

Aus der  
Klinik für Kardiologie, Pneumologie und Angiologie  
(Direktor: Univ.-Prof. Dr. med. Malte Kelm)  
der Medizinischen Fakultät  
der Heinrich-Heine-Universität Düsseldorf

## **Risikoadjustierte Strategien in interventioneller Kardiologie und kardiovaskulärer Intensivmedizin**

**Habilitationsschrift**  
zur Erlangung der Venia Legendi für das Fach  
Innere Medizin  
der Medizinischen Fakultät  
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von  
**Dr. med. Georg Ulrich Wolff**  
aus Ostercappeln

Düsseldorf 2023

*Meiner lieben Familie*



# 1 Inhaltsverzeichnis

|       |                                                                                                                                                                                                                          |     |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 1     | Inhaltsverzeichnis.....                                                                                                                                                                                                  | 3   |
| 2     | Der Habilitation zugrundeliegende Originalarbeiten.....                                                                                                                                                                  | 5   |
| 3     | Einleitung .....                                                                                                                                                                                                         | 7   |
| 3.1   | Chancen und Risiken evidenzbasierter kardiovaskulärer Medizin .....                                                                                                                                                      | 7   |
| 3.2   | Patientenindividuelle Risiko-/Nutzen-Abwägung mithilfe von Risikomodellen .....                                                                                                                                          | 9   |
| 3.3   | Populationsbasierte Risiko-/Nutzen-Abwägung mittels Meta-Analyse .....                                                                                                                                                   | 10  |
| 3.4   | Zielsetzung dieser Habilitationsschrift .....                                                                                                                                                                            | 11  |
| 4     | Dargestellte Arbeiten .....                                                                                                                                                                                              | 12  |
| 4.1   | Patientenindividuelle Risiko-/Nutzenabwägung mithilfe von Risikomodellen .....                                                                                                                                           | 12  |
| 4.1.1 | Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center .....                                              | 12  |
| 4.1.2 | National Cardiovascular Data Registry-Acute Kidney Injury (NCDR) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort ..... | 24  |
| 4.1.3 | Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort .....                                                                | 35  |
| 4.1.4 | Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients .....                                                                                     | 44  |
| 4.1.5 | Disease-course adapting machine learning prognostication models in critically ill elderly COVID-19 patients: a multi-centre cohort study with external validation .....                                                  | 54  |
| 4.2   | Populationsbasierte Risiko-/Nutzenabwägung mithilfe von Metaanalysen zur Evaluation interventioneller und adjunktiver Therapien .....                                                                                    | 69  |
| 4.2.1 | Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis .....                                                                                                     | 69  |
| 4.2.2 | Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients .....                                   | 83  |
| 4.2.3 | Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis .....                                              | 96  |
| 4.2.4 | Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke: A Meta-analysis.....                                                                                                                  | 108 |
| 4.2.5 | Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes .....                                                                                                                      | 114 |
| 5     | Diskussion.....                                                                                                                                                                                                          | 131 |
| 5.1   | Patientenindividuelles Risikoassessment in koronarvaskulären Herzkatheteruntersuchungen und in TAVI-Eingriffen .....                                                                                                     | 131 |

|       |                                                                                 |     |
|-------|---------------------------------------------------------------------------------|-----|
| 5.2   | Risikoadjustiertes Risikomanagement .....                                       | 133 |
| 5.3   | Optimierung von Risikomodellen unter Anwendung von künstlicher Intelligenz .... | 134 |
| 5.4   | Meta-Analyse als Methodik zur populationsbasierten Risiko-/Nutzenabwägung ...   | 135 |
| 6     | Zusammenfassung .....                                                           | 138 |
| 7     | Literaturverzeichnis .....                                                      | 139 |
| 8     | Verzeichnis eigener Publikationen und Kongressbeiträge .....                    | 146 |
| 8.1   | Originalarbeiten .....                                                          | 146 |
| 8.2   | Übersichtsartikel .....                                                         | 151 |
| 8.3   | Fallberichte und Kommentare .....                                               | 152 |
| 8.4   | Buchbeiträge / Zeitschriftenbeiträge ohne Pubmed-Listung .....                  | 153 |
| 8.5   | Kongressbeiträge .....                                                          | 153 |
| 8.5.1 | Posterpräsentationen .....                                                      | 153 |
| 8.5.2 | Vorträge .....                                                                  | 155 |
| 9     | Lebenslauf .....                                                                | 157 |
| 10    | Danksagung .....                                                                | 160 |

## 2 Der Habilitation zugrundeliegende Originalarbeiten

Die folgenden Originalarbeiten liegen dieser Habilitation zugrunde:

1. **Wolff G**, Lin Y, Quade J, Bader S, Kosejian L, Brockmeyer M, Karathanos A, Parco C, Krieger T, Heinen Y, Perings S, Albert A, Icks A, Kelm M, Schulze V. Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center. *Clin Res Cardiol.* 2020;109(2):235-45.
2. Parco C, Brockmeyer M, Kosejian L, Quade J, Trostler J, Bader S, Lin Y, Sokolowski A, Hoss A, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, **Wolff G**. National Cardiovascular Data Registry-Acute Kidney Injury (NCDRI) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort. *J Nephrol.* 2021;34(5):1491-500.
3. Parco C, Brockmeyer M, Kosejian L, Quade J, Trostler J, Bader S, Lin Y, Karathanos A, Krieger T, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, **Wolff G**. Modern NCDRI and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort. *Int J Cardiol.* 2021;329:28-35.
4. **Wolff G**, Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K, Maier O, Sedaghat A, Polzin A, Sugiura A, Jung C, Grube E, Westenfeld R, Icks A, Zeus T, Sinning JM, Baldus S, Nickenig G, Kelm M, Veulemans V. Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients. *Clin Res Cardiol.* 2021;110(3):368-76.
5. Jung C, Mamandipoor B, Fjolner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, **Wolff G**, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, De Lange DW, Guidet B, Flaatten H, Osmani V. Disease-Course Adapting Machine Learning Prognostication Models in Elderly Patients Critically Ill With COVID-19: Multicenter Cohort Study With External Validation. *JMIR Med Inform.* 2022;10(3):e32949.
6. Karathanos A, Lin Y, Dannenberg L, Parco C, Schulze V, Brockmeyer M, Jung C, Heinen Y, Perings S, Zeymer U, Kelm M, Polzin A, **Wolff G**. Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis. *Can J Cardiol.* 2019;35(11):1576-88.

7. Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, **Wolff G**, Dias S, Claessen B, Brouwer M, Tarantini G, Iliceto S, Brockmeyer M, Kowalewski M, Lin Y, Eikelboom J, Musumeci G, Lee L, Lip GY, Valgimigli M, Berti S, Kelm M. Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients. *Thromb Haemost.* 2015;114(5):933-44.
8. **Wolff G**, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP. Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. *Circ Heart Fail.* 2017;10(1).
9. Lin Y, Schulze V, Brockmeyer M, Parco C, Karathanos A, Heinen Y, Gliem M, Hartung HP, Antoch G, Jander S, Turowski B, Perings S, Kelm M, **Wolff G**. Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke: A Meta-analysis. *JAMA Neurol.* 2019;76(7):850-4.
10. **Wolff G**, Lin Y, Akbulut C, Brockmeyer M, Parco C, Hoss A, Sokolowski A, Westenfeld R, Kelm M, Roden M, Schlesinger S, Kuss O. Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes. *ESC Heart Fail.* 2022.

Die Arbeiten wurden mit freundlicher Genehmigung der Verlage als Teil dieser Arbeit gedruckt.

## 3 Einleitung

### 3.1 Chancen und Risiken evidenzbasierter kardiovaskulärer Medizin

Kardiovaskuläre Erkrankungen sind der weltweit führende Grund für Morbidität und Mortalität in entwickelten Ländern (1-3). In Deutschland sind im Jahr 2020 338.001 Patienten an einer kardiovaskulären Erkrankung verstorben (34% aller Todesfälle) (4), davon sind die ischämischen Herzkrankheiten (koronare Herzkrankheit (KHK) und Herzinfarkt) für >120.000 Todesfälle pro Jahr verantwortlich. Auch Herzinsuffizienz (in 2020 ~35.000 Todesfälle) und Herzklappenkrankheiten (in 2020 ~20.000 Todesfälle) haben große und über die Jahre zunehmende Bedeutung (5). Über 1,5 Millionen stationäre Krankenhausbehandlungen pro Jahr (5) zeigen die epidemiologische Relevanz kardiovaskulärer Erkrankungen, aber auch die Intensität der Symptomatik, unter welcher Patienten leiden, sowie die Komplexität der dafür angewandten Therapie.

Moderne Therapien sind das Ergebnis einer anhaltenden technischen und pharmakologischen Evolution mit Evaluation in randomisierten kontrollierten Studien (RCT): Die primäre perkutane Koronarintervention (PCI) im akuten ST-Strecken-Hebungsinfarkt (STEMI) hat die Sterblichkeit im Vergleich zur intravenösen Lysetherapie bedeutend reduziert (6, 7). Pharmakologische Strategien der Thrombozytenaggregationshemmung und Antikoagulation wurden weiterentwickelt (8-12), ebenso wie mehrere Generationen von koronaren Stents (13). Im Nicht-ST-Strecken-Hebungsinfarkt (NSTEMI) hat die *früh-invasive Strategie* in Hochrisiko-Patienten prognostische Vorteile gezeigt (14-17). Gleichzeitig profitieren Patienten mit niedrigerem ischämischem Risiko jedoch nicht immer (18, 19) und im chronischen Koronarsyndrom ist die Nutzen-Risiko-Abwägung einer Revaskularisierung besonders diffizil (20, 21). Der Transkatheter-Aortenklappenersatz (TAVI) hat sich als schonende und prognoserelevante Alternative zum chirurgischen Klappenersatz klinisch und technisch entwickelt (22), bis in Niedrig-Risiko-Kollektive hinein (23). In der kardiovaskulären Intensivmedizin wurden u.a. Therapiestrategien für die schwere Herzinsuffizienz (24-26) und den kardiogenen Schock evaluiert (27, 28), die Behandlung des akuten ischämischen Schlaganfalls revolutioniert (29) und nicht zuletzt wurde im Verlauf der COVID-Pandemie (30, 31) umfangreiche Evidenz zur Behandlung schwerer COVID-Pneumonien akkumuliert.

Die moderne evidenzbasierte kardiovaskuläre Medizin (32, 33) integriert zum Nutzen des Patienten die klinische Erfahrung des behandelnden Arztes, die Werte und Wünsche des Patienten und die beste vorhandene Evidenz zu einer Behandlungsentscheidung. In diesem Sinne sind Leitlinienempfehlungen als Grundlage für Nutzen-/Risikoabwägungen in vielen klinischen Situationen erarbeitet worden, z.B. im chronischen (34) oder akuten Koronarsyndrom (ACS) (35, 36), in der koronaren Revaskularisierung mittels PCI oder

koronarer Bypass-Chirurgie (CABG) (37, 38), in der Diagnostik und Therapie der Herzinsuffizienz (39, 40) und valvulärer Erkrankungen (39, 41).

Mit immer wirksameren Therapien entsteht jedoch auch ein immer größeres Potenzial für Nebenwirkungen – und Risiko-Nutzen-Abwägungen sind daher ein kritischer Teil der kardiovaskulären Medizin: Eine beständig im Fluss befindliche Studienlage, aber insbesondere auch der demographische Wandel in westlichen Gesellschaften mit älteren und morbideren kardiovaskulären Patienten mit gleichzeitig bestehendem Diabetes mellitus, Obesitas und chronischer Niereninsuffizienz (1, 2, 42, 43) machen individuelle Therapieentscheidungen hoch komplex.

Die Sicherheit einer Therapie für den Patienten hat eine ebenso große Bedeutung, wie die Effektivität der Therapie im Hinblick auf ihr Behandlungsziel.

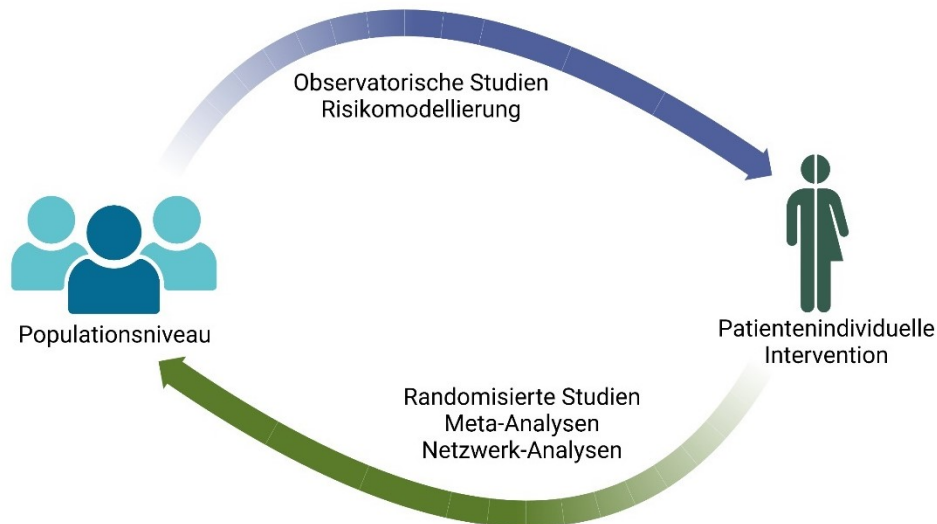
*“Primum non nocere, secundum cavere, tertium sanare.”*

*“Zuerst nicht schaden, zweitens vorsichtig sein, drittens heilen.”*

*Auguste François Chomel (1788-1858)*

Dieser Leitsatz der Medizin, dessen wortwörtlicher Ursprung a.e. auf A. Chomel zurückzuführen ist (44), wird inhaltlich dem *Corpus hippocraticum* zugeschrieben (45) und ermahnt diejenigen, die in der Heilkunst tätig sind, zu Vorsicht und Zurückhaltung in der Anwendung von Medizin – primär, um dem Patienten nicht zu schaden. Seine Ziele können jedoch auch ins Gegenteil umschlagen – ins sog. Risk-Treatment-Paradoxon: Im NSTEMI gibt es z.B. Hinweise (46), dass gerade Hochrisiko-Patienten – möglicherweise aus Angst vor Komplikationen – zurückhaltender behandelt werden, assoziiert mit einer schlechteren Prognose.

Diese Risiko-Nutzen-Abwägungen sind daher für den behandelnden Arzt eine große Herausforderung in der individuellen Therapie eines jeden Patienten und müssen bei einem hohen Anteil an Notfällen in der kardiovaskulären Medizin häufig unter Zeitdruck getroffen werden. Neben der klinischen Erfahrung des Behandlers können Methoden zur individuellen Risikovorhersage, aber auch meta-analytische Verfahren zur Integration klinischer Studiendaten eine bestmögliche Risiko-Nutzen-Abwägung unterstützen.



Graphischer Abstract: Daten aus randomisierten klinischen Studien, Meta- und Netzwerk-Analysen von patientenindividuellen Interventionen erlauben die Kalkulation von Effektschätzern für Risiko-/Nutzen-Abwägungen auf Populationsniveau. Daten aus Beobachtungsstudien großer Patientenkohorten erlauben individuelle Risiko-/Nutzen-Abwägungen mithilfe von Risikomodellen, geeignet für die Vorhersage von Ereignissen oder Auftreten von Komplikationen. Eigene Abbildung, erstellt mit BioRender.com.

### 3.2 Patientenindividuelle Risiko-/Nutzen-Abwägung mithilfe von Risikomodellen

Das individuelle Risiko eines Patienten für ein adverses Event (Tod, Blutung, Nierenversagen, Schlaganfall etc.) im Rahmen eines Eingriffs oder einer intensivmedizinischen Behandlung hängt von einer Vielzahl an Faktoren ab (47-50), u.a. von seinen demographischen Daten und klinischem Zustand (Alter, Geschlecht, Komorbiditäten etc.), dem Setting (z.B. Notfall vs. elektiv) und der Intensität seiner Symptomatik (z.B. kardiogener Schock vs. stabiler Kreislauf, Organversagen etc.), sowie prozeduralen und organisatorischen Faktoren (z.B. Tageszeit, Zugangsweg, Erfahrung des Operators etc.). Statistische Risikomodelle helfen mit Rückgriff auf große Datenbanken diese Faktoren zu integrieren, das Risiko zu objektivieren und dem Behandler eine Risikoabschätzung für adverse Events zu erleichtern. Es besteht gute Evidenz, dass ein systematisches Risikoassessment mithilfe solcher Risikomodelle der reinen klinischen Einschätzung des Patientenrisikos überlegen ist (51-54). Risikomodelle werden von kardiovaskulären Leitlinien im akuten Koronarsyndrom (STEMI (36) und NSTEMI (35)) und in der koronaren Revaskularisierung (38) empfohlen, sowie für die Durchführung von TAVI-Eingriffen (39, 41). Beispiele dafür sind die *Global Registry of Acute Coronary Events* (GRACE) (55-57) Modelle, die *Mehran Scores* (58, 59), oder die Risikomodelle des amerikanischen

*National Cardiovascular Data Registry* (NCDR) (60-64). In der Intensivmedizin sind Risikomodelle akzeptierter Standard für die Einschätzung von Krankheitsschweregrad und Prognose, z.B. mittels APACHE- (50), SAPS- (65) oder SOFA-Scores (66). In allen Bereichen soll eine akkurate Risikovorhersage helfen, risikoadjustierte Therapien zum Benefit des Patienten einzusetzen (67, 68).

Trotz der Verfügbarkeit und Empfehlungen dieser Methoden gibt es ein anhaltendes Defizit in der Anwendung solcher Risikomodelle. Dynamische Veränderungen der Behandlungsstandards, aber auch die Anwendung eines Risikomodells außerhalb einer validierten Patientenpopulation können die Vorhersage des Modells inakkurat (69, 70) und den Nutzen fraglich machen. Eine externe Validierung solcher Modelle ist daher von besonderer Bedeutung.

### 3.3 Populationsbasierte Risiko-/Nutzen-Abwägung mittels Meta-Analyse

Der evidenzbasierte Nutzen einer Intervention/Operation oder pharmakologischen Behandlung für einen Patienten geht im optimalen Fall (Evidenzgrad A) aus den übereinstimmenden Ergebnissen mehrerer randomisierter kontrollierter Studien im Vergleich zum Placebo oder einer Standardbehandlung hervor, und/oder aus Meta-Analysen solcher Studien (71, 72). Hieraus ermitteln sich auch durchschnittliche Risiken für Nebenwirkungen und adverse Events, so dass eine Risiko-/Nutzen-Abwägung für die beobachtete Population möglich wird. Dieser höchste Grad der Evidenz (Evidenzgrad A) liegt jedoch nur <15% aller Leitlinienempfehlungen der europäischen und amerikanischen kardiovaskulären Fachgesellschaften zugrunde (71, 72) – Gründe dafür sind mannigfaltig (73).

Meta-analytische Verfahren – angewandt seit den 1970er Jahren (74) – werden genutzt, die oftmals lückenhafte Evidenz zu einer Therapie systematisch zu analysieren, die Ergebnisse einzelner Studien qualitativ und quantitativ zu integrieren und mit höherer Sicherheit und Präzision zu einem Effektschätzer zu kommen, als die eingeschlossenen einzelnen Studien (75). Netzwerk-Analysen ermöglichen den Vergleich mehrerer Therapiestrategien miteinander (76). Der meta-analytische Vergleich relativer und absoluter Behandlungseffekte (77) und der Number-needed-to-treat (78) kann wichtige Einblicke in die Effektivität einer Behandlung und ihre Risiken geben.

Meta-analytische Methodik ist mittlerweile hoch standardisiert, z.B. bieten Arbeiten der *Cochrane Collaboration* (79) und das *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Statement (80) feste Leitfäden für Wissenschaftler. Die daraus resultierenden Ergebnisse für die evidenzbasierte Medizin sind hoch relevant, was sich in häufigen Zitationen meta-analytischer Arbeiten widerspiegelt (81).



### 3.4 Zielsetzung dieser Habilitationsschrift

Diese Habilitationsschrift fasst wissenschaftliche Arbeiten aus diesen zwei methodischen Bereichen zur Beurteilung risikoadjustierten Strategien in interventioneller Kardiologie und in kardiovaskulärer Intensivmedizin zusammen:

- a) Arbeiten zur individuellen Risiko-Vorhersage eines Patienten mithilfe von statistischen Risikomodellen, im Rahmen von koronarvaskulären Eingriffen, von TAVI-Eingriffen und in der Intensivmedizin. Hauptaugenmerk lag in diesen Arbeiten auf Leistungsindices der Risikoprädiktion von etablierten, leitlinienempfohlenen Modellen gegenüber modernen Alternativen in unterschiedlichen klinischen Settings. Weiterhin wurden Ansätze künstlicher Intelligenz für die Optimierung der individuellen Risikoprädiktion untersucht.
- b) Arbeiten zu meta-analytischen Methoden für populationsbasierte Risiko-/Nutzen-Abwägungen, insbesondere in adjunktiven Therapien in der interventionellen Kardiologie (Thrombozytenaggregationshemmung, Herzinsuffizienztherapie und Antikoagulation) und zu klinischen Outcomes von Eingriffen zur Revaskularisierung. Hauptaugenmerk lag in diesen Arbeiten auf der Auswahl von spezifischer Methodik.

Wissenschaftliche Arbeiten aus beiden Themengebieten werden in dieser Habilitationsschrift zunächst dargestellt und anschließend diskutiert.

## 4 Dargestellte Arbeiten

### 4.1 Patientenindividuelle Risiko-/Nutzenabwägung mithilfe von Risikomodellen

#### ***4.1.1 Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center***

**Wolff G**, Lin Y, Quade J, Bader S, Kosejian L, Brockmeyer M, Karathanos A, Parco C, Krieger T, Heinen Y, Perings S, Albert A, Icks A, Kelm M, Schulze V.

Clin Res Cardiol. 2020;109(2):235-45

Pubmed PMID: 31236693

DOI: [10.1007/s00392-019-01506-x](https://doi.org/10.1007/s00392-019-01506-x)

Ziel dieser Studie war eine Validierung von drei statistischen Risikomodellen (62, 63, 82, 83) aus dem amerikanischen *National Cardiovascular Data Registry* (NCDR) zur Vorhersage von Ereignissen (Tod, schwere Blutungen und akutes Nierenversagen) im Rahmen von Herzkatheteruntersuchungen in einem Düsseldorfer Patientenkollektiv. In einer retrospektiven Analyse von 1637 Patienten, welche zwischen 2014 und 2018 am Universitätsklinikum Düsseldorf für ST-Streckenhebungsinfarkte (STEMI, n=565), Nicht-ST-Streckenhebungsinfarkte (NSTEMI, N=572) oder aus elektiven Gründen (n=500) herzkathetert wurden, zeigten sich sehr gute (Tod: c-index 0,93) bis gute (Blutungen, Nierenversagen: c-index >0,82) Diskriminationen der NCDR-Risikomodelle zwischen Hoch- und Niedrigrisikopatienten in der Vorhersage aller drei Outcomes; die Kalibration aller drei Modelle war jedoch mäßig und überschätzte (Blutungen) bzw. unterschätzte (Tod, akutes Nierenversagen) Ereignisraten in diesem Kollektiv.

Zusammenfassend zeigte sich – mit Abstrichen bei der Genauigkeit der Wahrscheinlichkeitsvorhersage von Ereignissen – eine sehr gute Anwendbarkeit aller drei NCDR-Risikomodelle zum Zweck einer Vorhersage der wichtigsten Komplikationen von Herzkatheteruntersuchungen in Düsseldorf – vom elektiven Setting reichend bis zum akuten Notfall im Rahmen von Herzinfarkten. Aufbauend auf den Ergebnissen dieser Studie wurde ein interventionelles Risikomanagement an unserer Klinik etabliert, sowie weitere wissenschaftliche Untersuchungen angestellt, welche in Kapiteln 4.1.2 bis 4.2.4 dargestellt werden.



# Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center

Georg Wolff<sup>1</sup> · Yingfeng Lin<sup>1</sup> · Julia Quade<sup>1</sup> · Selina Bader<sup>1</sup> · Lucin Kosejian<sup>1</sup> · Maximilian Brockmeyer<sup>1</sup> · Athanasios Karathanos<sup>1</sup> · Claudio Parco<sup>1</sup> · Torben Krieger<sup>1</sup> · Yvonne Heinen<sup>1</sup> · Stefan Perings<sup>1</sup> · Alexander Albert<sup>3</sup> · Andrea Icks<sup>4,5,6</sup> · Malte Kelm<sup>1,2</sup> · Volker Schulze<sup>1</sup>

Received: 13 January 2019 / Accepted: 11 June 2019 / Published online: 24 June 2019  
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

## Abstract

**Background and purpose** The National Cardiovascular Data Registry (NCDR) risk scores for mortality, bleeding and acute kidney injury (AKI) are accurate outcome predictors of coronary catheterization procedures in North American populations. However, their application in German clinical practice remained elusive and we thus aimed to verify their use.

**Methods** NCDR scores for mortality, bleeding and AKI and corresponding clinical outcomes were retrospectively assessed in patients undergoing catheterization for ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or for elective coronary procedures at a German Heart Center from 2014 to 2017. Risk model performance was assessed using receiver-operating-characteristic curves (discrimination) and graphical analysis/logistic regression (calibration).

**Results** A total of 1637 patients were included, procedures were performed for STEMI (565 patients, 34.5%), NSTEMI (572 patients, 34.9%) and elective purposes (500 patients, 30.5%); 6% (13% of STEMI and 5% of NSTEMI patients) presented in cardiogenic shock and 3% with resuscitated cardiac arrest. Radial access was used in 38% of procedures and cross-over was necessary in 5%; PCI was performed in 60% of procedures. In-hospital mortality was 6.3% (STEMI 14.5%; NSTEMI 3.7%; elective 0%) and major bleedings occurred in 5.6% (STEMI 10.6%; NSTEMI 5.4%; elective 0.2%); AKI was detected in 18.1% of patients (STEMI 23.7%; NSTEMI 27.3%; elective 1.4%), amounting to KDIGO stage I/II/III in 11.5%/3.5%/3.2%. NCDR risk models discriminated very well for mortality [AUC 0.93 with 95% confidence interval (CI) 0.91–0.95] and well for major bleeding (AUC 0.82, CI 0.78–0.86) and any AKI (AUC 0.83, CI 0.81–0.86). Discrimination in the subgroup of patients with PCI was comparable (mortality: AUC 0.90; major bleeding: AUC 0.78; any AKI: AUC 0.79). However,

✉ Georg Wolff  
georg.wolff@med.uni-duesseldorf.de

<sup>1</sup> Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Medical Faculty, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany

<sup>2</sup> CARID-Cardiovascular Research Institute, Düsseldorf, Germany

<sup>3</sup> Clinic for Cardiovascular Surgery, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

<sup>4</sup> Institute for Health Services Research and Health Economics, Centre for Health and Society, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

<sup>5</sup> Institute for Health Services Research and Health Economics, German Diabetes Centre, Düsseldorf, Germany

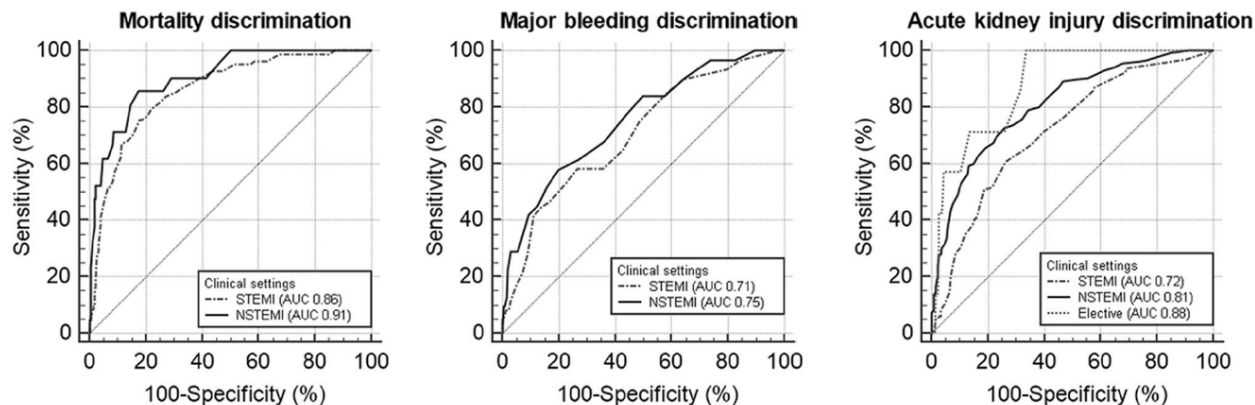
<sup>6</sup> German Institute for Diabetes Research, Neuherberg, Munich, Germany

calibration showed considerable underestimation of mortality and AKI in high-risk patients, while major bleeding was consistently overestimated (Hosmer–Lemeshow  $p < 0.02$  for all outcomes).

**Conclusions** The NCDR risk models showed excellent performance in discriminating high-risk from low-risk patients in contemporary German interventional cardiology. Model calibration for adverse event probability prediction, however, is limited and demands recalibration, especially in high-risk patients.

## Graphic abstract

### Validation of NCDR Risk Models for Mortality, Bleeding and Acute Kidney Injury in German Interventional Cardiology



**Keywords** NCDR · Risk prediction · Interventional cardiology · Mortality · Acute kidney injury · Bleeding

## Abbreviations

|        |                                                |
|--------|------------------------------------------------|
| AKI    | Acute kidney injury                            |
| AUC    | Area-under-the-curve                           |
| BARC   | Bleeding Academic Research Consortium          |
| BMI    | Body mass index                                |
| CABG   | Coronary artery bypass grafting                |
| CAD    | Coronary artery disease                        |
| CKD    | Chronic kidney disease                         |
| CVD    | Cardiovascular disease                         |
| DM     | Diabetes mellitus                              |
| GFR    | Glomerular filtration rate                     |
| N/A    | Not available                                  |
| NCDR   | National Cardiovascular Data Registry          |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| NYHA   | New York Heart Association                     |
| PAD    | Peripheral artery disease                      |
| PCI    | Percutaneous coronary intervention             |
| STEMI  | ST-segment elevation myocardial infarction     |

scoring models in the settings of acute coronary syndrome (ACS) (ST-segment elevation myocardial infarction (STEMI) [3, 4] and non-ST-segment elevation myocardial infarction (NSTEMI) [5, 6]) as well as in elective percutaneous coronary intervention (PCI) for stable coronary artery disease [7, 8]. Score-facilitated accurate patient risk assessment should help to guide pre-, peri- and postprocedural therapy.

The National Cardiovascular Data Registry (NCDR) risk models for prediction of adverse clinical outcomes incorporate details of clinical setting, patient characteristics and comorbidities and have been validated in the largest North American patient cohorts to date [9–13]. While this guarantees their accuracy and validity in the original populations, their applicability to German patients and contemporary daily clinical practice remains elusive.

We thus aimed to validate the NCDR scores for mortality, bleeding and acute kidney injury (AKI) in our local patient cohorts in different settings of contemporary interventional cardiology.

## Introduction

Multiple factors of procedural setting and patient comorbidities determine risk for adverse clinical outcomes [1, 2] in modern interventional cardiology. Cardiovascular societies recommend patient risk stratification by use of statistical risk

## Methods

This study was positively evaluated by the ethics committee of the Heinrich-Heine-University Düsseldorf (Study-no. 6050R, Registration-ID: 2017074349) and is registered at clinicaltrials.gov (NCT03671356).



## Patients, clinical settings and data collection

All patients undergoing coronary catheterization at University Hospital Düsseldorf between 2014 and 2017 in the clinical settings of STEMI, NSTEMI or elective coronary procedures were eligible for inclusion in a retrospective analysis. All patients were stratified into clinical setting subsets according to medical records and were then randomly selected for inclusion, distributed evenly across the inclusion period. Preliminary sample size calculation based on expected clinical outcome frequencies (~ 5% for mortality and major bleeding, ~ 15% for AKI) and previous validation studies [14–17] resulted in an estimate of a least 1500 patients to perform score validation.

Patient characteristics, details of clinical presentation and symptoms, comorbidities, catheterization procedural characteristics, other diagnostic testing (e.g., routine blood laboratory, echocardiography) and in-hospital clinical outcomes were identified in medical records and collected into a dedicated database for further evaluation.

## Cardiac catheterization procedures

All patients were treated according to guideline-recommended clinical practice at our heart center [3, 5, 8]. A team consisting of an interventionalist, assistant nurse and technician primarily performed the procedure; additional assistance was provided in case of emergencies by secondary interventionalists and intensive care unit personnel. The whole range of medical intensive care including mechanical assist devices and cardiac surgery was available.

## Clinical outcomes definitions

In-hospital clinical outcomes of mortality, bleeding, and AKI were evaluated. Mortality was defined as any post-procedural death within the same hospital admission. Bleeding events were assessed according to the Bleeding Academic Research Consortium (BARC) definitions [18] and classified into minor bleedings (BARC 1 + 2) and major bleedings (BARC 3–5). AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) definitions [19] and classified into AKI stages 1–3.

## Missing data

For medical history and clinical presentation variables, missing data were imputed to “no”; missing values of variables relevant for risk score calculation were imputed to the mean (continuous variables) or median/mode (ordinal/categorical variables) of the population. Missing procedural data were not imputed. Missing data details are reported in the results section.

## Statistics

Statistical and graphical data analysis was performed using Access and Excel 2016 (Microsoft), SPSS 21.0 (IBM), MedCalc 18.10 (MedCalc Software, Belgium) and Graphpad Prism 7.0 (Graphpad Software Inc.). Continuous data with normal distribution (according to Shapiro–Wilk tests) are presented as means  $\pm$  standard deviation (SD) and were compared using two-sided Student’s *t* tests; continuous data without normal distribution (according to Shapiro–Wilk tests) are presented as median and interquartile range and were compared using two-sided Mann–Whitney *U* tests; ordinal/categorical data are presented as counts and % of total and were compared using Chi-squared and Fisher’s exact tests (for expected values  $< 5$ ); receiver-operating-characteristic (ROC) curves were compared according to DeLong et al. [20]. Statistically significant differences of any test result were assumed at an  $\alpha$  probability  $< 0.05$ .

The NCDR risk scoring models for prediction of mortality [9], bleeding [11] and AKI [12] were calculated for individual patients. Parameters relevant for the mortality model were STEMI, age, BMI, CVD, PAD, chronic lung disease, prior PCI, diabetes mellitus, GFR, ejection fraction, cardiogenic shock/PCI status, NYHA class within 2 weeks and cardiac arrest within 24 h; parameters relevant for the bleeding model were STEMI, age, BMI, previous PCI, chronic kidney disease, shock, cardiac arrest within 24 h, female gender, Hb value and PCI status; parameters relevant for the AKI model were age, heart failure within 2 weeks, GFR, diabetes mellitus, prior heart failure, prior CVD, NSTEMI/unstable angina/STEMI, prior cardiogenic shock, prior cardiac arrest, anemia and intra-aortic balloon pump. Risk model performance was evaluated as follows: (1) all scoring variables were weighed according to model definitions; (2) weighed variables were summarized to obtain an individual summary risk score for each patient; (3) risk model discrimination accuracy was evaluated in a ROC analysis of clinical outcomes using a nonparametric approach [20]; *c*-index values [21]/areas-under-the-curve (AUC) with 95% confidence intervals (CI) are reported, with Youden indices [22] with respective sensitivity/specificity values; and (4) risk model calibration/goodness-of-fit was graphically analyzed by stratifying patients into risk deciles and comparison of observed vs. expected events within risk strata; it was formally tested using a logistic regression model and the Hosmer–Lemeshow goodness-of-fit test [23].

## Results

### Patient characteristics

Patient baseline characteristics are shown in Table 1: A total of 1637 patients [median age 70 (59–78) years, 69.3% male]

were included [565 with STEMI (34.5%), 572 with NSTEMI (34.9%), 500 with elective coronary procedures (30.5%)]. Cardiovascular risk factors of arterial hypertension, hyperlipoproteinemia, diabetes mellitus (DM) and chronic kidney disease (CKD) were frequent; more than half of the patients already suffered from some manifestation of cardiovascular disease (CVD) at presentation.

Patients from the STEMI subset were youngest [65 (54–76)], healthier and less frequently diagnosed with CVD, while NSTEMI patients were oldest [74 (65–81)] and suffered from most extensive comorbidities [e.g., prior heart failure (47.9%), DM (37.4%) and CKD  $\geq 3$  (41.6%)]. Patients with elective coronary procedures had the highest prevalence of known coronary artery disease (CAD,

66.8%) and prior coronary procedures (56.4% PCI, 6.8% CABG). NCDR scores for all outcomes were highest in STEMI and lowest in elective procedures. Interventionalists showed a preference of femoral over radial vascular access in higher risk patients: median NCDR scores for radial vs. femoral vascular access differed significantly for mortality, bleeding and AKI (all  $p < 0.001$ , data not shown).

A summary of symptoms at admission is reported in Table 2: Unstable angina pectoris was the dominant symptom in ACS patients and stable angina in elective coronary procedures. Severe circulatory deterioration with cardiogenic shock (6.2%), cardiac arrest within 24 h (3.4%) or need for endotracheal intubation (2.3%) occurred predominantly in STEMI patients.

**Table 1** Patient characteristics and comorbidities for the whole study population (left column) and separately for patient subsets of STEMI, NSTEMI and elective procedures

|                         | All ( $n = 1637$ ) | STEMI ( $n = 565$ ) | NSTEMI ( $n = 572$ ) | Elective ( $n = 500$ ) |
|-------------------------|--------------------|---------------------|----------------------|------------------------|
| Age (years)             | 70 (59–78)         | 65 (54–76)          | 74 (65–81)           | 70 (60–76)             |
| BMI                     | 26.7 (24.2–30.0)   | 26.0 (23.7–29.0)    | 27.0 (24.1–30.5)     | 27.5 (24.8–30.5)       |
| Male sex (%)            | 1,135 (69.3)       | 400 (70.8)          | 395 (69.1)           | 340 (68.0)             |
| Arterial hypertension   | 1,243 (75.9)       | 351 (62.0)          | 470 (82.2)           | 422 (84.4)             |
| Hyperlipoproteinemia    | 695 (42.4)         | 181 (32.0)          | 262 (45.8)           | 252 (50.4)             |
| Diabetes mellitus       | 475 (29.0)         | 113 (20.0)          | 214 (37.4)           | 148 (29.6)             |
| Insulin-dependent       | 146 (8.9)          | 26 (4.6)            | 81 (14.2)            | 39 (7.8)               |
| Baseline renal function |                    |                     |                      |                        |
| eGFR > 90 ml/min        | 853 (52.1)         | 184 (32.5)          | 264 (46.2)           | 405 (81.0)             |
| eGFR 60–90 ml/min       | 327 (20.0)         | 224 (39.6)          | 81 (14.2)            | 22 (4.4)               |
| eGFR 30–60 ml/min       | 358 (21.9)         | 125 (22.1)          | 173 (30.2)           | 60 (12.0)              |
| eGFR 15–30 ml/min       | 61 (3.7)           | 21 (3.7)            | 35 (6.1)             | 5 (1.0)                |
| eGFR 0–15 ml/min        | 39 (2.4)           | 12 (2.1)            | 19 (3.3)             | 8 (1.6)                |
| Chronic dialysis        | 38 (2.3)           | 11 (1.9)            | 21 (3.7)             | 6 (1.2)                |
| Chronic lung disease    | 195 (11.9)         | 45 (8.0)            | 86 (15.0)            | 64 (12.8)              |
| Known                   |                    |                     |                      |                        |
| CAD                     | 725 (44.3)         | 107 (18.9)          | 284 (49.7)           | 334 (66.8)             |
| PAD                     | 166 (10.1)         | 32 (5.7)            | 79 (13.8)            | 55 (11)                |
| Cerebrovasc. disease    | 90 (5.5)           | 7 (1.2)             | 47 (8.2)             | 36 (7.2)               |
| Heart failure           | 439 (26.8)         | 32 (5.7)            | 274 (47.9)           | 133 (26.6)             |
| Atrial fibrillation     | 290 (17.7)         | 54 (9.5)            | 147 (25.7)           | 89 (17.8)              |
| Prior                   |                    |                     |                      |                        |
| CABG                    | 118 (7.2)          | 4 (0.7)             | 80 (13.9)            | 34 (6.8)               |
| PCI                     | 471 (28.8)         | 20 (3.5)            | 169 (29.5)           | 282 (56.4)             |
| Myocardial infarction   | 290 (17.7)         | 19 (3.4)            | 122 (21.3)           | 149 (29.8)             |
| Stroke/TIA              | 141 (8.6)          | 16 (2.8)            | 82 (14.3)            | 43 (8.6)               |
| Mortality NCDR Score    | 35 (22–46)         | 48 (39–59)          | 36 (28–43)           | 17 (11–23)             |
| Bleeding NCDR Score     | 70 (45–90)         | 95 (80–115)         | 70 (51–85)           | 30 (20–45)             |
| AKI NCDR Score          | 19 (12–27)         | 23 (18–31)          | 22 (15–33)           | 9 (6–14)               |

Data presented as  $n$  (%) or as median (IQR)

AKI acute kidney injury, BMI body-mass-index, eGFR estimated glomerular filtration rate, CAD coronary artery disease, IQR interquartile range, PAD peripheral artery disease, CABG coronary artery bypass grafting, PCI percutaneous coronary intervention

## Procedural characteristics

Procedural characteristics are shown in Table 3: Elective procedures were frequently performed with the radial approach (59.2%), while operators predominantly used femoral access in STEMI (79.7%). Procedures were most complicated in STEMI patients (duration, contrast volume, etc.) and were most often associated with PCI (94.3%), more than in NSTEMI (47.6%) and elective procedures (35.6%). The use of glycoprotein IIb/IIIa inhibitors was most frequent in STEMI (19.6%); however, it was not significantly associated with major bleeding events. Need for cardiac assist devices was highest in STEMI patients (Impella® 4.8%, extracorporeal life support 6.4%).

## In-hospital clinical outcomes

In-hospital clinical outcomes are reported in Table 4: Death from any cause was most frequent in STEMI (14.5%), lower in NSTEMI (3.7%) and non-existent in elective coronary procedures. About 2/3rd of all deaths were classified as cardiac death. Major bleedings happened in 5.6% of patients overall, again with highest rates in STEMI (10.6%), followed by NSTEMI (5.4%) and elective procedures (0.2%). Gastrointestinal bleedings (1.4%) and access site bleedings (1.3%) were most frequent. There was a significant association of bleeding events with femoral rather than radial access ( $p < 0.001$ ), while prior oral anticoagulant intake showed no significant impact. Acute kidney injury was the most frequent adverse event (18.1%) predominantly in NSTEMI

**Table 2** Patient symptoms at admission for the whole study population (left column) and separately for patient subsets of STEMI, NSTEMI and elective procedures

|                            | All ( $n = 1637$ ) | STEMI ( $n = 565$ ) | NSTEMI ( $n = 572$ ) | Elective ( $n = 500$ ) |
|----------------------------|--------------------|---------------------|----------------------|------------------------|
| Stable angina              | 538 (32.9)         | 83 (14.7)           | 197 (34.4)           | 258 (51.6)             |
| Unstable angina            | 445 (27.2)         | 263 (46.5)          | 162 (28.3)           | 20 (4.0)               |
| Dyspnea NYHA IV            | 143 (8.7)          | 56 (9.9)            | 75 (13.1)            | 11 (2.2)               |
| Arrhythmia                 | 189 (11.5)         | 53 (9.4)            | 90 (15.7)            | 46 (9.2)               |
| Cardiac arrest within 24 h | 56 (3.4)           | 44 (7.8)            | 12 (2.1)             | 0 (0.0)                |
| Endotracheal intubation    | 37 (2.3)           | 21 (3.7)            | 16 (2.8)             | 0 (0.0)                |
| Cardiogenic shock          | 102 (6.2)          | 73 (12.9)           | 29 (5.1)             | 0 (0.0)                |

Data presented as  $n$  (%)

NYHA New York Heart Association Classification, CCS Canadian Cardiovascular Society Classification

**Table 3** Procedural characteristics for the whole study population (left column) and separately for patient subsets of STEMI, NSTEMI and elective procedures

|                                         | All ( $n = 1637$ ) | STEMI ( $n = 565$ ) | NSTEMI ( $n = 572$ ) | Elective ( $n = 500$ ) |
|-----------------------------------------|--------------------|---------------------|----------------------|------------------------|
| Vascular access                         |                    |                     |                      |                        |
| Radial (%)                              | 37.8               | 20.3                | 34.3                 | 59.2                   |
| Femoral (%)                             | 62.2               | 79.7                | 65.7                 | 40.8                   |
| Crossover (%)                           | 4.8                | 4.9                 | 6.4                  | 4.4                    |
| Femoral vascular closure device         | 249 (15.2)         | 78 (13.8)           | 110 (19.2)           | 61 (12.2)              |
| Glycoprotein IIb/IIIa inhibitor         | 131 (8.0)          | 111 (19.6)          | 14 (2.4)             | 6 (1.2)                |
| Procedure duration (min)                | 47 (32–64)         | 56 (41–77)          | 47 (32–66)           | 36 (24–53)             |
| Contrast volume (ml)                    | 140 (80–200)       | 200 (140–250)       | 125 (80–200)         | 80 (50–150)            |
| Fluoroscopy time (min)                  | 10.1 (5.7–17.1)    | 13.3 (8.6–21.7)     | 9.8 (5.6–16.3)       | 6.9 (3.4–13.4)         |
| Dose area product (Gy*cm <sup>2</sup> ) | 5442 (2959–9684)   | 7843 (4621–12,259)  | 5311 (2892–9065)     | 3672 (2146–6943)       |
| PCI                                     | 983 (60.0)         | 533 (94.3)          | 272 (47.6)           | 178 (35.6)             |
| LM/LAD (% of all/% of PCI)              | 27/46              | 46/49               | 21/45                | 13/37                  |
| RCX (% of all/% of PCI)                 | 12/20              | 14/15               | 12/25                | 10/28                  |
| RCA (% of all/% of PCI)                 | 21/34              | 34/36               | 14/30                | 13/37                  |
| Impella®                                | 34 (2.1)           | 27 (4.8)            | 6 (1.0)              | 1 (0.2)                |
| Extracorporeal life support             | 38 (2.3)           | 36 (6.4)            | 2 (0.3)              | 0 (0.0)                |

Data presented as  $n$  (%) or as median (IQR)

IQR interquartile range, PCI percutaneous coronary intervention, LM left main stem, LAD left anterior descending artery, RCX ramus circumflexus, RCA right coronary artery



(27.3%) and STEMI (23.7%) patients; the majority of AKI in all subsets were classified as stage 1. There was a highly significant association between contrast volume and development of AKI ( $p < 0.001$ ).

## Risk model performance

### Mortality

For risk prediction of in-hospital mortality, 2.4% missing data were imputed for variables of ejection fraction, NYHA class, glomerular filtration rate (GFR) and body mass index (BMI). Model discrimination was very accurate (Fig. 1a: AUC 0.93 with CI 0.91–0.95). The Youden index was 0.71 at > 49 summary risk points (corresponding to ~ 3% mortality risk; sensitivity 86.5%; specificity 84.7%). Comparative model discrimination in subsets (Fig. 2a) was less accurate in STEMI (AUC 0.86 with CI 0.82–0.90) than NSTEMI (AUC 0.91 with CI 0.85–0.97) without reaching statistical significance ( $p = 0.24$ ). Elective procedures could not be calculated separately due to lack of events. Model discrimination in the 981 patients with PCI was comparably exact (AUC 0.90 with CI 0.87–0.93).

Graphical analysis of model calibration (Fig. 1a) showed underestimation of events in higher risk deciles (6–10), and logistic regression returned inadequate goodness-of-fit (Hosmer–Lemeshow  $p < 0.001$ ).

### Bleeding

For risk prediction of in-hospital bleeding, 0.6% missing data were imputed for variables of BMI, PCI status and hemoglobin levels. Model discrimination for major bleeding (AUC 0.82 with CI 0.78–0.86; Fig. 1b) was more accurate than prediction of any bleeding (AUC 0.65 with CI

**Fig. 1** Model discrimination (ROC curves) and model calibration (observed vs. predicted event diagrams) for clinical outcomes of in-hospital mortality (a), major bleeding (b) and acute kidney injury (c). AUC area under the curve = c-index, AKI acute kidney injury

0.61–0.70) or minor bleeding (AUC 0.58 with CI 0.55–0.60). For major bleeding, the Youden index was 0.49 at > 85 summary risk points (~ 11.4% major bleeding risk; sensitivity 75%; specificity 74%). Comparative model discrimination for major bleeding in subsets (Fig. 2b) was less accurate in STEMI and NSTEMI (AUC 0.71 vs. 0.75;  $p = 0.40$ ), elective procedures could not be calculated separately due to lack of events. Discriminative model performance in the subset of patients receiving PCI was slightly lower overall (AUC 0.78 with CI 0.73–0.83), with slight advantages in NSTEMI over STEMI patient subsets (Table 5).

Graphical analysis of model calibration (Fig. 1b) for major bleeding showed an overestimation of events in all risk deciles; statistical testing agreed with limited goodness-of-fit (Hosmer–Lemeshow  $p = 0.02$ ).

### Acute kidney injury

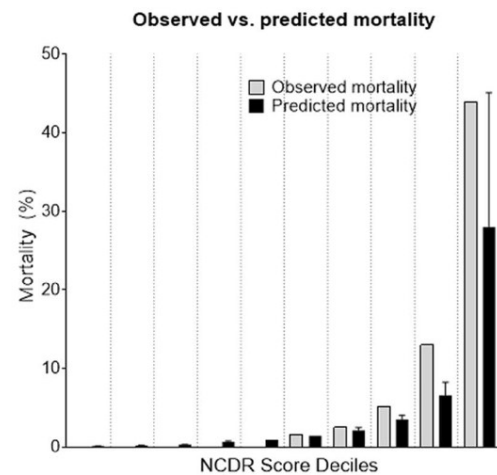
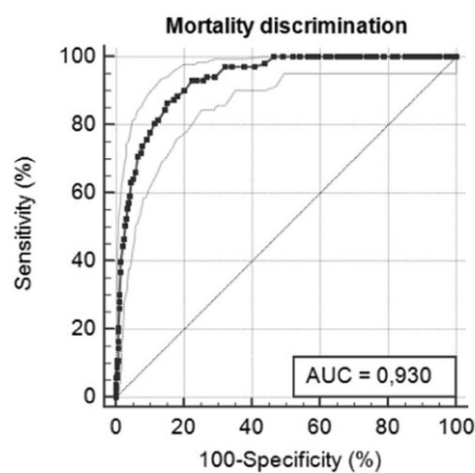
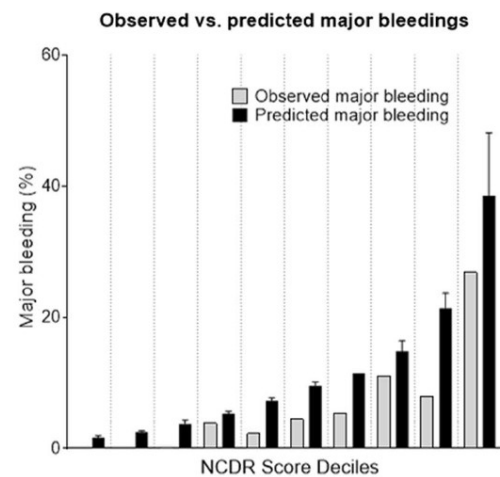
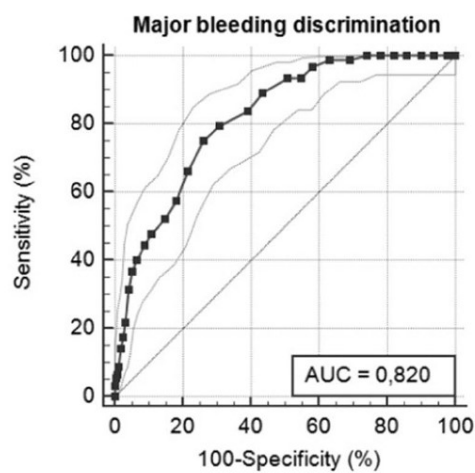
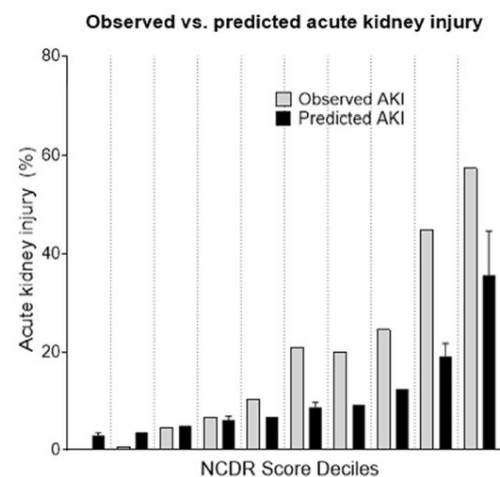
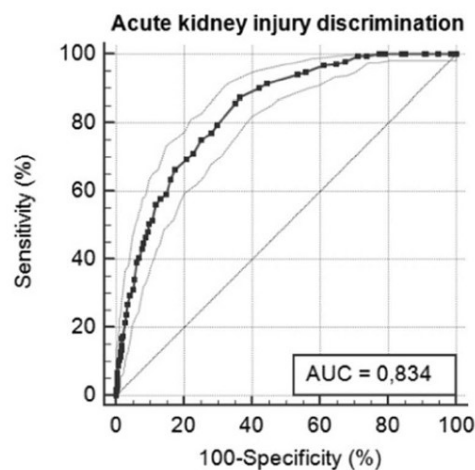
For risk prediction of in-hospital AKI, 0.7% missing data were imputed for variables of prior heart failure within 2 weeks and GFR. For any AKI prediction, model discrimination showed good accuracy (Fig. 1c: AUC 0.83 with CI 0.81–0.86). The Youden index was 0.51 at > 19 summary risk points (~ 6.7% AKI risk; sensitivity 88%; specificity 63%). Comparative model discrimination in subsets (Fig. 2c) was worst in STEMI (AUC 0.72 with CI 0.67–0.77), more accurate in NSTEMI (AUC 0.81 with CI 0.77–0.85;  $p = 0.2$ ) and significantly better in elective procedures (AUC 0.88 with CI 0.79–0.97;  $p$  vs. STEMI/NSTEMI  $< 0.01$ ). Again,

**Table 4** In-hospital clinical outcomes for the whole study population (left column) and separately for patient subsets of STEMI, NSTEMI and elective procedures

|                      | All ( $n = 1637$ ) | STEMI ( $n = 565$ ) | NSTEMI ( $n = 572$ ) | Elective ( $n = 500$ ) |
|----------------------|--------------------|---------------------|----------------------|------------------------|
| Death from any cause | 103 (6.3)          | 82 (14.5)           | 21 (3.7)             | 0 (0.0)                |
| Cardiac death        | 67 (4.1)           | 53 (9.4)            | 14 (2.4)             | 0 (0.0)                |
| Major bleeding       | 92 (5.6)           | 60 (10.6)           | 31 (5.4)             | 1 (0.2)                |
| Access site          | 22 (1.3)           | 12 (2.1)            | 9 (1.6)              | 1 (0.2)                |
| Intracranial         | 7 (0.4)            | 6 (1.1)             | 1 (0.2)              | 0 (0.0)                |
| Gastrointestinal     | 23 (1.4)           | 16 (2.8)            | 7 (1.2)              | 0 (0.0)                |
| Fatal                | 9 (0.5)            | 7 (1.2)             | 2 (0.3)              | 0 (0.0)                |
| Other                | 40 (2.4)           | 26 (4.6)            | 14 (2.4)             | 0 (0.0)                |
| Minor bleeding       | 135 (8.2)          | 47 (8.3)            | 61 (10.7)            | 27 (5.4)               |
| Acute kidney injury  | 297 (18.1)         | 134 (23.7)          | 156 (27.3)           | 7 (1.4)                |
| Stage 1              | 188 (11.5)         | 75 (13.3)           | 108 (18.9)           | 5 (1)                  |
| Stage 2              | 57 (3.5)           | 44 (7.8)            | 11 (1.9)             | 2 (0.4)                |
| Stage 3              | 52 (3.2)           | 15 (2.7)            | 37 (6.5)             | 0 (0.0)                |

Data presented as  $n$  (%)



**(A) Mortality****(B) Major bleeding****(C) Acute kidney injury**

model discrimination in patients receiving PCI was a little less exact (AUC 0.79 with CI 0.76–0.82). Model discrimination improved with AKI severity, from stage 1 (AUC 0.77 with CI 0.74–0.80) to stage 2 (AUC 0.80 with CI 0.76–0.85) and stage 3 AKI (AUC 0.90 with CI 0.86–0.94).

Graphical analysis of model calibration (Fig. 1c) for any AKI showed a considerable underestimation of events in higher risk deciles (6–10); statistical testing concurred (Hosmer–Lemeshow  $p < 0.001$ ).

## Discussion

We here present results of a performance analysis of NCDR risk prediction models for mortality, bleeding and acute kidney injury in interventional cardiology at our German Heart Center. Main results are: (1) discriminative abilities of NCDR risk scoring models for the three outcomes are excellent; (2) risk model calibration, however, has limited accuracy.

Main performance measures of any risk prediction model are (1) *discrimination* of low- and high-risk patients, and (2) *calibration/goodness-of-fit* of estimated and observed outcomes [24]—which is prediction of probabilities. Changes in clinical practice or application of a model to a different patient population may render risk models inaccurate [25, 26]. The NCDR risk scoring models for coronary catheterization procedures were developed in huge American populations of > 1,000,000 patients [9–12]. Most importantly, they are unique in their design for the whole range of coronary procedures—from low-risk elective settings to high-risk acute myocardial infarction and cardiogenic shock. Both qualities should render them particularly useful for routine application in interventional cardiology in Europe too, regardless of any specific setting. This study analyzes performance of risk models for all three clinical outcomes in our contemporary practice and across the whole range of coronary settings.

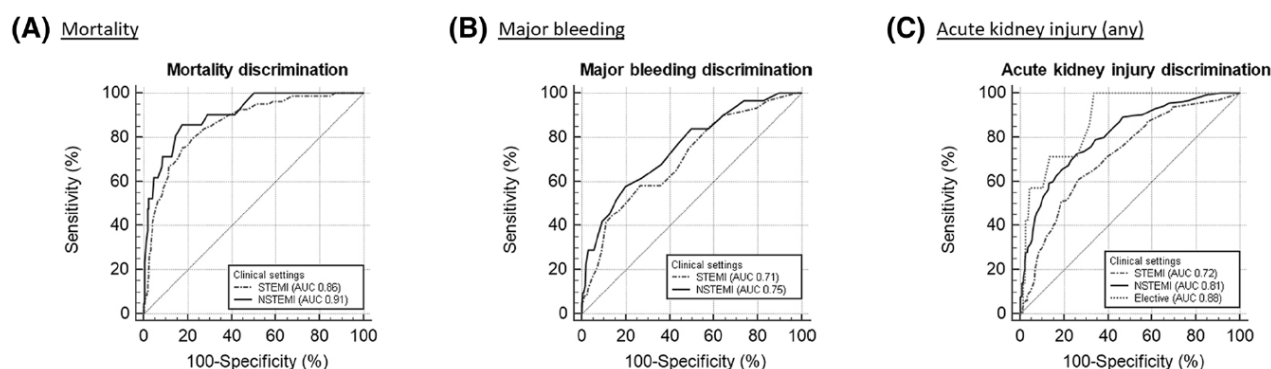
The NCDR models' discriminative performance was comparable—and for major bleeding and AKI even slightly superior—to the original NCDR populations [mortality: 0.93 (9); major bleeding: 0.77 (11); AKI: 0.71 (12)] in all patients. There was only little variance across clinical settings and diagnostic/interventional procedure status (Table 5 and Fig. 2). Interestingly, more serious outcomes [mortality (AUC 0.93), major bleeding (AUC 0.82), AKI stage 3 (AUC 0.90)] showed superior discrimination to less serious outcomes [minor bleeding (AUC 0.58), AKI stage 1 (AUC 0.77)]. There are several reports of external NCDR risk score validation studies: The mortality risk score has been validated in Portuguese (predominantly) STEMI patients of 2005–2013 [16], with comparable discrimination findings (AUC 0.87). The bleeding risk score has been evaluated

in a different US population (2009–2012; AUC 0.71) [27] and the AKI risk score was validated in Japanese patients (2008–2014; AUC 0.76) [15]. Our findings support these results and confirm accurate discrimination in our clinical practice and patients across the whole risk range.

In contrast to discrimination, calibration of all three risk models was inaccurate (Fig. 1): Graphical as well as statistical analysis confirmed overestimation of mortality and AKI in lower risk patients and underestimation in high-risk patients—while major bleedings were largely overestimated (Fig. 1). Corrupted calibration for mortality and AKI, especially in high-risk patients, has already been described in other validation studies [15, 16]—and is confirmed for all outcomes in this study. Fluctuations in risk model performance in interventional cardiology have been reported before [26]: Since data were collected in the original NCDR populations [9–12], interventional cardiology has undergone changes in device technology [28], pharmacologic management [29–32] and patient populations [33, 34]. More radial vascular access may reduce major bleedings [35] and AKI [36]; more emergency procedures and older/comorbid patients may increase mortality and acute kidney injury in high-risk patients. Additionally, we applied the slightly different BARC definition [18] rather than the NCDR definition [11] to assess bleedings, as its features allowed a more accurate event assessment in our medical records—however at the possible expense of calibration accuracy.

Our findings suggest that the risk factors incorporated into all three NCDR risk models very accurately discriminate patients at-risk vs. not-at-risk in our contemporary diagnostic and interventional procedures. However, the individual impact of these risk factors on exact adverse event probability estimation has limited accuracy. Applied weights within the risk model would need recalibration in a large contemporary patient cohort to obtain more accurate event probability prediction.

While the inclusion and differentiation of the whole range of patient risk are a particular strength of this study, it is limited by sample size: Separate conclusions in patients with elective procedures were impossible due to a very low adverse event rate in this subset (Tables 4, 5); calibration analysis especially in the lower risk range would improve with increasing patient numbers. The monocentric data collection limits generalizability of results and the mixture of femoral and radial access limits application of results to radial-only settings. The retrospective study design limits data quality and introduces need for imputation.



**Fig. 2** Comparative model discrimination (ROC curves) for patients in clinical settings of STEMI (dashed line), NSTEMI (solid line) and elective coronary procedures (dotted line), for clinical outcomes of in-hospital mortality (a), major bleeding (b) and any acute kidney injury (c)

**Table 5** Model discrimination performance for the whole study population (left column) and separately for patient subsets of STEMI, NSTEMI and elective procedures

| All procedures      | All ( <i>n</i> = 1637) | STEMI ( <i>n</i> = 565) | NSTEMI ( <i>n</i> = 572) | Elective ( <i>n</i> = 500) |
|---------------------|------------------------|-------------------------|--------------------------|----------------------------|
| Mortality           | 0.93 (0.91–0.95)       | 0.86 (0.82–0.90)        | 0.91 (0.85–0.97)         | N/A                        |
| Major bleeding      | 0.82 (0.78–0.86)       | 0.71 (0.64–0.78)        | 0.75 (0.67–0.84)         | N/A                        |
| Acute kidney injury | 0.83 (0.81–0.86)       | 0.72 (0.67–0.77)        | 0.81 (0.77–0.85)         | 0.88 (0.79–0.97)           |
| PCI only            | All ( <i>n</i> = 980)  | STEMI ( <i>n</i> = 532) | NSTEMI ( <i>n</i> = 272) | Elective ( <i>n</i> = 178) |
| Mortality           | 0.90 (0.87–0.93)       | 0.86 (0.82–0.90)        | 0.88 (0.80–0.96)         | N/A                        |
| Major bleeding      | 0.78 (0.73–0.83)       | 0.72 (0.64–0.79)        | 0.79 (0.69–0.88)         | N/A                        |
| Acute kidney injury | 0.79 (0.76–0.82)       | 0.72 (0.67–0.77)        | 0.80 (0.74–0.86)         | 0.95 (0.92–0.99)           |

Separate analyses for all procedures (top) and PCI only (bottom)

Data presented are area-under-the-curve (AUC) values of receiver-operating-characteristic (ROC) analyses (corresponding to *c*-indices) with 95% confidence intervals

N/A not available, PCI percutaneous coronary intervention

## Conclusion

The NCDR risk models are applicable to German clinical practice of coronary interventional cardiology to accurately discriminate patient risk of mortality, bleeding and acute kidney injury. Model calibration for exact adverse event probability prediction, however, is limited and demands recalibration, especially in high-risk patients.

**Author contributions** GW, MK and VS conceived and designed the study; JQ, SB and LK collected and analyzed data; GW and YL analyzed and interpreted data and drafted the manuscript; MB, AK, YH, CP, TK and SP supported data acquisition and analysis and critically revised the manuscript; MK, AI, AA and VS assumed project supervision, interpreted data and critically revised the manuscript. All authors read and accepted the submitted version of the manuscript.

**Funding** This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (no. 2018-32 to GW).

## Compliance with ethical standards

**Conflict of interest** All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## References

1. Block PC, Peterson ED, Krone R, Kesler K, Hannan E, O'Connor GT et al (1998) Identification of variables needed to risk adjust outcomes of coronary interventions: evidence-based guidelines for efficient data collection. *J Am Coll Cardiol* 32(1):275–282
2. Moscucci M, O'Connor GT, Ellis SG, Malenka DJ, Sievers J, Bates ER et al (1999) Validation of risk adjustment models for in-hospital percutaneous transluminal coronary angioplasty mortality on an independent data set. *J Am Coll Cardiol* 34(3):692–697
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al (2018) 2017 ESC guidelines for the management



- of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 39(2):119–177
4. American College of Emergency P, Society for Cardiovascular A, Interventions, O’Gara PT, Kushner FG, Ascheim DD et al (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(4):485–510
  5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F et al (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 37(3):267–315
  6. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr et al (2014) 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 130(25):e344–e426
  7. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B et al (2011) 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124(23):e574–e651
  8. Authors/Task Force M, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J et al (2014) 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 35(37):2541–2619
  9. Brennan JM, Curtis JP, Dai D, Fitzgerald S, Khandelwal AK, Spertus JA et al (2013) Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv* 6(8):790–799
  10. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV et al (2010) Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55(18):1923–1932
  11. Rao SV, McCoy LA, Spertus JA, Krone RJ, Singh M, Fitzgerald S et al (2013) An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI Registry. *JACC Cardiovasc Interv* 6(9):897–904
  12. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME et al (2014) Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc* 3(6):e001380
  13. Weintraub WS, Grau-Sepulveda MV, Weiss JM, DeLong ER, Peterson ED, O’Brien SM et al (2012) Prediction of long-term mortality after percutaneous coronary intervention in older adults: results from the National Cardiovascular Data Registry. *Circulation* 125(12):1501–1510
  14. Couto-Mallon D, Rodriguez-Garrido JL, Aldama-Lopez G, Calvino-Santos R, Pinon-Esteban P, Salgado-Fernandez J et al (2013) Validation of the National Cardiovascular Data Registry (NCDR) score for 30-day mortality prediction after Percutaneous Coronary Intervention (PCI) in a European cohort. *Eur Heart J* 34(suppl\_1):P1220
  15. Inohara T, Kohsaka S, Miyata H, Ueda I, Maekawa Y, Fukuda K et al (2016) Performance and validation of the US NCDR acute kidney injury prediction model in Japan. *J Am Coll Cardiol* 67(14):1715–1722
  16. Timoteo AT, Monteiro AV, Portugal G, Teixeira P, Aidos H, Ferreira ML et al (2016) Validation of two US risk scores for percutaneous coronary intervention in a single-center Portuguese population of patients with acute coronary syndrome. *Rev Port Cardiol* 35(2):73–78
  17. Wall JJS, Iqbal J, Andrews M, Teare D, Ghobrial M, Hinton T et al (2017) Development and validation of a clinical risk score to predict mortality after percutaneous coronary intervention. *Open Heart* 4(2):e000576
  18. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J et al (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 123(23):2736–2747
  19. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL et al (2012) Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2(1):1–138. <https://doi.org/10.1038/kisup.2012.1>
  20. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44(3):837–845
  21. Pencina MJ, D’Agostino RB Sr (2015) Evaluating discrimination of risk prediction models: the *C* statistic. *JAMA* 314(10):1063–1064
  22. Youden WJ (1950) Index for rating diagnostic tests. *Cancer* 3(1):32–35
  23. Hosmer DWJ, Lemeshow Sturdivant XR (2013) Applied logistic regression, 3rd edn. Wiley, Hoboken
  24. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N et al (2010) Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 21(1):128–138
  25. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS et al (2015) An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 162(4):266–275
  26. Matheny ME, Ohno-Machado L, Resnic FS (2005) Discrimination and calibration of mortality risk prediction models in interventional cardiology. *J Biomed Inform* 38(5):367–375
  27. Dobies DR, Barber KR, Cohoon AL (2015) Validity of a PCI Bleeding Risk Score in patient subsets stratified for body mass index. *Open Heart* 2(1):e000088
  28. Stefanini GG, Holmes DR Jr (2013) Drug-eluting coronary-artery stents. *N Engl J Med* 368(3):254–265
  29. Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, Wolff G, Dias S et al (2015) Comparative efficacy and safety of anti-coagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients. *Thromb Haemost* 114(5):933–944
  30. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S et al (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015

31. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C et al (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361(11):1045–1057
32. Hohnloser SH, Basic E, Nabauer M (2017) Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. *Clin Res Cardiol* 106(8):618–628
33. Grotti S, Bolognese L (2017) Interventional cardiology is changing: demographic, clinical and economic considerations. *J Cardiovasc Med (Hagerstown)* 18(Suppl 1):e67–e70
34. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M et al (2018) European Society of Cardiology: cardiovascular disease statistics 2017. *Eur Heart J* 39(7):508–579
35. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T et al (2015) Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 385(9986):2465–2476
36. Feldkamp T, Luedemann M, Spehlmann ME, Freitag-Wolf S, Gaensbacher J, Schulte K et al (2018) Radial access protects from contrast media induced nephropathy after cardiac catheterization procedures. *Clin Res Cardiol* 107(2):148–157

#### ***4.1.2 National Cardiovascular Data Registry-Acute Kidney Injury (NCDR) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort***

Parco C, Brockmeyer M, Kosejian L, Quade J, Tröstler J, Bader S, Lin Y, Sokolowski A, Hoss A, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, **Wolff G.**

J Nephrol. 2021 Oct;34(5):1491-1500

Pubmed PMID: 34363595

DOI: [10.1007/s40620-021-01124-9](https://doi.org/10.1007/s40620-021-01124-9)

In dieser Arbeit wurde – aufbauend auf der Validierungsstudie 4.1.1 – die Qualität der Risikovorhersage des NCDR-Risikomodells für Kontrastmittel-induziertes Nierenversagen (NCDR-AKI, (63)) im Rahmen von Herzkatheteruntersuchungen an unserer Klinik evaluiert und mit dem Goldstandard, dem Mehran-Risikomodell (58), verglichen.

Dazu wurden in 2067 Patienten Risikovorhersagen mittels NCDR-AKI- und Mehran-Modellen berechnet, sowie klinische Ereignisse von Kontrastmittel-induziertem Nierenversagen unterschiedlicher Stadien inkl. der Notwendigkeit für Dialysetherapie nach Herzkatheteruntersuchungen retrospektiv erhoben. Risikoprädiktion beider Modelle wurde anhand von Diskrimination (Genauigkeit des Modells in der Unterscheidung von Hoch- und Niedrigrisikopatienten) und Kalibration (Genauigkeit des Modells im Hinblick auf die Vorhersage der Ereigniswahrscheinlichkeit) verglichen.

Es zeigten sich sowohl für Kontrastmittel-induziertes Nierenversagen (c-index 0,75 vs. 0,69) als auch für die Notwendigkeit einer Dialysetherapie (c-index 0,85 vs. 0,75) bessere Diskriminationen des Risikos im NCDR-AKI- gegenüber dem Goldstandard Mehran-Risikomodell, wohingegen das Mehran-Modell besser kalibriert war.

Zusammenfassend zeigte das NCDR-AKI-Risikomodell eine hervorragende Leistung in der Vorhersage von akutem Nierenversagen inkl. Dialysetherapie im Rahmen von Herzkatheteruntersuchungen in unseren Patienten, bei denen es teilweise dem Goldstandard überlegen war.



# National Cardiovascular Data Registry-Acute Kidney Injury (NCDR) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort

Claudio Parco<sup>1</sup> · Maximilian Brockmeyer<sup>1</sup> · Lucin Kosejian<sup>1</sup> · Julia Quade<sup>1</sup> · Jennifer Tröstler<sup>1</sup> · Selina Bader<sup>1</sup> · Yingfeng Lin<sup>1</sup> · Alexander Sokolowski<sup>1</sup> · Alexander Hoss<sup>1</sup> · Yvonne Heinen<sup>1</sup> · Volker Schulze<sup>1</sup> · Andrea Icks<sup>2</sup> · Christian Jung<sup>1</sup> · Malte Kelm<sup>1</sup> · Georg Wolff<sup>1</sup>

Received: 17 December 2020 / Accepted: 12 July 2021 / Published online: 7 August 2021  
© The Author(s) 2021, corrected publication 2021

## Abstract

**Background** Contrast-induced nephropathy (CIN) is a major adverse event in patients undergoing coronary angiography. The Mehran risk model is the gold-standard for CIN risk prediction. However, its performance in comparison to more contemporary National Cardiovascular Data Registry-Acute Kidney Injury (NCDR-AKI) risk models remains unknown. We aimed to compare both in this study.

**Methods and results** Predictions of Mehran and NCDR-AKI risk models and clinical events of CIN and need for dialysis were assessed in a total of 2067 patients undergoing coronary angiography with or without percutaneous coronary intervention. Risk models were compared regarding discrimination (receiver operating characteristic analysis), net reclassification improvement (NRI) and calibration (graphical and statistical analysis). The NCDR risk model showed superior risk discrimination for predicting CIN (NCDR c-index 0.75, 95% CI 0.72–0.78; vs. Mehran c-index 0.69, 95% CI 0.66–0.72,  $p < 0.01$ ), and continuous NRI (0.22; 95% CI 0.12–0.32;  $p < 0.01$ ) compared to the Mehran model. The NCDR risk model tended to underestimate the risk of CIN, while the Mehran model was more evenly calibrated. For the prediction of need for dialysis, NCDR-AKI-D also discriminated risk better (c-index 0.85, 95% CI 0.79–0.91; vs. Mehran c-index 0.75, 95% CI 0.66–0.84;  $p_{\text{NCDRvsMehran}} < 0.01$ ), but continuous NRI showed no benefit and calibration analysis revealed an underestimation of dialysis risk.

**Conclusion** In German patients undergoing coronary angiography, the modern NCDR risk model for predicting contrast-induced nephropathy showed superior discrimination compared to the Mehran model while showing less accurate calibration. Results for the outcome ‘need for dialysis’ were equivocal.

✉ Georg Wolff  
Georg.Wolff@med.uni-duesseldorf.de

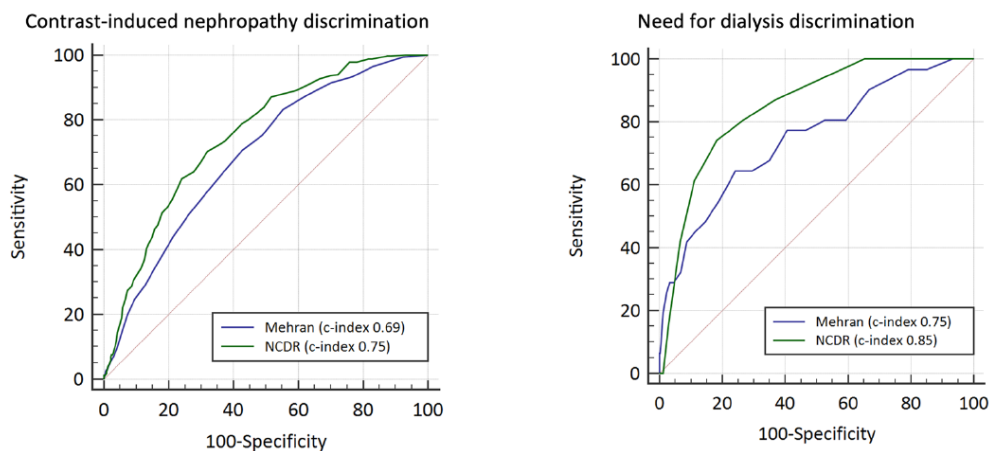
<sup>1</sup> Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Medical Faculty and University Hospital, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany

<sup>2</sup> Institute for Health Services Research and Health Economics, Medical Faculty and University Hospital, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany



## Graphic abstract

### NCDR vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort



**Keywords** NCDR · Mehran · Risk prediction · Acute kidney injury

#### Abbreviations

|        |                                                |
|--------|------------------------------------------------|
| AKI    | Acute kidney injury                            |
| AUC    | Area under curve                               |
| CI     | Confidence-interval                            |
| CIN    | Contrast-induced nephropathy                   |
| ROC    | Receiver operating characteristic              |
| PCI    | Percutaneous coronary intervention             |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| NRI    | Net reclassification improvement               |
| STEMI  | ST-segment elevation myocardial infarction     |

#### Introduction

Contrast-induced nephropathy (CIN) is a major adverse event for patients undergoing cardiac catheterization and is associated with increased mortality [1, 2]. CIN is defined as an impairment of renal function measured by an absolute ( $> 0.5$  mg/dl) or relative ( $> 25\%$ ) increase in serum creatinine within 48–72 h after application of iodinated contrast media [3]. CIN after coronary angiography heralds a higher patient risk for long-term decline in renal function [4] and thus has profound prognostic relevance.

Several risk factors have been found associated with an increased risk of developing CIN [5]. Taking the most

important risk factors (shock, congestive heart failure, older age, anemia, diabetes, contrast media volume, use of an intra-aortic balloon pump and chronic kidney disease) into account, in 2004 Mehran et al. developed a simple risk score to estimate the risk of developing CIN and need for dialysis [6]. To date, the original score has been validated in several cohorts [7, 8] and is the most established risk model for predicting CIN and need for dialysis. However, the more contemporary risk models of the National Cardiovascular Data Registry-Acute kidney Injury (NCDR-AKI) and NCDR-AKI-Dialysis (NCDR-AKI-D) based on data derived from 900,000 patients undergoing percutaneous coronary interventions (PCI) in the NCDR Cath-PCI Registry [9] showed promising performance in our external validation study [10]. The NCDR-AKI and NCDR-AKI-D models stratify the patients' risk of developing contrast-CIN by the following variables; age, acute decompensated heart failure, glomerular filtration rate, and diabetes, history of cardiovascular disease and heart failure, cardiogenic shock, cardiac arrest, anemia, use of an intra-aortic balloon pump.

Overall, identifying patients at risk and adequate preventive management remain key factors for improving patient outcomes. We thus aimed to compare the modern NCDR risk models to the established Mehran model for predicting contrast-induced nephropathy in a contemporary German patient cohort undergoing cardiac catheterization procedures with and without percutaneous coronary intervention.

## Methods

### Patient characteristics, clinical settings and data collection

Patients undergoing invasive coronary angiography at University Hospital Duesseldorf between 2014 and 2018 for reasons ranging from elective cardiac catheterization procedures to presentation with acute non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) were included in the study. All patients were treated according to current European guideline-recommended clinical practice for acute and chronic coronary syndromes [11–14]. Patient and procedural characteristics, as well as symptoms and results diagnostic testing were extracted from medical records and recorded into a dedicated database. History of chronic kidney disease was defined as a previous decline in renal function according to the current Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease guidelines [15].

### Clinical outcomes definitions

The main outcomes of interest were CIN and need for dialysis. CIN was defined as an absolute increase in creatinine of more than 0.5 mg/dl or more than 25% compared to the baseline value within 48–72 h after cardiac catheterization [6]. Need for dialysis was defined as renal replacement therapy due to insufficient urine output, high retention parameters, metabolic acidosis or relevant electrolyte disorders during hospitalization. CIN events in patients who underwent chronic renal replacement therapy were not considered. Secondary outcomes, e.g. in-hospital mortality, major bleeding or stroke are additionally reported (Table 2).

### Statistics

Data collection and descriptive statistics were done using Access (Microsoft), Excel (Microsoft) and SPSS 26 (IBM). Ordinal/categorical variables are presented as counts and % of total, continuous data are presented as means  $\pm$  standard deviation (SD). Statistical significance was assumed at a two-sided  $\alpha$  probability  $< 0.05$  for all analyses.

### Missing data

Missing data were imputed only if they were relevant for risk model calculation, either to the most common value (binary/ordinal/categorical variables) or to the mean (continuous variables) of the respective clinical

setting subgroup (NSTEMI, STEMI or elective). Details on missing variables as % of all model-relevant variables are reported in the Results section. Patients lacking information on relevant outcome variables (CIN or need for dialysis) were excluded. Sensitivity analysis of patients with complete datasets was additionally performed (no imputation).

### Risk model calculation

The Mehran B risk model was calculated to predict CIN and the need for dialysis [6]. The NCDR-AKI risk model was calculated to predict CIN [9], while the NCDR-AKI-D model was used to predict the need for dialysis [9]. For the calculation of individual risk scores, all relevant scoring parameters (Suppl. Tables 1–3) were weighted according to risk model definitions and summarized to obtain an individual summary risk score for each patient. Summary risk scores were assigned to event probabilities according to risk model definitions ([6, 9], Suppl. Tables 1–3).

### Risk model discrimination analysis

Risk model discrimination performance was analyzed using receiver operating characteristics (ROC) curves with area under the curve (AUC, c-index) comparisons using the non-parametric DeLong method [16]. All calculations were done using MedCalc v18.21 (MedCalc Software, Belgium). C-indices with 95% confidence intervals are reported [17, 18].

### Risk model reclassification analysis

Reclassification of patients with the NCDR risk models compared to the standard Mehran model was evaluated using the package PredictABEL for R Studio v4.0.3: net reclassification improvements (NRI; categorical and continuous) were calculated [19, 20] and tested for statistical significance. For categorical NRI, all patients were classified into arbitrary categories: predicted CIN risk of 0–10% (low risk), 10–20% (intermediate risk) and 20–100% (high-risk) and predicted dialysis risk of 0–1% (low risk), 1–5% (intermediate risk) and 5–100% (high risk) (Suppl. Tab. 4 and 5); both were tested for significant reclassification between groups.

### Risk model calibration analysis

Risk model calibration/goodness-of-fit was graphically analyzed [GraphPad Prism 8 (GraphPad Software Inc.)]

comparing observed events for patient quintiles of predicted risk based on historical event probabilities from the original derivation cohorts [6, 9]; it was formally tested with a logistic regression model and—where possible—the Hosmer–Lemeshow goodness-of-fit test [21] (MedCalc v18.21 (MedCalc Software, Belgium)). For the Mehran risk model for predicting contrast-induced nephropathy, assignment of score values to predicted risk were done according to extracted data from the central figure of the development cohort in the original publication [6].

## Results

### Patient and procedural characteristics

A total of 2,067 patients undergoing coronary angiography between 2014 and 2018 with and without PCI at University Hospital Duesseldorf were included. Patient characteristics and NCDR risk model performance indices of a sub-cohort of these patients ( $n = 1637$ ) have been previously published by our group [10]. Patients were divided into clinical setting subgroups of elective, NSTEMI and STEMI.

Mean age in the overall cohort was  $69 \pm 12.3$  years, 27.1% of the patients had a history of chronic kidney disease, 2.9% were treated with chronic dialysis. PCI was performed in 59.5% of all patients, the rest underwent diagnostic procedures alone. Mean applied contrast volume was  $154.7 \pm 97.0$  ml, most in STEMI and least in elective procedures. Mechanical circulatory support was used in 2.3% (Impella®) and 1.9% (Extracorporeal life support, ECLS), respectively. The predominant symptom at admission was angina pectoris. Patient and procedural characteristics for all patients and for respective subgroups are reported in Table 1.

### Contrast-induced nephropathy outcomes

Contrast-induced nephropathy occurred in 15.3% ( $n = 317$ ) of all patients, 1.5% ( $n = 31$ ) consecutively required renal replacement therapy. While CIN was relatively common in patients presenting with acute coronary syndrome (21.3% in NSTEMI patients, 17.9% in STEMI patients), only 0.6% of all patients undergoing elective procedures developed CIN, none of whom required dialysis. In-hospital clinical outcomes are reported in Table 2.

## Risk model performance evaluation

### Missing data

For the calculation of the Mehran risk model, 3.8% missing values were imputed for the following variables; hematocrit ( $n = 11$ ), contrast media volume ( $n = 108$ ), glomerular filtration rate ( $n = 15$ ), congestive heart failure ( $n = 1$ ), systolic blood pressure ( $n = 493$ ). For the calculation of the NCDR risk model, 0.12% missing values were imputed for these variables; hemoglobin ( $n = 11$ ), glomerular filtration rate ( $n = 15$ ), prior heart failure ( $n = 1$ ).

### Risk model discrimination (Fig. 1 and Table 3)

The NCDR risk models showed good discrimination of risk for CIN (c-index 0.75, 95% CI 0.72–0.78) and very accurate performance in predicting need for dialysis (c-index 0.85, 95% CI 0.79–0.91). The Mehran risk model showed mediocre performance for CIN (c-index 0.69, 95% CI 0.66–0.72) and good discrimination for need for dialysis (c-index 0.75, 0.66–0.84). For both outcomes, the NCDR-AKI and NCDR-AKI-D risk models performed superior to the Mehran model ( $p_{\text{NCDRvsMehran}} < 0.01$ ). The sensitivity analysis including only patients with complete datasets (no imputation,  $n = 1483$ ) confirmed these results for CIN (c-index 0.70; 95% CI 0.67–0.74 (NCDR) vs. c-index 0.66; 95% CI 0.62–0.69 (Mehran);  $p < 0.01$ ) and for need for dialysis (c-index 0.81; 95% CI 0.73–0.89 (NCDR) vs. 0.71; 95% CI 0.59–0.83 (Mehran);  $p = 0.03$ ).

### Risk model reclassification (Table 3 and Suppl. Tab. 4 + 5)

Reclassification analyses revealed a significant continuous NRI for the NCDR risk model compared to the Mehran risk model of 0.22 (95% CI 0.12–0.32;  $p < 0.01$ ; Table 3) for CIN, which was confirmed in patients with complete datasets alone (sensitivity analysis: continuous NRI 0.19; 95% CI 0.07–0.31;  $p < 0.01$ ). The continuous NRI for need for dialysis was not significant (NRI:  $-0.16$ ; 95% CI  $-0.50$  to  $0.18$ ;  $p = 0.35$ ). Categorical NRI analysis on CIN did not reveal significant differences between models (Suppl. Tab. 4), while Mehran classified better than NCDR-AKI-D for the chosen risk categories in need for dialysis (Suppl. Tab. 5).

### Risk model calibration (Fig. 2 and Table 3)

In the graphical analysis (Fig. 2A and C), the NCDR risk model tended to underestimate risk, especially in intermediate risk quintiles, while showing good calibration in high-risk patients. The Mehran risk model showed



**Table 1** Patient characteristics, comorbidities, symptoms at admission and procedural characteristics (left column) and separately for patient subsets of NSTEMI, STEMI and elective procedures

|                                                | All (n=2067) | NSTEMI<br>(n=1002, 48%) | STEMI (n=565, 27%) | Elective (n=500, 24%) |
|------------------------------------------------|--------------|-------------------------|--------------------|-----------------------|
| <b>Patient characteristics</b>                 |              |                         |                    |                       |
| Age (y)                                        | 69.2 ± 12.3  | 72.2 ± 11.3             | 65.1 ± 13.4        | 67.7 ± 11.3           |
| Body Mass Index (BMI)                          | 27.5 ± 5.1   | 27.6 ± 5.3              | 26.7 ± 4.8         | 28.1 ± 4.8            |
| Male sex                                       | 1439 (69.6)  | 700 (69.9)              | 399 (70.7)         | 340 (68.0)            |
| Diabetes mellitus                              | 608 (29.4)   | 365 (36.4)              | 95 (16.8)          | 148 (29.6)            |
| Chronic kidney disease (eGFR < 60 ml/min)      | 560 (27.1)   | 323 (32.2)              | 158 (28.0)         | 79 (15.8)             |
| Chronic dialysis                               | 60 (2.9)     | 43 (4.3)                | 11 (1.9)           | 6 (1.2)               |
| Coronary artery disease                        | 948 (45.9)   | 507 (50.6)              | 107 (19.0)         | 334 (66.8)            |
| Prior coronary artery bypass grafting (CABG)   | 191 (9.2)    | 153 (15.3)              | 4 (0.7)            | 34 (6.8)              |
| Prior percutaneous coronary intervention (PCI) | 611 (29.6)   | 309 (30.8)              | 20 (3.5)           | 282 (56.4)            |
| History of heart failure                       | 638 (30.9)   | 473 (47.2)              | 32 (5.7)           | 133 (26.6)            |
| Anemia                                         | 622 (30.1)   | 375 (37.4)              | 156 (27.6)         | 91 (18.2)             |
| <b>Symptoms at admission</b>                   |              |                         |                    |                       |
| Unstable angina                                | 674 (32.6)   | 391 (39.0)              | 263 (46.5)         | 20 (4.0)              |
| Dyspnea NYHA IV                                | 191 (9.2)    | 124 (12.4)              | 56 (9.9)           | 11 (2.2)              |
| Cardiac arrest within 24 h                     | 76 (3.7)     | 32 (3.2)                | 44 (7.8)           | 0                     |
| Endotracheal intubation                        | 58 (2.8)     | 37 (3.7)                | 21 (3.7)           | 0                     |
| Cardiogenic shock                              | 144 (7.0)    | 72 (7.2)                | 72 (12.7)          | 0                     |
| <b>Procedural characteristics</b>              |              |                         |                    |                       |
| PCI performed                                  | 1230 (59.5)  | 519 (51.8)              | 533 (94.3)         | 178 (35.6)            |
| Contrast media volume (ml)                     | 154.7 ± 97.0 | 148.9 ± 86.7            | 209.9 ± 105.8      | 107.3 ± 75.7          |
| Procedure duration (min)                       | 54.9 ± 33.9  | 56.1 ± 29.6             | 65.5 ± 43.4        | 41.0 ± 24.3           |
| Impella® mechanical support                    | 47 (2.3)     | 20 (2.0)                | 27 (4.8)           | 1 (0.2)               |
| Extracorporeal life support                    | 40 (1.9)     | 4 (0.4)                 | 36 (6.4)           | 0                     |

Data are presented as n (%) or as mean ± SD, unless specified differently

eGFR estimated glomerular filtration rate, (N)STEMI (Non) ST-segment elevation myocardial infarction, NYHA New York Heart Association

**Table 2** Overview of in-hospital clinical outcomes

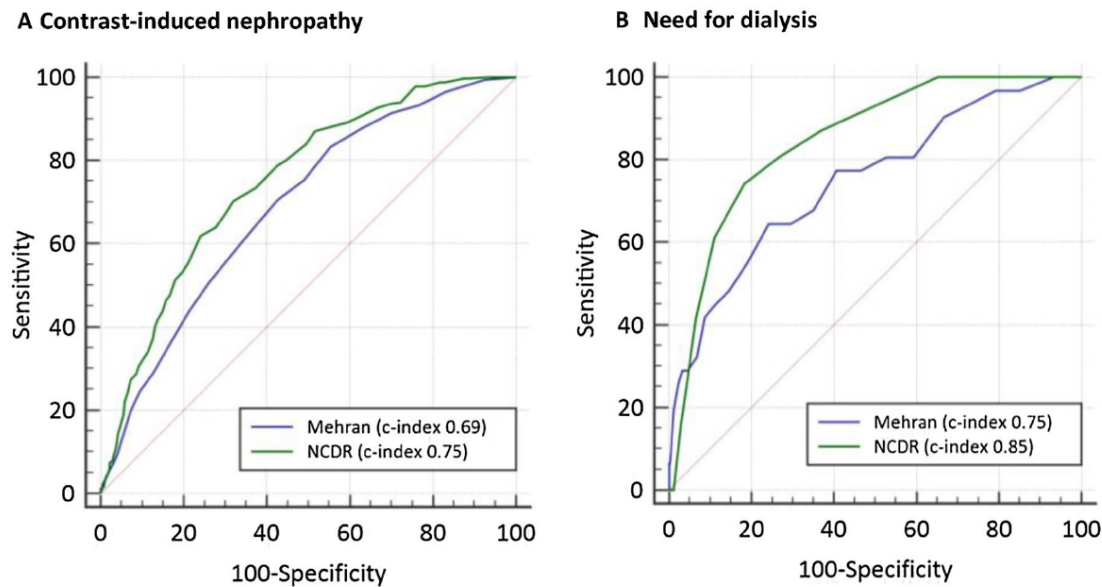
|                              | All (n=2067) | NSTEMI<br>(n=1002,<br>48%) | STEMI (n=565, 27%) | Elective<br>(n=500,<br>24%) |
|------------------------------|--------------|----------------------------|--------------------|-----------------------------|
| Contrast-induced nephropathy | 317 (15.3)   | 213 (21.3)                 | 101 (17.9)         | 3 (0.6)                     |
| Need for dialysis            | 31 (1.5)     | 15 (1.5)                   | 16 (2.8)           | 0                           |
| All-cause mortality          | 119 (5.8)    | 37 (3.7)                   | 82 (14.5)          | 0                           |
| Cardiovascular mortality     | 81 (3.9)     | 28 (2.8)                   | 53 (9.4)           | 0                           |
| Major bleeding               | 120 (5.8)    | 59 (5.9)                   | 60 (10.6)          | 1 (0.2)                     |
| Stroke                       | 6 (0.3)      | 3 (0.3)                    | 3 (0.5)            | 0                           |

Data are presented as n (%)

(N)STEMI (Non) ST-segment elevation myocardial infarction

more accurate calibration in the graphical calibration analysis and only overestimated risk in the highest risk quintile. The Hosmer–Lemeshow goodness-of-fit test showed  $p < 0.01$  for the NCDR-AKI as well as the Mehran risk model for predicting contrast-induced nephropathy.

Both risk models showed inaccurate calibration for the outcome of need for dialysis (Fig. 2B and D). The Hosmer–Lemeshow goodness-of-fit test showed  $p < 0.01$  for the NCDR-AKI-D model.



**Fig. 1** Comparative risk model discrimination performance analysis of ROC curves of National Cardiovascular Data Registry (NCDR) and Mehran risk models for A contrast induced nephropathy and B

need for dialysis. Statistical comparisons were performed using the DeLong method [16], results are also reported in Table 3

**Table 3** Comparative risk model performance analysis regarding model discrimination (a), reclassification (b) and calibration (c) for contrast-induced nephropathy and need for dialysis

|                                                                          | Contrast-induced nephropathy | Need for dialysis  |
|--------------------------------------------------------------------------|------------------------------|--------------------|
| Observed outcome events                                                  | 317 (15.3%)                  | 31 (1.5%)          |
| Risk model discrimination: areas-under-curve/c-indices                   |                              |                    |
| NCDR-AKI/NCDR AKI-D                                                      | 0.75 (0.72–0.78)             | 0.85 (0.79–0.91)   |
| Mehran                                                                   | 0.69 (0.66–0.72)             | 0.75 (0.66–0.84)   |
| Statistics                                                               | $p < 0.01$                   | $p < 0.01$         |
| Risk model reclassification: continuous net reclassification improvement |                              |                    |
| Mehran vs. NCDR-AKI/NCDR AKI-D                                           | 0.22 (0.12–0.32)             | –0.16 (–0.50–0.18) |
|                                                                          | $p < 0.01$                   | $p = 0.35$         |
| Risk model calibration: cohort mean risk prediction                      |                              |                    |
| NCDR-AKI/NCDR AKI-D                                                      | $11.6 \pm 10.6\%$            | $0.3 \pm 0.7\%$    |
| Mehran                                                                   | $17.7 \pm 14.0\%$            | $1.4 \pm 3.6\%$    |

Model discrimination is reported as areas-under-curve (AUC, c-indices) of receiver-operating characteristic (ROC) analyses with 95% confidence intervals; reclassification is reported as continuous net reclassification improvement (NRI) with 95% confidence intervals; mean risk prediction is reported as mean  $\pm$  standard deviation;  $p < 0.05$  was considered statistically significant

NCDR National Cardiovascular Data Registry

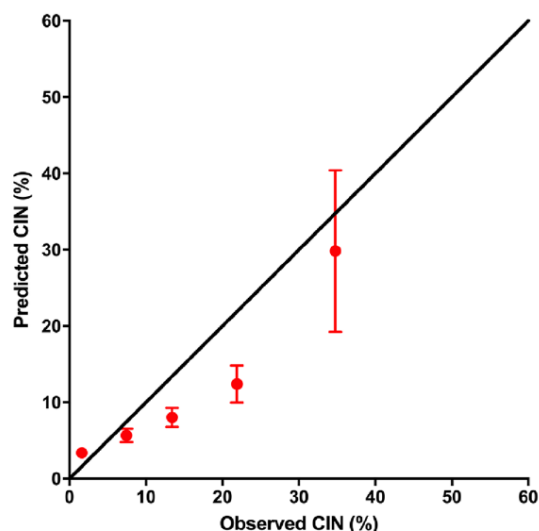
## Discussion

We herein present a comparative performance evaluation of NCDR and Mehran risk models for predicting contrast-induced nephropathy and need for dialysis in patients undergoing coronary angiography for elective and emergency indications. Main results are: (1) NCDR risk models for predicting CIN and need for dialysis (NCDR-AKI and

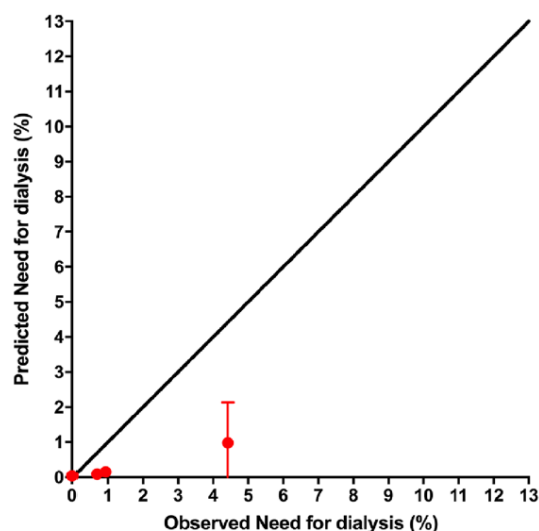
NCDR-AKI-D) discriminated risk superior to the Mehran model; (2) NCDR CIN prediction showed significant continuous reclassification improvement compared to the Mehran model; (3) Both risk models lacked calibration, especially in dialysis risk prediction. However, the Mehran risk model for predicting contrast-induced nephropathy showed slightly better calibration in the graphical analysis while the NCDR risk model tended to underestimate risk for CIN.

## NCDR-AKI / NCDR-AKI-D models

## A Contrast-induced nephropathy

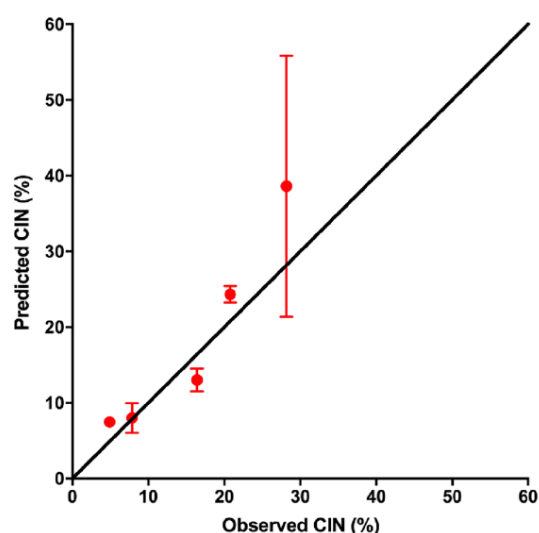


## B Need for dialysis

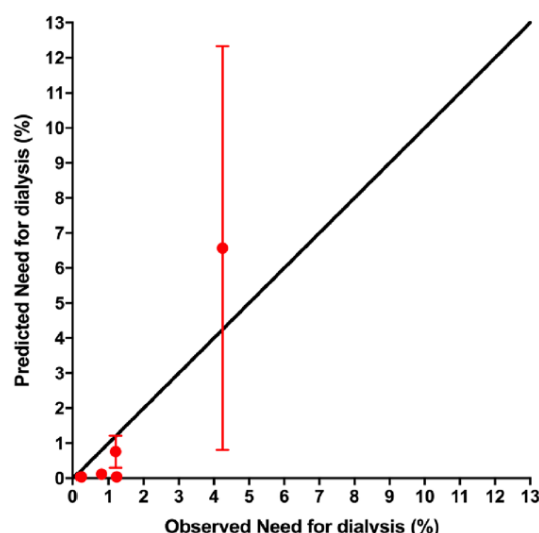


## Mehran model

## C Contrast-induced nephropathy



## D Need for dialysis



**Fig. 2** Risk model calibration for the National Cardiovascular Data Registry-Acute Kidney Injury (NCDR-AKI) and Dialysis (NCDR-AKI-D) and Mehran risk models, comparing observed and predicted

contrast-induced nephropathy and need for dialysis in risk quintiles of all patients. *CIN* contrast-induced nephropathy

Over the past decades, interventional cardiology has undergone tremendous changes in technology [22], pharmacological therapy [23–25] and demographic characteristics of patients [26]. But indications for invasive coronary angiography are also changing: interventional management of chronic coronary syndromes has become an increasingly controversial topic, taking the latest results from the

ISCHEMIA trial and a large meta-analysis into account [27, 28]. Thus, adequate risk assessment and management is an important part of daily clinical practice to improve patient outcomes. Temporal and external validation of established risk scores is necessary to optimize risk management and retain risk model performance. Standard risk scores developed in patient cohorts almost two decades ago – like the



Mehran risk model – might not be the most accurate option anymore.

The Mehran risk model for predicting contrast-induced nephropathy is well-established and was developed in 2004 by Mehran et al. in a cohort of 8357 patients [6]. The initial validation cohort showed similar risk discrimination performance (c-index of 0.67 [6]) for contrast-induced nephropathy compared to our cohort (c-index of 0.69). For predicting need for dialysis, the Mehran risk model also showed a reasonable discrimination performance (c-index 0.75). Graphical analysis revealed slightly better calibration for predicting contrast-induced nephropathy compared to the NCDR-AKI risk model, potentially due to similar rates of CIN (15.3% in our cohort vs. 13.1% in the development cohort [6]). Reasons for the inaccurate calibration regarding the outcome ‘need for dialysis’ may potentially lie in a limited number of events in our cohort ( $n=31$ ), a higher number of patients presenting with acute myocardial infarction (75.8% vs. 35.7% in the development cohort) and an overall older patient cohort (69.2 years vs. 63.8 years in the development cohort).

The National Cardiovascular Data Registry risk models for predicting acute kidney injury and need for dialysis were developed in a patient cohort of over 900,000 patients [9]. NCDR-AKI and NCDR-AKI-D showed good discrimination performance in the initial validation cohort with c-indices of 0.71 for NCDR-AKI and of 0.89 for NCDR-AKI-D [9]. We herein observed comparable results for predicting CIN (c-index 0.75) and need for dialysis (c-index 0.85). Calibration showed an underestimation of risk in the models (Fig. 2), especially for dialysis risk prediction. On the one hand, this may be related to a difference in risk (more myocardial infarction) with higher event rates: Tsai et al. [9] observed only 7.1% acute kidney injury in the validation cohort, compared to 15.3% in our cohort. On the other hand, the CIN outcome definition of Mehran et al. [6] used here is slightly different from the one by Tsai et al. [9], which may explain an offset in calibration.

Calibration as one of the performance measures of risk models is an important aspect of individualized risk prediction since it refers to the ability of a risk model to precisely forecast the true risk of a patient and therefore may also be seen as an indicator of whether the risk model fits the test data well. In our study, we observed a graphically more accurate risk model calibration for the Mehran risk model compared to the NCDR risk model, while statistical testing rendered both models inaccurate regarding calibration. Volatile calibration performance is often observed in external risk model validation studies: both NCDR models were externally validated in a Japanese patient cohort with over 11,000 patients [29], with similarly good discrimination performance, but also offsets in calibration [29]. Previous work from our group also observed corrupted calibration

[10, 30]. The methodical work of Matheny et al. [31] shows that volatile calibration in risk models in interventional cardiology is related to small changes in event risk and data assessment, while retained discrimination shows the stability of risk factors over time. They conclude that continuous recalibration of risk models is mandatory to achieve perfect calibration. Additionally, slight differences in endpoint definitions between CIN according to Mehran (used here [6]), AKIN (used in the original NCDR population [9]) and the contrast-induced acute kidney injury definition (according to KDIGO [32, 33]) may influence comparability of risk models regarding calibration.

Preprocedural risk assessment, as well as procedural and postprocedural risk management are critical stepping stones to improve patient outcomes. A major advantage of the NCDR risk models over the Mehran risk model is that both NCDR risk models allow calculation of risk from preprocedural characteristics—while Mehran is a postprocedural risk prediction model. Knowing the risk of CIN or dialysis before the procedure, the operator may undertake preventive measures (—periprocedural risk management). The clinical indication of the procedure can be critically reviewed and high-risk patients may benefit from more intense or prolonged postprocedural monitoring of urine output and retention parameters. Contrast media volume is a key factor for the development of CIN, especially in high-risk patients [34] and may be managed accordingly: the use of biplane angiography systems helps to reduce contrast media exposure [35]. There are technical devices which are efficient in reducing contrast media over-injection [36]. The use of intravascular ultrasound (IVUS) and physiological guidance [37] may help in decreasing contrast media volume exposure for high-risk patients. Periprocedural risk management also includes volume expansion, which is still common practice (European class IIa recommendation for preprocedural hydration with isotonic saline [14]), although several studies showed no significant difference in the rate of CIN in patients with and without prophylactic hydration [38, 39]. Other studies investigated the influence on statin administration for the prevention of contrast-induced nephropathy with divergent results [40, 41]. Taken together, knowing patient risk for CIN upfront may hold the key for initiating adequate preventive measures in high-risk patients. Future studies are needed to investigate potential outcome benefits from preprocedural risk assessment and periprocedural risk management.

Major limitations of our study are the retrospective single-center design, which limits generalizability to other patient cohorts, and the limited number of included patients and events. Therefore, results, especially for the outcome ‘need for dialysis’, have to be interpreted with caution, as they are not clearly in favor of the NCDR model. A further limitation is missing data and the simple method of data imputation, especially for the Mehran model. However,

sensitivity analysis in patients with complete data verified the overall results. There were almost no missing data for the calculation of the NCDR score, which underlines its usefulness as a preprocedural risk model.

Prospective validation of both risk models in a contemporary patient cohort is necessary to verify our results and help to further improve CIN risk management.

## Conclusion

In German patients undergoing coronary angiography, the modern NCDR risk model for predicting contrast-induced nephropathy showed superior discrimination performance compared to the established Mehran risk model. Both risk models showed inaccurate calibration, with slight advantages for the Mehran over the NCDR risk model for predicting contrast-induced nephropathy. Results for the outcome of ‘need for dialysis’ were equivocal. Further prospective studies are necessary to investigate patient outcome benefits from optimization in risk assessment and risk management.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s40620-021-01124-9>.

**Author contributions** CP and GW conceived and designed the study. JQ, JT, SB, CP and LK collected and analyzed data. GW and CP analyzed and interpreted data and drafted the manuscript. MB, YL, VS and CJ supported data acquisition and analysis and critically revised the manuscript. MK and AI assumed project supervision, interpreted data and critically revised the manuscript. AS and AH supported data analysis and revision of the manuscript during the submission process. All authors read and accepted the submitted version of the manuscript.

**Funding** Open Access funding enabled and organized by Projekt DEAL. This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich-Heine-University Düsseldorf for a Clinician Scientist track (No. 2018-32 to GW).

## Declarations

**Conflicts of interest** All authors declare: no support from any industry or third-party organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval** This study was positively evaluated by the Ethics committee of the Heinrich-Heine-University Düsseldorf (Study-No. 6050R, Registration-ID: 2017074349) and is registered at clinicaltrials.gov (NCT03671356). Informed consent was waived due to the retrospective design.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes

were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. Rihal CS et al (2002) Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 105(19):2259–2264
2. Weisbord SD et al (2006) Associations of increases in serum creatinine with mortality and length of hospital stay after coronary angiography. *J Am Soc Nephrol* 17(10):2871–2877
3. Mehran R, Nikolsky E (2006) Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 100:S11–S15
4. James MT et al (2010) Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. *Kidney Int* 78(8):803–809
5. Tsai TT et al (2014) Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. *JACC Cardiovasc Interv* 7(1):1–9
6. Mehran R et al (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 44(7):1393–1399
7. Araujo GN et al (2016) Comparison of two risk models in predicting the incidence of contrast-induced nephropathy after percutaneous coronary intervention. *J Interv Cardiol* 29(5):447–453
8. Abellas-Sequeiros RA et al (2016) Mehran contrast nephropathy risk score: is it still useful 10 years later? *J Cardiol* 67(3):262–267
9. Tsai TT et al (2014) Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc* 3(6):e001380
10. Wolff G et al (2019) Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center. *Clin Res Cardiol* 109:235–245
11. Ibanez B et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 39(2):119–177
12. Roffi M et al (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 37(3):267–315
13. Knuuti J et al (2020) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 41(3):407–477
14. Neumann FJ et al (2019) 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 40(2):87–165
15. Eknoyan G et al (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 3(1):5–14



16. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44(3):837–845
17. Pencina MJ, D'Agostino RB Sr (2015) Evaluating discrimination of risk prediction models: the C statistic. *JAMA* 314(10):1063–1064
18. Youden WJ (1950) Index for rating diagnostic tests. *Cancer* 3(1):32–35
19. Pencina MJ et al (2008) Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 27(2):157–172 (**discussion 207–212**)
20. Pencina MJ, D'Agostino RB Sr, Steyerberg EW (2011) Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 30(1):11–21
21. Hosmer DWJ, Lemeshow S, Sturdivant RX (2013) *Applied logistic regression*, 3rd edn. Wiley, Hoboken
22. Jorgensen E et al (2010) Sirolimus-eluting versus bare-metal stent implantation in patients with ostial lesions. *Int J Cardiol* 145(1):162–163
23. Andell P et al (2015) Ticagrelor versus clopidogrel in patients with acute coronary syndromes and chronic obstructive pulmonary disease: an analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *J Am Heart Assoc* 4(10):e002490
24. Schupke S et al (2019) Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 381(16):1524–1534
25. Navarese EP et al (2015) Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. *Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients*. *Thromb Haemost* 114(5):933–944
26. Grotti S, Bolognese L (2017) Interventional cardiology is changing: demographic, clinical and economic considerations. *J Cardiovasc Med (Hagerstown)* 18(Suppl 1):e67–e70
27. Maron DJ et al (2020) Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 382(15):1395–1407
28. Bangalore S et al (2020) Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and meta-analysis of randomized trials. *Circulation* 142(9):841–857
29. Inohara T et al (2016) Performance and validation of the US NCDR acute kidney injury prediction model in Japan. *J Am Coll Cardiol* 67(14):1715–1722
30. Wolff G et al (2020) Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients. *Clin Res Cardiol* 110:368–376
31. Matheny ME, Ohno-Machado L, Resnic FS (2005) Discrimination and calibration of mortality risk prediction models in interventional cardiology. *J Biomed Inform* 38(5):367–375
32. Mehran R, Dangas GD, Weisbord SD (2019) Contrast-associated acute kidney injury. *N Engl J Med* 380(22):2146–2155
33. Members KB (2012) KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements*
34. Brown JR et al (2010) Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? *Circ Cardiovasc Interv* 3(4):346–350
35. Smith K et al (2019) Bi-plane and single plane angiography: a study to compare contrast usage and radiation doses for adult cardiac patients in diagnostic studies. *Br J Radiol* 92(1093):20180367–20180367
36. Bruno RR et al (2019) Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. *Int J Cardiol Heart Vasc* 23:100377
37. Ali ZA et al (2016) Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. *Eur Heart J* 37(40):3090–3095
38. Nijssen EC et al (2017) Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet* 389(10076):1312–1322
39. Navarese EP et al (2017) Prevention of contrast-induced acute kidney injury in patients undergoing cardiovascular procedures—a systematic review and network meta-analysis. *PLoS ONE* 12(2):e0168726
40. Leoncini M et al (2014) Early high-dose rosuvastatin and cardioprotection in the protective effect of rosuvastatin and antiplatelet therapy on contrast-induced acute kidney injury and myocardial damage in patients with acute coronary syndrome (PRATO-ACS) study. *Am Heart J* 168(5):792–797
41. Jo SH et al (2008) Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. *Am Heart J* 155(3):499.e–8

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

#### ***4.1.3 Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort***

Parco C, Brockmeyer M, Kosejian L, Quade J, Tröstler J, Bader S, Lin Y, Karathanos A, Krieger T, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, **Wolff G**

Int J Cardiol. 2021 Jan 4;S0167-5273(20)34333-3.

Pubmed PMID: 33412182

DOI: [10.1016/j.ijcard.2020.12.085](https://doi.org/10.1016/j.ijcard.2020.12.085)

Diese Studie untersuchte – ebenfalls aufbauend auf der Validierungsstudie 4.1.1 – den Vergleich dreier Risikomodelle für die Vorhersage von Mortalität im akuten Koronarsyndrom in einem Düsseldorfer Patientenkollektiv.

In diesem klinischen Setting ist Risikoassessment fester Bestandteil der klinischen Routine: Seit über 10 Jahren ist das GRACE-Risikomodell für die Vorhersage der Krankenhaus- und 6-Monats-Sterblichkeit in den europäischen Leitlinien (35, 84, 85) verankert und wird unter anderem genutzt, um die Dringlichkeit invasiver Herzkatheteruntersuchungen bei hohem ischämischem Risiko zu evaluieren. Seine Validierung ist jedoch 10-20 Jahre alt (55, 57, 86), in diesem Zeitraum hat sich in der klinischen Routine viel gewandelt.

Wir haben daher die Leistungsindices zweier moderner Risikomodelle – des NCDR-Mortalitätsscores (82, 83) und des ACTION-Risikomodells (87, 88) – mit dem GRACE Modell in 1567 Düsseldorfer Patienten mit akutem Koronarsyndrom (n=1002 mit NSTEMI, n=565 mit STEMI) verglichen: Die besten Ergebnisse in der Risikodiskrimination aller drei Modelle erreichte der NCDR-Mortalitätsscore (c-index 0,89), auch in NSTEMI und STEMI Subgruppen; ACTION und GRACE Risikomodelle waren etwa gleichwertig mit trotzdem guter Performance (c-index 0,84). Die Kalibration des NCDR- und GRACE-Modells hatte Defizite, während ACTION hervorragend kalibriert war.

Durch einen kontinuierlichen Wandel von Patientenkollektiven, Kathetertechniken und Pharmakotherapie im akuten Koronarsyndrom sind ältere Risikomodelle nicht mehr zweifellos erste Wahl: Neue, moderne Modelle sind mindestens gleichwertig, insbesondere das NCDR-Mortalitätsmodell hat sich in diesem Düsseldorfer Patientenkollektiv bewährt. Rekalibrierung kann für eine akkurate Vorhersage von Ereigniswahrscheinlichkeiten notwendig sein, wenn ein Modell in neuen Kollektiven angewandt wird.



# Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort

Claudio Parco<sup>a,\*</sup>, Maximilian Brockmeyer<sup>a</sup>, Lucin Kosejian<sup>a</sup>, Julia Quade<sup>a</sup>, Jennifer Tröstler<sup>a</sup>, Selina Bader<sup>a</sup>, Yingfeng Lin<sup>a</sup>, Athanasios Karathanos<sup>a</sup>, Torben Krieger<sup>a</sup>, Yvonne Heinen<sup>a</sup>, Volker Schulze<sup>a</sup>, Andrea Icks<sup>b</sup>, Christian Jung<sup>a</sup>, Malte Kelm<sup>a</sup>, Georg Wolff<sup>a</sup>

<sup>a</sup> Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Düsseldorf, Germany

<sup>b</sup> Institute for Health Services Research and Health Economics, Heinrich-Heine-University, Düsseldorf, Germany

## ARTICLE INFO

### Article history:

Received 27 August 2020

Received in revised form 18 November 2020

Accepted 28 December 2020

Available online 4 January 2021

### Keywords:

NCDR

ACTION

GRACE

Risk prediction

Acute coronary syndrome

NSTEMI

Mortality

## ABSTRACT

**Background and purpose:** Risk prediction with the Global Registry of Acute Coronary Events (GRACE) risk model is guideline-recommended in acute coronary syndrome (ACS) patients. However, the performance of more contemporary scores derived from ACTION (Acute Coronary Treatment and Intervention Outcomes Network) and National Cardiovascular Data (NCDR) registries remains incompletely understood. We aimed to compare these models in German ACS patients.

**Methods and results:** A total of 1567 patients with (Non-)ST-segment elevation myocardial infarction (NSTEMI: 1002 patients, STEMI: 565 patients) undergoing invasive management at University Hospital Düsseldorf (Germany) from 2014 to 2018 were included. Overall in-hospital mortality was 7.5% (NSTEMI 3.7%, STEMI 14.5%). Parameters for calculation of GRACE 1.0, GRACE 2.0, ACTION and NCDR risk models and in-hospital mortality were assessed and risk model performance was compared. The GRACE 1.0 risk model for prediction of in-hospital mortality discriminated risk superior (c-index 0.84) to its successor GRACE 2.0 (c-index 0.79,  $p_{\text{GRACE1.0vsGRACE2.0}} = 0.0008$ ). The NCDR model performed best in discrimination of risk in ACS overall (c-index 0.89;  $p_{\text{ACTIONvsNCDR}} < 0.0001$ ;  $p_{\text{GRACEvsNCDR}} < 0.0001$ ) and showed superior performance compared to GRACE in NSTEMI and STEMI subgroups ( $p_{\text{GRACEvsNCDR}}$  both  $< 0.02$ ). ACTION and GRACE risk models performed comparable to each other (both c-index 0.84,  $p_{\text{GRACEvsACTION}} = 0.68$ ), with advantages for ACTION in NSTEMI patients (c-index 0.87 vs. 0.84 (GRACE);  $p_{\text{GRACEvsACTION}} = 0.02$ ). ACTION and GRACE 2.0 showed the most accurate calibration of all models.

**Conclusions:** In a contemporary German patient population with ACS, modern NCDR and ACTION risk models showed superior performance in prediction of in-hospital mortality compared to the gold-standard GRACE model.

© 2021 Elsevier B.V. All rights reserved.

**Abbreviation:** ACS, acute coronary syndrome; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; AUC, area-under-the-curve; CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; NCDR, National Cardiovascular Data Registry; NSTEMI, Non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; ROC, receiver operating characteristic; STEMI, ST-segment elevation myocardial infarction.

\* Corresponding author at: Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany.

E-mail address: [claudio.parco@med.uni-duesseldorf.de](mailto:claudio.parco@med.uni-duesseldorf.de) (C. Parco).

<https://doi.org/10.1016/j.ijcard.2020.12.085>

0167-5273/© 2021 Elsevier B.V. All rights reserved.

## 1. Introduction

Ischemic heart disease remains one of the leading causes of morbidity and mortality in Europe and worldwide [1,2]. Invasive management of acute coronary syndrome (ACS) has the potential to improve patient outcomes in acute myocardial infarction with (STEMI) and without (NSTEMI) ST-segment elevation [3–6]. However, this also carries various risks for complications depending on setting, procedural characteristics and patients' comorbidities. Adequate risk assessment and subsequent clinical management are thus mandatory to optimize patient outcomes: Both the European and American cardiac societies recommend patient risk stratification in ACS [3–7] by use of the Global Registry of Acute Coronary Events (GRACE) risk model [8–11], which



has been prospectively validated for this setting. More recently, the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) [12,13] and the National Cardiovascular Data Registry (NCDR) [14–19] risk models have been developed and validated in the setting of ACS. Both were derived from larger and more contemporary registry data and therefore may hold advantages over the GRACE model.

The performance of NCDR and ACTION models in comparison to the GRACE model – the gold-standard in ACS – in a contemporary patient cohort is unknown. We thus aimed to compare all three risk models in their performance for prediction of in-hospital mortality in German patients with acute coronary syndrome.

## 2. Methods

This study was positively evaluated by the Ethics committee of the Heinrich-Heine-University Düsseldorf (Study-No. 6050R, Registration-ID: 2017074349) and is registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03671356).

### 2.1. Patient characteristics, clinical settings and data collection

Patients presenting with NSTEMI and STEMI from 2014 to 2018 were eligible for inclusion in the study. Based on previous work by our group [19] and an estimated event-rate of ~5% for in-hospital mortality, at least 1500 included patients were deemed necessary to perform risk model evaluation. Patient and procedural characteristics, symptoms and clinical presentations and in-hospital clinical outcomes were extracted from medical records into a dedicated database. Patient characteristics and NCDR risk model performance of the STEMI and NSTEMI patient subgroups from 2014 to 2017 have been previously published by our group [19]. NSTEMI patients from 2018 were additionally added.

### 2.2. Catheterization procedure

All patients were treated at our tertiary care hospital according to European guideline-recommended clinical practice for acute coronary syndrome by an interventionalist team (physician, assistant nurse and technician). In case of emergencies, additional assistance was provided: Cardiovascular intensive care, mechanical circulatory support (Impella®, extracorporeal life support (ECLS), left ventricular assist devices (LVAD)) and also cardiac surgery were routinely available. Postprocedural treatment with optimal medical therapy [3,20] was continued on intensive or intermediate care units or on a normal care ward, depending on clinical stability of the patient and at the discretion of the interventionalist.

### 2.3. Clinical outcomes definitions

Primary outcome of interest for risk model performance evaluation was in-hospital mortality, which was defined as any post-procedural death within the same hospital admission (Table 3). Secondary outcomes of major bleeding events (according to BARC [21]), acute kidney injury (according to KDIGO [22]) and stroke are additionally reported (Suppl. Table 1).

## 3. Statistics

### 3.1. Missing data

Missing data for clinical presentation and medical history variables were imputed to “no”. Missing data relevant for risk model calculation were imputed to the mean (continuous variables) or median (ordinal/categorical variables) of the respective STEMI or NSTEMI subpopulations. Details on missing data imputation are reported in the results section, given as the percentage of all risk model data points (Suppl. Tables 2–4) which were imputed.

### 3.2. Data analysis

Data analysis was performed using Excel 2019 (Microsoft), SPSS 25 (IBM), MedCalc v18.21 (MedCalc Software, Belgium) and GraphPad Prism 6.0 (GraphPad Software Inc.). Reclassification statistics were calculated using the package PredictABEL in R Studio v4.0.3. Continuous data are presented as means  $\pm$  standard deviation (SD), ordinal or categorical variables are presented as counts and % of total. Continuous data were tested for normal distribution (according to Kolmogorov-Smirnov), all tested variables were non-normally distributed and thus compared using Mann-Whitney-U tests; categorical data were compared using Chi-squared and Fisher's exact tests (for expected values  $< 5$ ).

### 3.3. Risk model calculation and evaluation

The most updated versions of GRACE 1.0 [11], GRACE 2.0 [9], ACTION [12] and NCDR [14] risk scoring models for prediction of in-hospital mortality (Table 1) were applied to this ACS population for comparative performance evaluation. The scores were calculated for individual patients as follows: All relevant scoring variables were weighed according to model definitions (Suppl. Tables 2–4; [10,12,14]); weighed variables were then summarized, resulting in an individual summary risk score for each patient. The GRACE 2.0 risk model [9] was calculated using the GRACE ACS risk calculator available on the authors' website ([https://www.outcomes-umassmed.org/grace/acs\\_risk2/index.html](https://www.outcomes-umassmed.org/grace/acs_risk2/index.html)). After individual summary risk score calculation, the discrimination performance of each risk model for in-hospital mortality was analyzed using receiver operating characteristics (ROC) curves with area-under-the-curve (AUC = c-index) calculations as a cumulative measure; c-indices with 95% confidence intervals (CI) are reported. Risk model discrimination performance between models was compared using the DeLong method [23]; significant differences were assumed at an  $\alpha$  probability  $< 0.05$ . Subgroup analyses were performed for NSTEMI and STEMI subsets and for PCI-only patients, respectively (Table 3). Risk model calibration/goodness-of-fit was graphically analyzed by comparison of expected vs. observed events within risk strata (risk quintiles for GRACE 1.0, GRACE 2.0, NCDR and ACTION models [9–12,14]). For reclassification analyses, arbitrary risk categories (0–1%, 1–5% and 5–100%) were made and reclassification tables comparing NCDR and ACTION risk models to GRACE 1.0/GRACE 2.0 were analyzed for net reclassification improvements (NRI) and integrated discrimination improvements (IDI).

## 4. Results

### 4.1. Patient and procedural characteristics

A total of 1567 patients with invasive management of acute coronary syndrome of either NSTEMI ( $n = 1002$ , 63.9%) or STEMI ( $n = 565$ , 36.1%) were included; characteristics and NCDR risk model performance of the STEMI patient subgroup have been previously published by our group [19].

Patient and procedural characteristics are presented in Table 2. Unstable angina was the primary symptom at admission (41.7%). Cardiac arrest (4.9%; NSTEMI 3.2%; STEMI 7.8%) and cardiogenic shock (9.2%; NSTEMI 7.2%; STEMI 12.8%) were frequently observed (Table 2). Mechanical circulatory support was used in 87 patients (5.6%; NSTEMI 2.4%; STEMI 11.2%) with Impella® (3.0%) and/or extracorporeal life support (2.6%).

### 4.2. Clinical outcomes

In-hospital all-cause mortality (7.5%; NSTEMI 3.7%; STEMI 14.5%;  $p < 0.0001$ ) was the primary outcome of interest for risk model performance (Table 3) and significantly more frequent in STEMI patients. Secondary outcomes (Suppl. Table 1) of cardiovascular mortality (5.2%; NSTEMI 2.8%; STEMI 9.4%;  $p < 0.0001$ ) and major bleeding (7.6%;

**Table 1**  
Risk model characteristics.

| Risk model        | Year of publication (original / update) | Recruitment period | Recruitment region    | Development setting        | Development cohort size | Discrimination performance (c-indices) | External validation                                                            |
|-------------------|-----------------------------------------|--------------------|-----------------------|----------------------------|-------------------------|----------------------------------------|--------------------------------------------------------------------------------|
| GRACE 1.0 (10,11) | 2003 / 2009                             | 1999–2006          | Global (14 countries) | ACS (38% STEMI)            | 48,023                  | 0.84                                   | Global [8], India [35], Canada [34], Japan [36], Australia [37], Portugal [38] |
| GRACE 2.0 (9)     | 2014                                    | 2002–2007          | Global (14 countries) | ACS (36% STEMI)            | 32,037                  | 0.83 (1-year)                          | France [9], USA [40], Portugal [56], United Kingdom [57]                       |
| ACTION [12,13]    | 2011 / 2016                             | 2012–2013          | US                    | ACS (39% STEMI)            | 145,952                 | 0.88                                   | Spain [43], China [44]                                                         |
| NCDR [14,15]      | 2010 / 2013                             | 2009–2011          | US                    | All PCI (elective and ACS) | 724,883                 | 0.93                                   | Portugal [42], Germany [19]                                                    |

Risk model characteristics for the three models, including details on development, original performance and external validation. Unless specified otherwise, reported data belong to the most updated version of the respective model. STEMI = ST-segment elevation myocardial infarction; US = United States.

NSTEMI 5.9%; STEMI 10.6%;  $p = 0.001$ ) also occurred more frequently in STEMI patients, while acute kidney injury (22.8%; NSTEMI 22.1%; STEMI 23.7%;  $p = 0.51$ ) and stroke (0.4%; NSTEMI 0.3%; STEMI 0.5%;  $p = 0.48$ ) showed no differences.

#### 4.3. Risk model performance evaluation

Characteristics of the GRACE [9–11], ACTION [12,13] and NCDR [14,15] risk models for prediction of in-hospital mortality are reported in Table 1.

**Table 2**  
Patient and procedural characteristics.

|                                                         | All (n = 1567)     | NSTEMI (n = 1002, 64%) | STEMI (n = 565, 36%) |
|---------------------------------------------------------|--------------------|------------------------|----------------------|
| <b>Patient characteristics</b>                          |                    |                        |                      |
| Age (y)                                                 | 69.7 ± 12.5        | 72.2 ± 11.3            | 65.1 ± 13.4          |
| BMI                                                     | 27.3 ± 5.2         | 27.6 ± 5.3             | 26.7 ± 4.8           |
| Male sex                                                | 1099 (70.1)        | 700 (69.9)             | 399 (70.7)           |
| Arterial hypertension                                   | 1195 (76.3)        | 844 (84.2)             | 351 (62.1)           |
| Hyperlipoproteinemia                                    | 627 (40.0)         | 446 (44.5)             | 181 (32.0)           |
| Diabetes mellitus                                       | 460 (29.4)         | 365 (36.4)             | 95 (16.8)            |
| CKD (eGFR <60 ml/min)                                   | 481 (30.7)         | 323 (32.2)             | 158 (28.0)           |
| Chronic dialysis                                        | 54 (3.4)           | 43 (4.3)               | 11 (1.9)             |
| Chronic lung disease                                    | 236 (15.1)         | 191 (19.1)             | 45 (8.0)             |
| Coronary artery disease                                 | 614 (39.2)         | 507 (50.6)             | 107 (19.0)           |
| Peripheral artery disease                               | 188 (12.0)         | 149 (14.9)             | 39 (6.9)             |
| Prior CABG                                              | 157 (10.0)         | 153 (15.3)             | 4 (0.7)              |
| Prior PCI                                               | 329 (21.0)         | 309 (30.8)             | 20 (3.5)             |
| <b>Symptoms at admission</b>                            |                    |                        |                      |
| Unstable angina                                         | 654 (41.7)         | 391 (39.0)             | 263 (46.5)           |
| Cardiac arrest within 24 h                              | 76 (4.9)           | 32 (3.2)               | 44 (7.8)             |
| Endotracheal intubation                                 | 58 (3.7)           | 37 (3.7)               | 21 (3.7)             |
| Cardiogenic shock                                       | 144 (9.2)          | 72 (7.2)               | 72 (12.7)            |
| <b>Procedural characteristics</b>                       |                    |                        |                      |
| Primary vascular access radial / femoral / brachial (%) | 34.4 / 65.1 / 0.4  | 41.5 / 57.8 / 0.7      | 20.3 / 79.7 / 0      |
| PCI performed                                           | 1052 (67.1)        | 519 (51.8)             | 533 (94.3)           |
| PCI in LM                                               | 46.2 / 19.4 / 33.4 | 45.7 / 23.6 / 28.7     | 46.9 / 14.6 /        |
| +LAD/RCA/Bypass (%)                                     | / 1.0              | / 1.9                  | 38.5                 |
| Impella® mechanical support                             | 47 (3.0)           | 20 (2.0)               | 27 (4.8)             |
| Extracorporeal life support                             | 40 (2.6)           | 4 (0.4)                | 36 (6.4)             |

Patient characteristics, comorbidities, symptoms at admission and procedural characteristics for the ACS population (left column) and separately for patient subsets of NSTEMI and STEMI. Data are presented as n (%) or as mean ± SD, unless specified differently. (N)STEMI = (Non) ST-segment elevation myocardial infarction; BMI = body-mass-index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; LM = left main; LAD = left anterior descending artery; RCX = ramus circumflexus; RCA = right coronary artery.

#### 4.3.1. Missing data

For calculation of the GRACE risk models (Suppl. Table 2) 2.46% missing data for variables of systolic blood pressure ( $n = 145$ ), heart rate ( $n = 120$ ), creatinine ( $n = 13$ ) and cardiac enzyme levels ( $n = 30$ ) were imputed. For the ACTION risk model (Suppl. Table 3) 2.19% missing data for variables of systolic blood pressure ( $n = 145$ ), heart rate ( $n = 120$ ), creatinine clearance ( $n = 14$ ) and troponin ( $n = 30$ ) were imputed. For the NCDR risk model (Suppl. Table 4) 3.40% missing data for variables of body mass index ( $n = 61$ ), glomerular filtration rate ( $n = 14$ ), ejection fraction ( $n = 83$ ), troponin ( $n = 30$ ), heart rate ( $n = 120$ ), systolic blood pressure ( $n = 145$ ) and NYHA class ( $n = 440$ ) were imputed.

**Table 3**  
Risk model discrimination and calibration performance.

|                                                      | All (n = 1567)   | NSTEMI (n = 1002, 64%) | STEMI (n = 565, 36%) |
|------------------------------------------------------|------------------|------------------------|----------------------|
| In-hospital mortality                                | 119 (7.5)        | 37 (3.7)               | 82 (14.5)            |
| <b>Risk model discrimination</b>                     |                  |                        |                      |
| GRACE 1.0                                            | 0.84 (0.80–0.87) | 0.84 (0.78–0.89)       | 0.83 (0.79–0.88)     |
| GRACE 2.0                                            | 0.79 (0.75–0.83) | 0.74 (0.66–0.83)       | 0.83 (0.78–0.87)     |
| ACTION                                               | 0.84 (0.80–0.87) | 0.87 (0.83–0.92)       | 0.84 (0.80–0.89)     |
| NCDR                                                 | 0.89 (0.87–0.92) | 0.90 (0.86–0.94)       | 0.86 (0.82–0.90)     |
| <b>Statistical comparison</b>                        |                  |                        |                      |
| GRACE 1.0 vs. ACTION (P <sub>GRACEvsACTION</sub> )   | $p = 0.675$      | $p = 0.018$            | $p = 0.303$          |
| GRACE 1.0 vs. NCDR (P <sub>GRACEvsNCDR</sub> )       | $p < 0.0001$     | $p = 0.007$            | $p = 0.018$          |
| ACTION vs. NCDR (P <sub>ACTIONvsNCDR</sub> )         | $p < 0.0001$     | $p = 0.099$            | $p = 0.104$          |
| <b>Risk model calibration – Mean risk prediction</b> |                  |                        |                      |
| GRACE 1.0                                            | 12.2 ± 15.2%     | 11.1 ± 13.5%           | 14.3 ± 17.6%         |
| GRACE 2.0                                            | 6.5 ± 11.6%      | 6.2 ± 10.6%            | 7.2 ± 13.1%          |
| ACTION                                               | 7.0 ± 11.7%      | 6.7 ± 10.7%            | 7.5 ± 13.4%          |
| NCDR                                                 | 6.4 ± 11.3%      | 5.0 ± 10.1%            | 8.9 ± 12.7%          |

In-hospital mortality, comparative risk model discrimination performance analysis and calibration indices (mean risk prediction) presented for the ACS population (left column) and separately for patient subsets of STEMI and NSTEMI. Mortality is reported as n (%). Model discrimination is reported as areas-under-the-curve (AUC, c-indices) of receiver-operating-characteristic (ROC) analyses with 95% confidence intervals; mean risk prediction is reported as mean ± standard deviation. Statistical comparisons of c-indices were performed using the DeLong method [23];  $p < 0.05$  was considered statistically significant. (N)STEMI = (Non) ST-segment elevation myocardial infarction.



#### 4.3.2. Risk model discrimination (Fig. 1 and Table 3)

The GRACE 1.0 model discriminated risk significantly better than its successor GRACE 2.0 (c-index 0.84 vs. 0.79, 95% CI 0.75 to 0.83;  $p_{\text{GRACE1.0vsGRACE2.0}} = 0.0008$ , Fig. 1). All c-index comparisons of GRACE to ACTION and NCDR models thus were performed on GRACE 1.0 data.

In the overall ACS population, the GRACE (c-index 0.84, 95% CI 0.80 to 0.87) and ACTION (c-index 0.84, 95% CI 0.80 to 0.87;  $p_{\text{GRACEvsACTION}} = 0.657$ ) risk models showed good discrimination of risk for in-hospital mortality; the NCDR risk model (c-index 0.89, 95% CI 0.87 to 0.92) was significantly more accurate than both ( $p_{\text{GRACEvsNCDR}}$  and  $p_{\text{ACTIONvsNCDR}} < 0.0001$ ). Only the GRACE model thus met its original performance from development populations (Table 1), while ACTION and NCDR showed slightly lower c-indices (Table 3: GRACE/ACTION/NCDR original c-indices 0.84/0.88/0.93, respectively).

In the subpopulation of patients presenting with NSTEMI, the GRACE model (c-index 0.84, 95% CI 0.78 to 0.89) performed significantly inferior to ACTION (c-index 0.87, 95% CI 0.83 to 0.92;  $p_{\text{GRACEvsACTION}} = 0.018$ ) and especially NCDR models (c-index 0.90, 95% CI 0.86 to 0.94;  $p_{\text{GRACEvsNCDR}} = 0.007$ ). ACTION and NCDR models did not differ significantly ( $p_{\text{ACTIONvsNCDR}} = 0.099$ ). In STEMI patients, the GRACE model (c-index 0.83, 95% CI 0.79 to 0.88) also fell numerically behind ACTION (c-index 0.84, 95% CI 0.80 to 0.89;  $p_{\text{GRACE1vsACTION}} = 0.30$ ) and especially NCDR models (c-index 0.86, 95% CI 0.82 to 0.90;  $p_{\text{GRACEvsNCDR}} = 0.018$ ). ACTION and NCDR models again did not differ significantly ( $p_{\text{ACTIONvsNCDR}} = 0.10$ ). There were no significant within-model performance differences between subgroups of NSTEMI vs. STEMI patients (Table 3: ACTION  $p = 0.35$ ; NCDR  $p = 0.17$ ; GRACE  $p = 0.89$ ). In a sensitivity analysis restricted only to patients who received PCI ( $n = 1052$ ), results of GRACE (c-index 0.83), ACTION (c-index 0.84) and NCDR (c-index 0.88;  $p_{\text{GRACEvsNCDR}}$  and  $p_{\text{ACTIONvsNCDR}}$  both  $< 0.01$ ) comparisons were not different to the overall cohort (Table 3).

#### 4.3.3. Risk model calibration (Fig. 2 and Table 3)

Comparative graphical analysis of risk model calibration is depicted in Fig. 2: ACTION (Fig. 2C) showed the most accurate calibration, while GRACE 1.0 (Fig. 2A) overestimated and NCDR (Fig. 2D) underestimated mortality risk in our cohort, especially in high-risk patients. Compared to the GRACE 1.0 model, GRACE 2.0 was more evenly calibrated across risk quintiles (Fig. 2A and B). This was also evident in calculated mean risk for in-hospital mortality, which was  $12.2 \pm 15.2\%$  for GRACE 1.0,  $6.5 \pm 10.6\%$  for GRACE 2.0,  $7.6 \pm 11.9\%$  for ACTION and  $6.4 \pm 11.3\%$  for NCDR risk models, respectively (Table 3). On average, all models – least of them NCDR – tended to overestimate risk in NSTEMI patients, ACTION and GRACE underestimated risk in STEMI (Table 3).

#### 4.3.4. Risk model reclassification (Suppl. Tables 5–8)

The reclassification tables (Suppl. Tables 5 and 6) comparing NCDR and ACTION risk models to the GRACE 1.0 risk model revealed that NCDR and ACTION risk models tended to reclassify patients without events to lower risk categories, while there was no improvement in reclassification of patients with events to higher risk categories (Suppl. Table 5–6). Overall, the continuous (category-free) net reclassification improvement (NRI) for NCDR vs. GRACE 1.0 (NRI 0.267, 95% CI 0.102 to 0.431;  $p = 0.002$ ) was significant, while there was no significant continuous net reclassification improvement for ACTION vs. GRACE 1.0 (NRI 0.142, 95% CI -0.006 to 0.291;  $p = 0.06$ ) in the overall cohort. Comparison with the GRACE 2.0 risk model revealed a significant continuous net reclassification improvement for NCDR (NRI 0.328, 95% CI 0.145 to 0.508;  $p = 0.0004$ ) as well as ACTION (NRI 0.277, 95% CI 0.094 to 0.459;  $p = 0.003$ ) risk models (Suppl. Table 7–8).

## 5. Discussion

We here present a comparative performance evaluation of the GRACE [10,11,24], ACTION [12,13] and NCDR [14,15] risk models for prediction of in-hospital mortality in German patients with ACS. Main results are: 1) all three risk scores showed good performance in ACS; 2) the modern NCDR and – to a lesser extent – ACTION risk models discriminated superior to the GRACE models; 3) there were no significant within-model differences in performance for NSTEMI vs. STEMI patient subgroups.

An abundance of risk models for cardiovascular clinical practice developed from registry patient populations is available [25]. Application of such a model to a different patient population or to different clinical practice – e.g. due to progress in medical or interventional therapy [26–30] – may render risk model performance inaccurate [31], as either relative weights of risk factors within a model change or new risk factors demand incorporation. Temporal, geographical and domain validation of risk models is thus critical to retain performance [32], but only very few of the available cardiovascular risk models have been externally validated [33]. However, as risk stratification with ACS models – especially the gold-standard GRACE model – with scoring-dependent management is guideline-recommended clinical practice for ACS [3–7], reevaluation and improvement of risk model performance may have direct impact on patient outcomes and is thus of utmost importance to ensure quality of cardiovascular care in ACS.

The GRACE registry prospectively included a multinational cohort of >102,000 ACS patients from 30 countries and nearly 250 hospitals between 1999 and 2009. The GRACE 1.0 model for prediction of

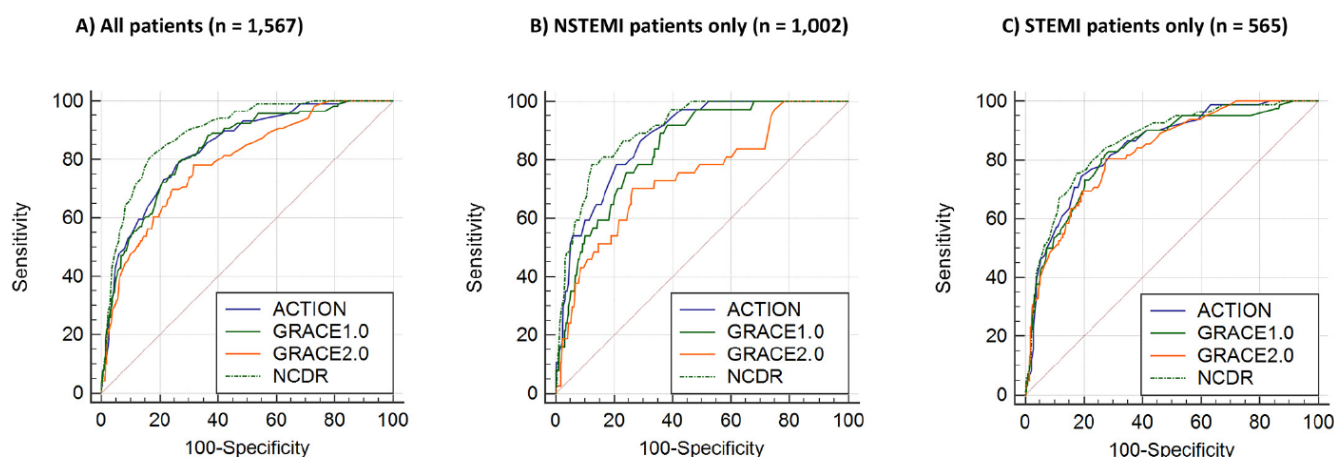


Fig. 1. Risk model discrimination. Comparative risk model discrimination performance analysis of ROC curves of ACTION, GRACE and NCDR risk models for in-hospital mortality, including all patients with ACS (A), and for the subsets of patients with NSTEMI (B) and STEMI (C), respectively. (N)STEMI = (Non) ST-segment elevation myocardial infarction. Statistical comparisons between models were performed using the DeLong method [20], results are reported in Table 3.

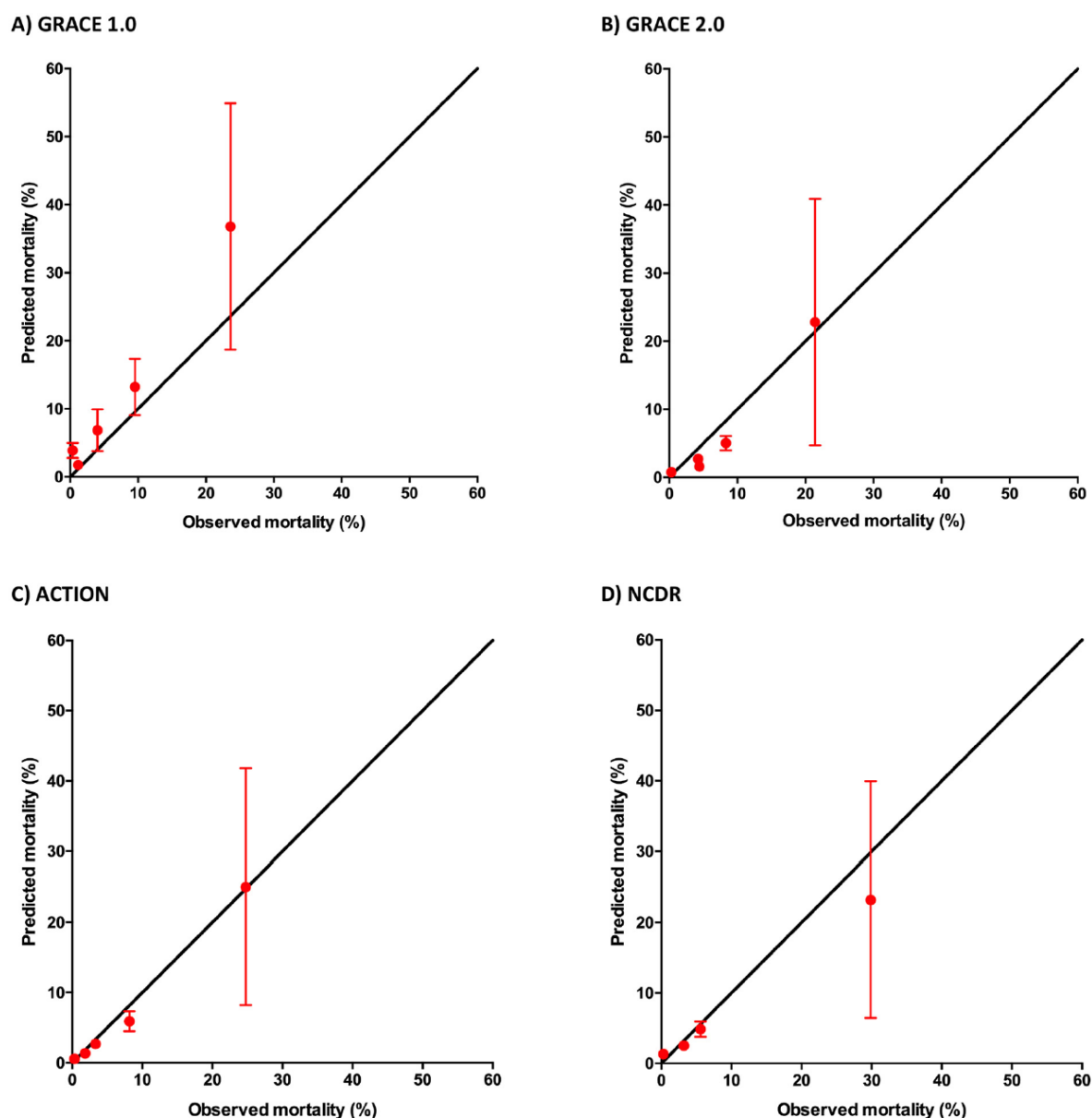


Fig. 2. Risk model calibration. Risk model calibration for A) GRACE 1.0, B) GRACE 2.0, C) ACTION and D) NCDR risk models, comparing observed and predicted mortality in risk quintiles of all patients with acute coronary syndrome.

in-hospital mortality was first developed in 11,389 ACS patients in 2003 [10] and later updated in 48,023 patients [11] (38% STEMI, c-index 0.84, Table 1). It underwent extensive external validation [34–37], including extension to 6-month and 1-year mortality prediction [8,38]; it has proven its value to judge early vs. delayed invasive management strategies in ACS [39]. Its successor – the GRACE 2.0 model [9] – implemented non-linear associations and improved ease-of-use for the bedside; it was also externally validated, including longer-term follow-ups up to 1 and 3 years [9,40]. However, its validation for in-hospital mortality – the outcome of interest in this study – cannot rival its predecessor, which may partly explain its inferior discrimination performance compared to GRACE 1.0 [11] for our in-hospital mortality analysis. We thus report transparent results for both models in the results section. Apart from extensive external validation, there is an ongoing study (UK GRACE Intervention Study, UKGRIS) to assess the effectiveness of the systematic clinical application of the GRACE risk score and the impact of GRACE risk score dependent management on clinical outcomes

[41]. The current guidelines of the European Society of Cardiology on the management of patients with non-ST-segment myocardial infarction contain a class IIa recommendation for risk stratification with the GRACE risk model [7].

The NCDR risk model for in-hospital mortality [15] was developed from a multicentric US registry population, including 181,775 PCI procedures in all risk categories – ranging from elective PCI to STEMI and cardiogenic shock. It was updated in 2013 in 724,883 patients to improve risk prediction in high-risk populations [14] and reached an unsurpassed c-index of 0.93 in its original cohort. It was externally validated in Portuguese [42] and German [19] populations. Longer-term follow-ups have not been evaluated thus far. Corresponding NCDR risk models for prediction of in-hospital acute kidney injury [17] and bleeding [16] events are also available.

The ACTION risk model for in-hospital mortality was developed from the homonymous multicentric US registry cohort of 65,668 patients with acute myocardial infarction (40% STEMI) [13]. It was updated in



2016 [12] with patients included from 2012 to 2013, reaching an excellent c-index of 0.88. The original model has been externally validated in a Spanish cohort [43], the update in China regarding prediction of 1-year mortality [44]. This is the first external validation of the updated score for in-hospital mortality [12]. A corresponding bleeding model is also available [45].

This study evaluated all three risk scores in a performance comparison in German patients with ACS – in a cohort of comparable risk (36% STEMI, 64% NSTEMI) to the GRACE and ACTION development cohorts (38% and 39% STEMI, respectively [11,12]). All three models discriminated risk well (Table 3 and Fig. 1), in NSTEMI as well as in STEMI, although a consistent loss of discrimination of ~0.04 in c-index compared to original cohorts was observed for NCDR and ACTION models (Tables 1 and 3). However, significant performance advantages over the GRACE model are evident, especially for the NCDR model (Table 3 and Fig. 1:  $p_{\text{GRACEvsNCDR}} < 0.05$  overall and for both NSTEMI and STEMI subgroups) and – to a lesser extent – for the ACTION model (Table 3 and Fig. 1:  $p = 0.02$  for NSTEMI patients). The NCDR model performed significantly better than the ACTION model in the overall cohort, however did not reach significance within subgroups (Table 3).

A similar study by Raposeiras-Roubin et al. compared ACTION and GRACE risk models in ACS patients, as well as the NCDR risk model in the subgroup of patients undergoing PCI [43]. Their analyses showed no difference between the ACTION and GRACE risk model and an inferior performance for the NCDR risk model. Reasons for the divergent results may lie in different patient cohorts, as the recruitment period was more than a decade ago. In the present study, we applied updated versions of the NCDR and ACTION risk models – published in 2013 and 2016 respectively [12,14] – to a more contemporary patient cohort.

This study thus finds first evidence that for prediction of in-hospital mortality in ACS – while still being a good tool – the GRACE model may not be the best choice anymore. Reasons may lie in the more contemporary and larger development cohorts of NCDR and ACTION models, potentially also in higher data quality in digitalized modern health services, which facilitate model development. Due to rapidly evolving medical technology and a society undergoing demographic change, clinical practice in interventional cardiology has changed tremendously since the original GRACE model was established: ACS patients more frequently undergo invasive management instead of medical therapy [3,5,46], PCI indications have expanded for multivessel- and left-main coronary artery disease [20,47–49], primary vascular access has shifted from transfemoral to transradial approaches [3,5,50]. Patients undergoing cardiac catheterization are now older and feature more comorbidities [51–53], pharmacological therapy (e.g. platelet inhibition) has changed [26,27,54] and modern drug-eluting stent systems have reduced coronary complications [29].

These findings may thus prompt additional studies on this important topic and eventually a reevaluation of recommendations for clinical practice. There is a need for randomized clinical trials evaluating the impact of risk-adjusted management on clinical outcomes especially for risk stratification based on the NCDR and ACTION risk models since data on this important topic are sparse.

Apart from in-hospital clinical outcomes, the prognosis after ACS is also determined by adverse events occurring during the first year or later [55]. Thus risk stratification is also recommended for longer-term mortality, in order to identify patients at risk after discharge from hospital [3–6]. In contrast to ACTION and NCDR risk models, GRACE risk models have also been prospectively validated to estimate long-term mortality up to three years [8,9,38,40], therefore providing a useful tool to identify patients with higher risk after discharge.

Particular strengths of our study are the inclusion of the whole range of risk in ACS from low-risk NSTEMI to highest-risk STEMI in cardiogenic shock, the good data quality with low need for imputation and the comprehensive comparison of the three risk models. Limitations lie in the retrospective and monocentric study design, which limits

generalizability and conclusions to German – or at best European – clinical practice. As long-term outcome data were not available for this cohort, our comparative analysis was limited to evaluation of in-hospital mortality prediction.

## 6. Conclusion

In a contemporary German patient population with acute coronary syndrome, modern NCDR and ACTION risk models show superior performance in prediction of in-hospital mortality compared to the gold-standard GRACE model – which nonetheless still performed well and remains the sole tool for long-term risk prediction in ACS.

## Contributors

CP and GW conceived and designed the study; JQ, JT, SB, CP and LK collected and analyzed data; GW and CP analyzed and interpreted data and drafted the manuscript; MB, AK, YL, TK, VS and CJ supported data acquisition and analysis and critically revised the manuscript; MK and AI assumed project supervision, interpreted data and critically revised the manuscript. All authors read and accepted the submitted version of the manuscript.

## Financial support

This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (No. 2018-32 to GW).

## Declaration of Competing Interest

All authors declare: no support from any industry or third-party organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## Acknowledgements

We thank Robert McNamara, lead author of the ACTION risk model [12], for his support of our work with unpublished data for the ACTION risk model calibration.

We thank Alexander Hoss from our group for statistical help during the revision process.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2020.12.085>.

## References

- [1] A. Timmis, N. Townsend, C.P. Gale, A. Torbica, M. Lettino, S.E. Petersen, et al., European Society of Cardiology: cardiovascular disease statistics 2019, *Eur. Heart J.* 41 (1) (2019) 12–85.
- [2] World Health Organization, Global Status Report on Noncommunicable Diseases 2010, 2011 ISBN: 978 92 4 156422 9.
- [3] M. Roffi, C. Patrono, J.P. Collet, C. Mueller, M. Valgimigli, F. Andreotti, et al., 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the Management of Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), *Eur. Heart J.* 37 (3) (2016) 267–315.
- [4] E.A. Amsterdam, N.K. Wenger, R.G. Brindis, D.E. Casey Jr., T.G. Ganiats, D.R. Holmes Jr., et al., 2014 AHA/ACC guideline for the Management of Patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, *J. Am. Coll. Cardiol.* 64 (24) (2014) e139–e228.



- [5] B. Ibanez, S. James, S. Agewall, M.J. Antunes, C. Buiccarelli-Ducci, H. Bueno, et al., 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), *Eur. Heart J.* 39 (2) (2018) 119–177.
- [6] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, D.E. Casey Jr., M.K. Chung, J.A. de Lemos, et al., 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, *J. Am. Coll. Cardiol.* 61 (4) (2013) e78–e140.
- [7] J.P. Collet, H. Thiele, E. Barbato, O. Barthelémy, J. Bauersachs, D.L. Bhatt, et al., ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, *Eur. Heart J.* 2020 (2020).
- [8] K.A. Fox, O.H. Dabbous, R.J. Goldberg, K.S. Pieper, K.A. Eagle, F. Van de Werf, et al., Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE), *BMJ*. 333 (7578) (2006) 1091.
- [9] K.A. Fox, G. Fitzgerald, E. Pyunmirat, W. Huang, K. Carruthers, T. Simon, et al., Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score, *BMJ Open* 4 (2) (2014), e004425.
- [10] C.B. Granger, R.J. Goldberg, O. Dabbous, K.S. Pieper, K.A. Eagle, C.P. Cannon, et al., Predictors of hospital mortality in the global registry of acute coronary events, *Arch. Intern. Med.* 163 (19) (2003) 2345–2353.
- [11] K.S. Pieper, J.M. Gore, G. Fitzgerald, C.B. Granger, R.J. Goldberg, G. Steg, et al., Validity of a risk-prediction tool for hospital mortality: the global registry of acute coronary events, *Am. Heart J.* 157 (6) (2009) 1097–1105.
- [12] R.L. McNamara, K.F. Kennedy, D.J. Cohen, D.B. Diercks, M. Moscucci, S. Ramee, et al., Predicting in-hospital mortality in patients with acute myocardial infarction, *J. Am. Coll. Cardiol.* 68 (6) (2016) 626–635.
- [13] C.T. Chin, A.Y. Chen, T.Y. Wang, K.P. Alexander, R. Mathews, J.S. Rumsfeld, et al., Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the acute coronary treatment and intervention outcomes network (ACTION) registry—get with the guidelines (GWTG) acute myocardial infarction mortality model and risk score, *Am. Heart J.* 161 (1) (2011) 113–122 (e2).
- [14] J.M. Brennan, J.P. Curtis, D. Dai, S. Fitzgerald, A.K. Khandelwal, J.A. Spertus, et al., Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry), *JACC Cardiovasc. Interv.* 6 (8) (2013) 790–799.
- [15] E.D. Peterson, D. Dai, E.R. DeLong, J.M. Brennan, M. Singh, S.V. Rao, et al., Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry, *J. Am. Coll. Cardiol.* 55 (18) (2010) 1923–1932.
- [16] S.V. Rao, L.A. McCoy, J.A. Spertus, R.J. Krone, M. Singh, S. Fitzgerald, et al., An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI registry, *JACC Cardiovasc. Interv.* 6 (9) (2013) 897–904.
- [17] T.T. Tsai, U.D. Patel, T.I. Chang, K.F. Kennedy, F.A. Masoudi, M.E. Matheny, et al., Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI registry, *J. Am. Heart Assoc.* 3 (6) (2014), e001380.
- [18] W.S. Weintraub, M.V. Grau-Sepulveda, J.M. Weiss, E.R. DeLong, E.D. Peterson, S.M. O'Brien, et al., Prediction of long-term mortality after percutaneous coronary intervention in older adults: results from the National Cardiovascular Data Registry, *Circulation*. 125 (12) (2012) 1501–1510.
- [19] G. Wolff, Y. Lin, J. Quade, S. Bader, L. Kosejian, M. Brockmeyer, et al., Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German heart center, *Clin. Res. Cardiol.* 109 (2019) 235–245.
- [20] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, et al., 2018 ESC/EACTS Guidelines on myocardial revascularization, *Eur. Heart J.* 40 (2) (2019) 87–165.
- [21] R. Mehran, S.V. Rao, D.L. Bhatt, C.M. Gibson, A. Caixeta, J. Eikelboom, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium, *Circulation*. 123 (23) (2011) 2736–2747.
- [22] P.M. Palevsky, K.D. Liu, P.D. Brophy, L.S. Chawla, C.R. Parikh, C.V. Thakur, et al., KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury, *Am. J. Kidney Dis.* 61 (5) (2013) 649–672.
- [23] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, *Biometrics*. 44 (3) (1988) 837–845.
- [24] V.M. Abazov, B. Abbott, M. Abolins, B.S. Acharya, D.L. Adams, M. Adams, et al., Observation and properties of the  $X(3872)$  decaying to  $J/\psi\pi^+\pi^-$  in pp collisions at  $\sqrt{s}=1.96$  TeV, *Phys. Rev. Lett.* 93 (16) (2004) 162002.
- [25] Tufts PACE Clinical Predictive Model Registry. Accessed April 27, 2020.
- [26] L. Wallentin, R.C. Becker, A. Budaj, C.P. Cannon, H. Emanuelsson, C. Held, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 361 (11) (2009) 1045–1057.
- [27] S.D. Wiviott, E. Braunwald, C.H. McCabe, G. Montalescot, W. Ruzyllo, S. Gottlieb, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 357 (20) (2007) 2001–2015.
- [28] S. Schupke, F.J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wohrle, et al., Ticagrelor or Prasugrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 381 (16) (2019) 1524–1534.
- [29] G.G. Stefanini, D.R. Holmes Jr., Drug-eluting coronary-artery stents, *N. Engl. J. Med.* 368 (3) (2013) 254–265.
- [30] M. Valgimigli, E. Frigoli, S. Leonardi, P. Vranckx, M. Rothenbuhler, M. Tebaldi, et al., Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial, *Lancet*. 392 (10150) (2018) 835–848.
- [31] M.E. Matheny, L. Ohno-Machado, F.S. Resnic, Discrimination and calibration of mortality risk prediction models in interventional cardiology, *J. Biomed. Inform.* 38 (5) (2005) 367–375.
- [32] Moons KGM, A.P. Kengne, D.E. Grobbee, P. Royston, Y. Vergouwe, D.G. Altman, et al., Risk prediction models: II. External validation, model updating, and impact assessment, *Heart*. 98 (9) (2012) 691.
- [33] A. Adibi, M. Sadatsafavi, Ioannidis JPA, Validation and utility testing of clinical prediction models: time to change the approach, *JAMA* 324 (2020) 235–236.
- [34] B. Elbarouni, S.G. Goodman, R.T. Yan, R.C. Welsh, J.M. Kornder, J.P. Deyoung, et al., Validation of the global registry of acute coronary event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada, *Am. Heart J.* 158 (3) (2009) 392–399.
- [35] A.R. Prabhudesai, M.A. Srilakshmi, M.J. Santosh, G.G. Shetty, K. Varghese, C.B. Patil, et al., Validation of the GRACE score for prognosis in Indian patients with acute coronary syndromes, *Indian Heart J.* 64 (3) (2012) 263–269.
- [36] K. Komiyama, M. Nakamura, K. Tanabe, H. Niikura, H. Fujimoto, K. Oikawa, et al., In-hospital mortality analysis of Japanese patients with acute coronary syndrome using the Tokyo CCU network database: applicability of the GRACE risk score, *J. Cardiol.* 71 (3) (2018) 251–258.
- [37] P.J. Bradshaw, J.M. Katzenellenbogen, F.M. Sanfilippo, M.S.T. Hobbs, P.L. Thompson, S.C. Thompson, Validation study of GRACE risk scores in indigenous and non-indigenous patients hospitalized with acute coronary syndrome, *BMC Cardiovasc. Disord.* 15 (1) (2015) 151.
- [38] Goncalves P. de Araujo, J. Ferreira, C. Aguiar, R. Seabra-Gomes, TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS, *Eur. Heart J.* 26 (9) (2005) 865–872.
- [39] S.R. Mehta, C.B. Granger, W.E. Boden, P.G. Steg, J.P. Bassand, D.P. Faxon, et al., Early versus delayed invasive intervention in acute coronary syndromes, *N. Engl. J. Med.* 360 (21) (2009) 2165–2175.
- [40] W. Huang, G. Fitzgerald, R.J. Goldberg, J. Gore, R.H. McManus, H. Awad, et al., Performance of the GRACE risk score 2.0 simplified algorithm for predicting 1-year death after hospitalization for an acute coronary syndrome in a contemporary multiracial cohort, *Am. J. Cardiol.* 118 (8) (2016) 1105–1110.
- [41] C.C. Everett, K.A. Fox, C. Reynolds, C. Fernandez, L. Sharples, D.D. Stocken, et al., Evaluation of the impact of the GRACE risk score on the management and outcome of patients hospitalised with non-ST elevation acute coronary syndrome in the UK: protocol of the UKGRIS cluster-randomised registry-based trial, *BMJ Open* 9 (9) (2019), e032165.
- [42] A.T. Timoteo, A.V. Monteiro, G. Portugal, P. Teixeira, H. Aidos, M.L. Ferreira, et al., Validation of two US risk scores for percutaneous coronary intervention in a single-center Portuguese population of patients with acute coronary syndrome, *Rev. Port. Cardiol.* 35 (2) (2016) 73–78.
- [43] S. Rasepseiras-Roubin, E. Abu-Assi, P. Cabanas-Grandio, R.M. Agra-Bermejo, S. Gestal-Romari, E. Pereira-Lopez, et al., Walking beyond the GRACE (Global Registry of Acute Coronary Events) model in the death risk stratification during hospitalization in patients with acute coronary syndrome: what do the AR-G (ACTION [Acute Coronary Treatment and Intervention Outcomes Network] Registry and GWTG [Get With the Guidelines] Database), NCDR (National Cardiovascular Data Registry), and EuroHeart Risk Scores Provide? *JACC Cardiovasc. Interv.* 5 (11) (2012) 1117–1125.
- [44] T. Yu, C. Tian, J. Song, D. He, Z. Sun, Z. Sun, ACTION (acute coronary treatment and intervention outcomes network) registry-GWTG (get with the guidelines) risk score predicts long-term mortality in acute myocardial infarction, *Oncotarget*. 8 (60) (2017) 102559–102572.
- [45] R. Mathews, E.D. Peterson, A.Y. Chen, T.Y. Wang, C.T. Chin, G.C. Fonarow, et al., In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION registry@-GWTGTM, *Am. J. Cardiol.* 107 (8) (2011) 1136–1143.
- [46] R.U. Shah, T.D. Henry, S. Rutten-Ramos, R.F. Garberich, M. Tighiouart, C.N. Bairey Merz, Increasing percutaneous coronary interventions for ST-segment elevation myocardial infarction in the United States: progress and opportunity, *JACC Cardiovasc. Interv.* 8 (1 Pt B) (2015) 139–146.
- [47] T. Makikallio, N.R. Holm, M. Lindsay, M.S. Spence, A. Erglis, I.B. Menown, et al., Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial, *Lancet*. 388 (10061) (2016) 2743–2752.
- [48] G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. Simonton, P. Genereux, J. Puskas, et al., Everolimus-eluting stents or bypass surgery for left Main coronary artery disease, *N. Engl. J. Med.* 375 (23) (2016) 2223–2235.
- [49] P.W. Serruys, M.C. Morice, A.P. Kappetein, A. Colombo, D.R. Holmes, M.J. Mack, et al., Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease, *N. Engl. J. Med.* 360 (10) (2009) 961–972.
- [50] M. Valgimigli, A. Gagnor, P. Calabro, E. Frigoli, S. Leonardi, T. Zaro, et al., Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial, *Lancet*. 385 (9986) (2015) 2465–2476.
- [51] S. Grotti, L. Bolognese, Interventional cardiology is changing: demographic, clinical and economic considerations, *J. Cardiovasc. Med. (Hagerstown)* 18 (Suppl. 1) (2017) e67–e70.

- [52] A. Timmis, N. Townsend, C. Gale, R. Grobbee, N. Maniadakis, M. Flather, et al., European Society of Cardiology: cardiovascular disease statistics 2017, *Eur. Heart J.* 39 (7) (2018) 508–579.
- [53] G. Wolff, D. Dimitroulis, F. Andreotti, M. Kolodziejczak, C. Jung, P. Scicchitano, et al., Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis, *Circ. Heart Fail.* 10 (1) (2017).
- [54] E.P. Navarese, F. Andreotti, M. Kolodziejczak, V. Schulze, G. Wolff, S. Dias, et al., Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients, *Thromb. Haemost.* 114 (5) (2015) 933–944.
- [55] T. Jernberg, P. Hasvold, M. Henriksson, H. Hjelm, M. Thuresson, M. Janzon, Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective, *Eur. Heart J.* 36 (19) (2015) 1163–1170.
- [56] S. Akyuz, S. Yazici, E. Bozbeyoglu, T. Onuk, O. Yildirimturk, D. Karacimen, et al., Validity of the updated GRACE risk predictor (version 2.0) in patients with non-ST-elevation acute coronary syndrome, *Rev. Port. Cardiol.* 35 (1) (2016) 25–31.
- [57] A. Anand, S. Cudmore, S. Robertson, J. Stephen, K. Haga, C.J. Weir, et al., Frailty assessment and risk prediction by GRACE score in older patients with acute myocardial infarction, *BMC Geriatr.* 20 (1) (2020) 102.

#### **4.1.4 Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients**

**Wolff G**, Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K, Maier O, Sedaghat A, Polzin A, Sugiura A, Jung C, Grube E, Westenfeld R, Icks A, Zeus T, Sinning JM, Baldus S, Nickenig G, Kelm M, Veulemans V.

Clin Res Cardiol 2021 Mar;110(3):368-376.

Pubmed PMID: 32851491

DOI: [10.1007/s00392-020-01731-9](https://doi.org/10.1007/s00392-020-01731-9)

Chirurgische Risikomodelle wie der EUROScore I/II (89, 90) oder der STS-Score (91) werden routinemäßig bei Patienten mit hochgradiger Aortenklappenstenose genutzt, um das Risiko eines Transkatheter-Aortenklappenersatzes (TAVI) einzuschätzen. Jedoch sind diese nicht in TAVI-Prozeduren entwickelt und validiert worden, weshalb ihre Leistung in diesem Patientenkollektiv häufig schlecht ist. TAVI-spezifische Modelle sind aus großen Kohorten entwickelt worden, um das präprozedurale Risikoassessment vor TAVI zu verbessern.

Ziel dieser Studie war es, die Vorhersage des Mortalitätsrisikos nach einem TAVI-Eingriff bei Patienten mit hochgradiger Aortenklappenstenose mittels dreier chirurgischer Risikomodelle (Logistischer EUROScore I, EUROScore II, STS PROM Score (89-91)) und dreier TAVI-spezifischer Risikomodelle (FRANCE-2, OBSERVANT, GAVS-2 (92-94)) einzuschätzen. Dafür wurden alle sechs Risikomodelle retrospektiv in einer TAVI-Kohorte von 2946 Patienten der Deutschen Rhein-Transregio-Aortenklappenkohorte berechnet und im Hinblick auf die Vorhersage von 30-Tages-Sterblichkeit untersucht. Dabei wurden transfemorale und transapikale TAVI-Eingriffe in Subanalysen unterschieden.

Die Risikodiskrimination der verschiedenen Modelle war – unabhängig, ob es sich um chirurgische oder TAVI-spezifische Scores handelte – gleichermaßen schlecht: C-Werte der ROC-Analysen reichten von 0,60 (OBSERVANT) bis 0,67 (STS PROM), ohne signifikante Unterschiede. Die Kalibration der Scores war ebenfalls schwankend: alle sechs Modelle überschätzten die Sterblichkeit (im Mittel 3,7%), teilweise sogar dramatisch (z.B. LogES I mit 23,4% ± 15,9%) und besonders in Hochrisiko-Patienten. Es ergaben sich keine Unterschiede zwischen transfemoralen und transapikalen Prozeduren.

Zusammenfassend zeigte sich, dass im Risikoassessment für den Transkatheter-Aortenklappenersatz – insbesondere im Vergleich zu den in 4.1.1 bis 4.1.3 evaluierten koronaren Risikomodellen – noch erhebliche Schwächen bestehen. Ursache kann sein, dass sich diese interventionellen Eingriffe noch sehr rasch weiterentwickeln und die zur Verfügung stehenden Entwicklungskohorten noch klein und heterogen sind. Neue Modelle oder Updates bestehender Modelle sind notwendig, um hier die Leistung zu verbessern.





# Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients

Georg Wolff<sup>1</sup> · Jasmin Shamekhi<sup>2</sup> · Baravan Al-Kassou<sup>2</sup> · Noriaki Tabata<sup>2</sup> · Claudio Parco<sup>1</sup> · Kathrin Klein<sup>1</sup> · Oliver Maier<sup>1</sup> · Alexander Sedaghat<sup>2</sup> · Amin Polzin<sup>1</sup> · Atsushi Sugiura<sup>2</sup> · Christian Jung<sup>1</sup> · Eberhard Grube<sup>2</sup> · Ralf Westenfeld<sup>1</sup> · Andrea Icks<sup>4</sup> · Tobias Zeus<sup>1</sup> · Jan-Malte Sinning<sup>2,5</sup> · Stephan Baldus<sup>3,5</sup> · Georg Nickenig<sup>2,5</sup> · Malte Kelm<sup>1,5</sup> · Verena Veulemans<sup>1</sup>

Received: 13 June 2020 / Accepted: 12 August 2020  
© The Author(s) 2020

## Abstract

**Background** Surgical risk prediction models are routinely used to guide decision-making for transcatheter aortic valve replacement (TAVR). New and updated TAVR-specific models have been developed to improve risk stratification; however, the best option remains unknown.

**Objective** To perform a comparative validation study of six risk models for the prediction of 30-day mortality in TAVR

**Methods and results** A total of 2946 patients undergoing transfemoral (TF,  $n = 2625$ ) or transapical (TA,  $n = 321$ ) TAVR from 2008 to 2018 from the German Rhine Transregio Aortic Diseases cohort were included. Six surgical and TAVR-specific risk scoring models (LogES I, ES II, STS PROM, FRANCE-2, OBSERVANT, GAVS-II) were evaluated for the prediction of 30-day mortality. Observed 30-day mortality was 3.7% (TF 3.2%; TA 7.5%), mean 30-day mortality risk prediction varied from  $5.8 \pm 5.0\%$  (OBSERVANT) to  $23.4 \pm 15.9\%$  (LogES I). Discrimination performance (ROC analysis,  $c$ -indices) ranged from 0.60 (OBSERVANT) to 0.67 (STS PROM), without significant differences between models, between TF or TA approach or over time. STS PROM discriminated numerically best in TF TAVR ( $c$ -index 0.66; range of  $c$ -indices 0.60 to 0.66); performance was very similar in TA TAVR (LogES I, ES II, FRANCE-2 and GAVS-II all with  $c$ -index 0.67). Regarding calibration, all risk scoring models—especially LogES I—overestimated mortality risk, especially in high-risk patients.

**Conclusions** Surgical as well as TAVR-specific risk scoring models showed mediocre performance in prediction of 30-day mortality risk for TAVR in the German Rhine Transregio Aortic Diseases cohort. Development of new or updated risk models is necessary to improve risk stratification.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00392-020-01731-9>) contains supplementary material, which is available to authorized users.

✉ Georg Wolff  
[Georg.Wolff@med.uni-duesseldorf.de](mailto:Georg.Wolff@med.uni-duesseldorf.de)

<sup>1</sup> Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Heinrich Heine University, Medical Faculty, Moorenstr. 5, 40225 Düsseldorf, Germany

<sup>2</sup> Department of Medicine II, Heart Center Bonn, University Hospital Bonn, Bonn, Germany

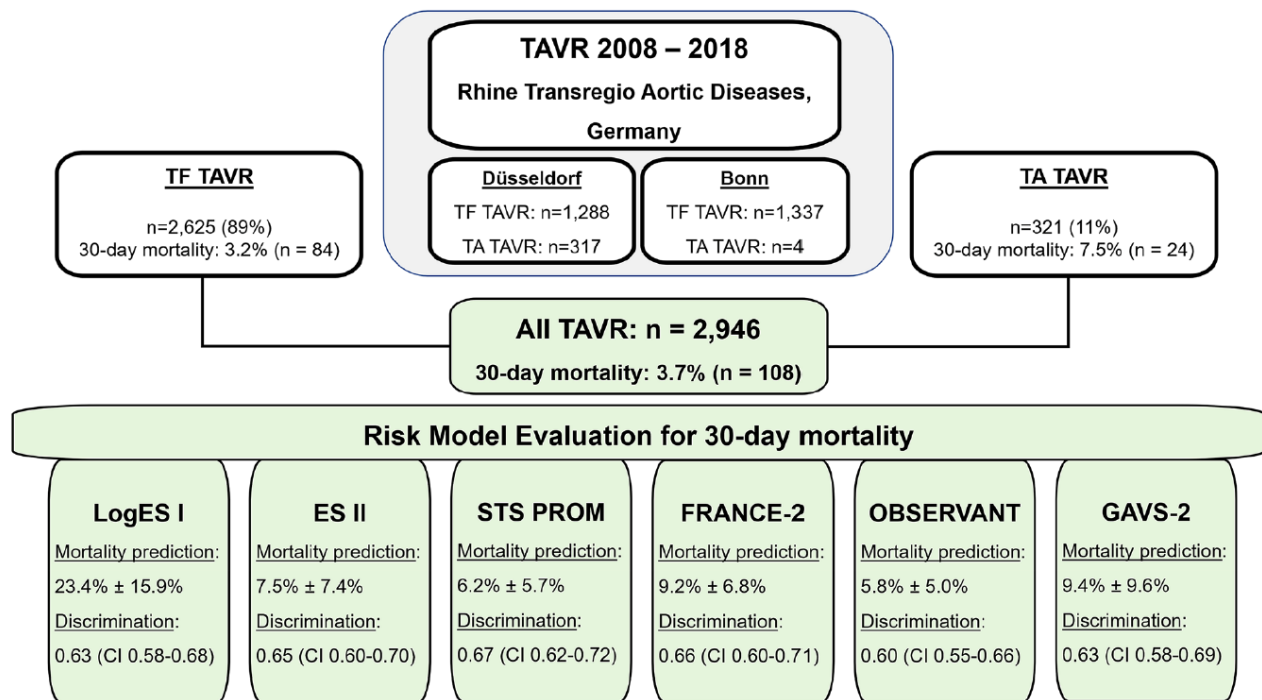
<sup>3</sup> Division of Cardiology, Pneumology, Angiology and Intensive Care, Department of Internal Medicine III, University of Cologne, Cologne, Germany

<sup>4</sup> Institute for Health Services Research and Health Economics, Centre for Health and Society, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

<sup>5</sup> Transregio 259: Aortic Diseases-Scientific Network of University Heart Centers in Düsseldorf/Bonn/Cologne, Düsseldorf/Bonn/Cologne, Germany



## Graphic abstract



**Keywords** TAVR · TAVI · Risk prediction · Mortality · EuroSCORE · GAVS

### Abbreviations

|            |                                                                                                                                                   |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| ES II      | EuroSCORE II                                                                                                                                      |
| EuroSCORE  | European System for Cardiac Operative Risk Evaluation                                                                                             |
| GAVS-II    | German Aortic Valve Score (2nd update)                                                                                                            |
| LogES I    | Logistic EuroSCORE I                                                                                                                              |
| OBSERVANT  | Observational study of appropriateness, efficacy and effectiveness of AVR-TAVR procedures for the treatment of severe symptomatic aortic stenosis |
| STS (PROM) | Society of Thoracic Surgeons Predicted Risk of Mortality                                                                                          |
| TAVR       | Transcatheter aortic valve replacement                                                                                                            |

### Introduction

Transcatheter aortic valve replacement (TAVR) is the treatment option of choice in inoperable and high-risk patients with severe aortic valve stenosis [1, 2] and recently showed favorable outcomes also in intermediate-risk [3, 4] and low-risk patients [5, 6]. Patient and procedural characteristics determine risk for adverse clinical outcomes. Cardiovascular societies recommend clinical decision-making for TAVR

within the Heart Team [1, 2], assisted by the use of statistical risk scoring models for individual patient risk stratification. Classical surgical risk models such as logistic EuroSCORE I (LogES I) [7, 8], its update EuroSCORE II (ES II) [9], or the Society of Thoracic Surgeons Predicted Risk of Mortality model (STS PROM) [10] are routinely used to gauge operative risk; however, they are known to overestimate mortality risk in TAVR [11–13]. Several TAVR-specific risk assessment models have been developed from national registry databases to optimize the predictive performance in the context of TAVR [14–16]. However, the optimal approach to risk prediction in TAVR still remains unknown, as their performance has been poor in validation studies [12, 17, 18].

We here aimed to evaluate the 30-day mortality prediction performance of six surgery- and TAVR-specific risk models (Table 1) in our German Rhine Transregio Aortic Diseases cohort of patients undergoing TAVR.

### Methods

#### Study population and data collection

This study was performed as an all-comer analysis of patients treated with either TF or TA TAVR between 2008

**Table 1** Risk model characteristics

| Risk model     | Year of publication | Recruitment period | Recruitment region              | Cohort size: development/validation (n) | Procedure characteristics             | Discrimination performance ( <i>c</i> -indices in validation cohort) |
|----------------|---------------------|--------------------|---------------------------------|-----------------------------------------|---------------------------------------|----------------------------------------------------------------------|
| LogES I [7, 8] | 1999/2003           | 1995               | Europe                          | 13,302/1479                             | Cardiac surgery                       | 0.76                                                                 |
| ES II [9]      | 2012                | 2010               | Worldwide, predominantly Europe | 16,828/5553                             | Cardiac surgery                       | 0.81                                                                 |
| STS PROM [10]  | 2009                | 2002–2006          | US                              | 65,855/43,904                           | Cardiac valve surgery                 | 0.80                                                                 |
| FRANCE-2 [15]  | 2014                | 2010–2011          | France + Monaco                 | 2552/1281                               | TAVR (TF 73.4%, TA 17.8%, other 8.8%) | 0.59                                                                 |
| OBSERVANT [14] | 2014                | 2010–2012          | Italy                           | 1256/622                                | TAVR                                  | 0.71                                                                 |
| GAVS-II [16]   | 2017                | 2011–2012          | Germany                         | 9027/9027                               | 55% surgical AVR, 45% TAVR            | 0.74                                                                 |

Characteristics of the analyzed risk models for the prediction of 30-day mortality risk in TAVR

and 2018 at the Heart Centers in Düsseldorf and Bonn, Germany, within the Rhine Transregio research consortium on aortic diseases. All patients were referred for TAVR procedures by local heart teams according to contemporary clinical practice and provided written informed consent for inclusion in prospective registries, with collection of clinical, procedural and follow-up data. The study was performed in accordance with the Declaration of Helsinki. The institutional Ethics Committee of the Heinrich-Heine University approved the study protocol (4080).

Clinical outcomes were systematically assessed using the Valve Academic Research Consortium consensus statement [19]. Primary clinical outcome of interest for risk model performance evaluation was 30-day mortality, secondary in-hospital outcomes are additionally reported.

## Statistics

Statistical and graphical data analysis was performed using Excel (Microsoft, USA), SPSS (version 23.0, SPSS Inc., Chicago, IL, USA), MedCalc 18.10 (MedCalc Software, Belgium) and GraphPad Prism (version 7.0, Graphpad Software, San Diego, CA, USA). Continuous data are described as means  $\pm$  standard deviation (SD), ordinal/categorical data as counts and % of total, and receiver-operating-characteristic (ROC) curve analysis is summarized as *c*-indices (area-under-the-curve) with 95% confidence intervals (CI). Continuous variables were evaluated for normal distribution using the Kolmogorov–Smirnov test and compared with either Student's *t* tests (for normally distributed samples) or Mann–Whitney–*U* tests; categorical data were compared with Chi-squared tests

or Fisher's exact tests (for expected values  $< 5$ ); ROC curves were compared using a non-parametric approach according to DeLong et al. [20]. All statistical tests were two tailed and an  $\alpha$  probability of  $p < 0.05$  was considered statistically significant.

Six risk models for the prediction of 30-day mortality (Table 1: LogES I [7, 8], ES II [9], STS PROM [10], FRANCE-2 [15], OBSERVANT [14] and GAVS-II [16]) were calculated for individual patients. LogES I, ES II and STS were routinely available in the databases and used for heart team decision-making. FRANCE-2, OBSERVANT and GAVS-II were calculated as follows: (1) relevant variables (for details, see Supplementary material) were weighed according to model definitions; (2) weighed variables were transformed into 30-day mortality probability predictions according to model definitions. Missing values necessary for risk model calculation were imputed to the mean (continuous) or median (categorical) of the whole population. Risk model discrimination accuracy was evaluated using ROC analysis and the *c*-index [area-under-the-curve (AUC)] as a cumulative measure; risk model calibration accuracy/goodness-of-fit was evaluated by stratification of patients into risk quintiles and comparison of observed vs. expected events within risk strata; additionally, it was formally tested by calculation of a logistic regression model for 30-day mortality, with the score value as independent variable and the Hosmer–Lemeshow goodness-of-fit test [21]. Prespecified analyses of patients stratified by TF vs. TA approach, time period of the procedure and prosthetic valve device types were additionally performed to account for learning curves and technical developments.

## Results

### Patient population

A total of 2,946 patients underwent TAVR between 2008 and 2018 at the German Heart Centers of Düsseldorf ( $n = 1605$ ) and Bonn ( $n = 1341$ ) and were included in this analysis, with 2,625 TF TAVR (89%) and 321 TA TAVR (11%) procedures, respectively. Mean age was  $80.9 \pm 6.1$  years (Suppl. Table 1), patients suffered from a high-cardiovascular-risk profile, including comorbidities of cardiovascular disease (67% coronary artery disease), previous cardiac interventional or surgical procedures (39% previous PCI, 15% previous CABG) and diabetes mellitus (30%). Characteristics differed significantly between patients treated with TF and TA TAVR procedures (Suppl. Table 1).

### Procedural characteristics across the TAVR era

TAVR developed from a rare procedure with high mortality (2008/2009:  $n = 61$  with ~10% mortality) to a high-volume routine procedure (2018:  $n = 538$  with 1.5% mortality) with low adverse events and shortened procedure duration (Table 2), which reflects a learning curve as well as continuous technical development. Patient age and estimated surgical mortality risk (LogES I) only declined marginally. TF TAVR became the primary access of choice (95.5% of procedures in 2018) over TA TAVR. The self-expandable Medtronic valves in different generations (early: CoreValve; newer generations: Evolut R and Evolut R Pro) were preferred to the balloon-expandable Edwards valves (early:

Sapien XT; newer generation: Sapien 3) in TF TAVR; the latter were the primary choice in TA TAVR (Suppl. Table 1).

### Clinical outcomes

The primary outcome of 30-day mortality occurred in 3.7% overall, more likely in TA vs. TF TAVR patients (7.5% vs. 3.2%;  $p < 0.0001$ ). Secondary clinical outcomes according to VARC-2 criteria are additionally reported in Suppl. Table 2.

### Risk model performance for the prediction of 30-day mortality

Risk model characteristics are provided in Table 1 and in the Supplementary material.

### Model discrimination

Risk model discrimination performance indices are reported in Table 3A, Fig. 1 and Table 4: ROC analyses showed mediocre performance of all risk models, without significant differences between them. Numerically, STS PROM ( $c$ -index 0.67, 95% CI 0.62–0.72) performed best, followed by FRANCE-2 ( $c$ -index 0.66, 95% CI 0.60–0.71) and ES II ( $c$ -index 0.65, 95% CI 0.60–0.70), OBSERVANT performed worst ( $c$ -index 0.60, 95% CI 0.55–0.66). All risk models performed worse than in their original validation cohorts (Table 1), except for FRANCE-2 ( $c$ -index 0.66 vs. 0.59 original). STS PROM showed the most consistent performance across TF and TA TAVR subgroups (both  $c$ -indices 0.66), while OBSERVANT performed numerically worst in both.

**Table 2** Patient and procedural characteristics across the study period

| Year    | Age, years     | LogES I         | Patient count, $n$ (%) | New gen. device, $n$ (%) | TF/TA TAVR, $n/n$ (% TF) | Procedure duration, min | Contrast volume, ml | 30-Day mortality, $n$ (%) |
|---------|----------------|-----------------|------------------------|--------------------------|--------------------------|-------------------------|---------------------|---------------------------|
| 2008    | $84.5 \pm 4.6$ | $31.7 \pm 17.6$ | 17 (0.6)               | 0 (0)                    | 17/0 (100)               | $59.1 \pm 24.0$         | $186.3 \pm 45.8$    | 1 (5.9)                   |
| 2009    | $79.1 \pm 6.7$ | $27.5 \pm 18.1$ | 44 (1.5)               | 0 (0)                    | 43/1 (97.7)              | $75.9 \pm 29.1$         | $217.1 \pm 76.8$    | 5 (11.4)                  |
| 2010    | $82.5 \pm 5.7$ | $26.4 \pm 14.5$ | 78 (2.6)               | 0 (0)                    | 60/18 (76.9)             | $82.6 \pm 46.1$         | $192.1 \pm 80.9$    | 5 (6.4)                   |
| 2011    | $80.9 \pm 6.3$ | $23.2 \pm 14.1$ | 188 (6.4)              | 0 (0)                    | 156/32 (83.0)            | $85.3 \pm 39.0$         | $166.9 \pm 75.1$    | 11 (5.9)                  |
| 2012    | $81.1 \pm 6.1$ | $22.6 \pm 14.2$ | 118 (4.0)              | 0 (0)                    | 88/30 (74.6)             | $88.6 \pm 30.7$         | $145.3 \pm 88.6$    | 9 (7.6)                   |
| 2013    | $81.5 \pm 6.1$ | $22.5 \pm 16.2$ | 212 (7.2)              | 15 (7.1)                 | 187/25 (88.2)            | $76.6 \pm 27.0$         | $128.7 \pm 27.0$    | 9 (4.2)                   |
| 2014    | $80.7 \pm 6.0$ | $21.0 \pm 15.0$ | 297 (10.1)             | 125 (42.1)               | 252/45 (84.8)            | $78.2 \pm 31.4$         | $143.7 \pm 60.2$    | 13 (4.4)                  |
| 2015    | $80.7 \pm 5.9$ | $26.0 \pm 17.9$ | 361 (12.3)             | 318 (88.1)               | 323/38 (89.5)            | $96.9 \pm 43.9$         | $138.7 \pm 49.8$    | 14 (3.9)                  |
| 2016    | $80.4 \pm 6.0$ | $24.6 \pm 15.8$ | 466 (15.8)             | 461 (98.9)               | 406/60 (87.1)            | $87.2 \pm 35.2$         | $121.7 \pm 39.3$    | 12 (2.6)                  |
| 2017    | $81.0 \pm 6.3$ | $23.7 \pm 16.1$ | 627 (21.3)             | 627 (100)                | 579/48 (92.3)            | $71.5 \pm 32.9$         | $119.9 \pm 46.5$    | 21 (3.4)                  |
| 2018    | $80.7 \pm 6.1$ | $21.0 \pm 15.0$ | 538 (18.3)             | 538 (100)                | 514/24 (95.5)            | $64.9 \pm 27.4$         | $106.1 \pm 46.1$    | 8 (1.5)                   |
| Overall | $80.9 \pm 6.1$ | $23.4 \pm 15.9$ | 2946 (100)             | 2084 (70.7)              | 2625/321 (89.1)          | $78.7 \pm 35.5$         | $130.3 \pm 56.0$    | 108 (3.7)                 |

Patient and procedural characteristics of TAVR from 2008 to 2018 and overall means/counts. Continuous variables are displayed as mean with standard deviation, categorical variables as  $n$  (%), unless specified differently

TF transfemoral, TA transapical, TAVR transcatheter aortic valve replacement, LogES I/Logistic EuroScore I



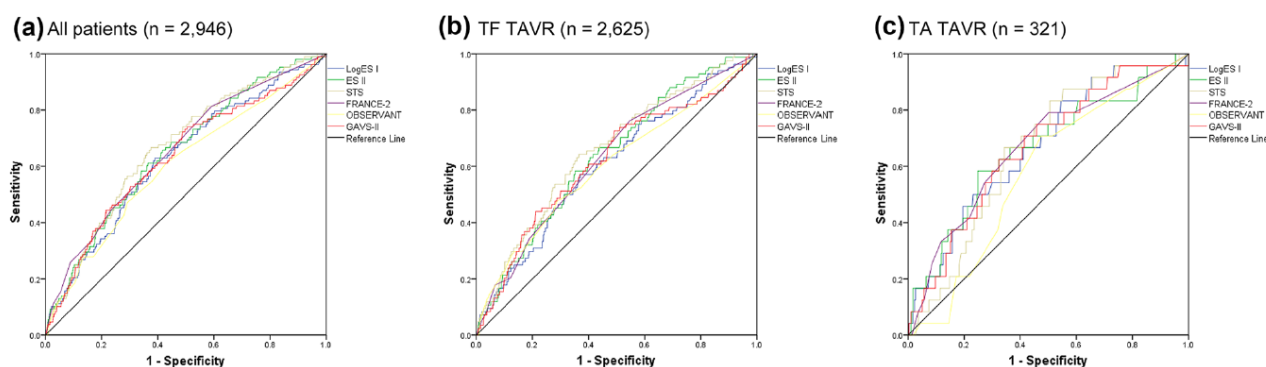
**Table 3** Risk model performance for the prediction of 30-day mortality risk in TAVR

| Risk model     | (A) Model discrimination: ROC analysis |                       |                      | (B) Model calibration: prediction of 30-day mortality risk |                            |                            |
|----------------|----------------------------------------|-----------------------|----------------------|------------------------------------------------------------|----------------------------|----------------------------|
|                | All patients<br>(n = 2946)             | TF TAVR<br>(n = 2625) | TA TAVR<br>(n = 321) | All patients<br>(n = 2946)                                 | TF TAVR<br>(n = 2625)      | TA TAVR (n = 321)          |
| LogES I [7, 8] | 0.63 (0.58–0.68)                       | 0.61 (0.55–0.67)      | 0.67 (0.56–0.78)     | 23.4 ± 15.9<br>(1.1–95.0)                                  | 22.8 ± 15.7*<br>(1.1–95.0) | 28.0 ± 16.9*<br>(2.5–88.4) |
| ES II [9]      | 0.65 (0.60–0.70)                       | 0.64 (0.58–0.70)      | 0.67 (0.55–0.79)     | 7.5 ± 7.4 (0.5–78.1)                                       | 7.3 ± 7.2* (0.5–78.1)      | 9.3 ± 8.8*<br>(1.0–56.1)   |
| STS PROM [10]  | 0.67 (0.62–0.72)                       | 0.66 (0.60–0.72)      | 0.66 (0.57–0.76)     | 6.2 ± 5.7 (0.5–69.3)                                       | 6.1 ± 5.6* (0.6–69.3)      | 7.5 ± 6.7*<br>(0.6–58.1)   |
| FRANCE-2 [15]  | 0.66 (0.60–0.71)                       | 0.63 (0.57–0.69)      | 0.67 (0.55–0.79)     | 9.2 ± 6.8 (4.0–62.0)                                       | 8.3 ± 5.6* (4.0–55.0)      | 16.3 ± 10.7*<br>(6.8–62.0) |
| OBSERVANT [14] | 0.60 (0.55–0.66)                       | 0.60 (0.54–0.67)      | 0.58 (0.47–0.68)     | 5.8 ± 5.0 (1.8–58.7)                                       | 5.7 ± 5.0 (1.8–58.7)       | 6.2 ± 4.9 (1.8–33.2)       |
| GAVS-II [16]   | 0.63 (0.58–0.69)                       | 0.62 (0.56–0.69)      | 0.67 (0.56–0.78)     | 9.4 ± 9.6 (1.0–89.8)                                       | 9.2 ± 9.1 (0.9–89.8)       | 10.9 ± 12.4<br>(1.1–80.8)  |

Summary of risk model performance indices for the prediction of 30-day mortality risk in TAVR. (A) Model discrimination, reported as *c*-indices (area-under-the-ROC-curve, Fig. 1) with 95% confidence intervals (in brackets); (B) model calibration reported as predicted mean 30-day mortality risk (in %) ± standard deviations (in %) and risk range (in brackets, in %)

TF transfemoral, TA transapical, TAVR transcatheter aortic valve replacement

\*Statistically significant differences between TF and TA TAVR groups



**Fig. 1** Risk model discrimination for the prediction of 30-day mortality. Model discrimination (ROC curves) of the six risk models for the prediction of 30-day mortality, for all studied patients (a), patients with TF TAVR only (b) and patients with TA TAVR only (c)

The stratified analyses for time period and for new vs. old generation devices (Table 4) showed no significant differences and also no visible performance trend in either risk model over the years.

### Model calibration

Mean predicted mortality risk (Table 3B) exceeded observed mortality in all models, ranging from 5.8 ± 5.0% (OBSERVANT) to 23.4 ± 15.9 (LogES I). Predictions were significantly higher in the TA TAVR subgroup for LogES I, ES II, STS PROM and FRANCE-2, while the OBSERVANT and GAVS-II models showed no differences between subgroups.

Graphical analysis of calibration is displayed in Fig. 2. Overestimation of mortality risk was especially pronounced in high-risk patients, while the lower risk quintiles were more adequately calibrated (e.g. STS PROM, ES II, OBSERVANT models). The classical LogES I surgical model grossly overestimated mortality in all risk strata.

Results of formal statistical testing for goodness-of-fit are displayed in Suppl. Table 3: STS PROM and GAVS-II showed significant Hosmer–Lemeshow *p* values (= inadequate calibration) of the respective logistic regression models for the whole population, GAVS-II also across TF and TA TAVR subgroups. OBSERVANT could not be calculated due to lack of events in some risk groups.

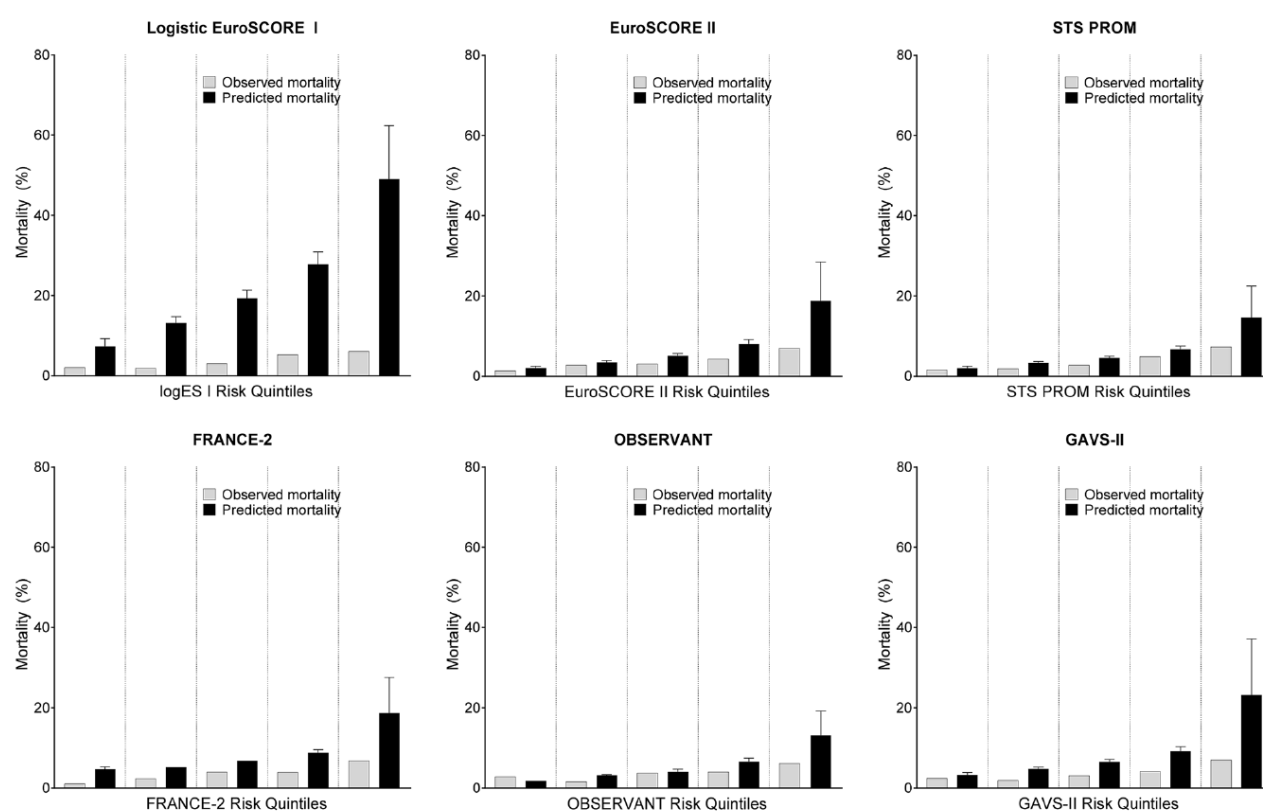


**Table 4** Risk model discrimination stratified by time period and device type

| Risk model     | 2008–2010<br>(n = 139) | 2011–2013<br>(n = 518) | 2014–2016<br>(n = 1124) | 2017–2018<br>(n = 1165) | Old-generation<br>TAVR device<br>(n = 862) | New-generation<br>TAVR device<br>(n = 2084) | Overall<br>(n = 2946) |
|----------------|------------------------|------------------------|-------------------------|-------------------------|--------------------------------------------|---------------------------------------------|-----------------------|
| LogES I [7, 8] | 0.67 (0.50–0.85)       | 0.59 (0.48–0.70)       | 0.68 (0.59–0.77)        | 0.57 (0.47–0.68)        | 0.63 (0.55–0.71)                           | 0.63 (0.56–0.71)                            | 0.63 (0.58–0.68)      |
| ES II [9]      | 0.65 (0.46–0.83)       | 0.57 (0.48–0.67)       | 0.70 (0.61–0.78)        | 0.65 (0.55–0.74)        | 0.63 (0.56–0.71)                           | 0.66 (0.59–0.73)                            | 0.65 (0.60–0.70)      |
| STS PROM [10]  | 0.53 (0.32–0.74)       | 0.64 (0.56–0.73)       | 0.67 (0.58–0.76)        | 0.64 (0.54–0.74)        | 0.63 (0.56–0.70)                           | 0.65 (0.57–0.72)                            | 0.67 (0.62–0.72)      |
| FRANCE-2 [15]  | 0.63 (0.49–0.76)       | 0.63 (0.51–0.74)       | 0.66 (0.57–0.75)        | 0.66 (0.57–0.76)        | 0.61 (0.53–0.69)                           | 0.68 (0.61–0.76)                            | 0.66 (0.60–0.71)      |
| OBSERVANT [14] | 0.61 (0.41–0.82)       | 0.53 (0.41–0.65)       | 0.68 (0.60–0.76)        | 0.57 (0.47–0.68)        | 0.57 (0.49–0.66)                           | 0.63 (0.56–0.70)                            | 0.60 (0.55–0.66)      |
| GAVS-II [16]   | 0.58 (0.37–0.79)       | 0.54 (0.42–0.66)       | 0.68 (0.60–0.77)        | 0.66 (0.57–0.76)        | 0.59 (0.50–0.68)                           | 0.67 (0.60–0.74)                            | 0.63 (0.58–0.69)      |

Risk model discrimination performance across the study period from 2008 to 2018, stratified by time period and device type, in comparison to the overall mean, displayed as c-indices (area-under-the-ROC-curve) with 95% confidence intervals (in brackets)

TAVR transcatheter aortic valve replacement



**Fig. 2** Risk model calibration for the prediction of 30-day mortality. Graphical model calibration comparison of the six risk models, stratified into risk quintiles for observed vs. predicted 30-day mortality

## Discussion

The main results of this comparative external validation study of six risk models for the prediction of 30-day mortality in patients undergoing TAVR at two German

high-volume Heart Centers from 2008 to 2018 are (1) surgical and TAVR-specific risk models showed similarly mediocre discrimination performance (*c*-indices 0.60–0.67); (2) all models overestimated 30-day mortality risk and were poorly calibrated, especially in high-risk

patients; (3) no significant influence of time of procedure or device type on the results could be found.

Patient risk stratification for coronary procedures is well established—ranging from the elective setting to acute coronary syndromes [22–24]—but the risk of TAVR procedures is thus far considerably less predictable: Patients suffer from a multitude of interdependent comorbid conditions, especially *frailty* as an essential risk factor is difficult to classify [25, 26]. The expansion of TAVR from highest risk/inoperable patients into intermediate- and lower risk groups introduces bias. On the procedural side, there are clear associations of center volume [27], operator experience [28], and choice of approach (TA vs. TF) [29] with clinical outcomes.

Classical surgical risk models (LogES I, STS PROM, ES II) have well-known limitations in TAVR [13]. LogES I is not recommended for use in TAVR anymore (1), we included the model for historical comparisons. National TAVR-registries have provided platforms for the development of TAVR-specific risk models [14–16], which were mostly developed in the “early years” of TAVR (Table 1). Resulting limitations in their performance have already been seen when applied outside of their original populations [30, 31], external validation studies with a similar design to our study were performed in the United Kingdom [12] and in the Netherlands [18]—and also retrieved disappointing results.

This analysis from the German Transregio Aortic Diseases cohort elucidates risk prediction in the whole era of TAVR, which has developed from an experimental procedure in 2008 to a routine and high-volume alternative to surgical aortic valve replacement in 2018. With steadily increasing operator experience and new-generation devices, procedure counts have dramatically increased and complication rates declined over the study period. The TF approach has become the routine access route.

Surgical risk models performed similar to expectations [13]: Discrimination analysis essentially showed similar performance of STS PROM [10], LogES I [7, 8] and ES II [9] models. None could even remotely match discrimination performance in their original surgical patient cohorts. Calibration analysis underlined the general overestimation of 30-day mortality risk—most pronounced in the LogES I model. Surgical models are thus confirmed to have severe limitations to judge TAVR risk.

However, dedicated TAVR-specific models also disappointed: FRANCE-2 (overall *c*-index 0.66, 95% CI 0.60–0.71) was better than in the original validation cohort (*c*-index 0.59 [15]) and in the UK (*c*-index 0.62 [12]) and Netherlands (*c*-index 0.63 [18]) external validation studies, but not superior to surgical models and slightly worse than in an Israeli external validation study (*c*-index 0.71 [30]). The model considerably overestimated risk (Fig. 2) in our patients. The GAVS-II model [16] derived from the German Aortic Valve Registry was expected to be most adapted

to German TAVR conditions, but it performed similar to the other models in the overall cohort (*c*-index 0.63) and in TF and TA subgroups and could not meet the performance in the development cohort (*c*-index 0.74), similar to the Dutch external validation study [18]. Numerically, its discrimination improved over time and in new vs. old generation devices (Table 4). The model also overestimated mortality (expected: 9.4%; Fig. 2). Reasons for the lower-than-expected performance may lie in the GAVS-II model being developed in 55% surgical/45% TAVR patients from 2011–2012 (Table 1), which significantly differed in age (74 vs. 81 years) and comorbidities from our population [16]. The OBSERVANT model [14] discriminated numerically worst in the overall cohort and in TF/TA subgroups, and could not match performance in the original population (*c*-index 0.71), which confirms findings in other external validation studies [12, 18, 30]. However—of all analyzed models—its mean mortality prediction (5.8%) came closest to observed events (3.7%).

Taken together, this analysis clarifies that risk prediction in TAVR is still an unsolved issue: all tested models are severely limited in their performance, and dedicated TAVR-specific models are not superior to decade-old surgical scores. Using any of these models for risk stratification is better than a coin-flip—but with ample room for improvement. A recently published analysis from the Netherlands [18] found similar results to the UK study [12] and to our results, which supports the validity of these findings across Europe. With TAVR evermore becoming a routine procedure and 30-day mortality rates reaching all-time-lows in high-volume Heart Centers, a re-calibration of existing risk models or a new development from growing registries is thus mandatory to improve accuracy [32, 33]. High-quality TAVR databases should enable us to produce risk models with performance comparable to surgical procedures or acute coronary syndrome. Incorporation of functional status/frailty assessment as important predictive factors may additionally improve model accuracy in the TAVR setting [34, 35].

## Study limitations

All conclusions from our study are limited to risk model performance in German—or at best European—TAVR patients, findings might be different in other patient populations and procedural conditions. Bias may originate from retrospective calculation of FRANCE-2, OBSERVANT and GAVS-II risk models. While data quality in our prospective databases was high at all times, there is unavoidable risk for bias by changes in clinical practice and adverse event rates from 2008 to 2018: We accounted for this with sub-analyses of patients stratified by time of procedure and device generations (Table 4); however, their statistical power is limited.

## Conclusions

Three surgical as well as three TAVR-specific risk scoring models showed mediocre performance in prediction of 30-day mortality risk for TAVR in the German Rhine Transregio Aortic Diseases cohort. Development of new or updated risk models is necessary to improve risk stratification.

**Acknowledgements** We thank Jenni Scharlau for substantial contribution in data acquisition.

**Funding** Open Access funding provided by Projekt DEAL. This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (No. 2018-32 to GW) for a Clinician Scientist Track and by the Deutsche Forschungsgemeinschaft for the collaborative research center Transregio 259: Aortic diseases. There was no financial or other support from the industry.

**Code availability** Not applicable.

## Compliance with ethical standards

**Conflict of interest** Georg Wolff, Christian Jung, Kathrin Klein, Amin Polzin, Ralf Westenfeld, Tobias Zeus, and Verena Veulemans have received consulting fees, travel expenses or study honoraria from Medtronic and/or Edwards Lifesciences. Jan-Malte Sinning and Georg Nickenig have received speaker honoraria and research grants from Abbott, Abiomed, Medtronic, Boston Scientific, and Edwards Lifesciences. Dr. Grube is a proctor for Medtronic and Boston Scientific. All other authors have nothing to disclose with regard to this project.

**Ethics approval** This study was ethics approved (see “Methods”) and performed in accordance with the Declaration of Helsinki.

**Consent to participate** All patients provided written informed consent to participate in TAVR registries at both sites.

**Consent for publication** All authors read and consented to the final manuscript version for publication.

**Availability of data and material** All authors had access to the data used in this study. Data can be made available upon request.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al (2017) 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 38(36):2739–2791
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA et al (2017) 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 70(2):252–289
3. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK et al (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 374(17):1609–1620
4. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M et al (2017) Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 376(14):1321–1331
5. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M et al (2019) Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 380(18):1695–1705
6. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D et al (2019) Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 380(18):1706–1715
7. Roques F, Michel P, Goldstone AR, Nashef SA (2003) The logistic EuroSCORE. *Eur Heart J* 24(9):881–882
8. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R (1999) European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 16(1):9–13
9. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR et al (2012) EuroSCORE II. *Eur J Cardiothorac Surg* 41(4):734–44 (discussion 44–5)
10. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB et al (2009) The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg* 88(1 Suppl):S23–42
11. Piazza N, Wenaweser P, van Gameren M, Pilgrim T, Tzikas A, Otten A et al (2010) Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons predicted risk of mortality score in patients implanted with the CoreValve ReValving system—a Bern-Rotterdam study. *Am Heart J* 159(2):323–329
12. Martin GP, Sperrin M, Ludman PF, de Belder MA, Gale CP, Toff WD et al (2017) Inadequacy of existing clinical prediction models for predicting mortality after transcatheter aortic valve implantation. *Am Heart J* 184:97–105
13. Wang TKM, Wang MTM, Gamble GD, Webster M, Ruygrok PN (2017) Performance of contemporary surgical risk scores for transcatheter aortic valve implantation: a meta-analysis. *Int J Cardiol* 236:350–355
14. Capodanno D, Barbanti M, Tamburino C, D'Errigo P, Ranucci M, Santoro G et al (2014) A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol* 113(11):1851–1858
15. Iung B, Laouenan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P et al (2014) Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart (British Cardiac Society)* 100(13):1016–1023
16. Schiller W, Barnewold L, Kazmaier T, Beckmann A, Masseli F, Welz A et al (2017) The German aortic valve score II. *Eur J Cardiothorac Surg* 52(5):881–887



17. Martin GP, Sperrin M, Mamas MA (2018) Pre-procedural risk models for patients undergoing transcatheter aortic valve implantation. *J Thoracic Dis* 10(Suppl 30):S3560–S3567
18. Al-Farra H, Abu-Hanna A, de Mol BAJM, ter Burg WJ, Houterman S, Henriques JPS et al (2020) External validation of existing prediction models of 30-day mortality after transcatheter aortic valve implantation (TAVI) in the Netherlands Heart Registration. *Int J Cardiol*
19. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH et al (2013) Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thoracic Cardiovasc Surg* 145(1):6–23
20. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44(3):837–845
21. Hosmer DWJ, Lemeshow SXS (2013) *Applied logistic regression*, 3rd edn. Wiley, Hoboken
22. Brennan JM, Curtis JP, Dai D, Fitzgerald S, Khandelwal AK, Spertus JA et al (2013) Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv* 6(8):790–799
23. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F et al (2006) Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 333(7578):1091
24. Wolff G, Lin Y, Quade J, Bader S, Kosejian L, Brockmeyer M et al (2019) Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center. *Clin Res Cardiol*
25. Flaatten H, De Lange DW, Morandi A, Andersen FH, Artigas A, Bertolini G et al (2017) The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients ( $\geq 80$  years). *Intensive Care Med* 43(12):1820–1828
26. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y et al (2017) Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation* 135(21):2013–2024
27. Wassef AWA, Rodes-Cabau J, Liu Y, Webb JG, Barbanti M, Munoz-Garcia AJ et al (2018) The learning curve and annual procedure volume standards for optimum outcomes of transcatheter aortic valve replacement: findings from an International Registry. *JACC Cardiovasc Interv* 11(17):1669–1679
28. Salemi A, Sedrakyan A, Mao J, Elmously A, Wijeyesundera H, Tam DY et al (2019) Individual operator experience and outcomes in transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 12(1):90–97
29. Kumar N, Khera R, Fonarow GC, Bhatt DL (2018) Comparison of outcomes of transfemoral versus transapical approach for transcatheter aortic valve implantation. *Am J Cardiol* 122(9):1520–1526
30. Halkin A, Steinvil A, Witberg G, Barsheshet A, Barkagan M, Assali A et al (2016) Mortality prediction following transcatheter aortic valve replacement: a quantitative comparison of risk scores derived from populations treated with either surgical or percutaneous aortic valve replacement. The Israeli TAVR Registry Risk Model Accuracy Assessment (IRRMA) study. *Int J Cardiol* 215:227–231
31. Pilgrim T, Franzone A, Stortecky S, Nietlispach F, Haynes AG, Tueller D et al (2017) Predicting mortality after transcatheter aortic valve replacement: external validation of the transcatheter valve therapy registry model. *Circ Cardiovasc Intervent* 10(11)
32. Hickey GL, Grant SW, Murphy GJ, Bhabra M, Pagano D, McAlister K et al (2013) Dynamic trends in cardiac surgery: why the logistic EuroSCORE is no longer suitable for contemporary cardiac surgery and implications for future risk models. *Eur J Cardiothorac Surg* 43(6):1146–1152
33. Matheny ME, Ohno-Machado L, Resnic FS (2005) Discrimination and calibration of mortality risk prediction models in interventional cardiology. *J Biomed Inform* 38(5):367–375
34. Martin GP, Sperrin M, Ludman PF, deBelder MA, Gunning M, Townend J et al (2018) Do frailty measures improve prediction of mortality and morbidity following transcatheter aortic valve implantation? An analysis of the UK TAVI registry. *BMJ Open* 8(6):e022543
35. van der Wulp K, van Wely MH, Schoon Y, Vart P, Olde Rikkert MGM, Morshuis WJ et al Geriatric assessment in the prediction of delirium and long-term survival after transcatheter aortic valve implantation. *J Thorac Cardiovasc Surg*



#### ***4.1.5 Disease-course adapting machine learning prognostication models in critically ill elderly COVID-19 patients: a multi-centre cohort study with external validation***

Jung C, Mamandipoor B, Fjølner J, Bruno R, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, **Wolff G**, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, De Lange DW, Guidet B, Flaatten H, Osmani V.

JMIR Med Inform. 2022 Mar 31;10(3):e32949.

Pubmed PMID: 35099394

DOI: [10.2196/32949](https://doi.org/10.2196/32949)

Die COVID-19 Pandemie hat weltweit die Gesundheitssysteme an die Grenzen ihrer Belastbarkeit gebracht. Insbesondere ältere Menschen waren davon besonders betroffen und eine Triage von Patienten nach Krankheitsschweregrad und Prognose fand in einigen Bereichen der Welt statt. Die Vorhersage der Prognose von schwerem COVID-19 ist jedoch schwierig, insbesondere bei kritisch kranken, älteren Patienten auf Intensivstationen.

In dieser Analyse aus der multizentrischen internationalen COVIP-Studie (95) haben wir 1432 kritisch kranke Patienten mit schwerem COVID-19 und  $\geq 70$  Jahren ausgewertet. Die 30-Tages-Sterblichkeit betrug 43,5%. Für deren Risikovorhersage wurden neben dem konventionellen SOFA-Score sog. Machine-learning Modelle angewandt, welche zunächst nur Baseline-Variablen bei Eintritt der Patienten auf die Intensivstation in logistische Regression, random forest und extreme gradient boosting (XGB) einschlossen und vergleichend untersucht wurden. Zu diesen Algorithmen wurden dann Ereignisse im klinischen Verlauf der Patienten inkl. deren „time-to-event“ Informationen zusätzlich eingeschlossen und die Genauigkeit der Modelle vergleichend untersucht.

Die finalen Modelle, welche den klinischen Verlauf der Patienten mit einschlossen, zeigten eine deutlich bessere Vorhersage der 30-Tages-Mortalität als sowohl der SOFA-Score als auch die Baseline-Modelle (c-index 0,77 vs. 0,65 im Mittel). Am besten schnitt das XGB Modell ab (c-index 0,81).

Diese Studie zeigte zusammenfassend, dass Risikomodelle unter Nutzung künstlicher Intelligenz in der Lage sind, Variablen zur Charakterisierung komplexer klinische Krankheitsverläufe automatisiert zu integrieren und zu besseren Risikovorhersagen zu kommen als übliche Scoring-Modelle. Zukünftig kann künstliche Intelligenz bei der Entscheidungsfindung in komplexen klinischen Situationen hilfreich sein.

## Original Paper

# Disease-Course Adapting Machine Learning Prognostication Models in Elderly Patients Critically Ill With COVID-19: Multicenter Cohort Study With External Validation

Christian Jung<sup>1</sup>, MD, PhD<sup>†</sup>; Behrooz Mamandipoor<sup>2</sup>, BSc; Jesper Fjølner<sup>3</sup>, MD; Raphael Romano Bruno<sup>1</sup>, MD<sup>†</sup>; Bernhard Wernly<sup>4</sup>, MD, PhD; Antonio Artigas<sup>5</sup>, MD; Bernardo Bollen Pinto<sup>6</sup>; Joerg C Schefold<sup>7</sup>; Georg Wolff<sup>1</sup>, MD; Malte Kelm<sup>1</sup>, MD; Michael Beil<sup>8</sup>; Sigal Sviri<sup>8</sup>, MHA; Peter V van Heerden<sup>9</sup>, MD, PhD; Wojciech Szczeklik<sup>10</sup>; Mirosław Czuczwar<sup>11</sup>; Muhammed Elhadi<sup>12</sup>; Michael Joannidis<sup>13</sup>; Sandra Oeyen<sup>14</sup>; Tilemachos Zafeiridis<sup>15†</sup>; Brian Marsh<sup>16</sup>; Finn H Andersen<sup>17,18</sup>; Rui Moreno<sup>19,20</sup>, MD, PhD; Maurizio Cecconi<sup>21</sup>; Susannah Leaver<sup>22</sup>; Dylan W De Lange<sup>23</sup>; Bertrand Guidet<sup>24,25</sup>; Hans Flaatten<sup>26,27</sup>; Venet Osmani<sup>2</sup>, PhD

<sup>1</sup>Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich-Heine-University Duesseldorf, University Hospital Duesseldorf, Duesseldorf, Germany

<sup>2</sup>Fondazione Bruno Kessler Research Institute, Trento, Italy

<sup>3</sup>Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark

<sup>4</sup>Department of Anaesthesiology, Paracelsus Medical University, Salzburg, Austria

<sup>5</sup>Department of Intensive Care Medicine, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Sabadell, Spain

<sup>6</sup>Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland

<sup>7</sup>Department of Intensive Care Medicine, Inselspital, Universitätsspital, University of Bern, Bern, Switzerland

<sup>8</sup>Department of Medical Intensive Care, Hadassah University Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

<sup>9</sup>Department of Anesthesia, Intensive Care and Pain Medicine, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

<sup>10</sup>Center for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland

<sup>11</sup>Second Department of Anesthesiology and Intensive Care, Medical University of Lublin, Lublin, Poland

<sup>12</sup>Faculty of Medicine, University of Tripoli, Tripoli, Libyan Arab Jamahiriya

<sup>13</sup>Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria

<sup>14</sup>Department of Intensive Care IK12IC, Ghent University Hospital, Ghent, Belgium

<sup>15</sup>Intensive Care Unit, General Hospital of Larissa, Larissa, Greece

<sup>16</sup>Mater Misericordiae University Hospital, Dublin, Ireland

<sup>17</sup>Department of Anaesthesia and Intensive Care, Ålesund Hospital, Ålesund, Norway

<sup>18</sup>Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

<sup>19</sup>Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

<sup>20</sup>Faculdade de Ciências Médicas de Lisboa, Nova Medical School - Faculdade de Ciências Médicas, Universidade da Beira Interior, Lisbon, Portugal

<sup>21</sup>Department of Anaesthesia, IRCCS Istituto Clinico Humanitas, Humanitas University, Milan, Italy

<sup>22</sup>General Intensive Care, St George's University Hospitals, NHS Foundation Trust, London, United Kingdom

<sup>23</sup>Department of Intensive Care Medicine, University Medical Center, Utrecht University, Utrecht, Belgium

<sup>24</sup>Épidémiologie Hospitalière Qualité et Organisation des Soins, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMR\_S 1136, Paris, France

<sup>25</sup>Service de Réanimation Médicale, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Paris, France

<sup>26</sup>Department of Clinical Medicine, University of Bergen, Bergen, Norway

<sup>27</sup>Department of Anesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway

<sup>†</sup>deceased<sup>‡</sup>COVID Study Group

## Corresponding Author:

Christian Jung, MD, PhD

Division of Cardiology, Pulmonology and Vascular Medicine

Medical Faculty, Heinrich-Heine-University Duesseldorf

University Hospital Duesseldorf

Moorenstraße 5

Duesseldorf, 40225  
Germany  
Phone: 49 2118118800  
Fax: 49 211 81 19520  
Email: [christian.jung@med.uni-duesseldorf.de](mailto:christian.jung@med.uni-duesseldorf.de)

## Abstract

**Background:** The COVID-19 pandemic caused by SARS-CoV-2 is challenging health care systems globally. The disease disproportionately affects the elderly population, both in terms of disease severity and mortality risk.

**Objective:** The aim of this study was to evaluate machine learning-based prognostication models for critically ill elderly COVID-19 patients, which dynamically incorporated multifaceted clinical information on evolution of the disease.

**Methods:** This multicenter cohort study (COVIP study) obtained patient data from 151 intensive care units (ICUs) from 26 countries. Different models based on the Sequential Organ Failure Assessment (SOFA) score, logistic regression (LR), random forest (RF), and extreme gradient boosting (XGB) were derived as baseline models that included admission variables only. We subsequently included clinical events and time-to-event as additional variables to derive the final models using the same algorithms and compared their performance with that of the baseline group. Furthermore, we derived baseline and final models on a European patient cohort, which were externally validated on a non-European cohort that included Asian, African, and US patients.

**Results:** In total, 1432 elderly ( $\geq 70$  years old) COVID-19-positive patients admitted to an ICU were included for analysis. Of these, 809 (56.49%) patients survived up to 30 days after admission. The average length of stay was 21.6 (SD 18.2) days. Final models that incorporated clinical events and time-to-event information provided superior performance (area under the receiver operating characteristic curve of 0.81; 95% CI 0.804-0.811), with respect to both the baseline models that used admission variables only and conventional ICU prediction models (SOFA score,  $P < .001$ ). The average precision increased from 0.65 (95% CI 0.650-0.655) to 0.77 (95% CI 0.759-0.770).

**Conclusions:** Integrating important clinical events and time-to-event information led to a superior accuracy of 30-day mortality prediction compared with models based on the admission information and conventional ICU prediction models. This study shows that machine-learning models provide additional information and may support complex decision-making in critically ill elderly COVID-19 patients.

**Trial Registration:** ClinicalTrials.gov NCT04321265; <https://clinicaltrials.gov/ct2/show/NCT04321265>

(*JMIR Med Inform* 2022;10(3):e32949) doi: [10.2196/32949](https://doi.org/10.2196/32949)

## KEYWORDS

machine-based learning; outcome prediction; COVID-19; pandemic; machine learning; prediction models; clinical informatics; patient data; elderly population

## Introduction

The COVID-19 pandemic caused by SARS-CoV-2 is continuing to challenge health care systems globally [1]. The disease disproportionately affects the elderly population, both in terms of disease severity and mortality risk [2]. In many countries, intensive care unit (ICU) capacity was increased during the pandemic to meet demand. In addition, novel treatment modalities were introduced [3]. A key challenge in clinical outcome prediction in a dynamic disease is that the response to a given treatment varies considerably from patient to patient, especially in the elderly population [4]. Baseline data alone are inadequate to predict prognosis with sufficient accuracy for an individual patient, as they cannot capture the dynamic nature of the underlying critical illness [5]. It is well established that various factors provide prognostic information that should be taken into consideration [6]. More elaborate methods are thus urgently needed for both sophisticated and concise risk stratification of severely affected individual ICU patients [7]. Biomarkers, frailty, and severity scores are validated in elderly critically ill patients [8-11]. However, all of these have important

limitations as they do not reflect the dynamics of the underlying disease pathophysiology, and as a result have limited prognostic power. Ultimately, it remains up to the physician to integrate all baseline data, the changing course of the disease, and subjective experience into a clinical decision [12]. However, physicians do not assess dynamically evolving processes perfectly, as they are influenced by numerous factors, including fatigue and other human factors, resulting in less objective and reproducible decision-making [13]. This aspect is especially relevant for new diseases such as COVID-19, where physician experience is lacking.

Therefore, a supportive prognostication model that can integrate baseline data with complex, dynamic processes in an objective manner is necessary. Machine learning (ML) algorithms could be used to address this need, as some have successfully been evaluated in clinical settings such as in cardiovascular intensive care [14]. Wernly et al [9] retrospectively analyzed arterial blood gas data from septic intensive care patients from a multicenter electronic ICU database as well as from a single-center MIMIC-III (Medical Information Mart for Intensive Care) data set to predict 96-hour mortality.



Izquierdo et al [15] combined classical epidemiological methods, natural language processing, and ML to examine the electronic health records of 10,504 patients with COVID-19. According to their analysis, the combination of easily obtainable clinical variables such as age, fever, and tachypnea predicted which patients would require ICU admission [15]. The observational study by Bolourani et al [16] had a similar aim. They used clinical and laboratory data commonly collected in the emergency department to train and validate three predictive models (two based on extreme gradient boosting [XGB] and one that used logistic regression [LR]) with cross-hospital validation. The XGB model had the highest mean accuracy to predict 48-hour respiratory failure [16]. Aktar et al [17] used ML to distinguish between healthy people and those with COVID-19 and subsequently to predict COVID-19 severity. They used decision tree, random forest (RF), variants of gradient boosting machine, support vector machine, k-nearest neighbor, and deep learning methods for blood samples. The developed analytical methods evidenced accuracy and precision scores >90% for disease severity prediction. To avoid locally aggregating raw clinical data across multiple institutions, Vaid et al [18] evaluated a federated learning ML technique using electronic health records from 5 hospitals. In brief, they used LR with L1 regularization/least absolute shrinkage and selection operator, and multilayer perceptron models that were trained using local data at each study site. The federated models outperformed the local models with regard to their accuracy in predicting the mortality in hospitalized patients with COVID-19 within 7 days. In a smaller study, Domínguez-Olmedo et al [19] selected 32 predictor laboratory features in 1823 patients with confirmed COVID-19 for an XGB algorithm. Similar to the other studies, using laboratory parameters resulted in excellent outcome prediction. Subudhi et al [20] used ensemble-based ML models to identify C-reactive protein, lactate dehydrogenase, and oxygen saturation as the most important factors for predicting ICU admission, with estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>, and neutrophil and lymphocyte percentages as the important factors for predicting mortality.

A recent systematic review by Syeda et al [21] identified more than 400 articles that investigated the role of ML in the field of COVID-19. For example, Pan et al [22] studied 123 ICU patients and identified eight important risk factors with high recognition ability using an XGB model. A similar approach was used by Kim et al [23], who established an XGB model in 4787 patients admitted to a hospital due to COVID-19. Furthermore, Burian et al [24] estimated the need for intensive care treatment in 65 patients with confirmed COVID-19, and Shahsikumar et al [25] investigated the performance of an algorithm to predict the need for mechanical ventilation on 402 patients with COVID-19, using cohorts with a wide age range (48 to 74 years).

Patients who are very old represent the most vulnerable intensive care subgroup [26]. However, to date, there are no studies investigating the role of ML models in this specific subgroup exclusively. To address this lack of evidence, the aim of this study was to evaluate whether ML models can reliably improve mortality prognostication in critically ill elderly patients with COVID-19 based on clinical baseline information, biomarkers,

accumulating events, and time-to-event information during the disease course.

## Methods

### Study Design

This was a retrospective analysis that included data from 1432 patients in a prospective multicenter study. The primary outcome was 30-day mortality. We also used the 3-month outcome to ensure consistency of the primary outcome and allay concerns of censoring bias [27]. We derived two groups of models: baseline and final models. Baseline models were derived using admission variables only, whereas the final model group incorporated clinical events such as catecholamine therapy, renal replacement therapy, noninvasive ventilation, invasive ventilation, prone position, and tracheostomy, in addition to the baseline variables. We evaluated both model groups using stratified 3-fold cross-validation to mitigate the variability of a single derivation-validation random split. Furthermore, we derived baseline and final models on an EU patient cohort and externally validated them on a non-EU cohort that included Asian, African, and US patients.

### Clinical Data Sources and Study Population

Patient data were obtained from 151 ICUs across 26 independent countries, including European ICUs, and from ICUs in Asia, Africa, and the United States as part of the multinational COVIP trial (NCT04321265). This study was conducted in line with the European Union General Data Privacy Regulation directive. As in previous successful studies [6,26,28], national coordinators recruited the ICUs, coordinated national and local ethical permissions, and supervised patient recruitment at the national level. In the COVIP studies, ethical approval was obligatory for study participation. The electronic case report form (eCRF) and database were hosted on a secure server in Aarhus University, Denmark. Data from 1432 elderly (aged 70 years and above) COVID-19-positive patients admitted to a participating ICU between February 4 and May 26, 2020, were recorded. The study protocol is available from the COVIP study website [29]. Patients were followed up until hospital discharge and survival at 3 months using telephone interviews.

### Ethical Considerations

The primary competent ethics committee was the Ethics Committee of the University of Duesseldorf, Germany. Institutional research ethics board approval was obtained from each study site. This was a prerequisite for participation in the study. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the local institutional and/or licensing committees. Informed consent was obtained from all subjects if not omitted by the ethics vote. The studies were all observational; no examinations (eg, blood sampling) or tissue sampling took place.

### Study Data

Demographic data included age, gender, weight, height, and BMI. Furthermore, information on admission characteristics prior to ICU hospitalization, duration of hospital stay, day of symptom onset, and comorbidities were available. Preexisting



comorbidities were recorded in the eCRF: diabetes, ischemic heart disease, renal insufficiency, arterial hypertension, pulmonary comorbidity, and chronic heart failure.

During the ICU stay, data on bacterial coinfection were noted, in addition to Sequential Organ Failure Assessment (SOFA) subscores (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems). Laboratory values included partial oxygen pressure and the fraction of inspired oxygen (FiO<sub>2</sub>), and their ratio. Six clinical events of interest (catecholamine therapy, renal replacement therapy, noninvasive and invasive ventilation, prone position, and tracheostomy) were recorded along with the time the event occurred.

### Model Derivation and Validation

We derived models based on XGB [30], RF [31], and LR [32]. As the best-performing model, the XGB algorithm provides robust prediction results using a method where new models are added to correct the errors made by existing models. Models are added sequentially and the combination of many models in the XGB model accommodates nonlinearity between input variables [30]. Hyperparameter tuning was performed by an exhaustive grid search directed toward maximizing the F1-score metric. Three-fold cross-validation was performed inside each grid option, and the optimal hyperparameter set was chosen based on the model in the grid search with the highest F1 score. Hyperparameters of the final model of the XGB are listed in

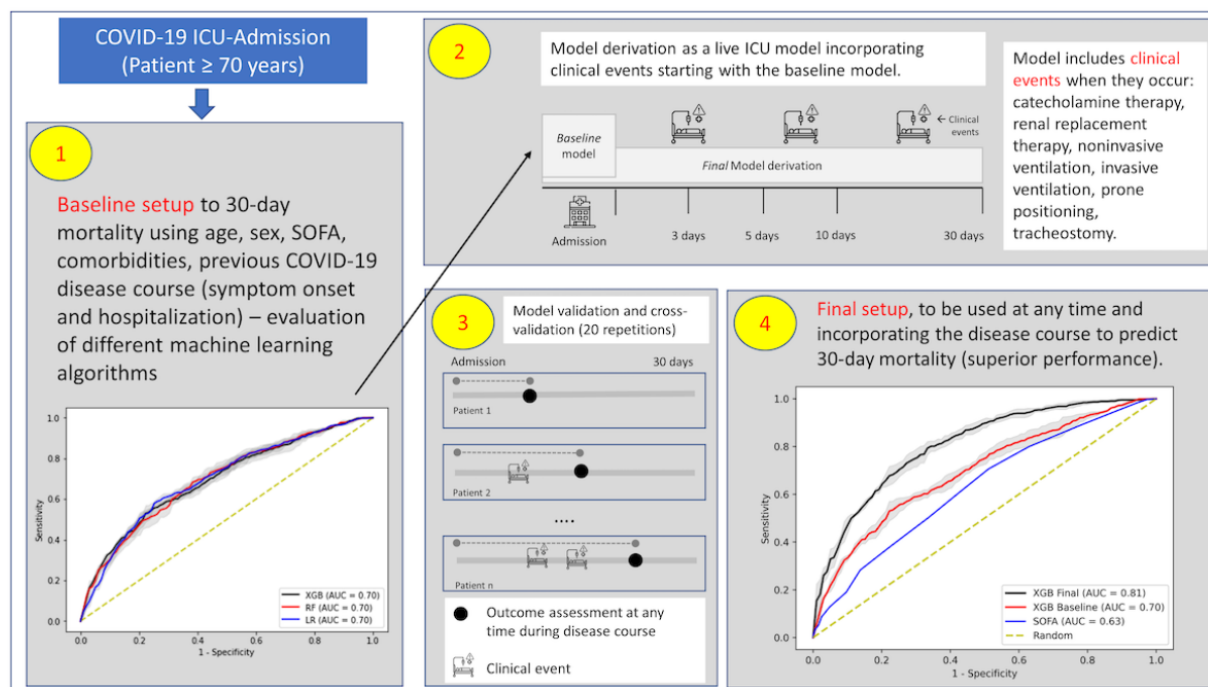
[Multimedia Appendix 1](#). To generate confidence intervals for the baseline and the final models, 3-fold cross-validation was performed with 20-times repetition with a randomly generated seed. To compare the performance of the XGB model, we also derived and validated two more predictive models based on LR and RF. This decision was driven by the fact that LR is typically considered a baseline algorithm, and RF has been previously used in other research with COVID-19 data [33]. Both LR and RF were optimized by an exhaustive grid search, similar to the XGB method.

To address noise and outliers in the data, we defined a clinically valid interval for each variable, and the values out of the valid scope were considered as missing values. For all models, the issue of missing values was addressed by removing variables with >90% missing values. We then used the median and zero to impute the missing data in the remaining continuous and categorical variables, respectively. All analyses were carried out using open-source software based on Python 3.6.8 with scikit-learn version 0.23.2.

### Experimental Evaluation

Performance evaluation of the models was based on 3-fold, stratified cross-validation with 20 repetitions using the area under the receiver operating characteristic curve (AUC; see step 3 in [Figure 1](#)) as well as area under the precision-recall curve (PRC), also known as average precision [34].

**Figure 1.** Graphical methods. (1) Study design, from admission to derivation and validation of baseline setup. (2) Derivation and validation of six models incorporating clinical events individually. Performance of individual models is shown in [Multimedia Appendix 2-5](#). (3) Derivation of the final model, including baseline variables as well as clinical events. (4) Evaluation of the final model in predicting 30-day outcomes. SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit.



The PRC shows the relationship between the positive predictive value (precision) and sensitivity (recall), measuring the performance of the model in correctly predicting mortality in patients with a high probability of dying. The area under the PRC is typically more informative than the AUC in the presence

of imbalanced outcomes [34]. Additional performance metrics are detailed in [Multimedia Appendix 2-5](#), including the positive predictive value (PPV), negative predictive value, F1 score (the balance between PPV and sensitivity), Matthews correlation coefficient (used to measure the quality of classification between

algorithms), and Brier score. Calibration quality was evaluated using Brier scores, where a lower score indicates a higher calibration quality, and we also present calibration plots (also known as reliability curves). The models were compared based on their AUC and PRC performance metrics for both the baseline data as well as the final models incorporating clinical events.

### Model Interpretation

We evaluated the ranking of variables that contributed toward the model description using shapely additive explanation (SHAP) scores. SHAP scores are a game-theoretic approach to model interpretability; they provide explanations of global model structures based on combinations of several local explanations for each prediction [35]. To interpret and rank the significance of input variables toward the final prediction of the model, mean absolute SHAP values were calculated for each variable across all observations in both the baseline model and the final model based on XGB. We also plotted SHAP interaction values that capture the contribution of pairwise interactions between unique

features to model prediction. To improve interpretability, especially in terms of the impact of clinical events, we defined a clinically meaningful day interval (0-3, 3-5, 5-10, and 10-30 days), and added a variable for each clinical event based on when the clinical event occurred; for example, "Tracheostomy-10-30" indicates that a tracheostomy was performed within the 10-30-day period. This allowed us to evaluate not only the importance of clinical events but also the time-to-event information. Naturally, these variables were only available in the final model.

## Results

### Study Population

Out of the total 1432 patients in the COVIP cohort, 809 (56.49%) patients survived up to 30 days after admission, with an average length of stay of 21.6 (SD 18.2) days. Patient baseline characteristics are given in [Table 1](#), with distribution of mortality and length of stay detailed in [Multimedia Appendix 6](#).

**Table 1.** Demographic characteristics, vital signs, and clinical events of patient cohorts (N=1432).

| Variables                                                           | Alive at 30 days (n=809) | Dead at 30 days (n=623) | P value |
|---------------------------------------------------------------------|--------------------------|-------------------------|---------|
| Sex (male), n (%)                                                   | 587 (72.6%)              | 463 (74.6%)             | .18     |
| Age (years), mean (SD)                                              | 75.0 (4.2)               | 76.5 (4.8)              | <.001   |
| Weight (kg), mean (SD)                                              | 81.3 (14.7)              | 81.0 (14.8)             | .42     |
| Height (cm), mean (SD)                                              | 169.7 (10.7)             | 169.8 (10.5)            | .06     |
| BMI (kg/m <sup>2</sup> ), mean (SD)                                 | 28.5 (6.5)               | 28.4 (5.7)              | .02     |
| Hospital stay prior to ICU <sup>a</sup> admission (days), mean (SD) | 3.8 (5.7)                | 3.5 (6.3)               | .002    |
| Symptoms prior to hospital admission (days), mean (SD)              | 7.2 (5.2)                | 6.6 (4.5)               | .10     |
| PaO <sub>2</sub> <sup>b</sup> (mmHg), mean (SD)                     | 87.3 (44.2)              | 84.3 (57.5)             | .003    |
| FiO <sub>2</sub> <sup>c</sup> (%), mean (SD)                        | 62.3 (31.0)              | 73.0 (24.0)             | <.001   |
| SOFA <sup>d</sup> score (points), mean (SD)                         | 5.2 (3.0)                | 6.7 (3.4)               | <.001   |
| <b>ICU treatment and outcome</b>                                    |                          |                         |         |
| Mechanical ventilation, n (%)                                       | 561 (69.3)               | 510 (81.9)              | <.001   |
| Vasopressors, n (%)                                                 | 525 (64.9)               | 515 (82.7)              | <.001   |
| Prone positioning, n (%)                                            | 309 (38.2)               | 279 (44.8)              | .10     |
| Tracheostomy, n (%)                                                 | 227 (28.1)               | 64 (10.3)               | <.001   |
| Noninvasive ventilation, n (%)                                      | 169 (20.9)               | 119 (19.1)              | .32     |
| Renal replacement therapy, n (%)                                    | 121 (15.0)               | 119 (19.1)              | .01     |
| Length of ICU stay (days), mean (SD)                                | 21.6 (18.2)              | 10.6 (7.6)              | <.001   |
| <b>Preexisting comorbidities, n (%)</b>                             |                          |                         |         |
| Diabetes mellitus                                                   | 268 (33.1)               | 240 (38.5)              | .01     |
| Ischemic heart disease                                              | 151 (18.7)               | 152 (24.4)              | .007    |
| Chronic renal insufficiency                                         | 91 (11.2)                | 130 (20.9)              | <.001   |
| Arterial hypertension                                               | 527 (65.1)               | 431 (69.2)              | .03     |
| Pulmonary disease                                                   | 175 (21.6)               | 145 (23.3)              | .07     |
| Chronic heart failure                                               | 98 (12.1)                | 103 (16.5)              | .01     |

<sup>a</sup>ICU: intensive care unit.<sup>b</sup>PaO<sub>2</sub>: partial oxygen pressure.<sup>c</sup>FiO<sub>2</sub>: fraction of inspired oxygen.<sup>d</sup>SOFA: Sequential Organ Failure Assessment.

## Model Derivation and Validation

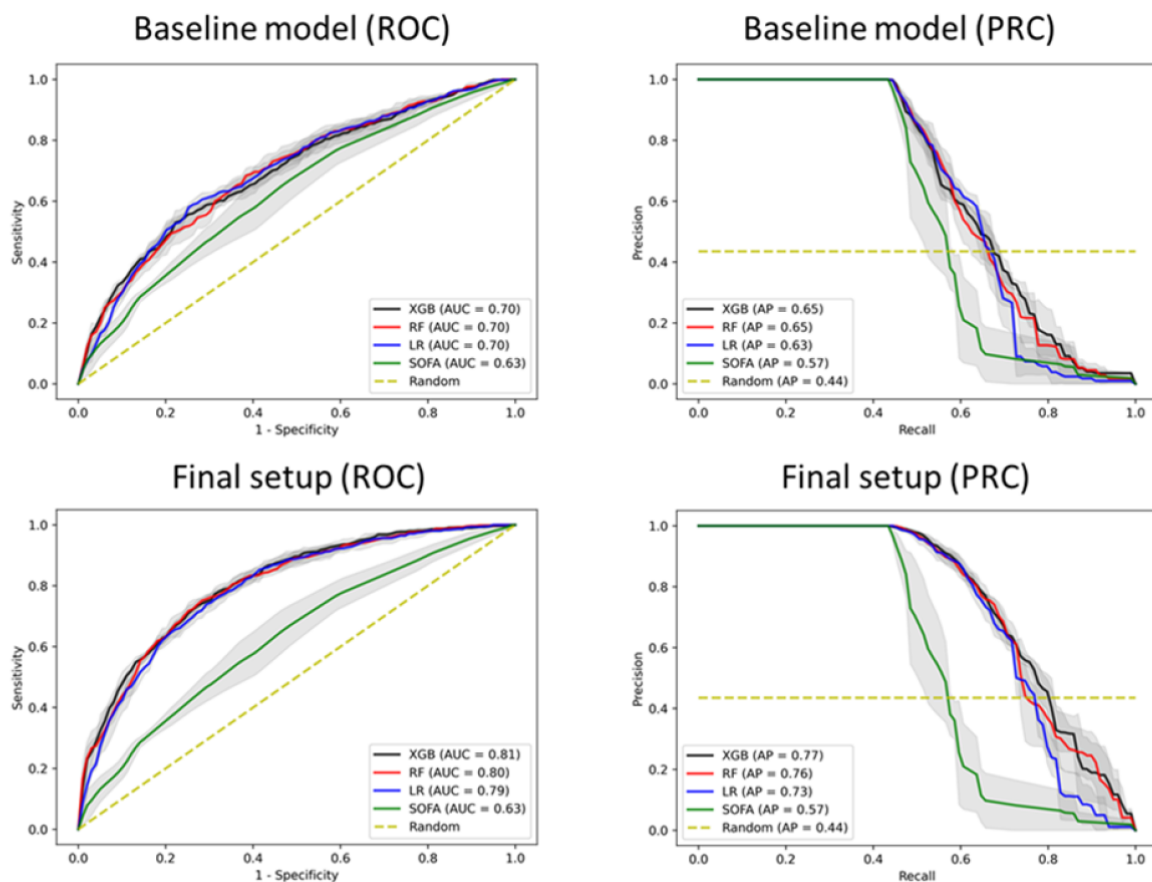
We evaluated the performance of *baseline setup* risk prognostication that included baseline variables only (see step 1 in Figure 1) and the *final setup*, which—in addition to baseline variables—included six key clinical events that occurred during the disease course and their time-to-event information: catecholamine therapy, renal replacement therapy, noninvasive ventilation, invasive ventilation, prone positioning, and tracheostomy (step 2 in Figure 1). The final set of selected variables is shown in Table 1. Furthermore, the baseline and the final setup were used to derive models on the EU cohort of

patients that were then externally evaluated using a non-EU cohort composed of Asian, African, and US patients.

Three risk prognostication models were derived from ML-based algorithms: LR and, for comparison, RF and XGB algorithms, as outlined in the Methods section [30,31].

The XGB algorithm achieved the numerically highest increase in discrimination performance from the *baseline setup* (AUC 0.70, 95% CI 0.692-0.701) to the *final setup* (AUC 0.81, 95% CI 0.804-0.811); average precision increased from 0.65 (95% CI 0.650-0.655) to 0.77 (95% CI 0.759-0.770) (Figure 2).

**Figure 2.** Performance of the baseline model (top) and improved performance in the final model (bottom) in response to clinical events with respect to the area under the receiver operating characteristic (ROC) curve (AUC) and area under the precision-recall curve (PRC). The PRC shows the relationship between the positive predictive value (precision) and sensitivity (recall) at all thresholds. XGB: extreme gradient boosting; RF: random forest; LR: logistic regression; SOFA: Sequential Organ Failure Assessment.



The LR (AUC 0.79, 95% CI 0.788-0.796) and RF (AUC 0.80, 95% CI 0.798-0.805) algorithms showed similar performance in the *baseline model* and improvement in the *final model*, comparable to XGB performance (see step 4 in Figure 1). The final XGB model provided superior performance compared to both the baseline model and SOFA score (both  $P < .001$ ).

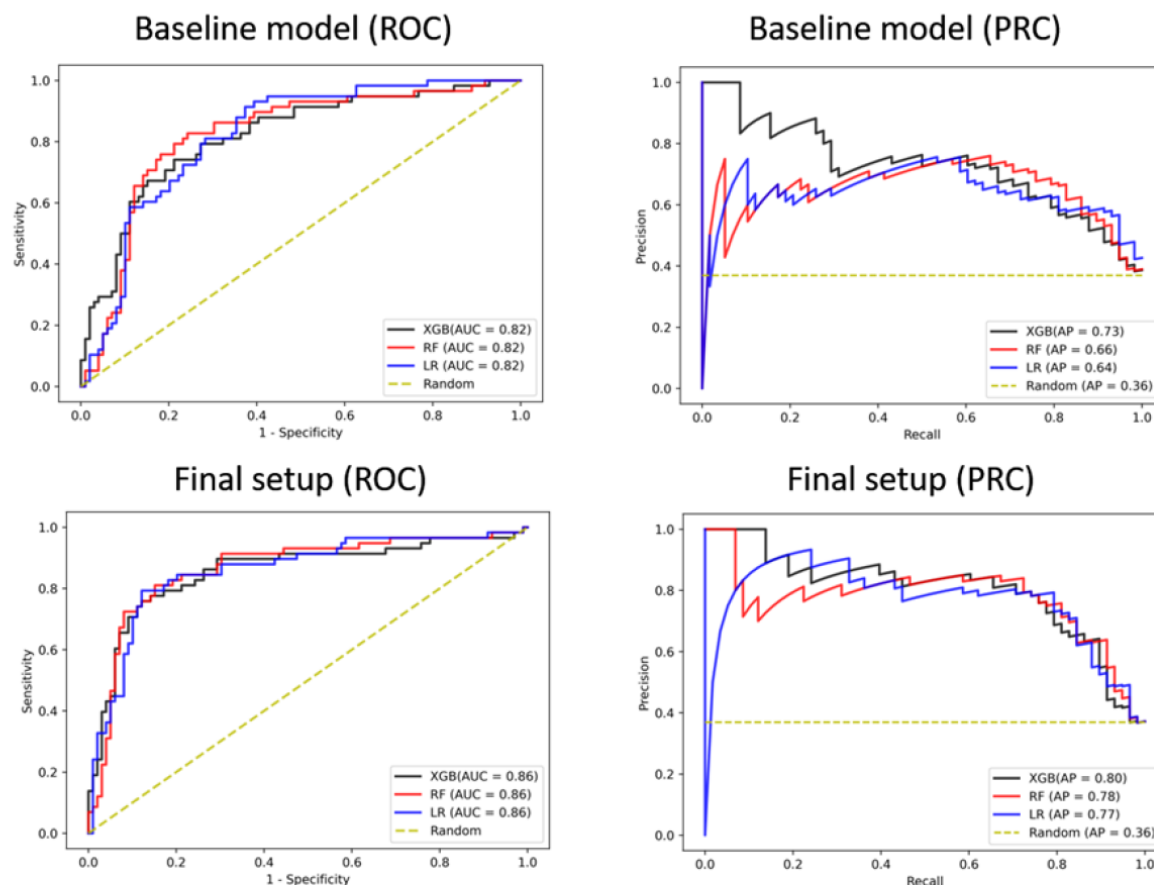
### Experimental Evaluation

In the external validation of the EU patient cohort, all three models achieved similar performance in the baseline and the final setup with an AUC of 0.82 and 0.86, respectively, when

evaluated on predicting the mortality of non-EU patients (Figure 3). One explanation for this performance on the external validation cohort might be that the patients in the non-EU cohort tended to gravitate toward two opposing health states of either being quite stable or very sick, making it easier for the model to discriminate between the two outcomes. To investigate this further, we plotted the distribution of the variable that had the highest impact on outcome prediction (FiO<sub>2</sub>) based on SHAP analysis (see Figure 4). As shown in Multimedia Appendix 7, the distribution for both outcomes was significantly skewed toward 21% for survivors and toward 100% for nonsurvivors.



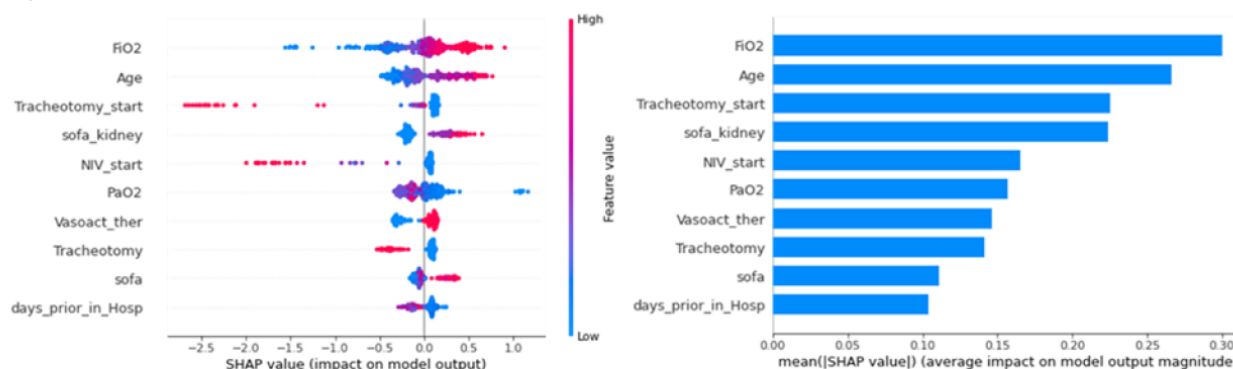
**Figure 3.** Performance of the final model derived using the EU patient cohort and externally validated on a non-EU patient cohort, comprising Asian, African, and US patients. Model performance is measured using area under the receiver operating characteristic (ROC) curve (AUC) and area under the precision-recall curve (PRC). XGB: extreme gradient boosting; RF: random forest; LR: logistic regression.



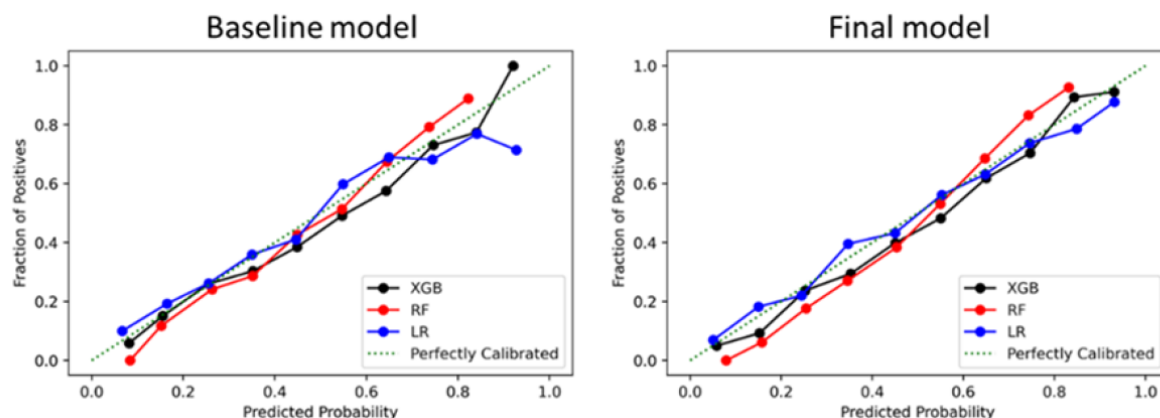
We also assessed the calibration of each model to ensure that the distribution of predicted outcomes matches the distribution of observed outcomes in our patient cohort. Baseline and final models were, in general, well calibrated (Figure 5), matching the estimated risk of outcome with observed risk. The final

setup for each algorithm was better calibrated (Brier score of 0.17) with respect to the baseline setup (Brier score 0.22). Full details of Brier scores for each algorithm are detailed in Multimedia Appendix 1.

**Figure 4.** Ranking of input variables of the final setup derived from the extreme gradient boost algorithm, using the shapely additive explanation (SHAP) method.



**Figure 5.** Calibration curves for each model and individual algorithms used to derive the model. XGB, extreme gradient boosting; RF: random forest; LR: logistic regression.



## Model Interpretation

The SHAP method was used to perform interpretability analysis, which explains model output by computing the contribution of each variable to the prediction. Among others, the SHAP method was applied on the best-performing model (XGB), where the FiO<sub>2</sub>, age, and tracheostomy had the highest impact on outcome prediction (Figure 4 and Multimedia Appendix 7).

We also report the model interpretability analysis for the RF and LR-based models in Multimedia Appendix 8 and 9, respectively. The top three variables remained common between XGB and RF, whereas for LR, only tracheostomy appeared in the top three, with the other two high-ranking variables being weight and BMI.

## Discussion

### Principal Findings and Comparison With Related Studies

This study demonstrates that individual prognostication accuracy based on patient baseline characteristics can be considerably improved with ML algorithms that incorporate occurrence and time-to-event information of clinical events along the course of a disease such as COVID-19 in elderly, critically ill patients. These results align with many previous studies that investigated ML approaches in patients suffering from COVID-19. The major difference between this COVIP study and others published previously lies in its focus on the especially vulnerable subgroup of very old intensive care patients [21]. The second important difference is that the current approach includes the risk for clinical events such as tracheostomy.

Subudhi et al [20] compared the ability of 18 different ML algorithms to predict the rate of admission and mortality of patients suffering from COVID-19. In their analysis, ensemble-based models were superior to other algorithms (including LR and XGB). Specific laboratory values and oxygen saturation were the most important factors for ICU admission, whereas impaired kidney function and differential blood count best predicted mortality [20]. However, this previous study primarily used data from patients, of all ages, presenting to the emergency room.

Domínguez-Olmedo et al [19] used data from 1823 patients with confirmed COVID-19 and established an XGB model. Their model found lactate dehydrogenase activity, C-reactive protein level, neutrophil count, and urea level to be the most important variables, reaching an AUC of 0.93 (95% CI 0.89-0.98) for sensitivity and 0.91 (95% CI 0.86-0.96) for specificity.

Pan et al [22] used data from 123 patients with COVID-19 admitted to an ICU to construct an XGB model, and identified eight factors (albumin level, creatinine, eosinophil percentage, lactate dehydrogenase, lymphocyte percentage, neutrophil percentage, prothrombin time, and total bilirubin) that were predictive for ICU mortality.

Vaid et al [18] utilized a different approach based on federated learning of electronic health records from five different hospitals, providing robust predictive models without compromising patient privacy.

Other studies focused primarily on peripheral blood samples. Aktar et al [17] developed ML and deep learning algorithms to predict the disease severity. Similarly, Kim et al [23] established an XGB model in 4787 hospital-admitted patients to predict their intensive care treatment requirements. Their model was significantly superior to the established CURB-65 (confusion, urea, respiratory rate, blood pressure) score.

### Applications

Immediate clinical applications are conceivable, especially given the limited number of ICU beds available. Our models may be used in several ways: ML could be used before ICU admission to offer objective support for complex allocation decisions. However, ML algorithms would mainly access data at presentation and few dynamic parameters, limiting the predictive power. ML algorithms could also be used in the context of time-limited trials (TLTs), which are common clinical practice in ICUs in some countries. This may be particularly helpful in patients for whom realistic therapeutic goals/outcomes are unclear at presentation. These patients could be admitted to the ICU under the premise of gaining more information about the patient and the initial response to treatment. This additional information could then be evaluated using ML algorithms [36] as already shown in patients with sepsis [9]. The ideal temporal

combination of a TLT and ML should be the subject of future, prospective studies [36,37].

In terms of practical applications, ML algorithms provide a potential strategy to improve decision confidence and predictive power over time. They are applicable at various time points during the disease course, predicting outcomes in a continuous manner. This approach is especially applicable when considering that the model was well calibrated in estimating outcomes. However, evaluation of the model with a diverse patient population would provide further evidence of its clinical applicability.

Clinical evaluations such as assessment of wakefulness, mobility, responsiveness, and independence are subjective and subject to interrater variability. Therefore, advances in digital technologies may support but not replace physicians' skills. ML can support physicians, especially in estimations on prognosis and achievement of therapy goals. Importantly, ethical problems become evident when ML is involved in matters of life and death [38], and it must be emphasized that ML should only support and aid medical decision-making. Our data show that dedicated modern algorithms can incrementally improve certainty during TLTs in elderly patients with COVID-19, and generalize well in an external patient cohort. These tools can enhance our ability to improve guidance of treatment and optimally allocate ICU resources. However, such a strategy can

only be viewed as complementary to clinical judgment and individual treatment goals, and form part of a holistic patient assessment.

### Limitations

This study has some methodological limitations in common with the other COVIP studies [11,26,39-42]. COVIP did not contain a control group of younger COVID-19 patients for comparison or a comparable age cohort of patients who were not or could not be admitted to the ICU. In addition, the COVIP database does not include information on pre-ICU care and triage decisions. These treatment limitations might also affect the care of older ICU patients [43]. Furthermore, COVIP recruited patients in 26 countries, and thus the participating countries varied widely in their care structure, resulting in considerable heterogeneity in treatments given.

### Conclusion

This study demonstrates that, in the particularly vulnerable subgroup of very old intensive care patients suffering from COVID-19, individual prognostication accuracy based on patient baseline characteristics can be improved with ML algorithms. These algorithms capture the dynamic course of the disease by including the occurrence and time-to-event information of clinical events, and thus reflect both disease severity and the need for intensive care treatment.

### Acknowledgments

The support of the study in France by a grant from Fondation Assistance Publique-Hôpitaux de Paris Pour la Recherche is greatly appreciated. In Norway, the study was supported by a grant from Health Region West. In addition, EOSCsecretariat.eu provided support and has received funding from the European Union's Horizon Programme call H2020-INFRAEOSC-05-2018-2019, grant agreement number 831644. This work was supported by the Forschungskommission of the Medical Faculty of Heinrich-Heine-University Düsseldorf (grant 2018-32 to GW and grant 2020-21 to RB for a Clinician Scientist Track). The complete list of COVIP collaborators is provided in [Multimedia Appendix 10](#).

### Authors' Contributions

BW, BM, JF, RB, VO, and CJ analyzed the data and wrote the first draft of the manuscript. AA, BBP, JCS, and GW contributed to the statistical analysis and improved the paper. MK, MB, SS, PVH, WS, MC, ME, MJ, SO, TZ, BM, FA, RM, MC, SL, DWDL, BG, and HF gave guidance and improved the paper. All authors read and approved the final manuscript.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Hyperparameters for each algorithm found through an exhaustive grid search.  
[\[DOCX File, 14 KB-Multimedia Appendix 1\]](#)

### Multimedia Appendix 2

Performance of the baseline model in terms of various performance metrics and 95% CIs: logistic regression (LR), random forest (RF), extreme gradient boosting (XGB).  
[\[DOCX File, 14 KB-Multimedia Appendix 2\]](#)

### Multimedia Appendix 3

Performance of the final model in terms of various performance metrics and 95% CIs: logistic regression (LR), random forest (RF), extreme gradient boosting (XGB).  
[\[DOCX File, 14 KB-Multimedia Appendix 3\]](#)



### Multimedia Appendix 4

Performance of the baseline model derived using the EU patient cohort and validated using a non-EU patient cohort in terms of various performance metrics and 95% CIs: logistic regression (LR), random forest (RF), and extreme gradient boosting (XGB). [\[DOCX File , 14 KB-Multimedia Appendix 4\]](#)

### Multimedia Appendix 5

Performance of the final model derived using the EU patient cohort and validated using a non-EU patient cohort in terms of various performance metrics and 95% CIs: logistic regression (LR), random forest (RF), and extreme gradient boosting (XGB). [\[DOCX File , 14 KB-Multimedia Appendix 5\]](#)

### Multimedia Appendix 6

Distribution of deaths over time and length of intensive care unit stay. [\[DOCX File , 56 KB-Multimedia Appendix 6\]](#)

### Multimedia Appendix 7

Distribution of fraction of inspired oxygen (FiO<sub>2</sub>) for outcomes of survivors (left) and nonsurvivors (right). FiO<sub>2</sub> was chosen as it was the variable that had the highest impact on the performance prediction, based on SHAP analysis. [\[DOCX File , 66 KB-Multimedia Appendix 7\]](#)

### Multimedia Appendix 8

Ranking of input variables of the final setup derived using the random forest-based model. [\[DOCX File , 161 KB-Multimedia Appendix 8\]](#)

### Multimedia Appendix 9

Ranking of input variables of the final setup derived using the logistic regression-based model. [\[DOCX File , 126 KB-Multimedia Appendix 9\]](#)

### Multimedia Appendix 10

List of COVIP-collaborators. [\[DOCX File , 56 KB-Multimedia Appendix 10\]](#)

## References

1. European Society of Intensive Care Medicine (ESICM), Global Sepsis Alliance (GSA), Society of Critical Care Medicine (SCCM). Reducing the global burden of sepsis: a positive legacy for the COVID-19 pandemic? *Intensive Care Med* 2021 Jul 16;47(7):733-736. [doi: [10.1007/s00134-021-06409-y](#)] [Medline: [34132841](#)]
2. Maltese G, Corsonello A, Di Rosa M, Soraci L, Vitale C, Corica F, et al. Frailty and COVID-19: a systematic scoping review. *J Clin Med* 2020 Jul 04;9(7):2106 [FREE Full text] [doi: [10.3390/jcm9072106](#)] [Medline: [32635468](#)]
3. Alkuzweny M, Raj A, Mehta S. Preparing for a COVID-19 surge: ICUs. *EClinicalMedicine* 2020 Aug;25:100502 [FREE Full text] [doi: [10.1016/j.eclim.2020.100502](#)] [Medline: [32835188](#)]
4. Chopra V, Flanders SA, Vaughn V, Petty L, Gandhi T, McSparron JJ, et al. Variation in COVID-19 characteristics, treatment and outcomes in Michigan: an observational study in 32 hospitals. *BMJ Open* 2021 Jul 23;11(7):e044921 [FREE Full text] [doi: [10.1136/bmjopen-2020-044921](#)] [Medline: [34301650](#)]
5. Mudatsir M, Fajar JK, Wulandari L, Soegiarto G, Ilmawan M, Purnamasari Y, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis. *F1000Res* 2020 Sep 9;9:1107. [doi: [10.12688/f1000research.26186.1](#)]
6. Flaatten H, De Lange DW, Morandi A, Andersen FH, Artigas A, Bertolini G, VIP1 study group. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). *Intensive Care Med* 2017 Dec 21;43(12):1820-1828. [doi: [10.1007/s00134-017-4940-8](#)] [Medline: [28936626](#)]
7. Zhao Z, Chen A, Hou W, Graham JM, Li H, Richman PS, et al. Prediction model and risk scores of ICU admission and mortality in COVID-19. *PLoS One* 2020 Jul 30;15(7):e0236618 [FREE Full text] [doi: [10.1371/journal.pone.0236618](#)] [Medline: [32730358](#)]
8. Jung C, Bruno RR, Wernly B, Wolff G, Beil M, Kelm M. Frailty as a prognostic indicator in intensive care. *Dtsch Arztebl Int* 2020 Oct 02;117(40):668-673. [doi: [10.3238/arztebl.2020.0668](#)] [Medline: [33357351](#)]
9. Wernly B, Mamandipoor B, Baldia P, Jung C, Osmani V. Machine learning predicts mortality in septic patients using only routinely available ABG variables: a multi-centre evaluation. *Int J Med Inform* 2021 Jan;145:104312. [doi: [10.1016/j.ijmedinf.2020.104312](#)] [Medline: [33126059](#)]



10. Masyuk M, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig JM, et al. Prognostic relevance of serum lactate kinetics in critically ill patients. *Intensive Care Med* 2019 Jan 26;45(1):55-61. [doi: [10.1007/s00134-018-5475-3](https://doi.org/10.1007/s00134-018-5475-3)] [Medline: [30478622](https://pubmed.ncbi.nlm.nih.gov/30478622/)]
11. Bruno RR, Wernly B, Flaatten H, Fjølner J, Artigas A, Bollen Pinto B, COVIP Study Group. Lactate is associated with mortality in very old intensive care patients suffering from COVID-19: results from an international observational study of 2860 patients. *Ann Intensive Care* 2021 Aug 21;11(1):128 [FREE Full text] [doi: [10.1186/s13613-021-00911-8](https://doi.org/10.1186/s13613-021-00911-8)] [Medline: [34417919](https://pubmed.ncbi.nlm.nih.gov/34417919/)]
12. Leeuwenberg AM, Schuit E. Prediction models for COVID-19 clinical decision making. *Lancet Digit Health* 2020 Oct;2(10):e496-e497 [FREE Full text] [doi: [10.1016/S2589-7500\(20\)30226-0](https://doi.org/10.1016/S2589-7500(20)30226-0)] [Medline: [32984794](https://pubmed.ncbi.nlm.nih.gov/32984794/)]
13. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res* 2020 Aug 16;32(8):1599-1608 [FREE Full text] [doi: [10.1007/s40520-020-01631-y](https://doi.org/10.1007/s40520-020-01631-y)] [Medline: [32557332](https://pubmed.ncbi.nlm.nih.gov/32557332/)]
14. Quer G, Arnaout R, Henne M, Arnaout R. Machine learning and the future of cardiovascular care: JACC state-of-the-art review. *J Am Coll Cardiol* 2021 Jan 26;77(3):300-313 [FREE Full text] [doi: [10.1016/j.jacc.2020.11.030](https://doi.org/10.1016/j.jacc.2020.11.030)] [Medline: [33478654](https://pubmed.ncbi.nlm.nih.gov/33478654/)]
15. Izquierdo JL, Ancochea J, Savana COVID-19 Research Group, Soriano JB. Clinical characteristics and prognostic factors for intensive care unit admission of patients with COVID-19: retrospective study using machine learning and natural language processing. *J Med Internet Res* 2020 Oct 28;22(10):e21801 [FREE Full text] [doi: [10.2196/21801](https://doi.org/10.2196/21801)] [Medline: [33090964](https://pubmed.ncbi.nlm.nih.gov/33090964/)]
16. Bolourani S, Brenner M, Wang P, McGinn T, Hirsch JS, Barnaby D, Northwell COVID-19 Research Consortium. A machine learning prediction model of respiratory failure within 48 hours of patient admission for COVID-19: model development and validation. *J Med Internet Res* 2021 Feb 10;23(2):e24246 [FREE Full text] [doi: [10.2196/24246](https://doi.org/10.2196/24246)] [Medline: [33476281](https://pubmed.ncbi.nlm.nih.gov/33476281/)]
17. Aktar S, Ahamad MM, Rashed-Al-Mahfuz M, Azad A, Uddin S, Kamal A, et al. Machine learning approach to predicting COVID-19 disease severity based on clinical blood test data: statistical analysis and model development. *JMIR Med Inform* 2021 Apr 13;9(4):e25884 [FREE Full text] [doi: [10.2196/25884](https://doi.org/10.2196/25884)] [Medline: [33779565](https://pubmed.ncbi.nlm.nih.gov/33779565/)]
18. Vaid A, Jaladanki SK, Xu J, Teng S, Kumar A, Lee S, et al. Federated learning of electronic health records to improve mortality prediction in hospitalized patients with COVID-19: machine learning approach. *JMIR Med Inform* 2021 Jan 27;9(1):e24207 [FREE Full text] [doi: [10.2196/24207](https://doi.org/10.2196/24207)] [Medline: [33400679](https://pubmed.ncbi.nlm.nih.gov/33400679/)]
19. Domínguez-Olmedo JL, Gragera-Martínez Á, Mata J, Pachón Álvarez V. Machine learning applied to clinical laboratory data in Spain for COVID-19 outcome prediction: model development and validation. *J Med Internet Res* 2021 Apr 14;23(4):e26211 [FREE Full text] [doi: [10.2196/26211](https://doi.org/10.2196/26211)] [Medline: [33793407](https://pubmed.ncbi.nlm.nih.gov/33793407/)]
20. Subudhi S, Verma A, Patel AB, Hardin CC, Khandekar MJ, Lee H, et al. Comparing machine learning algorithms for predicting ICU admission and mortality in COVID-19. *NPJ Digit Med* 2021 May 21;4(1):87. [doi: [10.1038/s41746-021-00456-x](https://doi.org/10.1038/s41746-021-00456-x)] [Medline: [34021235](https://pubmed.ncbi.nlm.nih.gov/34021235/)]
21. Syeda HB, Syed M, Sexton KW, Syed S, Begum S, Syed F, et al. Role of machine learning techniques to tackle the COVID-19 crisis: systematic review. *JMIR Med Inform* 2021 Jan 11;9(1):e23811 [FREE Full text] [doi: [10.2196/23811](https://doi.org/10.2196/23811)] [Medline: [33326405](https://pubmed.ncbi.nlm.nih.gov/33326405/)]
22. Pan P, Li Y, Xiao Y, Han B, Su L, Su M, et al. Prognostic assessment of COVID-19 in the intensive care unit by machine learning methods: model development and validation. *J Med Internet Res* 2020 Nov 11;22(11):e23128 [FREE Full text] [doi: [10.2196/23128](https://doi.org/10.2196/23128)] [Medline: [33035175](https://pubmed.ncbi.nlm.nih.gov/33035175/)]
23. Kim H, Han D, Kim J, Kim D, Ha B, Seog W, et al. An easy-to-use machine learning model to predict the prognosis of patients with COVID-19: retrospective cohort study. *J Med Internet Res* 2020 Nov 09;22(11):e24225 [FREE Full text] [doi: [10.2196/24225](https://doi.org/10.2196/24225)] [Medline: [33108316](https://pubmed.ncbi.nlm.nih.gov/33108316/)]
24. Burian E, Jungmann F, Kaissis G, Lohöfer FK, Spinner CD, Lahmer T, et al. Intensive care risk estimation in COVID-19 pneumonia based on clinical and imaging parameters: experiences from the Munich Cohort. *J Clin Med* 2020 May 18;9(5):1514 [FREE Full text] [doi: [10.3390/jcm9051514](https://doi.org/10.3390/jcm9051514)] [Medline: [32443442](https://pubmed.ncbi.nlm.nih.gov/32443442/)]
25. Shashikumar SP, Wardi G, Paul P, Carlile M, Brenner LN, Hibbert KA, et al. Development and prospective validation of a deep learning algorithm for predicting need for mechanical ventilation. *Chest* 2021 Jun;159(6):2264-2273 [FREE Full text] [doi: [10.1016/j.chest.2020.12.009](https://doi.org/10.1016/j.chest.2020.12.009)] [Medline: [33345948](https://pubmed.ncbi.nlm.nih.gov/33345948/)]
26. Jung C, Flaatten H, Fjølner J, Bruno RR, Wernly B, Artigas A, COVIP study group. The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. *Crit Care* 2021 Apr 19;25(1):149 [FREE Full text] [doi: [10.1186/s13054-021-03551-3](https://doi.org/10.1186/s13054-021-03551-3)] [Medline: [33874987](https://pubmed.ncbi.nlm.nih.gov/33874987/)]
27. Li Y, Sperrin M, Ashcroft DM, van Staa TP. Consistency of variety of machine learning and statistical models in predicting clinical risks of individual patients: longitudinal cohort study using cardiovascular disease as exemplar. *BMJ* 2020 Nov 04;371:m3919 [FREE Full text] [doi: [10.1136/bmj.m3919](https://doi.org/10.1136/bmj.m3919)] [Medline: [33148619](https://pubmed.ncbi.nlm.nih.gov/33148619/)]
28. Guidet B, de Lange DW, Boumendil A, Leaver S, Watson X, Boulanger C, VIP2 study group. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs:

- the VIP2 study. *Intensive Care Med* 2020 Jan 29;46(1):57-69 [FREE Full text] [doi: [10.1007/s00134-019-05853-1](https://doi.org/10.1007/s00134-019-05853-1)] [Medline: [31784798](https://pubmed.ncbi.nlm.nih.gov/31784798/)]
29. COVIP Study. VIPSTUDY. URL: <https://vipstudy.org/covip-study/> [accessed 2021-10-11]
  30. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. 2016 Presented at: 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining; August 2016; Machineryan Francisco, CA. [doi: [10.1145/2939672.2939785](https://doi.org/10.1145/2939672.2939785)]
  31. Ho TK. Random decision forests. 1995 Presented at: Third International Conference on Document Analysis and Recognition; August 14-16, 1995; Montreal p. 278-282. [doi: [10.1109/icdar.1995.598994](https://doi.org/10.1109/icdar.1995.598994)]
  32. McCullagh P, Nelder JA. Generalized Linear Models. 2nd edition. Milton Park, England: Routledge; 1989.
  33. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020 Apr 07;369:m1328 [FREE Full text] [doi: [10.1136/bmj.m1328](https://doi.org/10.1136/bmj.m1328)] [Medline: [32265220](https://pubmed.ncbi.nlm.nih.gov/32265220/)]
  34. Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. *PLoS One* 2015 Mar 4;10(3):e0118432 [FREE Full text] [doi: [10.1371/journal.pone.0118432](https://doi.org/10.1371/journal.pone.0118432)] [Medline: [25738806](https://pubmed.ncbi.nlm.nih.gov/25738806/)]
  35. Lundberg S, Lee SI. A unified approach to interpreting model predictions. arXiv. 2017. URL: <https://arxiv.org/abs/1705.07874> [accessed 2022-02-22]
  36. Vink EE, Azoulay E, Caplan A, Kompanje EJO, Bakker J. Time-limited trial of intensive care treatment: an overview of current literature. *Intensive Care Med* 2018 Sep 22;44(9):1369-1377. [doi: [10.1007/s00134-018-5339-x](https://doi.org/10.1007/s00134-018-5339-x)] [Medline: [30136140](https://pubmed.ncbi.nlm.nih.gov/30136140/)]
  37. Shrimme MG, Ferket BS, Scott DJ, Lee J, Barragan-Bradford D, Pollard T, et al. Time-limited trials of intensive care for critically ill patients with cancer: how long is long enough? *JAMA Oncol* 2016 Jan 01;2(1):76-83 [FREE Full text] [doi: [10.1001/jamaoncol.2015.3336](https://doi.org/10.1001/jamaoncol.2015.3336)] [Medline: [26469222](https://pubmed.ncbi.nlm.nih.gov/26469222/)]
  38. Beil M, Proft I, van Heerden D, Sviri S, van Heerden PV. Ethical considerations about artificial intelligence for prognostication in intensive care. *Intensive Care Med Exp* 2019 Dec 10;7(1):70 [FREE Full text] [doi: [10.1186/s40635-019-0286-6](https://doi.org/10.1186/s40635-019-0286-6)] [Medline: [31823128](https://pubmed.ncbi.nlm.nih.gov/31823128/)]
  39. Jung C, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, COVIP Study Group. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. *Crit Care* 2021 Sep 23;25(1):344 [FREE Full text] [doi: [10.1186/s13054-021-03739-7](https://doi.org/10.1186/s13054-021-03739-7)] [Medline: [34556171](https://pubmed.ncbi.nlm.nih.gov/34556171/)]
  40. Bruno RR, Wernly B, Homemann J, Flaatten H, Fjølner J, Artigas A, COVIP study group. Early evaluation of organ failure using MELD-XI in critically ill elderly COVID-19 patients. *Clin Hemorheol Microcirc* 2021;79(1):109-120. [doi: [10.3233/CH-219202](https://doi.org/10.3233/CH-219202)] [Medline: [34487039](https://pubmed.ncbi.nlm.nih.gov/34487039/)]
  41. Jung C, Bruno RR, Wernly B, Joannidis M, Oeyen S, Zafeiridis T, COVIP study group. Inhibitors of the renin-angiotensin-aldosterone system and COVID-19 in critically ill elderly patients. *Eur Heart J Cardiovasc Pharmacother* 2021 Jan 16;7(1):76-77 [FREE Full text] [doi: [10.1093/ehjcvp/pvaa083](https://doi.org/10.1093/ehjcvp/pvaa083)] [Medline: [32645153](https://pubmed.ncbi.nlm.nih.gov/32645153/)]
  42. Jung C, Wernly B, Fjølner J, Bruno RR, Dudzinski D, Artigas A, the COVIP study group. Steroid use in elderly critically ill COVID-19 patients. *Eur Respir J* 2021 Oct 25;58(4):2100979 [FREE Full text] [doi: [10.1183/13993003.00979-2021](https://doi.org/10.1183/13993003.00979-2021)] [Medline: [34172464](https://pubmed.ncbi.nlm.nih.gov/34172464/)]
  43. Flaatten H, deLange D, Jung C, Beil M, Guidet B. The impact of end-of-life care on ICU outcome. *Intensive Care Med* 2021 May 19;47(5):624-625. [doi: [10.1007/s00134-021-06365-7](https://doi.org/10.1007/s00134-021-06365-7)] [Medline: [33604761](https://pubmed.ncbi.nlm.nih.gov/33604761/)]

## Abbreviations

**AUC:** area under the receiver operating characteristic curve  
**CURB-65:** confusion, urea, respiratory rate, blood pressure  
**eCRF:** electronic case report form  
**FiO2:** fraction of inspired oxygen  
**ICU:** intensive care unit  
**LR:** logistic regression  
**MIMIC-III:** Medical Information Mart for Intensive Care  
**ML:** machine learning  
**PPV:** positive predictive value  
**PRC:** precision-recall curve  
**RF:** random forest  
**SHAP:** shapely additive explanation  
**SOFA:** Sequential Organ Failure Assessment  
**TLT:** time-limited trials  
**XGB:** extreme gradient boosting

*Edited by C Lovis; submitted 16.08.21; peer-reviewed by F Velayati, H Ayatollahi; comments to author 10.10.21; revised version received 22.10.21; accepted 04.12.21; published 31.03.22*

*Please cite as:*

Jung C, Mamandipoor B, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, Wolff G, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, De Lange DW, Guidet B, Flaatten H, Osmani V

*Disease-Course Adapting Machine Learning Prognostication Models in Elderly Patients Critically Ill With COVID-19: Multicenter Cohort Study With External Validation*

*JMIR Med Inform* 2022;10(3):e32949

URL: <https://medinform.jmir.org/2022/3/e32949>

doi: [10.2196/32949](https://doi.org/10.2196/32949)

PMID: [35099394](https://pubmed.ncbi.nlm.nih.gov/35099394/)

©Christian Jung, Behrooz Mamandipoor, Jesper Fjølner, Raphael Romano Bruno, Bernhard Wernly, Antonio Artigas, Bernardo Bollen Pinto, Joerg C Schefold, Georg Wolff, Malte Kelm, Michael Beil, Sigal Sviri, Peter V van Heerden, Wojciech Szczeklik, Mirosław Czuczwar, Muhammed Elhadi, Michael Joannidis, Sandra Oeyen, Tilemachos Zafeiridis, Brian Marsh, Finn H Andersen, Rui Moreno, Maurizio Cecconi, Susannah Leaver, Dylan W De Lange, Bertrand Guidet, Hans Flaatten, Venet Osmani. Originally published in JMIR Medical Informatics (<https://medinform.jmir.org>), 31.03.2022. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Medical Informatics, is properly cited. The complete bibliographic information, a link to the original publication on <https://medinform.jmir.org/>, as well as this copyright and license information must be included.

## 4.2 Populationsbasierte Risiko-/Nutzenabwägung mithilfe von Metaanalysen zur Evaluation interventioneller und adjunktiver Therapien

### **4.2.1 Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis**

Karathanos A, Lin Y, Dannenberg L, Parco C, Schulze V, Brockmeyer M, Jung C, Heinen Y, Perings S, Zeymer U, Kelm M, Polzin A, **Wolff G.**

Can J Cardiol. 2019;35(11):1576-1588.

Pubmed PMID: 31542257

DOI: [10.1016/j.cjca.2019.05.003](https://doi.org/10.1016/j.cjca.2019.05.003)

Die antithrombozytäre Therapie mit Glykoprotein IIb/IIIa Inhibitoren (GPI) ist im ST-Strecken-Hebungsinfarkt (STEMI) seit Jahrzehnten eine etablierte Therapieoption, die zwar im Falle einer koronaren Thrombose eine sehr rasche und potente Thrombozytenhemmung ermöglicht, gleichzeitig aber das Blutungsrisiko des Patienten stark erhöht. Mit Entwicklung modernerer oraler P2Y12-Hemmer zur Thrombozytenaggregationshemmung wurden die Leitlinienempfehlungen für GPI im STEMI von der „Routine-Therapie“ zur „bail-out“ Therapie nur in bestimmten Situationen zurückgestuft (36). Ziel unserer Arbeit war es, die Gesamtheit der Datenlage zur Routine-GPI-Therapie im STEMI zu überprüfen.

Wir führten ein systematisches Review aller RCT durch, welche Routine-GPI im STEMI gegen Placebo oder Standardtherapie verglichen hatten; sowohl Beobachtungsstudien als auch Studien ohne „Routineanwendung von GPI“ wurden ausgeschlossen. Primärer Endpunkt war die 30-Tages-Mortalität, sekundäre ischämische Endpunkte (erneuter Herzinfarkt, erneute Revaskularisierung) und sekundäre Blutungsendpunkte (Minor-/Major-Blutung) wurden ebenfalls analysiert. Insgesamt umfasste die Analyse 21 RCTs mit 8585 randomisierten Patienten, welche die GPI Tirofiban, (10 Studien), Abciximab (9 Studien) oder Eptifibatid (1 Studie) untersuchten.

Routine-GPI waren über alle Studien hinweg mit einer signifikanten Reduktion der 30-Tages-Mortalität assoziiert (2,4% vs. 3,2%), sowie einer signifikanten Reduktion sekundärer ischämischer Endpunkte – jedoch auch mit signifikant mehr Major- und Minor-Blutungen. Hauptlimitation der Analyse blieb, dass die meisten der eingeschlossenen Studien vor Einführung moderner oraler P2Y12-Hemmer (Prasugrel, Ticagrelor) durchgeführt wurden.

Zusammenfassend lässt sich sagen, dass Routine-GPI potenziell die Sterblichkeit im STEMI verringern, insbesondere, wenn Blutungskomplikationen vermieden werden. Ihr Einsatz sollte in RCTs unter gleichzeitiger Nutzung moderner, oraler Therapie erneut evaluiert werden.



## Systematic Review/Meta-analysis

# Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis

Athanasios Karathanos, MD,<sup>a</sup> Yingfeng Lin, MD,<sup>a</sup> Lisa Dannenberg, MD,<sup>a</sup> Claudio Parco, MD,<sup>a</sup> Volker Schulze, MD,<sup>a</sup> Maximilian Brockmeyer, MD,<sup>a</sup> Christian Jung, MD,<sup>a</sup> Yvonne Heinen, MD,<sup>a</sup> Stefan Perings, MD,<sup>a</sup> Uwe Zeymer, MD,<sup>b</sup> Malte Kelm, MD,<sup>a,c</sup> Amin Polzin, MD,<sup>a,†</sup> and Georg Wolff, MD<sup>a,†</sup>

<sup>a</sup> University Düsseldorf, Heinrich Heine University, Düsseldorf, Germany

<sup>b</sup> Heart Center Ludwigshafen, Clinic for Cardiology, Pulmonology, Vascular and Intensive Care Medicine, Ludwigshafen, Germany

<sup>c</sup> CARID—Cardiovascular Research Institute Düsseldorf, Düsseldorf, Germany

### ABSTRACT

**Background:** Guidelines recommend adjunct glycoprotein IIb/IIIa inhibitors (GPIs) only in selected patients with acute ST-segment elevation myocardial infarction (STEMI). This study aimed to evaluate routine GPI use in STEMI treated with primary percutaneous coronary intervention.

**Methods:** Online databases were searched for randomized controlled trials of routine GPI vs control therapy in STEMI. Data from retrieved studies were abstracted and evaluated in a comprehensive meta-analysis. Twenty-one randomized controlled trials with 8585 patients

### RÉSUMÉ

**Contexte :** Les lignes directrices recommandent le traitement d'appoint par des inhibiteurs des glycoprotéines IIb-IIIa (IGP) uniquement chez certains patients ayant subi un infarctus du myocarde avec élévation du segment ST (STEMI) aigu. Cette étude visait à évaluer l'utilisation systématique des IGP chez les patients ayant subi un STEMI traité par une intervention coronarienne percutanée primaire.

**Méthodologie :** Une recherche dans les bases de données en ligne a été entreprise pour trouver des études contrôlées à répartition aléatoire ayant comparé l'administration systématique d'IGP à un

Early reperfusion therapy preferably with primary percutaneous coronary intervention (pPCI) has substantially contributed to the improvement of prognosis in acute ST-segment elevation myocardial infarction (STEMI).<sup>1</sup> Adjunct anticoagulants and antiplatelet therapy are routinely used to facilitate dissolution of intracoronary thrombi, reduce microvascular obstruction, and reduce the rate of recurrent ischemic events.<sup>2,3</sup>

Glycoprotein IIb/IIIa inhibitors (GPIs) are potent and rapidly acting intravenous or intracoronary antiplatelet agents and have been an integral part of STEMI management for decades.<sup>4,5</sup> With the advent of the more potent oral P2Y<sub>12</sub> receptor inhibitors prasugrel and ticagrelor,<sup>6,7</sup> however,

American, Canadian, and European cardiovascular society guidelines have gradually scaled back GPI recommendations from routine therapy<sup>4,5,8</sup> to bail-out-use/selected-patients-only in contemporary iterations,<sup>2,3,9</sup> but the evidence base for these changes remains elusive. Contemporary randomized controlled trials (RCTs) with these agents are lacking, and meta-analyses are largely out-of-date and have focused on a mixture of clinical settings and GPI indications.<sup>10–13</sup>

The conceptual design of this systematic review and meta-analysis thus aimed at evaluating all available RCT evidence on routine GPI therapy in STEMI managed with pPCI, in order to elucidate risk-benefit ratios and improve guidance of intravenous adjunct antiplatelet therapy.

Received for publication January 31, 2019. Accepted May 1, 2019.

<sup>†</sup>These authors contributed equally to this work and share senior authorship.

Corresponding author: Dr Athanasios Karathanos, Moorenstr. 5, 40219 Düsseldorf, Germany. Tel.: +49-211-811-8800.

E-mail: ath.karathanos@med.uni-duesseldorf.de

See page 1586 for disclosure information.

### Methods

This work was performed by independent investigators in compliance with accepted standards defined by the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for

were included: 10 trials randomized tirofiban, 9 abciximab, 1 trial eptifibatide, and 1 trial used abciximab+tirofiban; only 1 trial used dual antiplatelet therapy with prasugrel/ticagrelor.

**Results:** Routine GPI use was associated with a significant reduction in all-cause mortality at 30 days (2.4% [GPI] vs 3.2%; risk ratio [RR], 0.72;  $P = 0.01$ ) and 6 months (3.7% vs 4.8%; RR, 0.76;  $P = 0.02$ ), and a reduction in recurrent myocardial infarction (1.1% vs 2.1%; RR, 0.55;  $P = 0.0006$ ), repeat revascularization (2.5% vs 4.1%; RR, 0.63;  $P = 0.0001$ ), thrombolysis in myocardial infarction flow <3 after percutaneous coronary intervention (5.4% vs 8.2%; RR, 0.61;  $P < 0.0001$ ), and ischemic stroke (RR, 0.42;  $P = 0.04$ ). Major (4.7% vs 3.4%; RR, 1.35;  $P = 0.005$ ) and minor bleedings (7.2% vs 5.1%; RR, 1.39;  $P = 0.006$ ) but not intracranial bleedings (0.1% vs 0%; RR, 2.7;  $P = 0.37$ ) were significantly increased under routine GPI.

**Conclusions:** Routine GPI administration in STEMI resulted in a reduction in mortality, driven by reductions in recurrent ischemic events—however predominantly in pre-prasugrel/ticagrelor trials. Trials with contemporary STEMI management are needed to confirm these findings.

reporting systematic reviews and meta-analyses in health care interventions.<sup>14,15</sup>

### Study design, trial eligibility, and outcome selection

All available prospective RCTs of routine GPI therapy vs control (placebo or no GPI therapy) in unselected patients with STEMI managed with pPCI were eligible for inclusion. Studies had to provide an abstract in English; however, no restrictions on publication date, country, patient characteristics, or reported outcomes were imposed. Observational studies were excluded, as well as trials without pPCI, trials in non-STEMI settings, trials of nonroutine GPI therapy (eg, preselected patients with STEMI or bail-out GPI only), and trials randomizing anticoagulants in addition to GPI (Supplemental Table S1 and Fig. S1).

The primary outcome of interest was all-cause mortality. Efficacy outcomes were recurrent myocardial infarction (MI), repeat revascularization, thrombolysis in myocardial infarction (TIMI) flow grade at the end of pPCI and ischemic stroke; safety outcomes were major and minor bleeding events (defined according to the published report or—where possible—Bleeding Academic Research Consortium [BARC]<sup>16</sup>), access site bleeding, transfusions, and hemorrhagic stroke.

### Data sources, search strategy, and study identification

Three investigators (G.W., A.K., and Y.L.) performed the systematic review process. Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar,

traitement témoin chez des patients ayant subi un STEMI. Les données tirées des études trouvées ont été résumées et évaluées dans le cadre d'une méta-analyse exhaustive. Vingt-et-une études contrôlées à répartition aléatoire, auxquelles ont participé 8 585 patients, ont été incluses : dix études sur le tirofiban, neuf études sur l'abciximab, une étude sur l'eptifibatide et une autre sur l'association abciximab + tirofiban; une seule étude a utilisé le traitement antiplaquettaire double par l'association prasugrel + ticagrelor.

**Résultats :** L'utilisation systématique d'IGP a été associée à une réduction significative de la mortalité toutes causes confondues à 30 jours (2,4 % [IGP] vs 3,2 %; rapport des risques [RR] : 0,72;  $p = 0,01$ ) et à 6 mois (3,7 % vs 4,8 %; RR : 0,76;  $p = 0,02$ ), ainsi qu'à une réduction de l'infarctus du myocarde récurrent (1,1 % vs 2,1 %; RR : 0,55;  $p = 0,0006$ ), de la répétition de la revascularisation (2,5 % vs 4,1 %; RR : 0,63;  $p = 0,0001$ ), d'un flux dont le grade TIMI (*Thrombolysis in Myocardial Infarction*) est inférieur à 3 après une intervention coronarienne percutanée (5,4 % vs 8,2 %; RR : 0,61;  $p < 0,0001$ ) et de l'accident vasculaire cérébral (AVC) ischémique (RR : 0,42;  $p = 0,04$ ). Les hémorragies majeures (4,7 % vs 3,4 %; RR : 1,35;  $p = 0,005$ ) et mineures (7,2 % vs 5,1 %; RR : 1,39;  $p = 0,006$ ) ont nettement augmenté avec l'administration systématique d'IGP, mais pas les hémorragies intracrâniennes (0,1 % vs 0 %; RR : 2,7;  $p = 0,37$ ).

**Conclusions :** L'administration systématique d'un IGP à des patients ayant subi un STEMI s'est traduite par une réduction de la mortalité, principalement attribuable à la diminution du nombre d'événements ischémiques récurrents. Cette réduction a néanmoins été surtout observée dans les études menées avant l'avènement de l'association prasugrel + ticagrelor. Il est nécessaire de mener des études sur les modalités de prise en charge actuelles du STEMI pour confirmer ces résultats.

clinicaltrials.gov, and EU Clinical Trials Register were systematically searched up until December 2018 for relevant publications. Search terms included but were not limited to glycoprotein inhibitor IIb/IIIa, GPI, STEMI, acute myocardial infarction, tirofiban, eptifibatide, abciximab, NSTEMI. Clinical trials in humans were used as a filter. Screening was primarily performed at the title and/or abstract level and was continued in full-text reports. Conference proceedings and bibliographic references of identified studies and reviews were additionally checked, and relevant citations were added. Positively evaluated studies were finally selected for inclusion in the meta-analysis. All relevant studies provided a full text in English. All divergences were resolved by consensus.

### Data collection and quality assessment

Information on the following was extracted from each included trial into prespecified forms (G.W., A.K., Y.L., and C.P.): trial characteristics (eg, details on trial conduct, publication, intervention, procedures, follow-up, and bias), patient characteristics (eg, age, sex, and comorbidities), and clinical outcomes of interest. The most updated and/or inclusive intention-to-treat data were used, where possible. Cross-checking between investigators ensured internal data validity. Bias assessment was performed by 2 investigators (Y.L. and M.B.) according to the Cochrane collaboration guidelines,<sup>14</sup> who again cross-checked each other for errors. Divergences at any stage of the data collection process were resolved by consensus.

**Table 1. Characteristics of included studies**

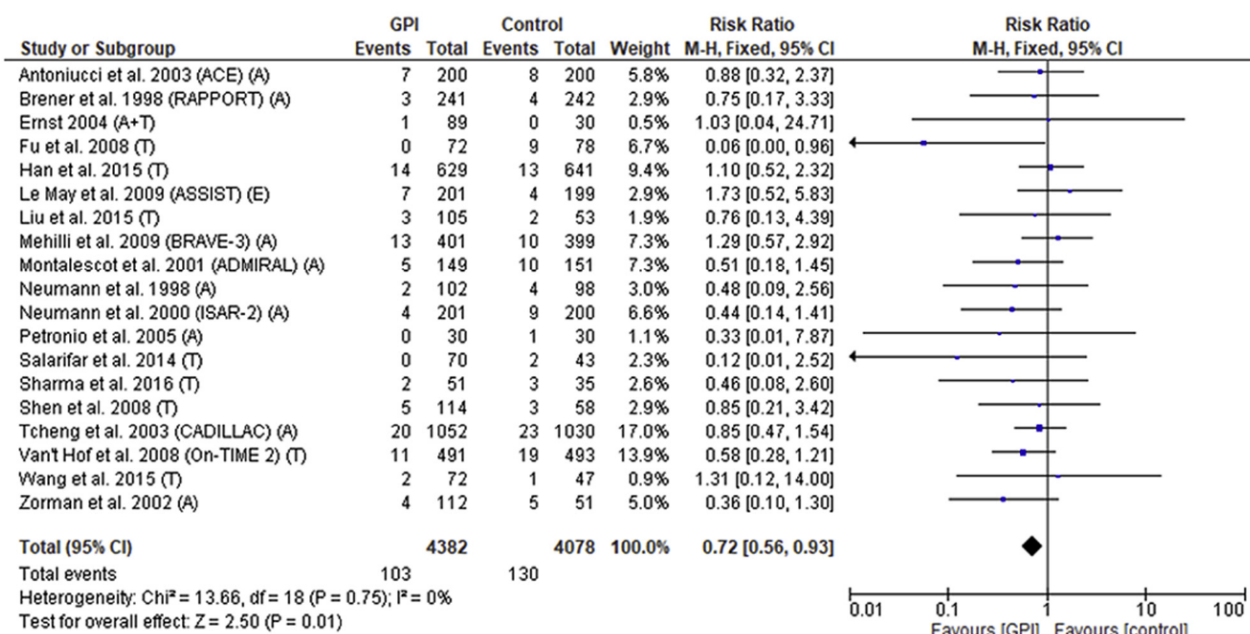
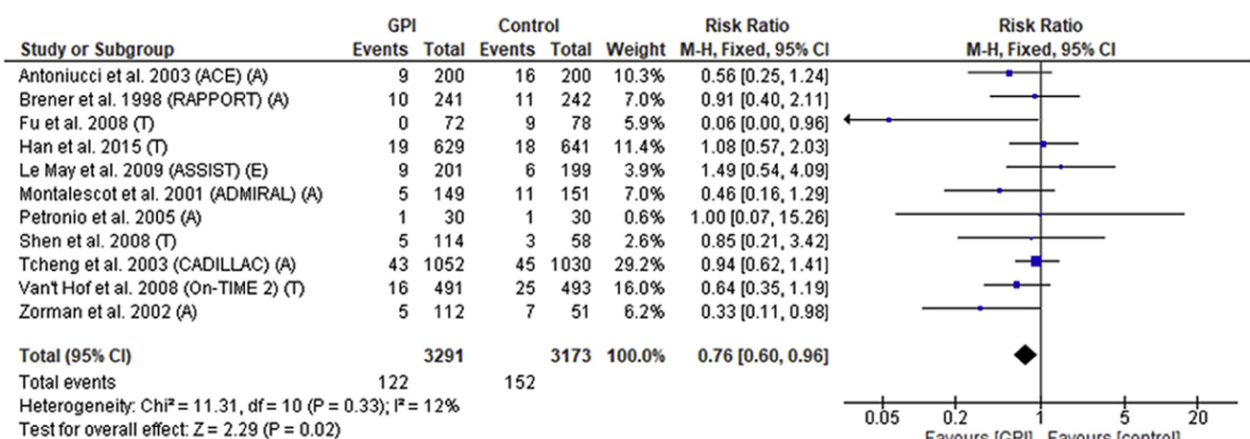
| Study                                                          | Journal                              | Multicentre trial<br>(no. of centres) | Enrollment | Year of<br>publication | No. of patients<br>(per group) | Randomization                                                                                                                                                                                        | Oral platelet<br>inhibitors             | Anticoagulant | pPCI<br>details     | Vascular<br>access         | Follow-up<br>duration |
|----------------------------------------------------------------|--------------------------------------|---------------------------------------|------------|------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------|---------------------|----------------------------|-----------------------|
| Antonucci<br>et al. <sup>39,40</sup> (ACE)                     | <i>Circulation/</i><br><i>JACC</i>   | Yes (n.a.)                            | 2001-2002  | 2003/2004              | 200/200                        | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs nothing                                                                                                                             | Aspirin,<br>ticlopidine,<br>clopidogrel | Heparin       | BMS                 | —                          | 30 d, 6 mo, 1 y       |
| Brener et al. <sup>20</sup><br>(RAPPORT)                       | <i>Circulation</i>                   | Yes (36)                              | 1995-1997  | 1998                   | 241/242                        | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs nothing                                                                                                                             | Aspirin, 18%<br>ticlopidine             | Heparin       | PTCA, 7% BMS        | —                          | 30 d, 6 mo            |
| Ernst et al. <sup>21</sup>                                     | <i>JACC</i>                          | No                                    | 2002-2003  | 2004                   | 30/30/29/30                    | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs tirofiban<br>10 µg/kg bolus + 0.15<br>µg/kg/min for 12 h vs<br>tirofiban 25 µg/kg/<br>bolus + 0.15 µg/kg/min<br>for 12 h vs nothing | Aspirin,<br>clopidogrel                 | Heparin       | —                   | —                          | In-hospital           |
| Fu et al. <sup>22</sup>                                        | <i>Chin Med J</i>                    | No                                    | 2005-2007  | 2008                   | 72/78                          | Tirofiban 10 µg/kg/<br>bolus + 0.15 µg/kg/min<br>for 24 h vs placebo                                                                                                                                 | Aspirin,<br>clopidogrel                 | Heparin       | —                   | Radial                     | 6 mo                  |
| Han et al. <sup>23</sup><br>(BRIGHT)                           | <i>JAMA</i>                          | Yes (82)                              | 2012-2013  | 2015                   | 629/641                        | Tirofiban 10 µg/kg/<br>bolus + 0.15 µg/kg/min<br>for 18-36 h vs nothing                                                                                                                              | Aspirin,<br>clopidogrel                 | Heparin       | 96% DES             | 78% radial,<br>22% femoral | 30 d, 1 y             |
| Le May et al. <sup>24</sup><br>(ASSIST)                        | <i>Circ Cardiovasc</i><br><i>Int</i> | Yes (3)                               | 2005-2008  | 2009                   | 201/199                        | Eptifibatide 180 µg/kg 2×<br>bolus + 2 µg/kg/min for<br>18 h vs nothing                                                                                                                              | Aspirin,<br>clopidogrel                 | Heparin       | 76% BMS,<br>17% DES | 87% Femoral                | 30 d, 6 mo            |
| Liu et al. <sup>25</sup>                                       | <i>Int J Clin Exp</i><br><i>Med</i>  | No                                    | 2013-2014  | 2015                   | 52/53/53                       | Tirofiban 10 µg/kg bolus<br>IC + 0.15 µg/kg/min<br>for 24 h vs tirofiban 10<br>µg/kg bolus + 0.075<br>µg/kg/min for 24 h vs<br>nothing                                                               | Aspirin,<br>ticagrelor                  | Heparin       | DES                 | 92% Radial                 | 30 d                  |
| Martinez-Rios<br>et al. <sup>26</sup><br>(SASTRE)              | <i>Am J Cardiol</i>                  | Yes (7)                               | 2000-2002  | 2004                   | 36/36                          | Tirofiban 0.4 µg/kg/min<br>for 30 min + 0.1 µg/kg/<br>min for 36 h vs nothing                                                                                                                        | Aspirin,<br>clopidogrel                 | Heparin       | BMS                 | —                          | 30 d                  |
| Mehilli et al. <sup>27</sup><br>(BRAVE-3)                      | <i>Circulation</i>                   | Yes (5)                               | 2003-2008  | 2009                   | 401/399                        | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs placebo                                                                                                                             | Aspirin,<br>clopidogrel                 | Heparin       | 49% BMS,<br>44% DES | —                          | 30 d                  |
| Montalescot<br>et al. <sup>28</sup><br>(ADMIRAL) <sup>29</sup> | <i>NEJM</i>                          | Yes (26)                              | 1997-1998  | 2001                   | 149/151                        | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs placebo                                                                                                                             | Aspirin,<br>ticlopidine                 | Heparin       | BMS                 | —                          | 30 d, 6 mo            |
| Neumann et al. <sup>29</sup><br>(ISAR-2)                       | <i>Circulation</i>                   | No                                    | —          | 1998                   | 102/98                         | Abciximab 0.25 mg/kg/<br>bolus + 10 µg/min for<br>12 h vs placebo                                                                                                                                    | Aspirin,<br>ticlopidine                 | Heparin       | BMS                 | —                          | 30 d                  |
| Neumann et al. <sup>30</sup><br>(ISAR-2)                       | <i>JACC</i>                          | No                                    | —          | 2000                   | 201/200                        | Abciximab 0.25 mg/kg/<br>bolus + 10 µg/min for<br>12 h vs placebo                                                                                                                                    | Aspirin,<br>ticlopidine                 | Heparin       | BMS                 | —                          | 30 d                  |
| Perron et al. <sup>41</sup>                                    | <i>Am Heart J</i>                    | No                                    | —          | 2005                   | 30/30                          | Abciximab 0.25 mg/kg/<br>bolus + 0.125 µg/kg/<br>min for 12 h vs nothing                                                                                                                             | Aspirin,<br>clopidogrel                 | Heparin       | BMS                 | 90% Radial                 | 30 d, 6 mo            |
| Salarifar et al. <sup>31</sup>                                 | <i>Iran Red Cres</i><br><i>Med J</i> | No                                    | —          | 2014                   | 70/43                          | Tirofiban 25 µg/kg/<br>bolus + 0.15 µg/kg/min<br>for 12-18 h vs nothing                                                                                                                              | Aspirin,<br>clopidogrel                 | Heparin       | 51% BMS, 30%<br>DES | —                          | 30 d                  |



|                                                  |                             |          |           |           |           |                                                                  |                      |         |                   |                   |
|--------------------------------------------------|-----------------------------|----------|-----------|-----------|-----------|------------------------------------------------------------------|----------------------|---------|-------------------|-------------------|
| Sharma et al. <sup>32</sup>                      | <i>Natl J Physiol Pharm</i> | No       | —         | 2016      | 51/35     | Tirofiban 25 µg/kg bolus + 0.15 µg/kg/min for 24–48 h vs nothing | Aspirin, clopidogrel | Heparin | —                 | 30 d              |
| Shen et al. <sup>33</sup>                        | <i>Coron Artery Dis</i>     | No       | 2005–2006 | 2008      | 114/58    | Tirofiban 10 µg/kg bolus + 0.15 µg/kg/min for 36 h vs nothing    | Aspirin, clopidogrel | Heparin | DES               | 30 d, 6 mo        |
| Steen et al. <sup>34</sup>                       | <i>Am Heart J</i>           | No       | 2000–2002 | 2005      | 24/29     | Tirofiban 10 µg/kg bolus + 0.15 µg/kg/min for 18 h vs nothing    | Aspirin, clopidogrel | Heparin | BMS               | In-hospital       |
| T'cheng et al. <sup>35,36</sup><br>(CADILLAC)    | <i>NEJM Circulation</i>     | Yes (76) | 1997–1999 | 2002/2003 | 1052/1030 | Abciximab 0.25 mg/kg bolus + 0.125 µg/kg/min for 12 h vs placebo | Aspirin, ticlopidine | Heparin | 42% PTCA, 58% BMS | 30 d, 1 y         |
| Van't Hof et al. <sup>37,43</sup><br>(On-TIME 2) | <i>The Lancet JACC</i>      | Yes (24) | 2006–2007 | 2008/2010 | 491/493   | Tirofiban 25 µg/kg bolus + 0.15 µg/kg/min for 18 h vs placebo    | Aspirin, clopidogrel | Heparin | 24% DES, 78% BMS  | 30 d, 1 y         |
| Wang et al. <sup>38</sup>                        | <i>Cell Biochem Biophys</i> | No       | 2011–2013 | 2015      | 72/47     | Tirofiban 10 µg/kg bolus IC + 0.15 µg/kg/min for 48 h vs nothing | Aspirin, clopidogrel | Heparin | DES               | 14 d              |
| Zorman et al. <sup>42</sup>                      | <i>Am J Cardiol</i>         | No       | 1998–2001 | 2002      | 112/51    | Abciximab 0.25 mg/kg bolus + 0.125 µg/kg/min for 12 h vs nothing | Aspirin              | Heparin | 64% BMS           | In-hospital, 6 mo |

ACE, Abciximab and Carbostent Evaluation; ADMIRAL, Abciximab Before Direct angioplasty and Stenting Myocardial Infarction Registering Acute Long-term Follow-up; ASSIST, A Safety and Efficacy Study of Integrilin-Facilitated Versus Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial; BMS, bare-metal stent; BRAVE-3, BAVARIAN Reperfusion Alternatives Evaluation-3; BRIGHT, Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; CADILLAC, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; DES, drug-eluting stent; IC, intracoronary; ISAR-2, Intracoronary Stenting and Antithrombotic Regimen-2; n.a., nonavailable; On-TIME 2, Ongoing Tirofiban in Myocardial Infarction Evaluation 2; pPCI, primary percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RAPPORT, ReoPro and Primary PTCA Organization and Randomized Trial.



**A 30-day all-cause mortality****B 6-months all-cause mortality**

**Figure 1.** All-cause mortality outcome of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction: (A) all-cause mortality at a median of 30 days; (B) all-cause mortality at a median of 6 months. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a fixed-effects model.

**Data synthesis and statistical analysis**

Microsoft Excel, SPSS version 23 (SPSS, Chicago, IL), and Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) were used for statistical computations.

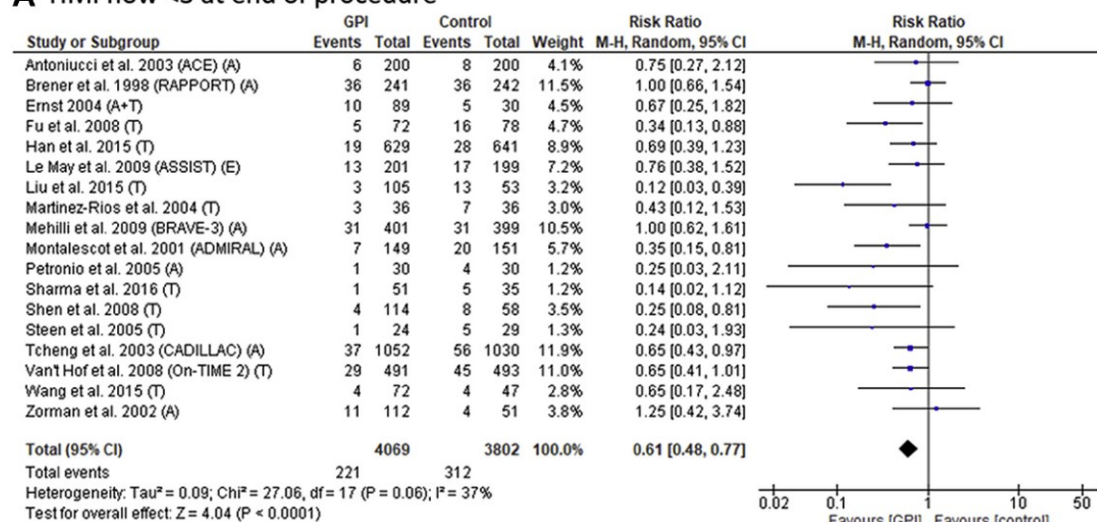
Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated as individual and summary statistics for effect size. Heterogeneity was assessed by the Cochran *Q* test,<sup>17</sup> and statistical heterogeneity was summarized by the *I*<sup>2</sup> statistic.<sup>18</sup> A fixed-effect meta-analysis model was applied for *I*<sup>2</sup> < 20%; higher statistical heterogeneity prompted the use of the conservative DerSimonian and Laird random-effects model.<sup>19</sup>

Prespecified sensitivity analyses were performed to differentiate the 3 GPI drugs. The statistical level of significance of the Cochran-Mantel-Haenszel statistics estimate for the summary treatment effect was assumed at a 2-tailed *P*-value of < 0.05.

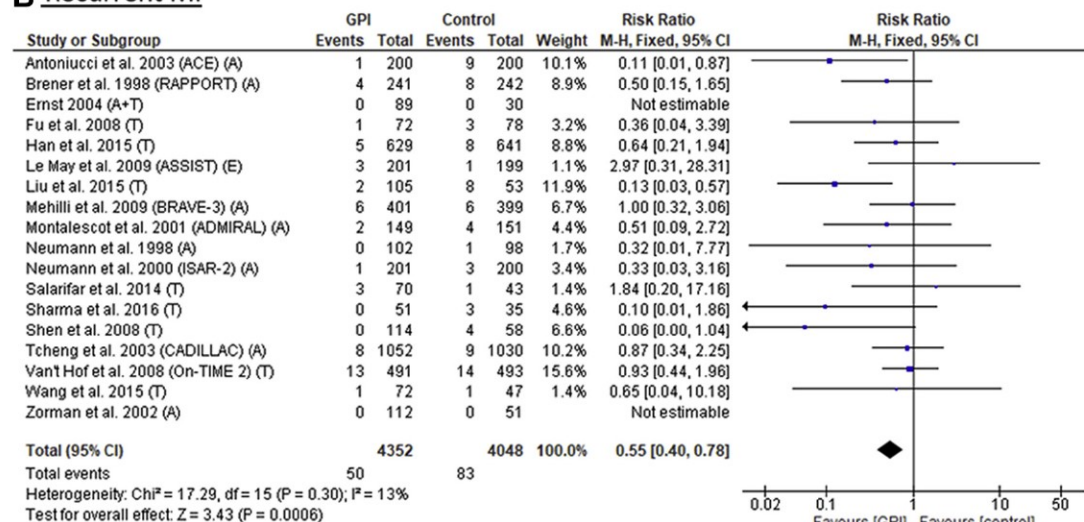
**Results**

The systematic literature search, screening, and selection process are described in a PRISMA flow chart (Supplemental Fig. S1): primary searches revealed a total of 2140 sources, which were subsequently condensed to 21 RCTs published between 1998 and 2016 with a total of 8585 patients.<sup>20-42</sup>

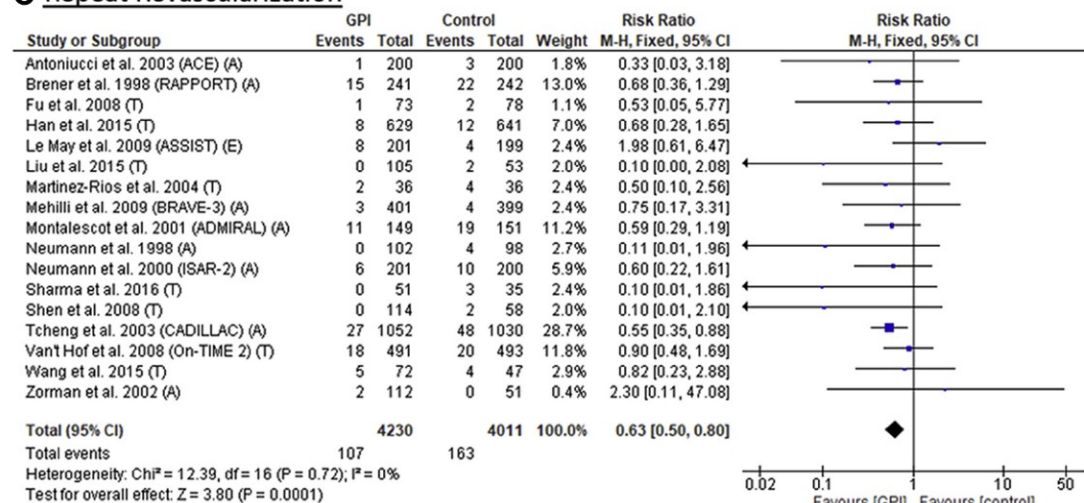
# A TIMI flow <3 at end of procedure



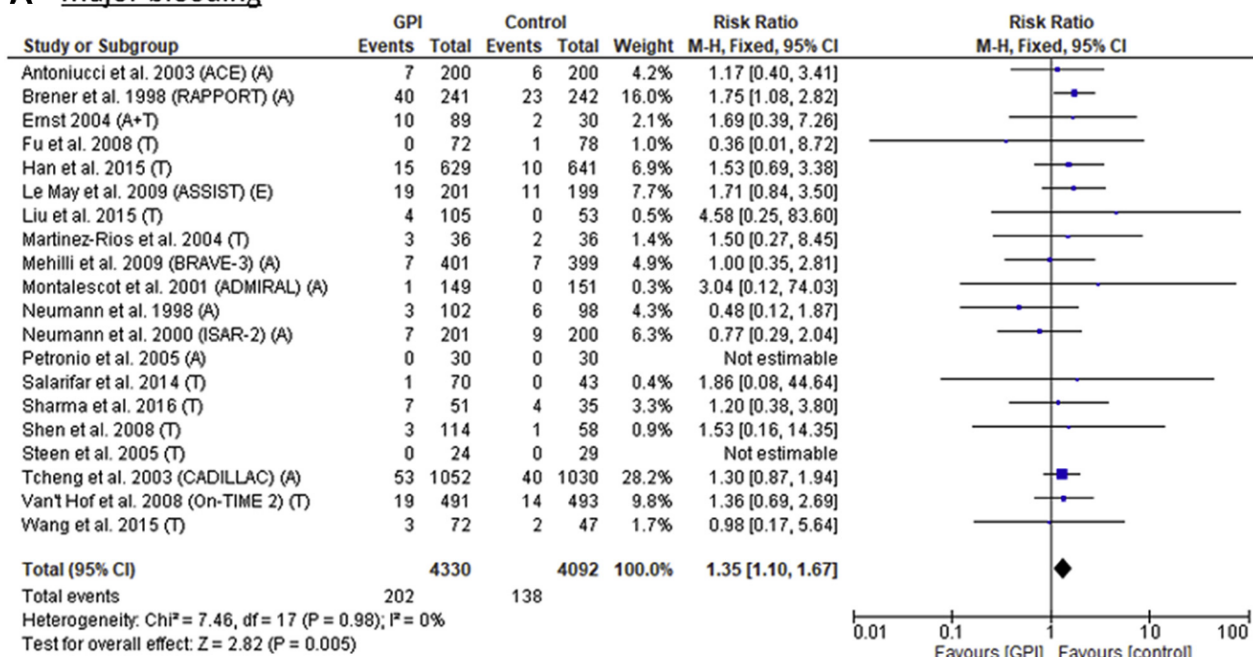
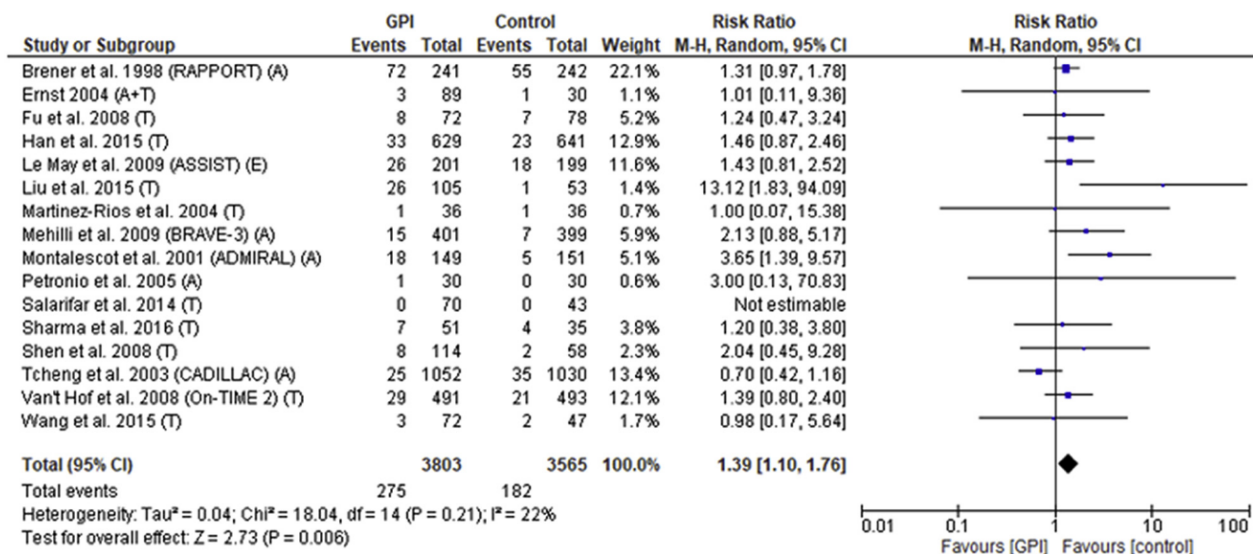
# B Recurrent MI



# C Repeat Revascularization



**Figure 2.** Efficacy outcomes of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction at a median follow-up of 30 days: **(A)** thrombolysis in myocardial infarction (TIMI) flow < 3 at the end of procedure; **(B)** recurrent myocardial infarction (MI); and **(C)** repeat revascularization. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a random-effects model used for  $I^2 > 20\%$ .

**A Major bleeding****B Minor bleeding**

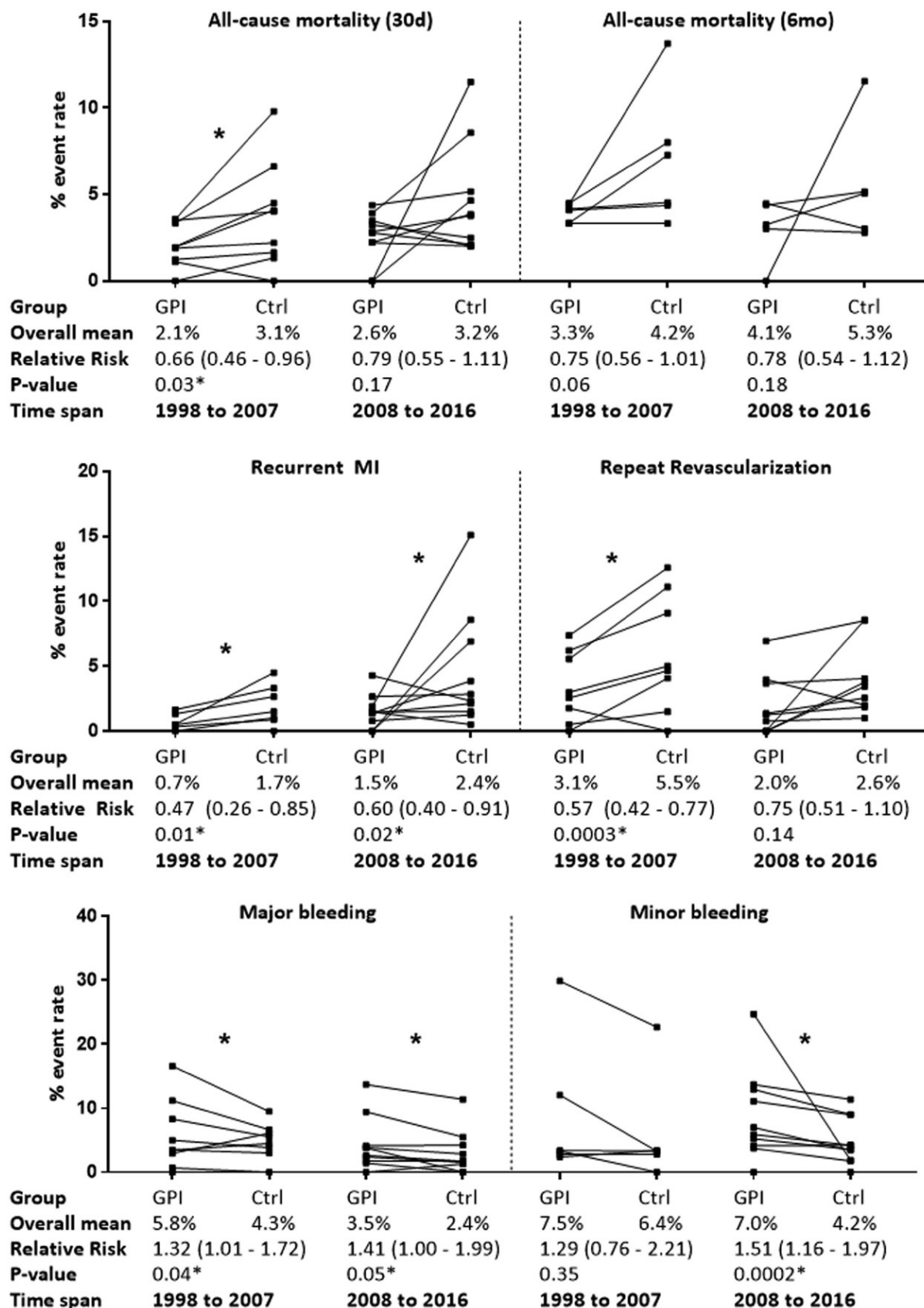
**Figure 3.** Safety outcomes of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction at a median follow-up of 30 days: (A) major bleeding; (B) minor bleeding. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a random-effects model used for  $I^2 > 20\%$ .

Excluded studies and reasons for exclusion are listed in Supplemental Table S1.

Study characteristics are reported in Table 1. The largest included RCT was Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC)<sup>35,36</sup> with 2082 patients and the smallest was by Steen et al.<sup>34</sup> with 53 patients. Eleven trials randomized tirofiban,<sup>21-23,25,26,31-34,37,38,43</sup> 10 trials abciximab,<sup>20,21,27-30,36,39-42</sup> and 1 trial eptifibatide<sup>24</sup> as the investigated GPI to either placebo (8 trials) or standard therapy

(13 trials). GPI was initiated as a bolus either upstream to the procedure in 7 trials<sup>22,27,31,33,37,42</sup> or periprocedural for all others; 2 trials administered the intracoronary bolus instead of intravenous.<sup>25,38</sup> The duration of postprocedural GPI infusion varied between 12 and 48 hours. Tirofiban groups of trials randomizing different dosages to control were analysed together.<sup>21,25</sup> Vascular access information was available only in 5 trials.<sup>23-25,33,41</sup> All but one study<sup>22</sup> reported median follow-ups of 30 days; 11 trials provided follow-ups up to 1 year.<sup>20,22-24,28,33,36,37,39-42</sup> Six studies





**Figure 4.** Summary of glycoprotein IIb/IIIa inhibitor (GPI) effect comparisons stratified by the period of study publication (1998-2007 vs 2008-2016), at a median follow-up of 30 days unless specified otherwise. \*Statistical significance. MI, myocardial infarction; RR, relative risk calculated from Mantel-Haenszel estimate and confidence intervals in parentheses.



were partly financed through Eli Lilly (Bad Homburg, Germany), the company producing ReoPro (abciximab). Many of the trials received financial support from the pharmaceutical industry; 3 trials received support from the local government.<sup>19,22,35</sup> Two trials declared no conflicts of interest,<sup>28,29</sup> and there was no financial disclosure provided or it was unclear in 4 of the trials<sup>18,38,31,39</sup> (for details, see Supplemental Table S2).

Patient characteristics are reported in Supplemental Table S3: the majority of patients were male, median age was 60 years, and cardiovascular comorbidities and smoking were frequent. Medical care for STEMI was heterogeneous across studies (Table 1): pPCI techniques in older trials featured balloon dilatation only or bare-metal stents, whereas later trials used drug-eluting stents. P2Y12 inhibitor therapy in addition to aspirin consisted of clopidogrel (14 trials), ticlopidine (5 trials), and ticagrelor (1 trial); 2 trials predominantly used aspirin monotherapy.<sup>20,42</sup> Heparin was used for anticoagulation in all trials, initiated with a bolus of 60 to 100 U/kg and titrated to an activated clotting time of >250 seconds; heparin dosage after pPCI and during GPI infusion was not consistently reported.

The risk of bias of included RCTs is shown in Supplemental Table S4. Bias originated primarily from the lack of blinding of participants or study personnel and unreported methods of randomization and group allocation of patients. Outcome assessors were blinded in 11 of 21 trials, and there was overall little evidence for incomplete outcome data or selective reporting. Funnel plot graphical analysis for the most relevant outcome of 30-day all-cause mortality revealed no evidence for publication bias (Supplemental Fig. S2).

### All-cause mortality

Nineteen RCTs including 8460 patients reported 30-day all-cause mortality.<sup>20-25,27-33,35-43</sup> The pooled analysis (Fig. 1A) resulted in a significant reduction in the risk for mortality for routine GPI compared with control (2.4% vs 3.2%; RR, 0.72; 95% CI, 0.56-0.93;  $I^2 = 0\%$ ;  $P = 0.01$ ). Sensitivity analyses for abciximab vs control (10 trials<sup>20,21,27-30,36,39-42</sup>; Supplemental Fig. S3: 2.3% vs 3.0%; RR, 0.74; 95% CI, 0.53-1.04;  $I^2 = 0\%$ ;  $P = 0.08$ ) and tirofiban vs control (9 trials<sup>21-23,25,31-33,37,38,43</sup>; Supplemental Fig. S3B: 2.3% vs 3.5%; RR, 0.64; 95% CI, 0.42-0.96;  $I^2 = 0\%$ ;  $P = 0.03$ ) exhibited similar results.

Mortality after a median follow-up of 6 months was reported in 11 trials,<sup>20,22-24,28,33,35-37,39-43</sup> resulting in a similarly significant reduction in the risk for GPI (3.7% vs 4.8%; RR, 0.76; 95% CI, 0.60-0.96;  $I^2 = 12\%$ ;  $P = 0.02$ ; Fig. 1B).

### Efficacy outcomes of TIMI flow, recurrent MI, repeat revascularization, and ischemic stroke

The meta-analysis of 18 RCTs reporting TIMI flow grades at the end of pPCI showed a highly significant reduction in the risk for suboptimal TIMI flow with GPI vs control (5.4% vs 8.2%; RR, 0.61; 95% CI, 0.48-0.78;  $P < 0.0001$ ; Fig. 2A), albeit with considerable statistical heterogeneity (heterogeneity  $P = 0.06$ ;  $I^2 = 37\%$ ) in a random-effects model. There was a modest difference in sensitivity analyses of abciximab (RR, 0.78;  $P = 0.09$ ) and tirofiban (RR, 0.46;  $P < 0.0001$ ; data not shown).

Eighteen RCTs reported recurrent MI events;<sup>20-25,27-33,35-40,42,43</sup> their meta-analysis showed a highly significant reduction in the risk for recurrent MI with routine GPI compared with control (1.1% vs 2.1%; RR, 0.55; 95% CI, 0.40-0.78;  $I^2 = 13\%$ ;  $P = 0.0006$ ; Fig. 2B). Similar results were found for sensitivity analyses in abciximab (RR, 0.55;  $P = 0.02$ ) and tirofiban (RR, 0.46;  $P = 0.04$ ) trials only (data not shown).

Seventeen RCTs reported repeat revascularizations.<sup>20,22-33,35-40,42,43</sup> A highly significant risk reduction was seen in the pooled analysis with GPI vs control therapy (2.5% vs 4.1%; RR, 0.63; 95% CI, 0.5-0.8;  $I^2 = 0\%$ ;  $P = 0.0001$ ; Fig. 2C). Abciximab (RR, 0.58;  $P = 0.0004$ ) and tirofiban alone were equally effective (RR, 0.64;  $P = 0.04$ ; data not shown).

Seven trials reported ischemic stroke events.<sup>23,24,27,30,35-37,40,43</sup> The pooled meta-analyses resulted in a significant reduction in the risk for this rare event under GPI therapy (0.2% vs 0.6%; RR, 0.42; 95% CI, 0.19-0.96;  $I^2 = 0\%$ ;  $P = 0.04$ ; data not shown).

### Safety outcomes of bleeding events and intracranial haemorrhage

Bleeding events were reported in all trials.<sup>20-43</sup> The risk of major bleedings was significantly increased under GPI therapy compared with control (Fig. 3A: 4.7% vs 3.4%; RR, 1.35; 95% CI, 1.1-1.67;  $I^2 = 0\%$ ;  $P = 0.005$ ). Similar results, albeit with higher heterogeneity, were observed for minor bleedings (Fig. 3B: 7.2% vs 5.1%; RR, 1.39; 95% CI, 1.10-1.76;  $I^2 = 22\%$ ; random-effects model,  $P = 0.006$ ). Access site bleedings were reported in 6 trials<sup>20,22,24,28,31,41</sup> and were significantly more frequent under GPI (8.5% vs 3.5%; RR, 2.34; 95% CI, 1.51-3.60;  $I^2 = 14\%$ ;  $P = 0.0001$ ; data not shown); the same was true for transfusions (9 trials<sup>20,22,24,27,29,33,35-37,41-43</sup>: 5.1% [GPI] vs 4.0% [control]; RR, 1.3; 95% CI, 1.02-1.66;  $I^2 = 0\%$ ;  $P = 0.03$ ; data not shown).

Intracranial haemorrhage reported in 10 trials<sup>20,21,23,25-27,29,35,36,39-41</sup> was extremely rare: 3 events in total were reported under GPI therapy vs control (0.1% vs 0%; RR, 2.7; 95% CI, 0.3-24.4;  $P = 0.37$ ; data not shown).

### Number-needed-to-treat and number-needed-to-harm of GPI therapy

The number-needed-to-treat of GPI therapy to prevent 1 death was 125 during the first 30 days and 91 during the 6-month follow-up. The number-needed-to-harm with major bleeding under GPI therapy was 77 and 1000 for intracranial bleeding.

### Impact of study publication period on GPI effects for clinical outcomes

To account for the time span across which studies were included in this analysis (1998-2016), a dichotomous analysis of studies from 1998 to 2007 and from 2008 to 2016 was performed (Fig. 4): GPI reduced 30-day and 6-month all-cause mortality in both older and younger trials (RR, 0.66-0.78;  $P = 0.03$ -0.18), which was similarly true for recurrent ischemic events (MI and repeat revascularization: RR, 0.47-0.75;  $P = 0.01$ -0.14). All outcomes showed a slight trend

towards lower GPI efficacy in the younger trial group. Overall, major bleedings became less frequent in the contemporary period; GPI still significantly increased bleeding risk (Fig. 4).

## Discussion

The main findings of this meta-analysis of routine GPI use in STEMI were as follows: (1) GPI significantly reduced the risk for mortality compared with control at 30-day and 6-month follow-up; (2) GPI significantly reduced recurrent ischemic events; and (3) GPI significantly increased risk for all bleeding outcomes, except for intracranial haemorrhage.

In high thrombus burden scenarios of STEMI with microvascular obstruction and no-reflow phenomenon, adverse outcomes ensue.<sup>44</sup> Routine thrombus aspiration in this setting has shown limited benefits<sup>45,46</sup> and is not recommended in current guidelines.<sup>2</sup> In this acute setting, oral antiplatelet agents have not yet managed to achieve optimal inhibition related to time, opioid use, and poor gastric absorption in shock. The impressive rapid onset of action of ticagrelor and prasugrel in healthy volunteers<sup>47,48</sup> is not applicable in the acute setting of STEMI, where effective platelet inhibition is achieved not earlier than 2 to 4 hours after oral administration.<sup>49-51</sup> Clopidogrel—still the only option in some subgroup of patients—has considerably slower pharmacokinetics.<sup>52,53</sup> Alternative therapy with intravenous cangrelor<sup>54,55</sup> achieved rapid platelet inhibition leading to a guidelines recommendation for P2Y<sub>12</sub>-naïve patients; nonetheless, high cost hinders large-scale routine application, and it should be considered that the medication was tested mostly on patients receiving clopidogrel. This renders the “old” GPI therapy “new” and interesting again, something that led us to perform this meta-analysis.

Previous meta-analyses studied different routes of administration of GPI or GPI after thrombectomy, but routine GPI therapy in STEMI has not been analysed.<sup>13,56,57</sup> This meta-analysis confirmed GPI efficacy in this setting, finding a robust reduction of recurrent MI, repeat revascularization, and suboptimal TIMI flow after pPCI compared with control. This finding was irrespective of the use of an antibody (abciximab) or small-molecule (tirofiban and eptifibatide) GPI, which is in line with previous analyses.<sup>58</sup> Ischemic strokes were also significantly reduced, reminiscent of the use of GPI in stroke—even though the event rate was low overall.

Compared with oral platelet inhibitors, GPIs have been shown to increase bleeding complications<sup>20,36</sup> leading European guidelines recommending only bail-out use in case of high thrombus burden (class IIa).<sup>2</sup> American guidelines (class IIa/IIb) stress the missing evidence of GPI in combination with modern DAPT,<sup>59</sup> similar to current Canadian guidelines.<sup>9</sup> This meta-analysis made similar observations with an increase in the relative risk of approximately 40% for major and minor bleedings and transfusions in studies predominantly featuring clopidogrel as the second antiplatelet agent in DAPT. Only 1 small trial on GPI therapy as a routine adjunct to modern DAPT with ticagrelor was available.<sup>25</sup>

Overall, this meta-analysis confirms an advantageous bleeding risk vs ischemic benefit balance of routine GPI in patients with STEMI in the pre-prasugrel/ticagrelor era, evident in a significant reduction of approximately 25% in

30-day and 6-month all-cause mortality. Such survival benefit was observed despite low overall mortality in these trials. Results of formal tests of heterogeneity were considered alongside a qualitative assessment of the combinability of studies in this review. Considering heterogeneity present among study designs, protocols, and study size, we analysed the relationship of study size, precision, and treatment effect (see Supplemental Fig. S1), and we accounted for heterogeneity by performing sensitivity analysis and choosing the conservative random-effects method. In addition, no major risk for publication bias or bias within studies could be found. With trials funded from various institutions, the risk of bias was present. Because the impact of trial funding cannot be assessed quantitatively, we included all studies independent of funding. An additional limitation that should be mentioned is the long time span across included studies with evolutions in pPCI techniques and oral antiplatelet therapy. Even with valid results, this meta-analysis cannot overcome the lack of evidence on GPI in combination with modern potent DAPT. This limitation notwithstanding, contemporary access-site management and transradial vascular access<sup>60,61</sup> are bound to reduce bleeding events and increase net GPI benefits. In a contemporary registry of patients with STEMI, we found no differences in bleeding events with or without GPI.<sup>62</sup> That said, we have to consider that GPIs have been shown to be slightly more efficient in older trials (Fig. 4) and might further lose efficacy in ischemic reduction in a setting of modern DAPT and stent technology. Because current evidence is not able to answer these open questions, we think that RCTs of routine GPI in contemporary STEMI management are warranted. Such trials should deliver evidence on clot burden, lesion complexity, and time delay through thrombectomy, while subgroup analyses to identify groups of patients with the largest benefit through such an approach would be of interest, for example, an analysis for patients treated via a transradial vs transfemoral approach. A further consideration would be to test shorter time intervals of GPI infusions, which could further decrease bleeding complications without compromising efficacy. Coadministration of GPIs with cangrelor for the duration of infusion might be another interesting option to increase efficacy while giving an option for fast reversal in case of bleeding.

## Conclusions

Routine GPI administration as an adjunct to pPCI in patients with STEMI was found to result in mortality reduction, which was driven by a reduction in recurrent ischemic events. Nevertheless, the majority of trials included were conducted before the era of potent P12Y2 inhibitors. New trials in a contemporary setting of STEMI management are warranted to confirm clinical benefits of routine GPI therapy.

## Acknowledgements

G.W., A.K., and V.S. conceived and designed the study, in collaboration with A.P., L.D., and C.J. on a larger GPI project; A.K., Y.L., M.B., C.P., and G.W. collected sources, selected studies, and abstracted data; M.B., C.P., A.K., Y.L., Y.H., and V.S. performed double checks. G.W. and Y.L.



performed the statistical analysis. A.K., G.W., A.P., C.J., U.Z., and M.K. drafted and revised the manuscript. All authors analysed and interpreted the data and critically revised the manuscript. All authors read and accepted the submitted version of the manuscript.

### Funding Sources

This work was supported by academic research grants from the Forschungskommission of the Medical Faculty, Heinrich Heine University Düsseldorf, Germany (No. 2018-32 to G.W. for a Clinician Scientist Track) and the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich [SFB] 1116 to M.K., A.P., and C.J.) for a collaborative research project on acute myocardial infarction. None of the authors received industry funding for this work; design, conduct, and reporting are thus free from influence.

### Disclosures

C.J. received an unrestricted research grant outside of the submitted work to the institution (MediCure, Canada) on a related topic. The rest of the authors have no relevant conflicts of interest to disclose.

### References

1. Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J* 2017;38:3056-65.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119-77.
3. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2016;133:1135-47.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004;110:588-636.
5. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;24:28-66.
6. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
7. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
8. Welsh RC, Travers A, Huynh T, Cantor WJ, Canadian Cardiovascular Society Working Group. Canadian Cardiovascular Society Working Group: providing a perspective on the 2007 focused update of the American College of Cardiology and American Heart Association 2004 guidelines for the management of ST elevation myocardial infarction. *Can J Cardiol* 2009;25:25-32.
9. Wong GC, Welsford M, Ainsworth C, et al. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology guidelines on the acute management of ST-elevation myocardial infarction: focused update on regionalization and reperfusion. *Can J Cardiol* 2019;35:107-32.
10. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J* 2010;31:35-49.
11. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb/IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J* 2009;30:2705-13.
12. Montalescot G, Antoniucci D, Kastrati A, et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J* 2007;28:443-9.
13. Elbadawi A, Elgendy IY, Megaly M, et al. Meta-analysis of randomized trials of intracoronary versus intravenous glycoprotein IIb/IIIa inhibitors in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2017;120:1055-61.
14. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: <http://www.handbook.cochrane.org>.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-47.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
18. Grizzle JE. Analysis of data from multiclinic trials. *Control Clin Trials* 1987;8:392-3.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;45:139-45.
20. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation* 1998;98:734-41.
21. Ernst NM, Suryapranata H, Miedema K, et al. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;44:1187-93.
22. Fu XH, Hao QQ, Jia XW, et al. Effect of tirofiban plus clopidogrel and aspirin on primary percutaneous coronary intervention via transradial

- approach in patients with acute myocardial infarction. *Chin Med J (Engl)* 2008;121:522-7.
23. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;313:1336-46.
24. Le May MR, Wells GA, Glover CA, et al. Primary percutaneous coronary angioplasty with and without eptifibatide in ST-segment elevation myocardial infarction: a safety and efficacy study of integrilin-facilitated versus primary percutaneous coronary intervention in ST-segment elevation myocardial infarction (ASSIST). *Circ Cardiovasc Interv* 2009;2:330-8.
25. Liu Y, Liu H, Hao Z, et al. Efficacy and safety of different doses of tirofiban combined with ticagrelor on diabetic patients with AMI receiving in emergency percutaneous coronary intervention (PCI). *Int J Clin Exp Med* 2015;8:11360-9.
26. Martinez-Rios MA, Rosas M, Gonzalez H, et al. Comparison of reperfusion regimens with or without tirofiban in ST-elevation acute myocardial infarction. *Am J Cardiol* 2004;93:280-7.
27. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009;119:1933-40.
28. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895-903.
29. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-701.
30. Neumann FJ, Kastrati A, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 2000;35:915-21.
31. Salarifar M, Mousavi M, Yousefpour N, et al. Effect of early treatment with tirofiban on initial TIMI grade 3 flow of patients with ST elevation myocardial infarction. *Iran Red Crescent Med J* 2014;16:e9641.
32. Sharma S, Gupta S, Bhat S, Gillani Z, Kumar D, Kumar R. Efficacy and safety of tirofiban as an adjunctive therapy in patients with acute ST-segment elevation myocardial infarction undergoing percutaneous transluminal coronary angioplasty. *Natl J Physiol Pharm Pharmacol* 2016;6:531-6.
33. Shen J, Zhang Q, Zhang RY, et al. Clinical benefits of adjunctive tirofiban therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Coron Artery Dis* 2008;19:271-7.
34. Steen H, Lehrke S, Wiegand UK, et al. Very early cardiac magnetic resonance imaging for quantification of myocardial tissue perfusion in patients receiving tirofiban before percutaneous coronary intervention for ST-elevation myocardial infarction. *Am Heart J* 2005;149:564.
35. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957-66.
36. Tcheng JE, Kandzari DE, Grines CL, et al. Benefits and risks of abciximab use in primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation* 2003;108:1316-23.
37. Van't Hof AW, Ten Berg J, Heestermaans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;372:537-46.
38. Wang K, Zuo G, Zheng L, et al. Effects of tirofiban on platelet activation and endothelial function in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Cell Biochem Biophys* 2015;71:135-42.
39. Antoniucci D, Migliorini A, Parodi G, et al. Abciximab-supported infarct artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infarct artery stenting plus abciximab with stenting alone. *Circulation* 2004;109:1704-6.
40. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1879-85.
41. Petronio AS, De Carlo M, Ciabatti N, et al. Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005;150:1015.
42. Zorman S, Zorman D, Noc M. Effects of abciximab pretreatment in patients with acute myocardial infarction undergoing primary angioplasty. *Am J Cardiol* 2002;90:533-6.
43. Ten Berg JM, van't Hof AW, Dill T, et al. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol* 2010;55:2446-55.
44. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J* 2016;37:1024-33.
45. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;369:1587-97.
46. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015;372:1389-98.
47. Giorgi MA, Cohen Arazi H, Gonzalez CD, Di Girolamo G. Beyond efficacy: pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. *Expert Opin Pharmacother* 2011;12:1285-95.
48. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009;30:1964-77.
49. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013;61:1601-6.
50. Valgimigli M, Tebaldi M, Campo G, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012;5:268-77.
51. Zeymer U, Mochmann HC, Mark B, et al. Double-blind, randomized, prospective comparison of loading doses of 600 mg clopidogrel versus 60 mg prasugrel in patients with acute ST-segment elevation myocardial infarction scheduled for primary percutaneous intervention: the ETAMI trial (early thienopyridine treatment to improve primary PCI in patients



- with acute myocardial infarction). *JACC Cardiovasc Interv* 2015;8:147-54.
52. Heestermans AA, van Werkum JW, Taubert D, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. *Thromb Res* 2008;122:776-81.
  53. Souckova L, Opatrilova R, Suk P, et al. Impaired bioavailability and antiplatelet effect of high-dose clopidogrel in patients after cardiopulmonary resuscitation (CPR). *Eur J Clin Pharmacol* 2013;69:309-17.
  54. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009;361:2330-41.
  55. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009;361:2318-29.
  56. Wu JH, Hao PP, Chen YG, Li RJ. Intracoronary glycoprotein IIb/IIIa inhibitors improve short-term mortality and reinfarction in East Asian patients with ST-segment elevation myocardial infarction after thrombus aspiration: a meta-analysis. *Evid Based Complement Alternat Med* 2018;2018:5174714.
  57. Rafique AM, Nayyar P, Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a network meta-analysis. *JACC Cardiovasc Interv* 2016;9:1036-46.
  58. Gurm HS, Tamhane U, Meier P, Grossman PM, Chetcuti S, Bates ER. A comparison of abciximab and small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention: a meta-analysis of contemporary randomized controlled trials. *Circ Cardiovasc Interv* 2009;2:230-6.
  59. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:529-55.
  60. Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;385:2465-76.
  61. Vranckx P, Frigoli E, Rothenbuhler M, et al. Radial versus femoral access in patients with acute coronary syndromes with or without ST-segment elevation. *Eur Heart J* 2017;38:1069-80.
  62. Dannenberg L, Wolff G, Naguib D, et al. Safety and efficacy of tirofiban in STEMI-patients. *Int J Cardiol* 2019;274:35-9.

### Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at [www.onlinecjc.ca](http://www.onlinecjc.ca) and at <https://doi.org/10.1016/j.cjca.2019.05.003>.

#### **4.2.2 Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients**

Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, **Wolff G**, Dias S, Claessen B, Brouwer M, Tarantini G, Iliceto S, Brockmeyer M, Kowalewski M, Lin Y, Eikelboom J, Musumeci G, Lee L, Lip GY, Valgimigli M, Berti S, Kelm M.

Thromb Haemost. 2015;114(5):933-44.

Pubmed PMID: 26177601

DOI: [10.1160/TH14-12-1066](https://doi.org/10.1160/TH14-12-1066)

Im akuten Koronarsyndrom sind von internationalen Leitlinien verschiedene Optionen der parenteralen Antikoagulation empfohlen (84, 96-98). Da jedoch direkte Vergleiche zwischen diesen verschiedenen Medikamentenklassen aus randomisierten Studien häufig fehlten, war unklar, welche Option die beste in diesem Setting ist.

Wir haben ein systematisches Review mit anschließender Netzwerk-Metaanalyse von insgesamt 42 randomisierten, kontrollierten Studien mit insgesamt 117.353 eingeschlossenen Patienten durchgeführt, welche sechs verschiedene Antikoagulantien miteinander verglichen haben: 1) Unfraktioniertes Heparin + Glykoprotein-Inhibition (GPI), 2) Unfraktioniertes Heparin ± GPI, 3) Bivalirudin, 4) Niedermolekulare Heparine, 5) Otamixaban und 6) Fondaparinux. Relevante klinische Endpunkte waren Tod, Myokardinfarkt, Revaskularisierung, Blutungsereignisse und Stentthrombose innerhalb von 30 Tagen. Subanalysen zu verschiedenen klinischen Settings (ST-Strecken- und Nicht-ST-Strecken-Hebungsinfarkte) wurden zusätzlich durchgeführt.

Es ergaben sich in unserer Netzwerk-Analyse keine signifikanten Unterschiede in der Mortalität zwischen allen sechs Strategien: Bivalirudin reduzierte verglichen mit Heparinen + GPI und Heparinen ± GPI das Blutungsrisiko, mit jedoch seinerseits erhöhtem Risiko für Myokardinfarkt und Stentthrombose, welche ihrerseits bei Heparinen (insbesondere Heparinen + GPI) niedriger waren.

Zusammenfassend zeigte sich in unserer bis dato größten Netzwerk-Metaanalyse der Antikoagulationsstrategien im akuten Koronarsyndrom keine eindeutig beste Option. Vielmehr muss anhand des individuellen Blutungsrisikos und des ischämischen Risikos des Patienten die beste Strategie abgewogen werden.

# Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes

## Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients

Eliano Pio Navarese<sup>1,14</sup>; Felicita Andreotti<sup>2,13</sup>; Michalina Kołodziejczak<sup>1,3,14</sup>; Volker Schulze<sup>1,14</sup>; Georg Wolff<sup>1,14</sup>; Sofia Dias<sup>4,14</sup>; Bimmer Claessen<sup>5,14</sup>; Marc Brouwer<sup>6,14</sup>; Giuseppe Tarantini<sup>7</sup>; Sabino Iliceto<sup>7</sup>; Maximilian Brockmeyer<sup>1,14</sup>; Mariusz Kowalewski<sup>8</sup>; Yingfeng Lin<sup>1,14</sup>; John Eikelboom<sup>9</sup>; Giuseppe Musumeci<sup>10</sup>; Leong Lee<sup>11</sup>; Gregory Y. H. Lip<sup>11</sup>; Marco Valgimigli<sup>12</sup>; Sergio Berti<sup>13,14</sup>; Malte Kelm<sup>1,14</sup>

<sup>1</sup>Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Düsseldorf, Germany; <sup>2</sup>Department of Cardiovascular Sciences, Catholic University of the Sacred Heart, Rome, Italy; <sup>3</sup>Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland; <sup>4</sup>University of Bristol, School of Social and Community Medicine, Bristol, UK; <sup>5</sup>Department of Cardiology, Academisch Medisch Centrum, Universiteit van Amsterdam, Netherlands; <sup>6</sup>Department of Cardiology, UMC St Radboud, Nijmegen, Netherlands; <sup>7</sup>Department of Cardiac, Thoracic and Vascular Sciences, University of Padua Medical School, Padua, Italy; <sup>8</sup>Department of Cardiology, 10th Military Research Hospital and Polyclinic, Bydgoszcz, Poland; <sup>9</sup>Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; <sup>10</sup>Azienda Ospedaliera Papa Giovanni XXIII Bergamo, Lombardia, Italy; <sup>11</sup>University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; <sup>12</sup>Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; <sup>13</sup>Cardiothoracic Department, Heart Hospital, Fondazione Toscana Gabriele Monasterio, Massa, Italy; <sup>14</sup>Systematic Investigation and Research on Interventions and Outcomes (SIRIO)-Medicine Research Network

### Summary

International guidelines differ in strengths of recommendation for anticoagulation strategies in acute coronary syndromes (ACS). We performed a comprehensive network meta-analysis (NMA) of randomised controlled trials (RCTs) to investigate the comparative efficacy and safety of parenteral anticoagulants in ACS. MEDLINE, Cochrane, EMBASE, Google Scholar, major cardiology websites, and abstracts/presentations were searched. Six treatments were identified: 1) unfractionated heparin (UFH) + glycoprotein IIb/IIIa inhibitor (GPI) [UFH+GPI], 2) UFH±GPI, 3) bivalirudin, 4) low-molecular-weight heparins (LMWHs), 5) otamixaban, and 6) fondaparinux. Prespecified outcomes (death, myocardial infarction [MI], revascularisation, major bleeding [MB], minor bleeding, and stent thrombosis [ST]) were evaluated up to 30 days. Forty-two RCTs involving 117,353 patients were included. No significant differences in mortality rates were found among strategies. Compared to UFH+GPI, bivalirudin reduced the

odds of MB but increased the odds of ST and MI. LMWHs vs bivalirudin reduced MI risk at the price of MB excess. UFH±GPI significantly increased the odds of MI vs LMWHs, of ST vs UFH+GPI, and of MB vs bivalirudin. Reduced ST risk with otamixaban vs UFH±GPI and vs bivalirudin was offset by a marked 2.5- to four-fold MB excess. Fondaparinux showed an intermediate profile. Results for ST-segment elevation MI were consistent with the overall findings. Early anticoagulant strategies for ACS differ in efficacy and safety, with UFH+GPI and LMWHs reducing ischaemic but increasing bleeding risk, and bivalirudin reducing MB but increases MI and ST. The findings support individualised therapy based on patients' bleeding and ischaemic risks.

### Keywords

Acute coronary syndrome, parenteral anticoagulant, network meta-analysis

### Correspondence to:

Department of Internal Medicine  
Division of Cardiology, Pulmonology and Vascular Medicine  
Heinrich-Heine-University, Düsseldorf, Germany  
E-mail: elianonavarese@gmail.com

### Financial support:

Part of this study was supported by the Collaborative Research Center 1116 Masterswitches in Myocardial Ischemia, funded by the German Research Council (Deutsche Forschungsgemeinschaft).

Received: December 20, 2014

Accepted after major revision: May 19, 2015

Epub ahead of print: July 16, 2015

<http://dx.doi.org/10.1160/TH14-12-1066>

Thromb Haemost 2015; 114: 933–944

Note: The review process for this manuscript was fully handled by Christian Weber, Editor in Chief.

## Introduction

Contemporary guidelines recommend parenteral anticoagulants for the initial management of patients with myocardial infarction (MI) or high-risk unstable angina (1–4). Options span from anti-thrombin-mediated coagulation inhibitors – that comprise unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and the synthetic pentasaccharide fondaparinux – to

the direct thrombin inhibitor, bivalirudin; a direct factor Xa inhibitor, otamixaban, has also been investigated. These strategies have been tested in phase II and III randomised controlled trials (RCTs) against each other, but direct comparisons among all of them are incompletely available. The lack of direct evidence has led to variable interpretations and uncertainty, reflected by a range of guideline recommendation for each agent (1–4). Even when apparently large, head-to-head comparisons exist, the available



evidence is still underpowered to draw conclusions with respect to individual outcomes (5–8).

Network meta-analyses (NMAs), also known as mixed treatment comparisons, are novel methods comparing different treatments in a connected network (9). They allow probability inferences on the best treatment even when direct comparisons are unavailable, by integrating data from direct and indirect comparisons, while maintaining the randomisation design (10). In addition to analysing direct within-trial comparisons between treatments (such as A vs B), the network framework incorporates indirect comparisons (such as A vs C) from trials having one treatment in common (such as A vs B and B vs C), thereby comparing agents not directly analysed within an individual trial. The role of NMAs in clinical research is well established, as they provide an overview of the available evidence on the largest possible scale (11). We report the first comprehensive NMA of RCTs investigating the efficacy and safety of parenteral anticoagulant strategies in patients with acute coronary syndromes (ACS).

## Methods

### Data source and search strategy

Established methods were used in compliance with the PRISMA (Preferred Reporting of Items for Systematic reviews and Meta-Analyses) statement in health care interventions (12). Relevant RCTs were searched until December 2014 through MEDLINE (Suppl. Table 1, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)), Cochrane, EMBASE and Google Scholar databases and through [www.tctmd.com](http://www.tctmd.com), [www.clinicaltrials.gov](http://www.clinicaltrials.gov), [www.clinicaltrialresults.org](http://www.clinicaltrialresults.org), and [www.cardiosource.com](http://www.cardiosource.com) websites. Previous meta-analyses and abstracts/presentations from annual meetings of major cardiovascular societies (American Heart Association, American College of Cardiology, Society of Cardiovascular Angiography and Intervention, Transcatheter Cardiovascular Therapeutics, European Society of Cardiology, Euro-PCR, and China Interventional Therapeutics) were also screened. Keywords were: randomised trials, UFH, bivalirudin, LMWHs, fondaparinux, otamixaban, GPI, abciximab, eptifibatide, tirofiban, ACS, ST-segment elevation MI, non ST-segment elevation MI, and unstable angina. MeSH terms are listed in Suppl. Table 2 (available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)). No language, date, or other publication restriction was imposed. The most updated/inclusive data for each study were used for abstraction.

### Selection criteria and quality assessment

To provide the most comprehensive analysis, as formally recommended by the Cochrane Collaboration (13), the efficacy and safety of all parenteral anticoagulants currently approved by the Food and Drug administration (FDA) in ACS were compared - UFH+GPI, UFH±GPI, bivalirudin, LMWHs, fondaparinux - as well as the non-FDA approved otamixaban. Citations were screened at title/abstract level and retrieved as full reports. Inclusion criteria were: 1) human studies; 2) randomised trials and sub-

sequent analyses comparing the above strategies; 3) studies reporting prespecified outcomes of interest; 4) trials conducted in the setting of ACS, and 5) for RCTs conducted in mixed populations (stable coronary artery disease and ACS), availability of ACS data. Exclusion criteria were: 1) non-randomised registries; 2) elective percutaneous coronary intervention (PCI) or mixed population studies without reported outcomes in the ACS subset; 3) upstream administration by study design of another anticoagulant prior to randomisation; 4) fibrinolytic therapy; 5) follow-up not relevant to the meta-analysis. Rivaroxaban and vitamin K antagonists were not included among the investigated treatments because administered orally and not parenterally.

Three authors (EPN, MK, VS) independently assessed the trials' eligibility and risk of bias, and extracted the data. Disagreements were resolved by consensus. Risk of bias was assessed using the components recommended by the Cochrane Collaboration, i.e. random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting and other sources of bias (13). Trials with high or unclear risk for any of the first three components were considered at high risk of bias; otherwise, they were considered at low risk of bias.

### Data extraction and synthesis

Six treatments contributed to the final network: UFH+GPI, UFH±GPI, bivalirudin, LMWHs, otamixaban and fondaparinux. Studies were considered of UFH+GPI if GPI was a routine part of the randomisation protocol. Prespecified outcomes were evaluated up to 30 days after randomisation and included: death, MI, revascularisation, protocol major bleeding (MB), protocol minor bleeding, and definite stent thrombosis (ST). A prespecified analysis of MB according to the Thrombolysis in Myocardial Infarction (TIMI) criteria was also performed. ST was defined by Academic Research Consortium criteria (14). Protocol definitions of MB were largely available across the included trials.

### Statistical analysis

NMA methods on all available networks of treatment comparisons were used to compare different strategies. Outcome analyses were compared by odds ratios (ORs) and 95% credible intervals (CrIs) using a Bayesian hierarchical random-effects model that takes into account multi-arm trials. A random-effects rather than a fixed-effect model was adopted, as this is likely the most appropriate and conservative, accounting for differences among trials. Posterior median rates of efficacy and safety outcomes, with corresponding CrIs, were calculated from the original trials incorporated in the network. Heterogeneity was defined as the variability of results across trials over and above chance, with  $\tau^2 < 0.04$  indicating low and  $\tau^2 > 0.4$  high heterogeneity. Model fit was assessed by comparing the posterior mean of the residual deviance with the number of data points (15, 16). Inconsistency was formally assessed by comparing the results of the direct evidence on a pairwise contrast with the estimates from the indirect evidence incorporated in the NMA using node-split



(17). Analysis was based on noninformative prior distributions for effect sizes (Normal(0,100<sup>2</sup>)) and between-studies standard deviation (Uniform(0,2)), which yield results that are comparable to those obtained from conventional statistical analysis. Convergence was achieved at 20,000 iterations for all outcomes; lack of autocorrelation was checked and confirmed. A further 40,000 iterations were taken on two chains. In the Bayesian framework, the results for which 95% CrI of the OR did not include the unit value were regarded as significant. Treatment hierarchy was assessed by surface under the cumulative ranking (SUCRA) curves, expressed as efficacy or safety percentage of each intervention relative to an imaginary intervention that is always the best without uncertainty; a SUCRA of 90% means that the drug of interest achieves 90% of the effectiveness or safety of this imaginary drug; thus, the larger the SUCRA value, the higher the rank of the treatment, indicating a more effective or safer intervention.

### Additional analyses

To further corroborate the robustness of the data, Bayesian posterior-probability curves were generated for each strategy, with UFH+GPI as reference; these curves provide a ranking of competing anticoagulant strategies with respect to overall safety and efficacy. Additional prespecified sensitivity analyses included computations with the fixed effect method, in STEMI patients only, and after excluding trials with high risk of bias.

## Results

### Study selection and characteristics

The study selection process is shown in Suppl. Figure 1 (available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)). Baseline study characteristics, MB definitions, patient demographics, clinical diagnoses, antiplatelet regimens, concomitant GPI (routine, provisional, bail-out), vascular access, proportion undergoing PCI, and proportion of drug eluting stent placement are listed in Suppl. Tables 3 and 4 (available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)). The risk of bias is shown in Suppl. Table 5 (available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)). Forty two RCTs involving 117,353 patients entered the final analysis. ►Figure 1 illustrates the network geometry.

### Mortality at 30 days

A total of 42 studies (n=117,353) contributed to the analysis of 30-day mortality (►Figure 2A). All studies showed a good fit to the NMA model, with a posterior mean of the residual deviance = 86.5, which is close to the number of data points = 88. There was no evidence of inconsistency (Suppl. Table 6, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)) or of high heterogeneity among trials ( $\tau^2=0.01$ ). None of the strategies, compared to each other, showed significantly improved survival; posterior median 30-day death rates were comparable (►Table 1). The treatment hierarchy for death (highest to lowest SUCRA) was: fondaparinux, followed

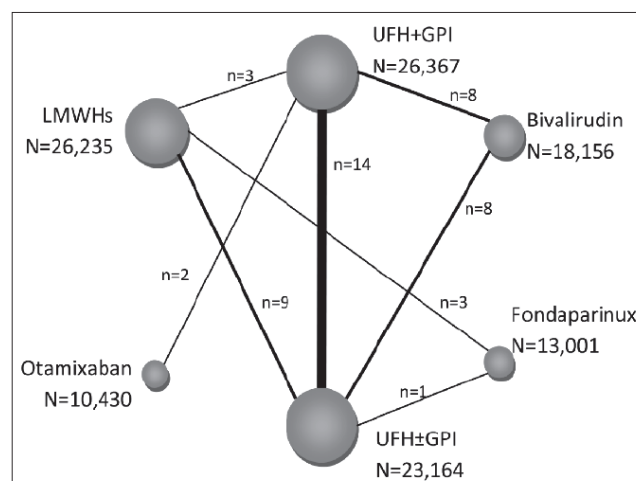


Figure 1: Geometry of the network meta-analysis comparing anticoagulants strategies.

by UFH+GPI, LMWHs, bivalirudin, otamixaban, and UFH±GPI (►Figure 3A).

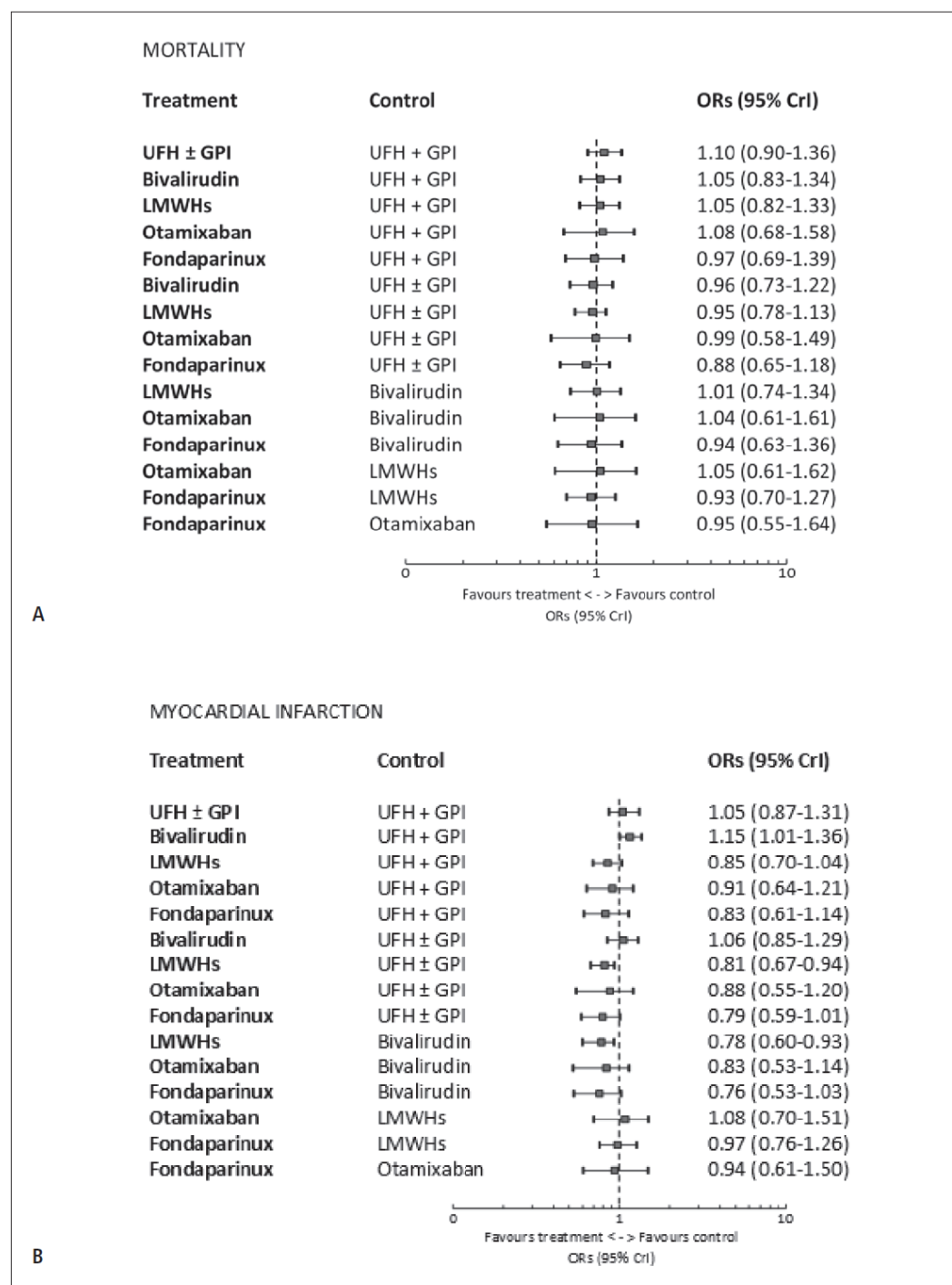
### Myocardial infarction and revascularisation at 30 days

Forty-one studies (n=117,153) contributed to the analysis of MI at 30 days (►Figure 2B). All studies had a good fit to the NMA model (posterior mean of the residual deviance = 94.9, which is close to the number of data points = 86). There was no evidence of inconsistency (Suppl. Table 6, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)) or of high heterogeneity among trials for MI ( $\tau^2=0.01$ ). Compared to UFH+GPI, bivalirudin was associated with a significant 15% increase in the odds of MI. LMWHs yielded significant 22% and 19% reductions in the odds of MI in comparison to bivalirudin and UFH±GPI, respectively (►Figure 2B). Median MI rates are displayed in ►Table 1. Treatment hierarchy for MI (highest to lowest SUCRA) was: fondaparinux, followed by LMWHs, otamixaban, UFH+GPI, UFH±GPI, and bivalirudin (►Figure 3B).

Thirty-three trials including 73,621 patients contributed to the analysis of revascularisation at 30 days. All studies had a good fit to the NMA model (posterior mean of the residual deviance = 76.0, which is close to the number of data points = 68). There was no evidence of high heterogeneity among trials ( $\tau^2=0.06$ ). Consistent with the MI results, LMWHs provided significant 29% and 19% reductions in the odds of revascularisation in comparison to bivalirudin and UFH±GPI, respectively (►Figure 2C). Median revascularisation rates are shown in ►Table 1.

### Major and minor bleeding at 30 days

Forty-one studies (n=116,952) contributed to the analysis of MB (►Figure 2D). All studies had a good fit to the NMA model (posterior mean of the residual deviance = 51.1, which is close to the number of data points = 53). There was no evidence of inconsistency (Suppl. Table 6, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)).



**Figure 2: Pooled odds ratio and 95 % credible intervals for 30 day outcomes. A) mortality; B) myocardial infarction; C) coronary revascularisation; D) major bleeding; E) minor bleeding; F) definite stent thrombosis.**

com) or of high heterogeneity among trials ( $\tau^2=0.11$ ). Bivalirudin provided significant 48% and 39% reductions in the odds of MB compared to UFH+GPI and UFH±GPI, respectively (► Figure 2D). Otamixaban showed the highest posterior median 30-day rate of MB (12.07% [6.64 to 20.31]) and bivalirudin the lowest rate (3.44% [2.46 to 4.61]) (► Table 1). Otamixaban significantly increased the odds of MB vs all other strategies except LMWHs.

Treatment hierarchy for MB (highest to lowest SUCRA) was: bivalirudin, followed by fondaparinux, UFH±GPI, UFH+GPI, LMWHs, otamixaban (► Figure 3C). Results for minor bleeding were consistent with those observed for MB (► Figure 2E and ► Table 1). Fondaparinux, UFH±GPI, and bivalirudin were associated with significant reductions in the odds of minor bleeding compared to UFH+GPI, LMWHs and otamixaban.

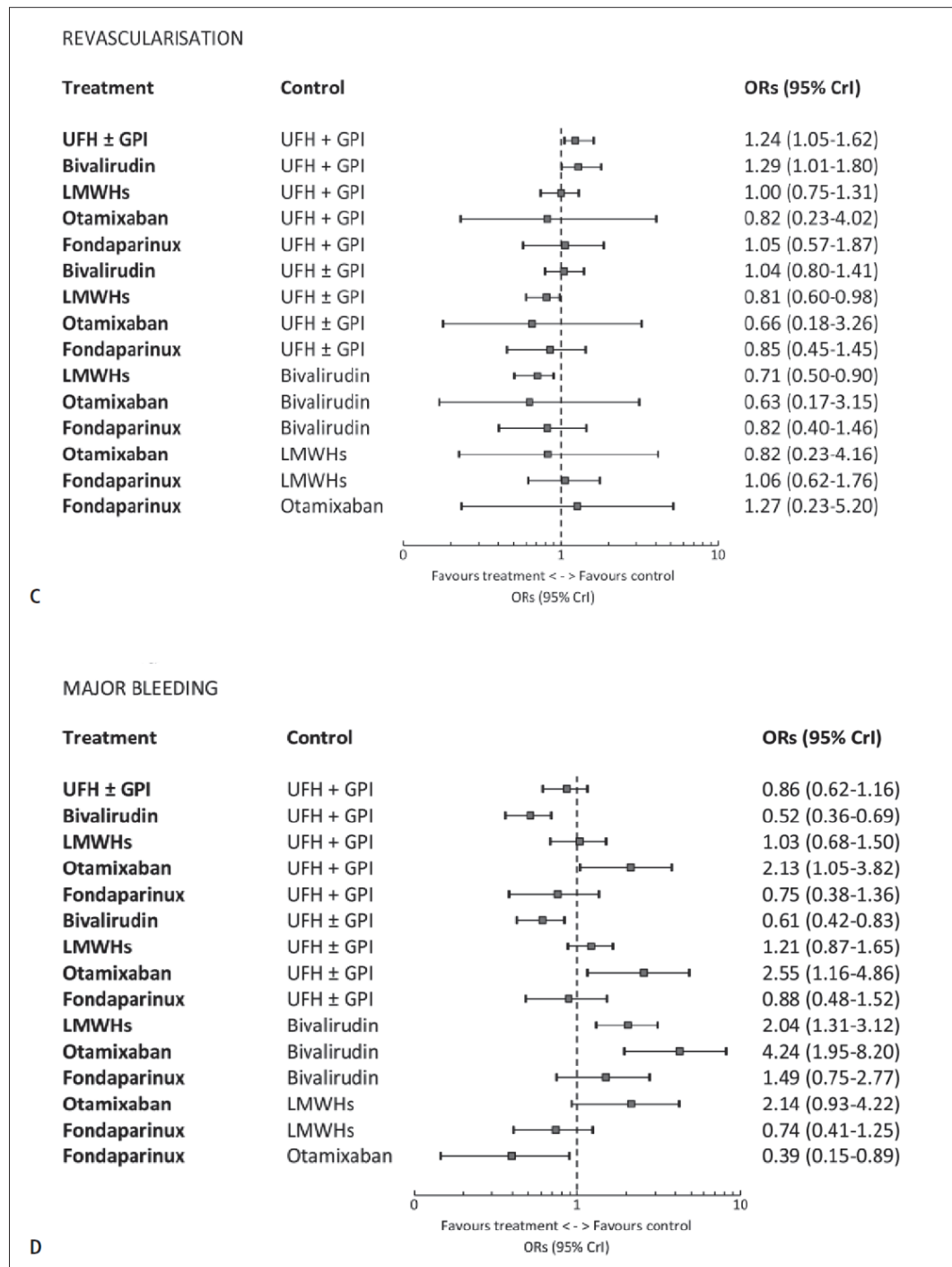


Figure 2: continued

### Stent thrombosis at 30 days

ST results were available in only 12 studies including 39,622 patients (► Figure 2F). ST data were not available for fondaparinux, and only one direct comparison was available for LMWHs. Compared to UFH+GPI and otamixaban, bivalirudin and UFH±GPI

were associated with significant increases in ST rates (► Figure 2F). Median ST rates are displayed in ► Table 1.

### Sensitivity analyses and posterior probability curves

Results for STEMI only were consistent with the overall findings (Suppl. Table 7, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)).

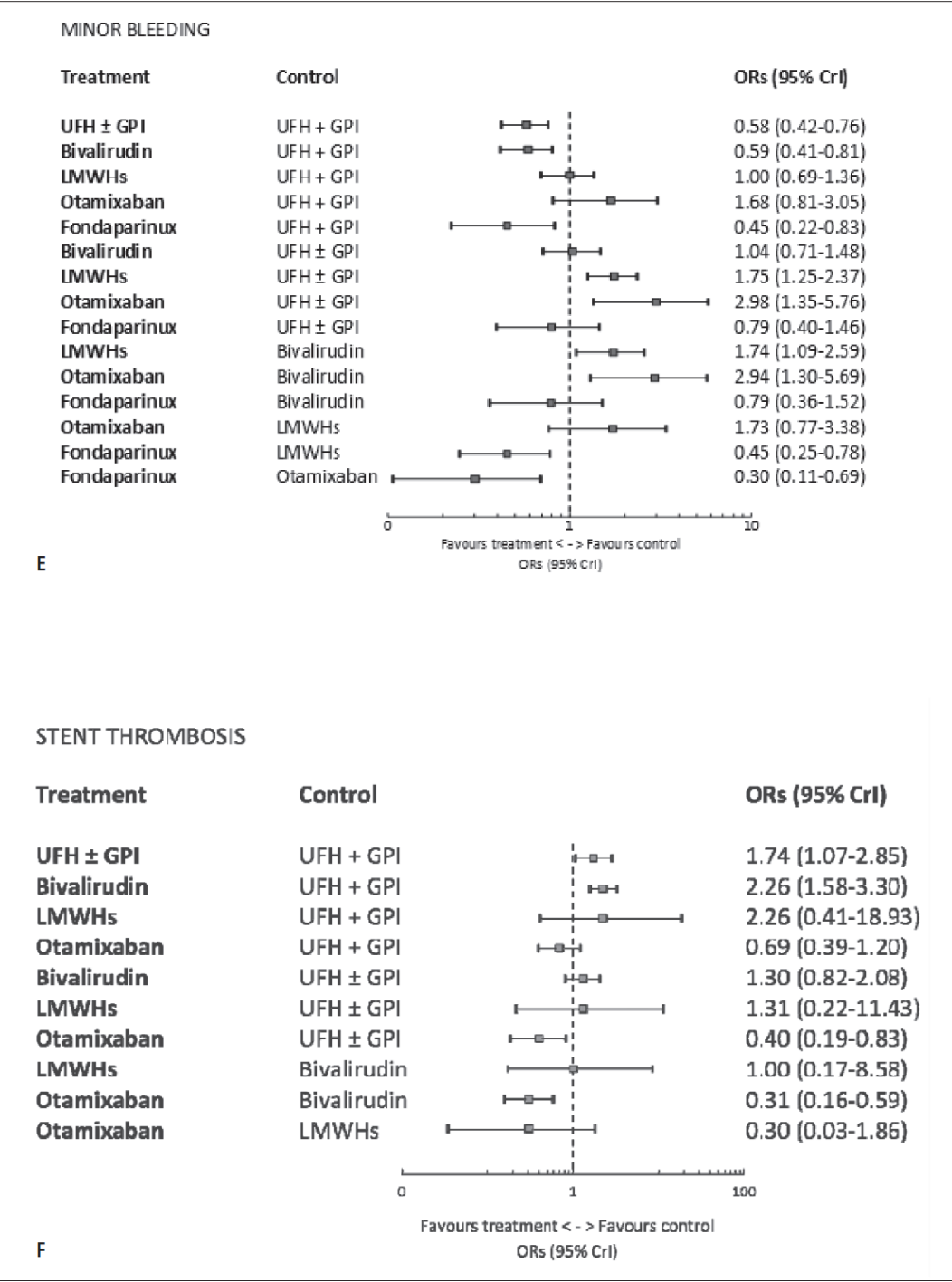


Figure 2: continued

Analyses for TIMI MB (Suppl. Figure 2, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)) showed a significant 42 % reduction in the odds with bivalirudin compared to UFH+GPI but not compared to UFH±GPI. Analyses based on the fixed effect model and exclusion of studies with high risk of bias did not significantly change the results of the NMA (Suppl. Tables 8 and 9, available online at [www.thrombosis-online.com](http://www.thrombosis-online.com)).

The Bayesian posterior-probability curves for the main outcomes (death, MI and MB) provided further confirmation of the findings (► Figure 4A-C). These curves allow probability inferences associated with specific thresholds of risk as compared to the reference treatment (in this case UFH+GPI). Thus, as compared to UFH+GPI, fondaparinux showed a low (12.5 %) probability to reduce by at least 20 % (cut-off point at OR estimate of 0.80) the



**Table 1: Event rates with different anticoagulants.** Numbers are percent (95% credible intervals).

|                       | UFH + GPI              | UFH ± GPI             | Bivalirudin          | LMWHs                  | Otamixaban             | Fondaparinux         |
|-----------------------|------------------------|-----------------------|----------------------|------------------------|------------------------|----------------------|
| Death                 | 1.84 (1.53 to 2.19)    | 2.00 (1.54 to 2.63)   | 1.91 (1.43 to 2.57)  | 1.90 (1.42 to 2.56)    | 1.94 (1.21 to 2.98)    | 1.75 (1.22 to 2.62)  |
| Myocardial infarction | 4.04 (3.58 to 4.54)    | 4.17 (3.38 to 5.36)   | 4.37 (3.59 to 5.55)  | 3.43 (2.74 to 4.32)    | 3.66 (2.55 to 4.93)    | 3.30 (2.44 to 4.65)  |
| Revascularisation     | 2.18 (0.18 to 2.55)    | 2.69 (2.06 to 3.62)   | 2.80 (2.08 to 4.00)  | 2.17 (1.56 to 2.94)    | 1.80 (0.50 to 8.20)    | 2.28 (0.12 to 4.0)   |
| Major bleeding        | 6.32 (5.74 to 6.93)    | 5.18 (3.50 to 7.44)   | 3.44 (2.46 to 4.61)  | 5.76 (3.63 to 8.91)    | 12.07 (6.64 to 20.31)  | 4.25 (2.24 to 7.97)  |
| Minor bleeding        | 16.78 (15.88 to 17.71) | 10.34 (7.74 to 13.42) | 10.50 (7.66 to 14.1) | 16.67 (12.21 to 21.65) | 24.35 (14.07 to 38.16) | 7.93 (4.26 to 14.37) |
| Stent thrombosis      | 1.00 (0.60 to 1.42)    | 1.72 (0.92 to 3.14)   | 2.23 (1.31 to 3.71)  | 2.22 (0.39 to 16.43)   | 0.69 (0.34 to 1.33)    | NA                   |

GPI – glycoprotein IIb/IIIa inhibitor; LMWHs – low-molecular-weight heparins; UFH – unfractionated heparin. NA = not available.

odds of dying within 30 days. Fondaparinux and LMWHs showed probabilities of 47 % and 29 %, respectively, to reduce by at least 20 % the odds of MI as compared to the reference treatment (► Figure 4B). Bivalirudin was associated with a 100 % probability to reduce MB by at least 20 % as compared to UFH+GPI (► Figure 4C). Similar curves for ST were not constructed, given the lack of data for fondaparinux and the limited number of comparisons for LMWHs. Visual inspection of funnel plots did not suggest any small study effects or publication bias.

## Discussion

The present report involving 117,353 patients from 42 randomised controlled trials represents the largest and most comprehensive analysis to date assessing the relative efficacy and safety of contemporary parenteral anticoagulant strategies in the spectrum of ACS. Although previous meta-analyses have compared UFH to LMWHs (18, 19), a rigorous assessment of how newer agents such as fondaparinux, bivalirudin or otamixaban perform in relation to these older agents has not been done.

The main findings of this analytical overview are that: 1) the odds of death at 30-days does not differ significantly among strategies; 2) the odds of MI and revascularisation are reduced by LMWHs, compared to bivalirudin and UFH±GPI, and by UFH+GPI compared to bivalirudin; the latter on the other hand reduces the odds of major bleeding when compared to UFH+GPI, UFH±GPI and LMWHs; 3) UFH+GPI additionally reduces the odds of 30-day definite ST as compared to bivalirudin and UFH±GPI; 4) a reduction in the odds of ST with otamixaban is heavily offset by a marked increase in bleeding outcomes. These results - showing that contemporary anticoagulant strategies have divergent effects on ischaemic and bleeding complications – do not support the paradigm that one drug fits all.

A key finding of the current report is the significantly increased incidence of MI with bivalirudin as compared to UFH+GPI and to LMWHs. The recently published Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI) trial (20), a single-centre study comparing bivalirudin to UFH alone in all-comers with STEMI, reported a numerical increase in major bleeding and a significantly higher rate of major

adverse cardiac events with bivalirudin compared to UFH alone. The excess of major adverse cardiac events was attributed mainly to higher rates of MI in the bivalirudin group. The results on MI in our report are corroborated by the analysis of definite ST: in the setting of ACS, bivalirudin was indeed associated with a significant 126 % increase in the odds of 30-day ST as compared to UFH+GPI.

The finding in the present network meta-analysis of a reduced bleeding risk with bivalirudin at the price of an increased propensity for MI and ST compared to most of the other strategies can be explained in several ways, mainly, the pharmacokinetics of the drug and the protocol of its administration. Bivalirudin is a reversible direct thrombin inhibitor with a half-life of ≈25 minutes – therefore, thrombin activity is restored rapidly when the infusion stops. The increase in stent thrombosis, driven by the increased number of events in the early phase, may reflect a gap in anti-thrombotic protection from the waning anti-thrombin effect of bivalirudin upon early discontinuation after intervention and the delayed onset of platelet inhibition by clopidogrel or the newer P2Y<sub>12</sub> inhibitors.

Another important finding of the present report is the reduced incidence of MI with LMWHs compared to both UFH±GPI and bivalirudin. The Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up (ATOLL) (21) trial compared the efficacy of enoxaparin to that of UFH in STEMI; ATOLL found a significant reduction in the composite endpoint of death, recurrent ACS, or urgent revascularisation with enoxaparin vs. UFH (relative rates: 7 % vs 11 %) but was underpowered for individual outcomes such as MI (relative rates: 4 % vs 6 %). The potential explanation for the benefit observed with LMWHs in ACS patients receiving PCI might be the pharmacokinetic and pharmacodynamic properties of enoxaparin: as compared to UFH, LMWHs have a four-fold greater activity against activated factor X, that is crucial for the production of thrombin, and have a much more predictable anticoagulant effect than UFH as they do not bind to plasma proteins. The ATOLL findings were corroborated by a meta-analysis showing greater efficacy of LMWHs compared to UFH in STEMI patients treated with primary PCI, with a significant relation between patient risk profile and clinical benefits (18).

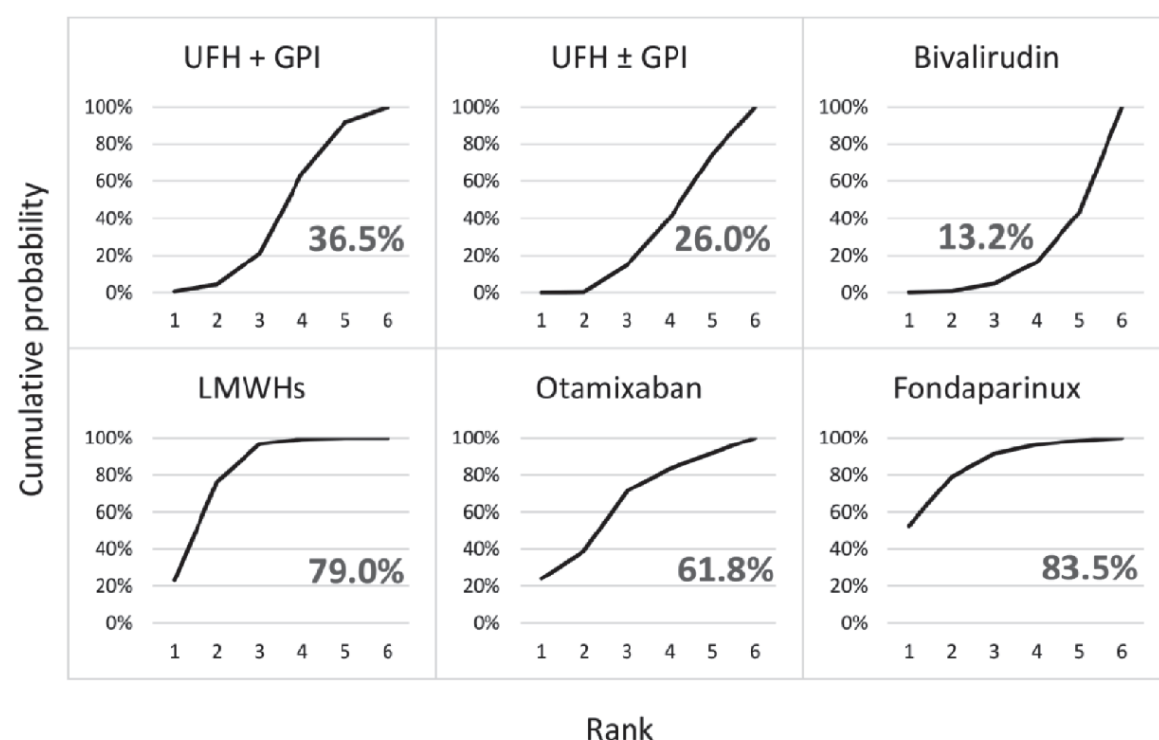
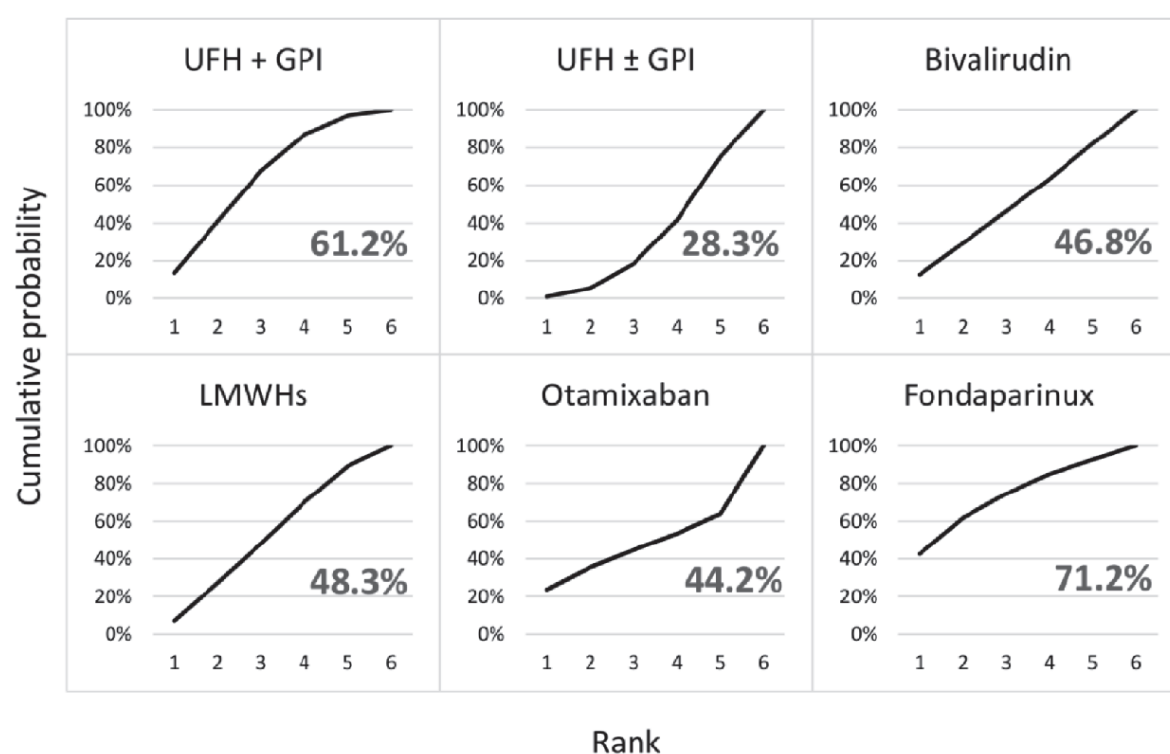


Figure 3: Hierarchy of treatments for 30-day outcomes using surface under cumulative ranking (SUCRA) curves: A) mortality; B) myocardial infarction; C) major bleeding; D) definite stent thrombosis. The higher the SUCRA, the better the treatment rank.

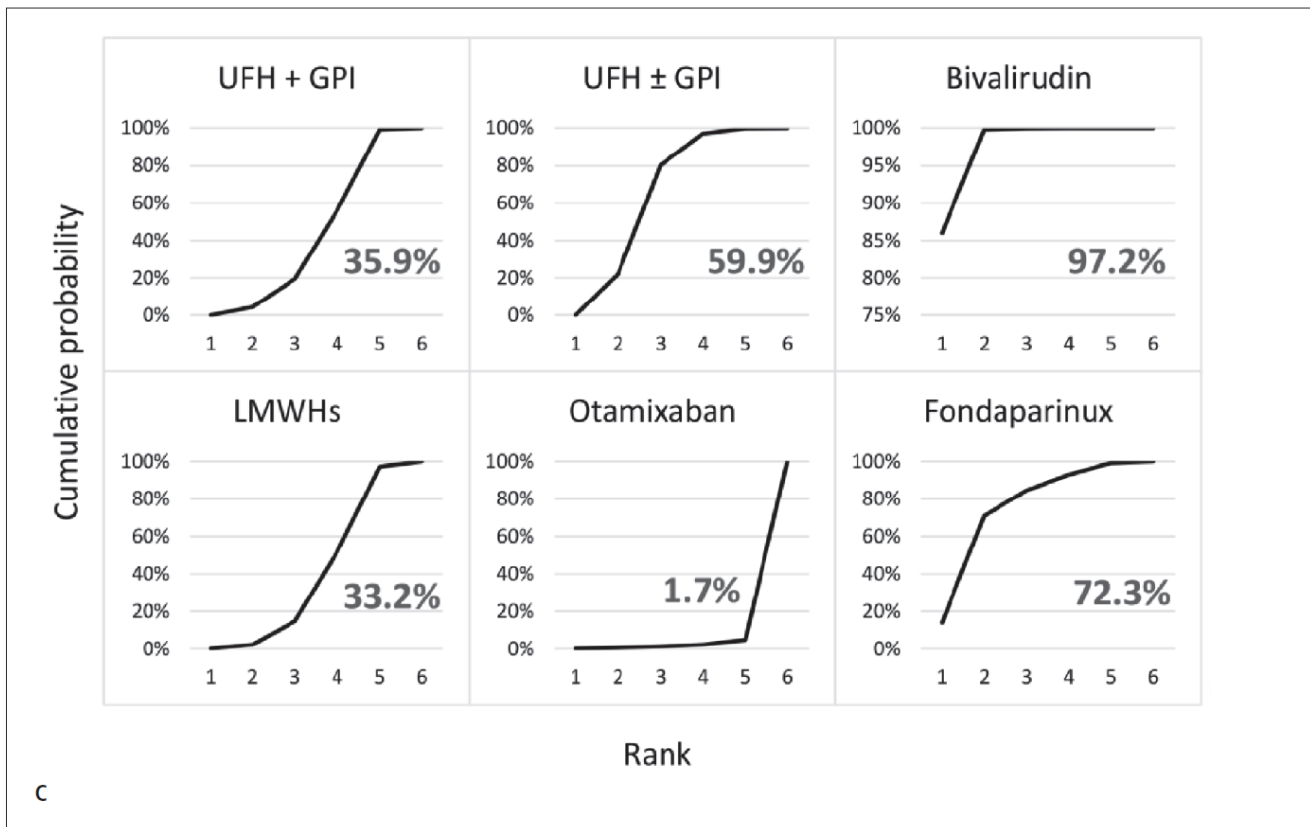


Figure 3: continued

Fondaparinux, another indirect anticoagulant, is a synthetic pentasaccharide and inhibitor of factor Xa with a lower risk of heparin induced thrombocytopenia compared to heparins. In patients with non ST-elevation ACS, fondaparinux has been found to improve survival and reduce major bleeding risk compared to heparins. In the present network meta-analysis, fondaparinux was associated with a numerical but not significant reduction of major bleeding risk and of ischaemic complications compared to heparins. However, data on ST were not available for this agent. The odds of minor bleeds were significantly reduced by fondaparinux (as well as by UFH±GPI and bivalirudin) as compared to UFH+GPI, LMWHs and otamixaban. On treatment hierarchy, fondaparinux had the most balanced profile out of the six strategies, ranking high for both efficacy and safety.

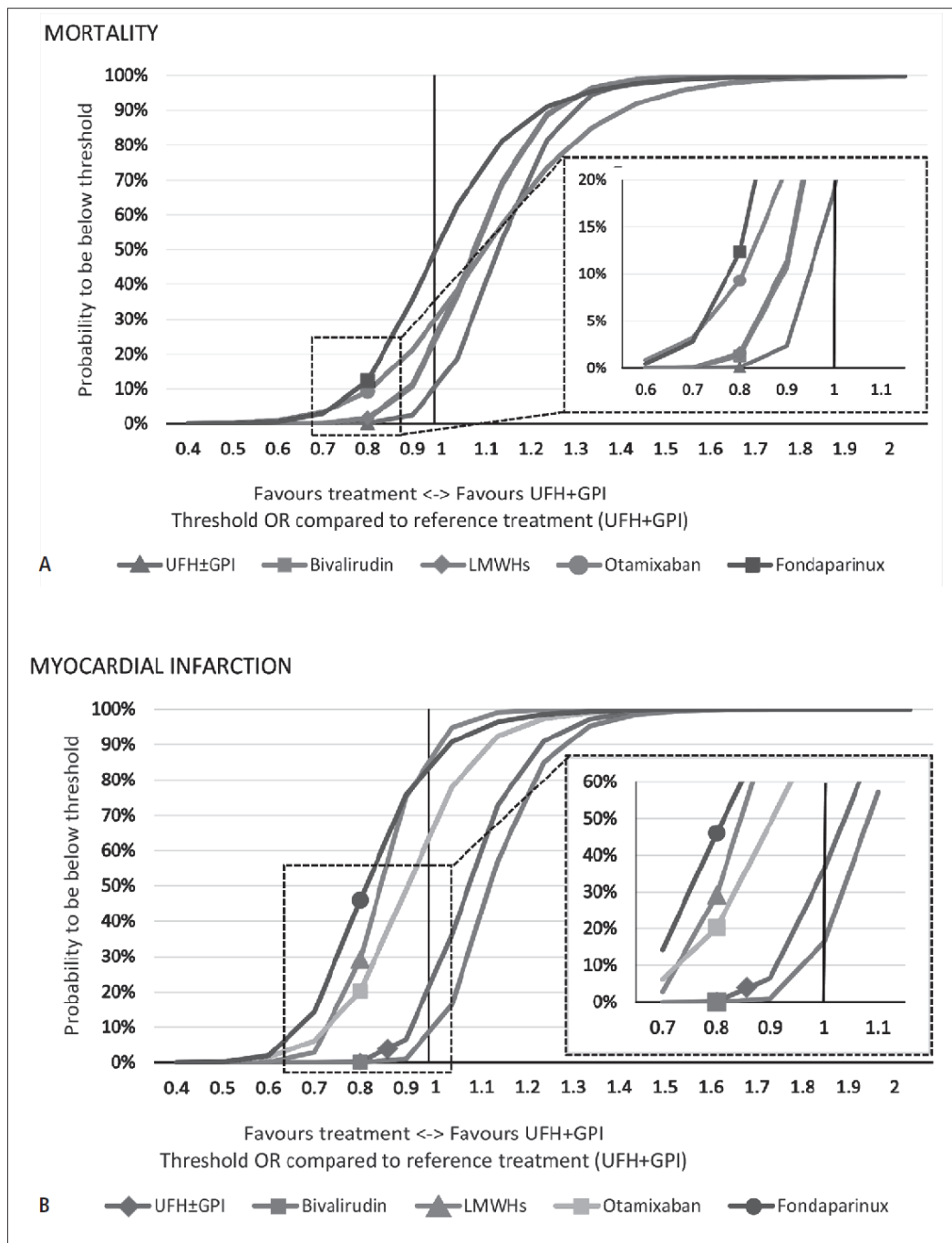
UFH±GPI, at the doses used in the included studies, did not emerge as a highly superior strategy; the odds of 30-day major and minor bleeding were reduced compared to LMWHs and otamixaban, but at the price of an increased risk of MI and revascularisation compared to LMWHs, and of ST compared to UFH+GPI (and otamixaban). Lastly, otamixaban, a direct factor Xa inhibitor, was found to provide the highest reduction of ST risk counterbalanced however by the highest propensity for bleeding compared to other strategies.

This meta-analysis agrees with the findings of two important recent pairwise meta-analyses comparing bivalirudin vs UFH (22,

23); the current meta-analysis, however, substantially differs in design from the latter by incorporating the most recent evidence on all parenteral anticoagulant strategies in ACS, instead of focusing on one comparison alone. Thus, with a total of 117,353 patients, this represents the largest anticoagulant database ever analysed and the first overview of the relative merits and limitations of such strategies in the setting of ACS.

The results of the current analysis support the paradigm that ischaemic and bleeding risks represent the extremes of a continuum in ACS patients. Both early thrombotic and bleeding events have been found to increase mortality. Thrombotic events may increase mortality from PCI by leading to post-procedural (type 4) MI or stroke. The potential link between bleeding complications and adverse outcomes can be explained not only by the blood loss and organ damage due to hypoperfusion but also – and equally importantly – by the direct effect of blood transfusions with stored red cells and by the discontinuation of antithrombotic therapies in patients who bleed (24). The neutral findings on mortality found in our report therefore can be potentially explained by the divergent effect of different anticoagulation strategies on major bleeding and thrombotic complications – less major bleeding counterbalanced by higher thrombotic rates as with bivalirudin; conversely, potentially less thrombotic events counterbalanced by increased bleeding complications as with otamixaban. The current network meta-analysis provides in a comprehensive way a unified hierarchy of





**Figure 4:** Posterior probabilities of developing an adverse outcome (y axis) for each anticoagulant strategy (coloured curves) at specific risk thresholds (odds ratios on x axis) compared to a reference treatment (UFH+GPI, vertical line). The probability of each anticoagulant to reduce the outcome by 20% (OR=0.8) compared to UFH+GPI is marked with a dot. All strategies show similarly low probabilities (0%-12.5%) of reducing the odds of death (A) by at least 20% (OR=0.8) as compared to UFH+GPI. Fondaparinux, LMWHs and otamixaban show probabilities of 47.5%, 29% and 20%, respectively, of reducing by at least 20% the odds of myocardial infarction, whereas bivalirudin and UFH±GPI show 80% and 90% probabilities of increasing these odds by at least 20% (OR=1.2) (B). Improved efficacy and safety profiles, indicated by greatest leftward shift, are displayed by bivalirudin and fondaparinux with regard to major bleeding (C).

evidence-based efficacy and safety profiles of potential anticoagulant therapies used during the early management of patients with ACS. The use of state of the art Bayesian methods account for multi-arm trials and for uncertainties of the estimates through appropriately conservative models. The results of this large-scale network meta-analysis indicate that there is no current specific agent that can provide optimal antiischaemic efficacy with reduced bleeding complication.

### Study limitations

Common to most meta-analyses is the lack of individual patient data which precludes detailed exploration of adjunctive therapies and other covariates which might have had an impact on bleeding and thrombotic outcomes, such as type, dose and duration of P2Y12 inhibitor administration (25), and radial or femoral vascular access site. The probability statements should be interpreted



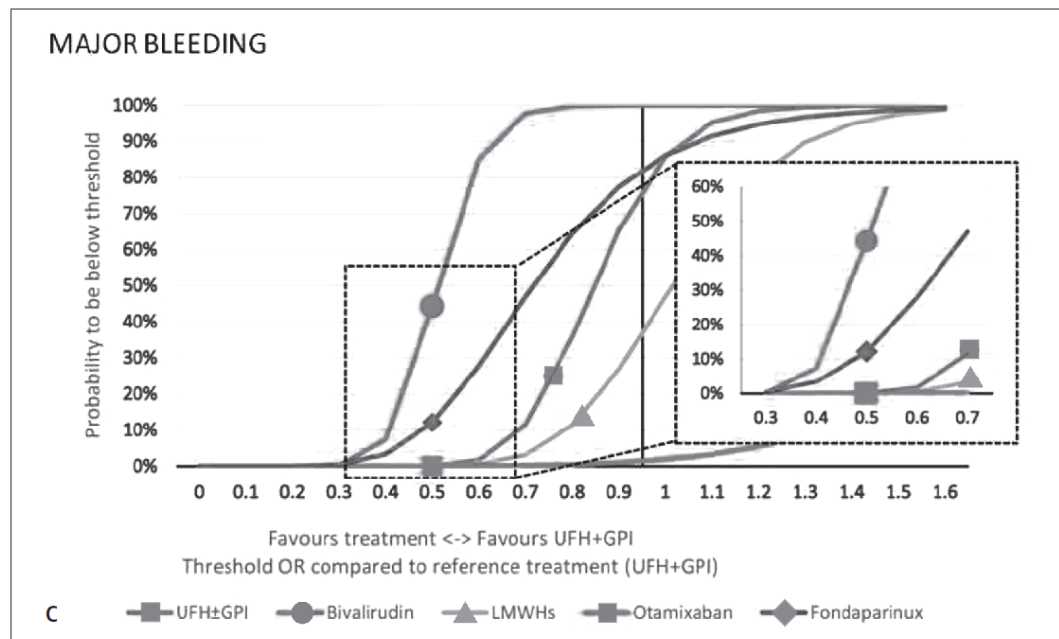


Figure 4:continued

with caution. Data on stent thrombosis were reported in a minority of trials and were not available for fondaparinux, precluding the possibility to perform further consistency analyses. Nonetheless, the results of the sensitivity analyses (direct and indirect estimates, fixed and random effect models) confirmed that the overall effects are robust and justified. Moreover, additional statistical approaches were used, relying on probabilities and event rates, with consistent findings in all the analyses performed.

## Conclusions

Parenteral anticoagulant strategies in ACS demonstrate a range of profiles, with no specific regimen providing optimal protection against ischaemic events along with low bleeding complications. Based on these results, the choice of therapy should be individualised taking into consideration the patient's bleeding and ischaemic risk profile.

## Acronyms and Abbreviations

ACS = acute coronary syndrome; CrI = credible interval; GPI = GPIIb/IIIa inhibitor; LMWHs = low-molecular-weight heparins; MB = major bleeding; MI = myocardial infarction; NMA = network meta-analysis; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; SUCRA = surface under the cumulative ranking; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; UFH = unfractionated heparin.

## Conflicts of interest

FA has received consulting fees and/or honoraria from Amgen, Bayer, Boehringer Ingelheim, BMS-Pfizer, and Daiichi Sankyo-Eli Lilly. GYHL served as Consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo; speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. JE has received Consulting fees and/or honoraria from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis, grants and/or in-kind support from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis. MV has received honoraria for lectures/advisory boards and research grants from Merck, Iroko, Eli Lilly and Medtronic; honoraria for advisory boards and lectures from The Medicines Company, Eli Lilly Co and Daiichi Sankyo.

## References

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 64: e139-e228.
2. American College of Emergency, Physicians Society for Cardiovascular and Angiography Interventions, O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61: e78-140.
3. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes

- (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32: 2999–3054.
4. Task Force on the management of S.T. segment elevation acute myocardial infarction of the European Society of Cardiology, Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
  5. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007; 50: 1742–1751.
  6. Stone G, McLaurin B, Cox D, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355: 2203–2216.
  7. Stone G, Witzensbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; 358: 2218–2230.
  8. Yusuf S, Mehta S, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *J Am Med Assoc* 2006; 295: 1519–1530.
  9. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 1: introduction. *Med Decision Making* 2013; 33: 597–606.
  10. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105–3124.
  11. Navarese EP, Tandjung K, Claessen B, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *Br Med J* 2013; 347: f6530.
  12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W65–94.
  13. Higgins J, Green D. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0. Cochrane Collaboration, 2011. [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
  14. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115: 2344–2351.
  15. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decision Making* 2013; 33: 607–617.
  16. Welton NJ, Sutton AJ, Cooper NJ, et al. *Evidence synthesis for decision making in healthcare* 2012. New York, Wiley.
  17. Dias S, Welton N, Caldwell D, et al. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; 29: 932–944.
  18. Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis. *J Thromb Haemost* 2011; 9: 1902–1915.
  19. Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J* 2007; 28: 2077–2086.
  20. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014; Epub ahead of print.
  21. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 2011; 378: 693–703.
  22. Navarese EP, Schulze V, Andreotti F et al. Comprehensive meta-analysis of safety and efficacy of bivalirudin versus heparin with or without routine glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome. *JACC Cardiovasc Interv* 2015; 8: 201–213.
  23. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. *Lancet* 2014; 384: 599–606.
  24. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011; 32: 1854–1864.
  25. Navarese EP, Andreotti F, Schulze V et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *Br Med J* 2015; Epub ahead of print.

#### **4.2.3 Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis**

**Wolff G**, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP.

Circ Heart Fail. 2017;10(1):e003255

Pubmed PMID: 28087687

DOI: [10.1161/CIRCHEARTFAILURE.116.003255](https://doi.org/10.1161/CIRCHEARTFAILURE.116.003255)

In der Herzinsuffizienz mit eingeschränkter linksventrikulärer Ejektionsfraktion ( $\leq 40\%$ ) aufgrund einer koronaren Herzerkrankung (KHK) war lange unklar, welchen Stellenwert die Revaskularisierungstherapie hat. Insbesondere, ob in diesem Setting eine aortocoronare Bypass-OP (CABG), eine perkutane Koronarintervention (PCI) oder konservative medikamentöse Therapie besser sei, war nicht bekannt.

Wir führten daher ein systematisches Review mit anschließender Meta-Analyse aller vorhandenen randomisierten kontrollierten Studien durch, welche zwei oder alle der drei Optionen in diesem Setting miteinander verglichen hatten: Wir konnten in 21 Studien mit 16.191 Patienten zeigen, dass CABG gegenüber medikamentöser Therapie eine signifikante Reduktion der Mortalität erbrachte (Hazard Ratio (HR) 0,66), ebenso PCI vs. medikamentöse Therapie (HR 0,82). Im direkten Vergleich zeigte CABG Vorteile gegenüber PCI für das Überleben (HR 0,82).

Diese Meta-Analyse zeigte Überlebensvorteile für die Revaskularisierung gegenüber medikamentöser Therapie bei KHK mit Herzinsuffizienz mit eingeschränkter LV-Funktion, mit Vorteilen für CABG gegenüber PCI.

## Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease

### A Meta-Analysis

Georg Wolff, MD; Dimitrios Dimitroulis, MD; Felicita Andreotti, MD, PhD, FESC;  
Michalina Kołodziejczak, MD; Christian Jung, MD, PhD; Pietro Scicchitano, MD;  
Fiorella Devito, MD; Annapaola Zito, MD; Michele Occhipinti, MD;  
Battistina Castiglioni, MD; Giuseppe Calveri, MD; Francesco Maisano, MD;  
Marco M. Ciccone, MD; Stefano De Servi, MD; Eliano P. Navarese, MD, PhD, FESC

**Background**—Heart failure with reduced ejection fraction caused by ischemic heart disease is associated with increased morbidity and mortality. It remains unclear whether revascularization by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) carries benefits or risks in this group of stable patients compared with medical treatment.

**Methods and Results**—We performed a meta-analysis of available studies comparing different methods of revascularization (PCI or CABG) against each other or medical treatment in patients with coronary artery disease and left ventricular ejection fraction  $\leq 40\%$ . The primary outcome was all-cause mortality; myocardial infarction, revascularization, and stroke were also analyzed. Twenty-one studies involving a total of 16 191 patients were included. Compared with medical treatment, there was a significant mortality reduction with CABG (hazard ratio, 0.66; 95% confidence interval, 0.61–0.72;  $P < 0.001$ ) and PCI (hazard ratio, 0.73; 95% confidence interval, 0.62–0.85;  $P < 0.001$ ). When compared with PCI, CABG still showed a survival benefit (hazard ratio, 0.82; 95% confidence interval, 0.75–0.90;  $P < 0.001$ ).

**Conclusions**—The present meta-analysis indicates that revascularization strategies are superior to medical treatment in improving survival in patients with ischemic heart disease and reduced ejection fraction. Between the 2 revascularization strategies, CABG seems more favorable compared with PCI in this particular clinical setting. (*Circ Heart Fail.* 2017;10:e003255. DOI: 10.1161/CIRCHEARTFAILURE.116.003255.)

**Key Words:** coronary artery bypass ■ coronary artery disease ■ heart failure  
■ meta-analysis ■ myocardial infarction

Heart failure (HF) remains a major cause of morbidity and mortality worldwide.<sup>1–4</sup> With an incidence expected to rise steadily in the coming years, it represents an increasing public health issue.

#### See Editorial by DeVore and Velazquez See Clinical Perspective

Systolic HF, also termed HF with reduced ejection fraction (HFrEF), accounts for  $\approx 50\%$  of the overall HF burden.<sup>1,3,5</sup>

HFrEF is commonly defined as a reduction in left ventricular ejection fraction (LVEF) to  $\leq 40\%$ , with coronary artery disease (CAD) causing approximately two thirds of cases.<sup>1,6</sup> Recurrent or prolonged ischemic events lead to maladaptive remodeling of cardiomyocytes and expanding extracellular matrix, culminating in cavity dilation and systolic dysfunction.<sup>7</sup>

Previous studies have reported improved survival by revascularization with coronary artery bypass grafting (CABG)

Received May 2, 2016; accepted December 5, 2016.

From the Systematic Investigation and Research on Interventions and Outcomes (SIRIO) MEDICINE Research Network, Milan, Italy (G.W., D.D., F.A., M.K., C.J., P.S., F.D., A.Z., M.O., M.M.C., S.D.S., E.P.N.); Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Düsseldorf, Germany (G.W., D.D., C.J.); Institute of Cardiology, Catholic University, Rome, Italy (F.A.); Collegium Medicum in Bydgoszcz, University of Nicolaus Copernicus, Toruń, Poland (M.K.); Department of Emergency and Organ Transplantation, Section of Cardiovascular Diseases, School of Medicine, University of Bari, Italy (P.S., F.D., A.Z.); Department of Heart Science, Ospedale di Circolo e Fondazione Macchi, University of Insubria, Varese, Italy (M.O., B.C., G.C.); Department of Cardiosurgery, University of Zurich, Switzerland (F.M.); Department of Emergency and Organ Transplantation, Section of Cardiovascular Diseases, School of Medicine, University of Bari, Italy (M.M.C.); and Department of Cardiology, Multimedica IRCCS, Milan, Italy (S.D.S., E.P.N.).

The Data Supplement is available at <http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.116.003255/-/DC1>.

Correspondence to Eliano P. Navarese, MD, PhD, FESC, Department of Cardiology, Multimedica IRCCS Via Milanese 300, 20099 Milan, Italy. E-mail [elianonavarese@gmail.com](mailto:elianonavarese@gmail.com)

© 2017 American Heart Association, Inc.

*Circ Heart Fail* is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.116.003255



compared with medical treatment (MT)<sup>8–10</sup> for patients with CAD and HFrEF, with CABG becoming the recommended strategy; however, other potential therapeutic options currently include percutaneous coronary interventions (PCIs) and intensified, evidence-based MT; moreover, single studies in the setting of HF have been underpowered to draw definite conclusions, ultimately contributing to the uncertainty of current recommendations on the optimal strategy for patients with CAD and HFrEF.<sup>1,3</sup> We aimed to perform an analysis of the totality of evidence of both randomized and observational studies evaluating the impact on mortality of available treatment options (CABG, PCI, and MT) for patients with HFrEF and CAD.

## Methods

### Data Sources and Search Strategy

The meta-analysis was performed according to the established methods recommended by the Cochrane guidelines<sup>11</sup> and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for conducting systematic reviews and meta-analyses in healthcare interventions.<sup>12</sup>

A systematic literature search of articles until July 5, 2016, was performed, using the medical databases MEDLINE, EMBASE, Google Scholar, Web of Science, and the Cochrane Controlled Trials Register, as well as congress proceedings from major cardiovascular societies (American College of Cardiology [ACC], American Heart Association [AHA] Scientific Sessions, and European Society of Cardiology [ESC] Congress). Search terms according to the medical subjects headings included revascularization, impaired ejection fraction, LVEF, severe left ventricular dysfunction, reduced ejection fraction, heart failure, ischemic cardiomyopathy, percutaneous coronary intervention, coronary artery bypass grafting, and medical therapy. A bibliography search within landmark articles and guidelines of cardiac societies on the subject was additionally performed, and relevant articles were added. Relevant citations were screened at the title/abstract level and retrieved as full-text reports, where possible.

### Study Design, Selection Criteria, and Outcome Measures

We designed the current meta-analysis to compare CABG, PCI, and MT treatment strategies for patients with ejection fraction  $\leq 40\%$ . All randomized or observational trials comparing at least 2 of the 3 treatment modalities against each other with a minimum follow-up of 12 months and reporting all-cause mortality were eligible for inclusion. No language or publication status restriction was imposed. Exclusion criteria were (1)  $<12$  months of follow-up, (2) mortality not reported, and (3) single-arm study.

The primary clinical end point was mortality; secondary end points were myocardial infarction (MI), repeat revascularization (RR), and stroke. RR was considered to be any revascularization, including target vessel revascularization.

### Data Abstraction and Quality Assessment

The most updated or inclusive data for each study were used for abstraction. Two independent investigators (D.D. and G.W.), who were not personally involved in any of the included trials, abstracted data from each report into prespecified forms. Data were abstracted according to the intention-to-treat principle, where possible. Internal validity was independently appraised by 2 investigators (D.D. and G.W.); divergences were resolved by discussion with a third investigator (E.P.N.). Bias assessment was performed based on the Cochrane Handbook recommendations.<sup>11</sup> Additional sensitivity analyses were conducted to account for different types of emerging bias.

## Statistical Analyses

Presented data are time-to-event outcomes. For meta-analyses of these outcomes, the most appropriate statistic to use is the hazard ratio (HR), which takes into account both the number of events and the time to these events. HR and 95% confidence intervals (CIs) were derived from survival parameters in each study and used as summary statistics. Heterogeneity was assessed by the Cochran Q test, and statistical heterogeneity was summarized by the  $I^2$  statistic, which quantifies the percent of variation in study results that is because of heterogeneity rather than to chance.<sup>13</sup>  $I^2$  values  $>50\%$  indicate substantial heterogeneity. Pooled HR for all outcomes were calculated using the more conservative DerSimonian and Laird random-effects model.<sup>11,14</sup>

To validate the overall analyses of the primary mortality outcome, 3 prespecified sensitivity analyses were performed, namely studies with matched patients only (either randomized or propensity score matched), studies comparing CABG against drug-eluting stent (DES)-PCI, and studies published in 2010 or later.

Statistical significance for the summary HRs was assumed at a 2-tailed  $P$  value  $<0.05$ . Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ) was used for statistical analyses.

## Results

### Study Selection and Patient Populations

Article screening and selection is described in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (Figure 1). Of 1108 articles retrieved from the primary searches using prespecified keywords, 879 were excluded for unmet inclusion criteria.

Twenty-one studies published between 1983 and July 2016 were finally included in the meta-analysis (Table 1), of which 16 available as full-text reports.<sup>10,15,16,18–24,26,29–35</sup> For the remaining 5 articles, data were abstracted from the study summaries.<sup>8,17,25,27,28</sup> Patient baseline characteristics are shown in Table 2. Of a total of 16 191 patients (mean age 64 years, 79% male), 7335 underwent CABG, 4439 underwent PCI, and 4417 received MT. Three trials involving 1779 patients had a randomized design, and 6 observational studies involving 2611 patients used propensity score or case-control matching, contributing to a total of 4410 patients in randomized or matched groups. For articles reporting both crude and propensity score-matched populations (Yang et al<sup>35</sup> and Velazquez et al<sup>34</sup>), these groups were included separately in the overall and sensitivity analyses. Median follow-up was 36 months. Only a minority of studies performed viability testing in over 50% of patients.

The risks of bias of the included randomized and observational studies are shown in Tables I and II in the [Data Supplement](#), respectively. Overall, bias was low across randomized controlled trials and moderate in observational studies.

### Mortality With CABG, PCI, or MT

Eight studies, of which 2 had a randomized design,<sup>21,31</sup> involved 6896 patients and reported mortality with CABG compared with contemporary MT (Figure 2A). A statistically significant reduction in mortality was observed with the use of CABG, 31.91% (791 of 2479 patients), compared with MT, 38.31% (1692 of 4417 patients; HR, 0.66; 95% CI, 0.61–0.72;  $P<0.001$ ; heterogeneity  $P<0.001$ ;  $I^2=77\%$ ).

Two studies involved 931 patients and compared PCI versus MT (Figure 2B). A statistically significant mortality reduction was observed with PCI 34.70% (178 of 513 patients)

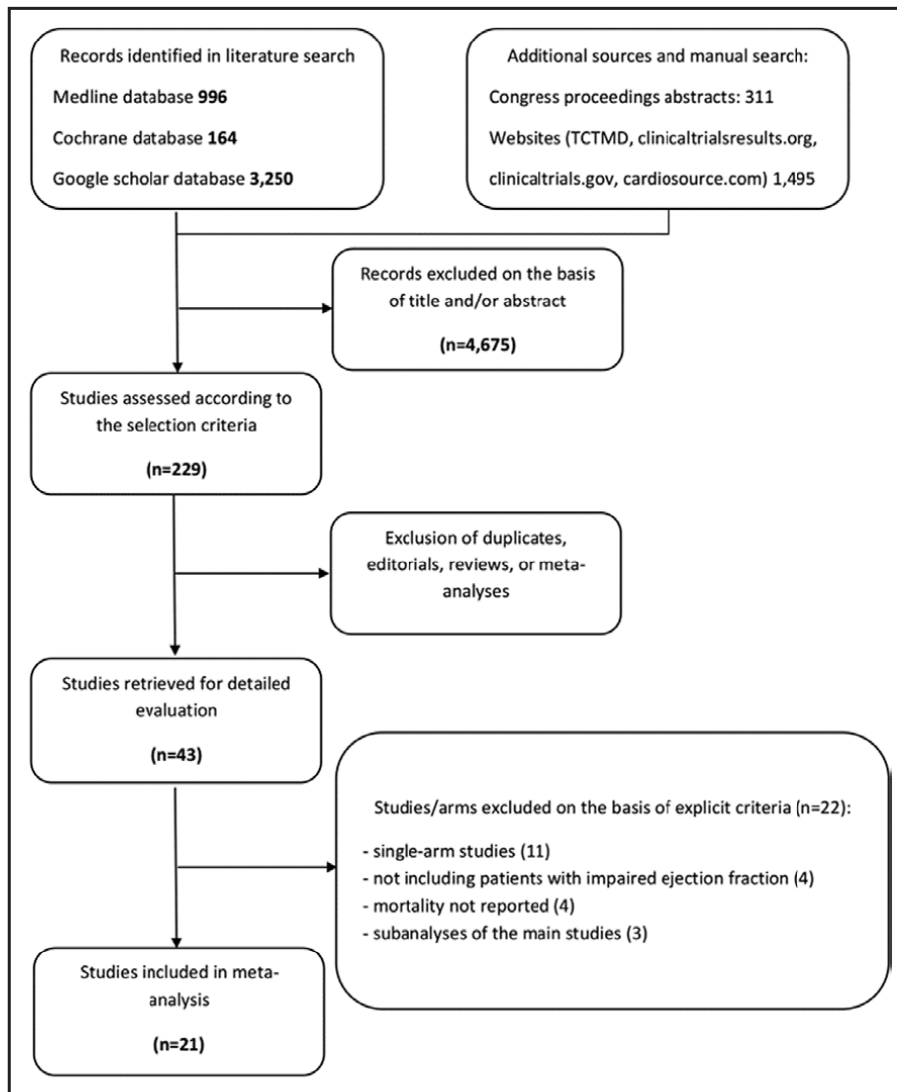


Figure 1. Flow diagram of meta-analysis.

compared with MT 46.41% (194 of 418 patients; HR, 0.73; 95% CI, 0.62–0.85;  $P<0.001$ ; heterogeneity  $P=0.96$ ;  $I^2=0\%$ ).

Sixteen studies involving 8782 patients and including 2 randomized controlled trials compared CABG versus PCI (Figure 2C). There was a statistically significant reduction in mortality with CABG compared with PCI; the respective mortality rates were 18.95% (920 of 4856 patients) and 24.45% (960 of 3926 patients; HR, 0.82; 95% CI, 0.75–0.90;  $P<0.001$ ; heterogeneity  $P=0.01$ ;  $I^2=47\%$ ).

A sensitivity analysis limited to the randomized or matched cohorts was performed (Figure I in the [Data Supplement](#)). The results of CABG versus MT were confirmed by 3 studies<sup>21,31,34</sup> involving 1779 patients (HR, 0.75; 95% CI, 0.60–0.93;  $P=0.01$ ; Figure IA in the [Data Supplement](#)). Seven studies<sup>18,20,21,28–30,35</sup> involving 2656 patients confirmed the results on CABG versus PCI (HR, 0.86; 95% CI, 0.77–0.96;  $P=0.009$ ; Figure IB in the [Data Supplement](#)). Only 1 small randomized trial was available for the PCI versus MT comparison (Figure IC in the [Data Supplement](#)).

To account for the procedural and pharmacological progress made over the last years, a sensitivity analysis including only studies published since 2010 was performed (Figure II in the [Data Supplement](#)). The survival benefit seen in the

overall analysis for CABG versus MT was confirmed by 5 studies<sup>21,26,27,31,34</sup> involving 3366 patients (HR, 0.67; 95% CI, 0.51–0.86;  $P=0.002$ ; Figure IIA in the [Data Supplement](#)) and for CABG versus PCI by 10 studies<sup>17,20–22,25,27–29,35</sup> involving 5279 patients (HR, 0.79; 95% CI, 0.71–0.88;  $P<0.001$ ; Figure IIB in the [Data Supplement](#)).

## Secondary End Points With CABG Versus PCI

### Myocardial Infarction

Eight studies with a total of 5122 patients reported data on first or recurrent MI (Figure 3A). Treatment with CABG resulted in a statistically significant reduction in MI compared with PCI; rates were 2.11% (62 of 2938) and 4.26% (93 of 2184), respectively (HR, 0.50; 95% CI, 0.36–0.68;  $P<0.001$ ; heterogeneity  $P=0.51$ ;  $I^2=0\%$ ).

### Repeat Revascularization

Seven studies, involving 3886 patients, provided data on RR (Figure 3B).<sup>20,22,23,25,28,30,33,35</sup> There was a statistically significant reduction in RR with CABG compared with PCI treatment; the respective rates were 5.82% (116 of 1991 patients) and 20.74% (371 of 1788 patients; HR, 0.34; 95% CI, 0.24–0.47;  $P<0.001$ ; heterogeneity  $P=0.03$ ;  $I^2=57\%$ ).

**Table 1. Characteristics of Included Studies**

| Study                          | Year      | Type               | Patients, Total | Comparison        | FU, mo | Reported Outcomes                                                              |
|--------------------------------|-----------|--------------------|-----------------|-------------------|--------|--------------------------------------------------------------------------------|
| Ahn et al <sup>15</sup>        | 2011      | Registry           | 327             | CABG vs PCI       | 36     | Mortality, major adverse cardiac or cerebrovascular events                     |
| Appoo et al <sup>16</sup>      | 2004      | Registry           | 2169            | CABG vs MT        | 12     | Mortality                                                                      |
| ASAN-MAIN <sup>17</sup>        | 2015      | Registry           | 213             | CABG vs PCI       | 24     | Mortality                                                                      |
| AWESOME <sup>18,19</sup>       | 2004      | RCT/Registry       | 386             | CABG vs PCI       | 36     | Mortality, survival free of angina, RR                                         |
| Bangalore et al <sup>20</sup>  | 2015      | Registry           | 396             | CABG vs PCI       | 35     | Mortality, MI, stroke, RR                                                      |
| Bounous et al <sup>8</sup>     | 1988      | Registry           | 710             | CABG vs MT        | 36     | Mortality                                                                      |
| CASS <sup>10</sup>             | 1983      | Registry           | 651             | CABG vs MT        | 36     | Mortality, functional limitation                                               |
| Cleland et al <sup>21</sup>    | 2011      | RCT                | 109             | CABG vs PCI vs MT | 59     | Mortality                                                                      |
| CREDO-Kyoto <sup>22</sup>      | 2014      | Registry           | 293             | CABG vs PCI       | 60     | Mortality, cardiac mortality, sudden death, readmission for HF, stroke, MI, RR |
| Gioia et al <sup>23</sup>      | 2007      | Registry           | 220             | CABG vs PCI       | 15     | Mortality, cardiac mortality, MI, TVR, NYHA                                    |
| Hannan et al <sup>24</sup>     | 2008      | Registry           | 2673            | CABG vs PCI       | 18     | Mortality, MI                                                                  |
| IRIS-MAIN <sup>25</sup>        | 2015      | Registry           | 364             | CABG vs PCI       | 12     | Mortality, cardiac mortality, MI, RR, TVR, stroke                              |
| Kwon et al <sup>26</sup>       | 2012      | Registry           | 450             | CABG vs MT        | 70     | Mortality                                                                      |
| LaBarbera et al <sup>27</sup>  | 2012      | Registry           | 1345            | CABG vs PCI vs MT | 60     | Mortality                                                                      |
| Nagendran et al <sup>28</sup>  | 2013      | Registry           | 1436            | CABG vs PCI       | 180    | Mortality, RR                                                                  |
| REAL <sup>29</sup>             | 2013      | Registry           | 296             | CABG vs PCI       | 60     | Mortality                                                                      |
| REHEAT <sup>30</sup>           | 2007      | Case-control study | 107             | CABG vs PCI       | 12     | Mortality, MI, arrhythmia, angina, RR, stroke                                  |
| STICH/STICHES <sup>31,32</sup> | 2011/2016 | RCT                | 1212            | CABG vs MT        | 118    | Mortality, cardiovascular mortality                                            |
| Toda et al <sup>33</sup>       | 2002      | Registry           | 117             | CABG vs PCI       | 36     | Mortality, MI, TVR, HF                                                         |
| Velazquez et al <sup>34</sup>  | 2012      | Registry           | 763             | CABG vs MT        | 120    | Mortality                                                                      |
| Yang et al <sup>35</sup>       | 2013      | Registry           | 953             | CABG vs PCI       | 28     | Mortality, MI, stroke, RR, TVR                                                 |

Characteristics of included studies. ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CABG, coronary artery bypass graft; CASS, Coronary Artery Surgery Study; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; FU, follow-up; HF, heart failure; IRIS-MAIN, Observational Study for Left Main Disease Treatment; MI, myocardial infarction; MT, medical therapy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; RR, repeat revascularization; STICH/STICHES, Surgical Treatment for Ischemic Heart Failure; and TVR, target vessel revascularization.

### Stroke

Four studies, comprising 2113 patients, were included in the analysis of stroke (Figure 3C). The rates did not differ significantly between the 2 groups: 5.21% (58 of 1112 patients) who underwent CABG and 4.13% (37 of 894 patients) who underwent PCI (HR, 0.79; 95% CI, 0.52–1.18;  $P=0.24$ ; heterogeneity  $P=0.76$ ;  $I^2=0\%$ ).

### CABG Versus PCI in Patients Stratified by Disease or Treatment Characteristics

We investigated whether CABG or PCI favored special patient populations or patients preferably treated with DESs in the PCI group.

Four studies, with a total of 987 patients, reported a prevalence of left main/proximal left anterior descending disease >50% in both groups (Figure 4A). Mortality was still significantly reduced with CABG versus PCI, with respective rates of 17.08% (103 of 603 patients) and 25.0% (96 of 384 patients; HR, 0.76; 95% CI, 0.59–0.98;  $P=0.03$ ; heterogeneity  $P=0.96$ ;  $I^2=0\%$ ).

Seven studies involving 2695 patients reported a prevalence of 3-vessel disease >50% in both groups (Figure 4B).<sup>18,21–23,28,33</sup> The overall incidence of all-cause mortality did not differ significantly between the 2 revascularization strategies: 27.85% (379 of 1361) among patients undergoing CABG and 30.51% (407 of 1334) among patients



**Table 2. Baseline Patient Characteristics**

| Study                          | Age, y | Male (%) | HTN (%) | DM (%) | HLP (%) | CKD (%) | Previous CABG (%) | Previous PCI (%) | Previous MI (%) | DES Use >50% | Left Main/Proximal LAD >50% | 3-Vessel Disease >50% | Viability Test >50% |
|--------------------------------|--------|----------|---------|--------|---------|---------|-------------------|------------------|-----------------|--------------|-----------------------------|-----------------------|---------------------|
| Ahn et al <sup>15</sup>        | ...    | ...      | ...     | ...    | ...     | ...     | ...               | ...              | ...             | yes          | no                          | yes                   | no                  |
| Appoo et al <sup>16</sup>      | 64     | 85       | 50      | 26     | 39      | 4       | 12                | 8                | 61              | no           | no                          | no                    | no                  |
| ASAN-MAIN <sup>17</sup>        | ...    | ...      | ...     | ...    | ...     | ...     | ...               | ...              | ...             | no           | yes                         | no                    | no                  |
| AWESOME <sup>18,19</sup>       | 65     | ...      | 66      | 33     | ...     | ...     | 29                | 23               | ...             | no           | no                          | yes                   | no                  |
| Bangalore et al <sup>20</sup>  | 65     | 72       | ...     | 40     | ...     | 5       | 0                 | ...              | 41              | yes          | no                          | no                    | no                  |
| Bounous et al <sup>8</sup>     | ...    | ...      | ...     | ...    | ...     | ...     | ...               | ...              | ...             | no           | no                          | no                    | no                  |
| CASS <sup>10</sup>             | 55     | 89       | ...     | ...    | ...     | ...     | ...               | ...              | ...             | no           | no                          | yes                   | no                  |
| Cleland et al <sup>21</sup>    | 67     | 93       | 50      | 36     | 59      | ...     | 8                 | 8                | 73              | no           | no                          | yes                   | yes                 |
| CREDO-Kyoto <sup>22</sup>      | 69     | 77       | 87      | 57     | ...     | 11      | ...               | ...              | 44              | yes          | yes                         | yes                   | no                  |
| Gioia et al <sup>23</sup>      | 68     | 81       | 69      | 43     | 68      | ...     | 17                | 20               | 56              | yes          | no                          | yes                   | no                  |
| Hannan et al <sup>24</sup>     | 66     | 70       | ...     | ...    | 36      | 4       | ...               | ...              | 42              | yes          | no                          | no                    | no                  |
| IRIS-MAIN <sup>25</sup>        | 66     | 79       | ...     | ...    | ...     | ...     | ...               | ...              | ...             | no           | yes                         | no                    | no                  |
| Kwon et al <sup>26</sup>       | 63     | 74       | 51      | 37     | 49      | ...     | 20                | ...              | ...             | no           | no                          | no                    | yes                 |
| LaBarbera et al <sup>27</sup>  | ...    | ...      | ...     | ...    | ...     | ...     | ...               | ...              | ...             | no           | no                          | no                    | no                  |
| Nagendran et al <sup>28</sup>  | 65     | 81       | 63      | 34     | 62      | 5       | 6                 | 8                | 66              | no           | no                          | yes                   | no                  |
| REAL <sup>29</sup>             | ...    | 78       | 78      | 26     | ...     | 5       | ...               | ...              | 29              | no           | no                          | no                    | no                  |
| REHEAT <sup>30</sup>           | 61     | 77       | 62      | 25     | 66      | ...     | ...               | ...              | 62              | no           | no                          | no                    | yes                 |
| STICH/STICHES <sup>31,32</sup> | 60     | 88       | 60      | 40     | 60      | 8       | 3                 | ...              | 77              | no           | yes                         | yes                   | no                  |
| Toda et al <sup>33</sup>       | 64     | 74       | ...     | 42     | ...     | 3       | 20                | 26               | 23              | no           | yes                         | yes                   | no                  |
| Velazquez et al <sup>34</sup>  | 64     | 75       | ...     | 34     | ...     | 4       | 30                | 21               | 39              | no           | no                          | no                    | no                  |
| Yang et al <sup>35</sup>       | 66     | 76       | 60      | 50     | 27      | 13      | 5                 | 25               | 29              | yes          | no                          | no                    | no                  |

ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CABG, coronary artery bypass graft; CASS, Coronary Artery Surgery Study; CKD, chronic kidney disease; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; DES, drug-eluting stent; DM, diabetes mellitus; HLP, hyperlipoproteinemia; HTN, hypertension; IRIS-MAIN, Observational Study for Left Main Disease Treatment; LAD, left anterior descending; MI, myocardial infarction; PCI, percutaneous coronary intervention; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; and STICH/STICHES, Surgical Treatment for Ischemic Heart Failure.

who underwent PCI (HR, 0.92; 95% CI, 0.82–1.03;  $P=0.16$ ; heterogeneity  $P=0.66$ ;  $I^2=0\%$ ).

Six studies comprising 4827 patients used only DES in the PCI group, allowing a comparison of CABG against contemporary PCI (Figure 4C). Revascularization by CABG still resulted in a statistically significant reduction of all-cause mortality compared with revascularization by PCI, with respective rates of 13.73% (380 of 2767) and 16.70% (344 of 2060; HR, 0.82; 95% CI, 0.69–0.96;  $P=0.01$ ; heterogeneity  $P=0.79$ ;  $I^2=0\%$ ).

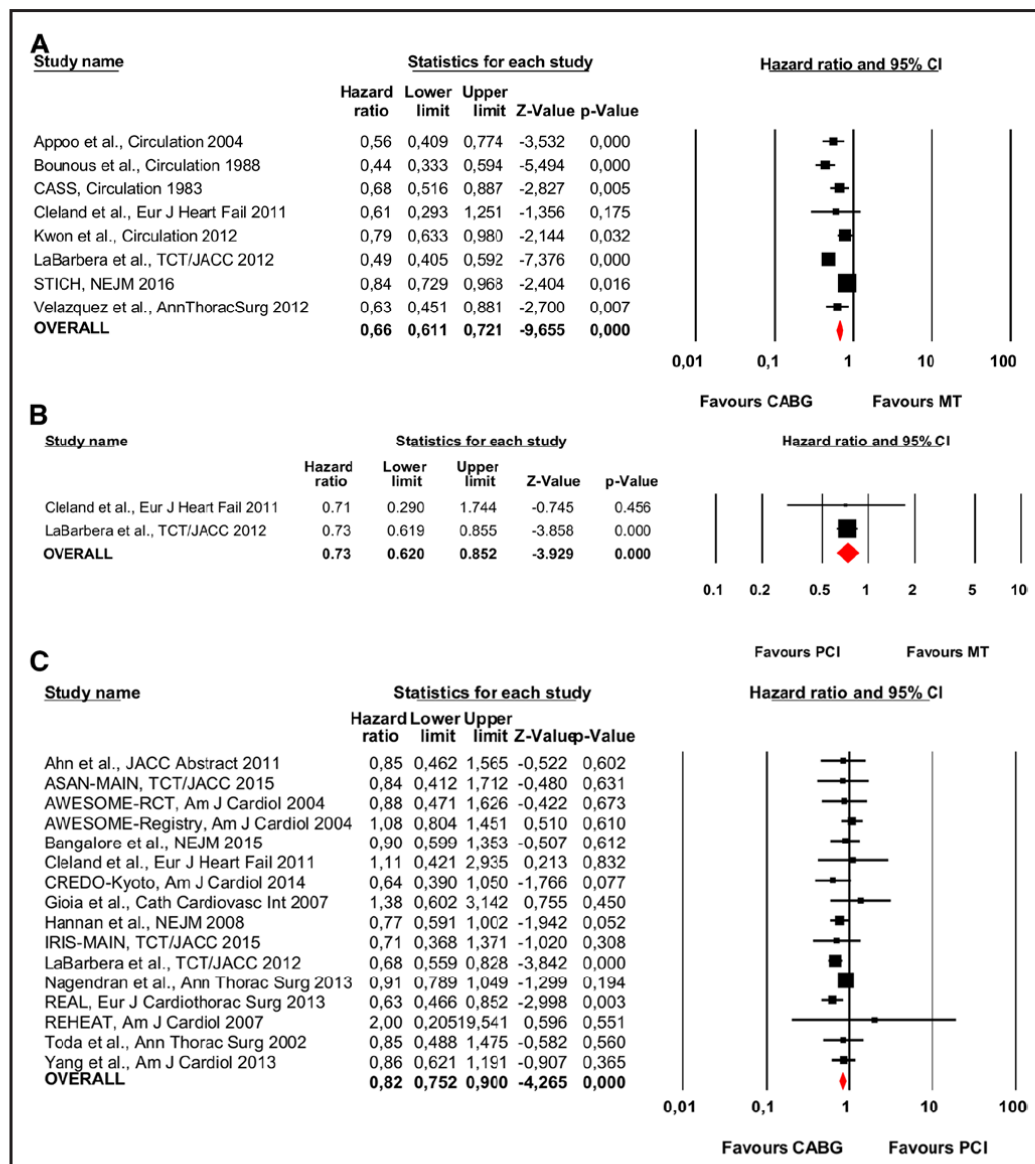
## Discussion

The present article, to the best of our knowledge, represents the largest evidence base comparing mortality outcome after surgical, percutaneous, or conservative treatment of HFrEF and CAD. The main findings of this analysis are that (1) revascularization with either CABG or PCI carried a significant improvement in long-term survival over MT, (2) CABG showed a significantly improved survival compared with PCI, that persisted among patients with left main/proximal left anterior descending disease and in studies conducted after the advent of DES, and (3) CABG compared with PCI was

associated with a significant reduction in the risk of MI or need for RR, albeit with a numerically higher rate of stroke.

There are potential anatomic and functional reasons for the described different mortality rates among the investigated patients' cohorts. (1) A complete revascularization can be more frequently reached with CABG than with PCI<sup>36</sup>; completeness of revascularization by removing the ischemic burden might be a pivotal driver of improved prognosis, in particular in high-risk patients with HF caused by ischemic CAD. Although in the last years advances have been made in MT, the results on clinical outcomes offered by a complete revascularization could not be equalized by the sole MT in the high-risk subset with HFrEF. (2) In HF patients, CAD tends to be more complex and diffuse, leading to higher need for RRs and MI rates after coronary stenting than with CABG.<sup>37,38</sup> (3) CABG revascularization of prolonged epicardial segments versus PCI performed only on specific stenotic lesion can yield a better vessel patency due to often extensively diseased arteries in ischemic HF. (4) In HF patients with low cardiac reserve, it is conceivable that in-stent restenosis would be more negatively impacting in this group than in others without severe dysfunction. (5) Improved survival after CABG could





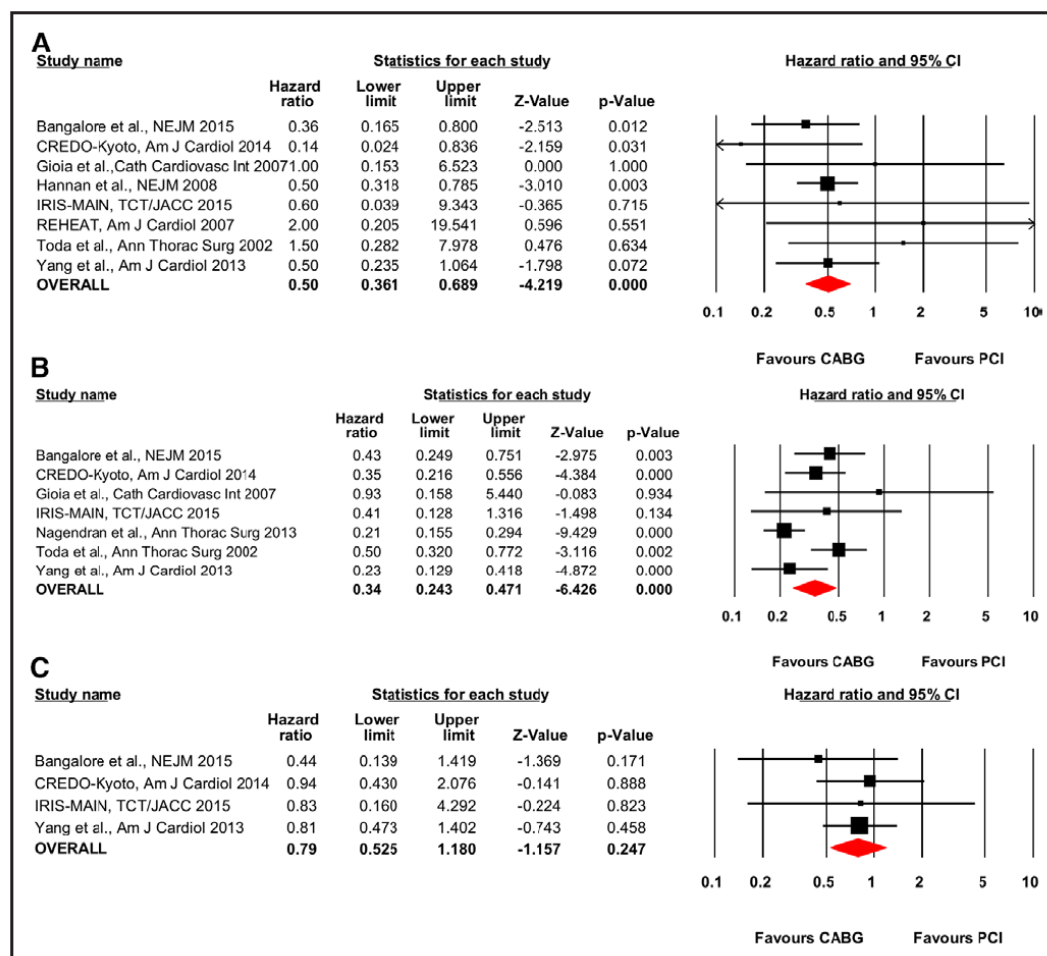
**Figure 2.** Individual and summary hazard ratios for mortality of studies stratified by treatment comparison: **(A)** coronary artery bypass grafting (CABG) vs medical treatment (MT)<sup>8,10,16,21,26,27,31,32,34</sup>; **(B)** percutaneous coronary intervention (PCI) vs MT<sup>21,27</sup>; and **(C)** CABG vs PCI.<sup>15,17–25,27–30,33,35</sup> ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CASS, Coronary Artery Surgery Study; CI, confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; IRIS-MAIN, Observational Study for Left Main Disease Treatment; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; and STICH, Surgical Treatment for Ischemic Heart Failure.

be related to fewer lethal ventricular arrhythmias or to reverse remodeling. The risk of contrast-induced acute nephropathy after PCI is also increased in more complex patients with HFrEF, potentially contributing to higher mortality rates when compared with CABG.<sup>39</sup>

Findings from early randomized trials comparing medical therapy to CABG for the treatment of stable angina cannot be automatically extrapolated to the care of CAD patients with HF because this is a specific population that was largely excluded from the early stable angina trials.<sup>31</sup> The only randomized trial specifically addressing HF patients is STICH (Surgical Treatment for Ischemic Heart Failure), with its recently published 10-year extended follow-up (STICHES).<sup>32</sup> For similar reasons, the randomized trials comparing PCI to CABG in CAD patients have failed to provide definite answers on patients with comorbid HF. Indeed, only ≈2% of patients

enrolled in the SYNTAX trial (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) had LVEF <30%.<sup>40</sup> More recently, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) reported similar outcomes with PCI using DESs and CABG in patients with LVEF <40%, but only 32 patients (2.5%) were in this prespecified subgroup.<sup>41</sup> Thus, the available randomized data comparing PCI and CABG in patients with severe left ventricular dysfunction are insufficient.

Current guidelines from the American and European cardiac societies are not uniform with respect to the class and level of treatment recommendations for CAD patients with HFrEF. The ESC guidelines recommend CABG over PCI for patients with HFrEF and significant CAD in the



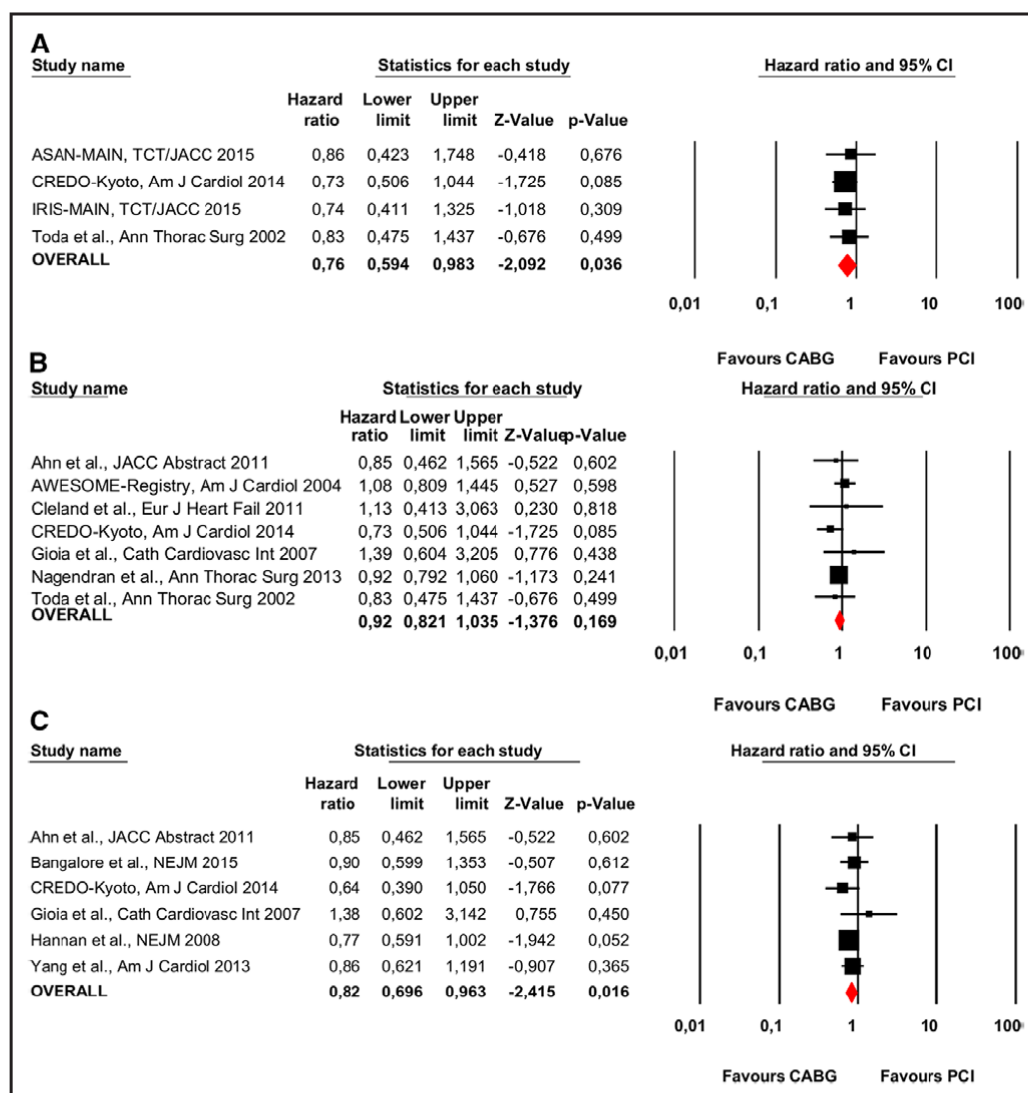
**Figure 3.** Individual and summary hazard ratios for secondary end points of studies comparing coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI): **(A)** myocardial infarction<sup>20,22–25,30,33,35</sup>; **(B)** repeat revascularization<sup>20,22,23,25,28,33,35</sup>; and **(C)** stroke.<sup>20,22,25,35</sup> CI indicates confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; IRIS-MAIN, Observational Study for Left Main Disease Treatment; and REHEAT, Revascularization in Heart Failure Trial.

presence of angina or viable myocardium.<sup>42</sup> PCI receives IIb C strength of recommendations for patients unsuitable for surgery, who have viable myocardium or significant left main stenosis or 2/3-vessel disease. The American College of Cardiology Foundation (ACCF)/AHA guidelines take a more liberal approach, suggesting CABG or PCI in patients with left main or multivessel disease in the case of angina and suitable coronary anatomy.<sup>3</sup> However, for patients with severely impaired left ventricular function and significant CAD in the absence of angina, only CABG is recommended as an alternative to MT, even in the absence of myocardial viability (Class IIb; Level of Evidence B).<sup>3</sup> The discrepancy among international recommendations, stemming from the lack of evidence from adequately powered randomized trials, challenges physicians in choosing the optimal strategy.<sup>1,3,42,43</sup> Our findings derived from a large-scale analysis agree with those from STICH, unequivocally supporting the revascularization option in this high-risk group of patients. Our data for the first time add comprehensive information on the efficacy of percutaneous revascularization versus medical therapy, providing evidence that revascularization, irrespective of modality, in this specific population has the potential to improve the patients' outcomes. Moreover, they further expand current evidence by investigating the comparison between surgical and percutaneous revascularization,

with a consistent long-term survival benefit provided by the surgical revascularization strategy. According to our meta-analysis and to the results of the STICH trial, surgical revascularization should be regarded as the preferred revascularization modality in these high-risk patients, followed by percutaneous interventions. These results suggest that current international guidelines should upgrade CABG to receive a higher class of recommendation and a higher level of evidence over PCI or MT.

An interesting finding of our study is that a significant mortality reduction is observed not only for patients with a classical indication for surgical revascularization (left main disease or 3-vessel disease), but possibly for all patients with significant CAD and impaired left ventricular function.

The comparison of CABG and PCI in patients with HFrEF shows a significant survival benefit for CABG in the present analysis. The low heterogeneity and the narrow 95% CIs suggest consistency of the findings that remained statistically significant in the subanalyses of CABG versus PCI using DES and of the randomized/matched cohorts. The reduction in mortality, however, was numerically smaller for CABG versus PCI than for CABG versus MT, in line with the findings of the present article on the benefits of PCI over MT. In a subanalysis of secondary end points, we found significantly reduced risk for MI and RR in patients treated with CABG versus PCI.



**Figure 4.** Individual and summary hazard ratios for mortality in studies comparing coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI) stratified by patient characteristics or treatment: **(A)** in patients with left main/proximal left anterior descending disease<sup>17,22,25,33</sup>; **(B)** in patients with 3-vessel disease<sup>15,18,19,21–23,28,33</sup>; and **(C)** in studies using drug-eluting stents in the PCI group.<sup>15,20,22–24,35</sup> ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CI, confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; and IRIS-MAIN, Observational Study for Left Main Disease Treatment.

Although left main and 3-vessel disease have long been a domain of CABG rather than PCI for revascularization, because of an established prognostic benefit of CABG, 3 recent randomized trials, LE MANS (Left Main Coronary Artery Stenting),<sup>44</sup> SYNTAX,<sup>45</sup> and PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease)<sup>46</sup> and subsequent meta-analyses<sup>47</sup> have suggested that intermediate-term mortality after interventional revascularization using modern stent systems is comparable to CABG, with a reduced risk of stroke but a higher need for RR. Revascularization guidelines<sup>42,43</sup> have thus expanded PCI indications in stable coronary heart disease, leaving the sole CABG recommendation to complex coronary anatomy with high SYNTAX scores or diabetes mellitus.<sup>41,48</sup> Our findings indicate that surgical revascularization in patients with HFrEF should be regarded as the preferred strategy, with significant survival benefits in patients with left

main/proximal left anterior descending disease and a numeric but nonsignificant mortality reduction in patients with 3-vessel disease.

Another important finding of the present report is that the significant survival improvement with CABG over MT or PCI occurred in patients largely without previous viability testing. The indication for revascularization in patients with HFrEF is most often based on clinical symptoms, for example, angina or decompensation, in the presence of significant CAD. The relevance of myocardial viability testing to determine the benefit/risk ratio of revascularization remains uncertain, with only a minority of studies providing signal for possible benefit<sup>49</sup> and guidelines generally recommending it as a reasonable procedure.<sup>1,3</sup> European guidelines clearly advise against revascularization with either CABG or PCI in patients who have neither angina nor viable myocardium.<sup>1,40</sup> American guidelines instead take a differing approach, giving a IIb recommendation to CABG,



independent of viable myocardium.<sup>3</sup> The present meta-analysis of all available studies on the topic shows a clear survival benefit for revascularization techniques (CABG as well as PCI) compared with MT, largely independent of viability testing. Our results are thus in line with current recommendations from American guidelines with respect to this point and suggest a minor role of viability testing in CAD patients with HFrEF.

In conclusion, this large-scale article emphasizes in patients with HF and CAD the mortality benefits of revascularizations over medical therapy; these findings prompt an update of international guidelines, with higher class and evidence of recommendations assigned to surgical revascularizations to these high-risk patients.

### Limitations

The availability of individual patient data would have improved the results of our meta-analysis, especially of potential subgroup analyses. Only few randomized controlled trials were available, with the majority of studies being observational. The observational design has the advantage of adhering to the real world, more appropriately reflecting current practice of unselected higher risk patients versus those derived from randomized trials. Nonetheless, many sensitivity analyses were performed, including those limited to patients randomized or well matched, and were consistent with the main findings, suggesting that the overall effect is justified.

Data on single treatments in the medical therapy group were available only in a minority of studies; therefore, precise description of the adherence to standard guidelines for medical therapy in this patient cohort is not possible. On the other hand, a sensitivity analysis done with the more contemporary studies only confirmed the overall results. Moreover, additional sensitivity analyses in studies using randomization or patient matching have been conducted, generating highly matched patients in terms of allocated MTs; the findings are directionally convergent and have consistent magnitude with the main findings. Caution should be prompted when interpreting subgroup analyses that should be regarded as exploratory, given the degree of variability in patient background characteristics.

### Conclusions

This meta-analysis provides evidence that revascularization, irrespective of modality, compared with medical therapy, significantly improves survival and other outcomes in patients with ejection fraction  $\leq 40\%$  and significant CAD. CABG seems to be the most favorable option in this setting, although PCI may have its advantages in special patients and situations. Careful assessment of procedural risk and discussion of the optimal treatment strategy within a heart team is mandatory and recommended by current guidelines. Additional randomized trials will be necessary to further define the most beneficial treatment for these high-risk patients.

### Disclosures

None.

### References

- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787–1847. doi: 10.1093/eurheartj/ehs104.
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322. doi: 10.1161/CIR.000000000000152.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327. doi: 10.1016/j.jacc.2013.05.019.
- Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137–1146. doi: 10.1136/hrt.2003.025270.
- Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis*. 2005;47:320–332.
- Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation*. 1998;97:282–289.
- Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation*. 2000;101:2981–2988.
- Bounous EP, Mark DB, Pollock BG, Hlatky MA, Harrell FE Jr, Lee KL, Rankin JS, Wechsler AS, Pryor DB, Califf RM. Surgical survival benefits for coronary disease patients with left ventricular dysfunction. *Circulation*. 1988;78(3 pt 2):1151–1157.
- Killip T, Passamani E, Davis K. Coronary Artery Surgery Study (CASS): a randomized trial of coronary bypass surgery. Eight years follow-up and survival in patients with reduced ejection fraction. *Circulation*. 1985;72(6 pt 2):V102–V109.
- Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, Levine F, Schloss M. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation*. 1983;68:785–795.
- The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions/Cochrane Community (Beta) [Internet]. 2016. <http://community.cochrane.org/handbook>. Accessed May 2, 2016.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi: 10.1136/bmj.327.7414.557.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
- Ahn J-M, Oh J-H, Sun BJ, Cho SW, Kim YR, Lee CH, Hwang KW, Song H, Kim WJ, Lee JY, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Comparisons of drug-eluting stents vs. coronary artery bypass grafting for patients with multi-vessel disease and severely compromised ventricular dysfunction. *Am J Cardiol*. 2011;8(suppl):87A.
- Appoo J, Norris C, Merali S, Graham MM, Koshal A, Knudtson ML, Ghali WA. Long-term outcome of isolated coronary artery bypass surgery in patients with severe left ventricular dysfunction. *Circulation*. 2004;110(11 suppl 1):II13–II17. doi: 10.1161/01.CIR.0000138345.69540.ed.



17. Kim MS, Kang SH, Park H, Bae BJ, Cheon SS, Roh JH, Lee PH, Chang M, Park HW, Yoon SH, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Left main revascularization for patients with reduced left ventricular ejection fraction; comparison of outcome after PCI versus CABG from ASAN-MAIN registry. *J Am Coll Cardiol*. 2015;65(suppl):S18.
18. Sedlis SP, Ramanathan KB, Morrison DA, Sethi G, Sacks J, Henderson W; Department of Veterans Affairs Cooperative Study No 385, Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) Investigators. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). *Am J Cardiol*. 2004;94:118–120. doi: 10.1016/j.amjcard.2004.03.041.
19. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, Esposito R, Ramanathan K, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Barbiere C, Lewis D; Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study No 385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol*. 2001;38:143–149. doi: 10.1016/S0735-1097(01)01366-3.
20. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med*. 2015;372:1213–1222. doi: 10.1056/NEJMoa1412168.
21. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail*. 2011;13:227–233. doi: 10.1093/eurjhf/hfq230.
22. Marui A, Kimura T, Nishiwaki N, Mitsudo K, Komiya T, Hanyu M, Shiomi H, Tanaka S, Sakata R; CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Comparison of five-year outcomes of coronary artery bypass grafting versus percutaneous coronary intervention in patients with left ventricular ejection fractions  $\leq 50\%$  versus  $>50\%$  (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol*. 2014;114:988–996. doi: 10.1016/j.amjcard.2014.07.007.
23. Gioia G, Matthai W, Gillin K, Dralle J, Benassi A, Gioia MF, White J. Revascularization in severe left ventricular dysfunction: outcome comparison of drug-eluting stent implantation versus coronary artery bypass grafting. *Catheter Cardiovasc Interv*. 2007;70:26–33. doi: 10.1002/ccd.21072.
24. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med*. 2008;358:331–341. doi: 10.1056/NEJMoa071804.
25. Park H-S, Roh J-H, Lee PH, Chang M, Yoon S-H, Ahn J-M, Lee B-K, Kang S-J, Park D-W, Lee S-W, Kim Y-H, Lee CW, Park S-W, Park S-J. Percutaneous coronary intervention versus coronary-artery bypass grafting for left main coronary disease with reduced left ventricular ejection fraction. *J Am Coll Cardiol*. 2015;66(suppl):B196–B197.
26. Kwon DH, Hachamovitch R, Popovic ZB, Starling RC, Desai MY, Flamm SD, Lytle BW, Marwick TH. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. *Circulation*. 2012;126(11 suppl 1):S3–S8. doi: 10.1161/CIRCULATIONAHA.111.084434.
27. LaBarbera M, Hui P, Shaw R. Coronary artery disease in patients with reduced left ventricular systolic function treated with medicine, surgery, or percutaneous coronary intervention: a retrospective review of outcomes within a multicenter healthcare system. *J Am Coll Cardiol*. 2012;60:B107.
28. Nagendran J, Norris CM, Graham MM, Ross DB, Macarthur RG, Kieser TM, Maitland AM, Southern D, Meyer SR; APPROACH Investigators. Coronary revascularization for patients with severe left ventricular dysfunction. *Ann Thorac Surg*. 2013;96:2038–2044. doi: 10.1016/j.athoracsur.2013.06.052.
29. Fortuna D, Nicolini F, Guastaroba P, De Palma R, Di Bartolomeo S, Saia F, Pacini D, Grilli R; RERIC (Regional Registry of Cardiac Surgery); REAL (Regional Registry of Coronary Angioplasties) Investigators. Coronary artery bypass grafting vs percutaneous coronary intervention in a 'real-world' setting: a comparative effectiveness study based on propensity score-matched cohorts. *Eur J Cardiothorac Surg*. 2013;44:e16–e24. doi: 10.1093/ejcts/ezt197.
30. Buszman P, Szkróbka I, Gruszka A, Parma R, Tendera Z, Leśko B, Wilczyński M, Bochenek T, Wojakowski W, Bochenek A, Tendera M. Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. *Am J Cardiol*. 2007;99:36–41. doi: 10.1016/j.amjcard.2006.07.056.
31. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yui M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364:1607–1616. doi: 10.1056/NEJMoa1100356.
32. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374:1511–1520. doi: 10.1056/NEJMoa1602001.
33. Toda K, Mackenzie K, Mehra MR, DiCorte CJ, Davis JE, McFadden PM, Ochsner JL, White C, Van Meter CH Jr. Revascularization in severe ventricular dysfunction ( $15\% < \text{OR} = \text{LVEF} < 30\%$ ): a comparison of bypass grafting and percutaneous intervention. *Ann Thorac Surg*. 2002;74:2082–2087, discussion 2087.
34. Velazquez EJ, Williams JB, Yow E, Shaw LK, Lee KL, Phillips HR, O'Connor CM, Smith PK, Jones RH. Long-term survival of patients with ischemic cardiomyopathy treated by coronary artery bypass grafting versus medical therapy. *Ann Thorac Surg*. 2012;93:523–530. doi: 10.1016/j.athoracsur.2011.10.064.
35. Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Jeong DS, Sung K, Kim WS, Lee YT, Gwon HC. Long-term outcomes of drug-eluting stent implantation versus coronary artery bypass grafting for patients with coronary artery disease and chronic left ventricular systolic dysfunction. *Am J Cardiol*. 2013;112:623–629. doi: 10.1016/j.amjcard.2013.04.035.
36. Schwann TA, Engoren M, Bonnell M, Clancy C, Habib RH. Comparison of late coronary artery bypass graft survival effects of radial artery versus saphenous vein grafting in male and female patients. *Ann Thorac Surg*. 2012;94:1485–1491. doi: 10.1016/j.athoracsur.2012.05.029.
37. Navarese EP, Kowalewski M, Kandzari D, Lansky A, Górny B, Koltowski L, Waksman R, Berti S, Musumeci G, Limbruno U, van der Schaaf RJ, Kelm M, Kubica J, Suryapranata H. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. *Open Heart*. 2014;1:e000064. doi: 10.1136/openhrt-2014-000064.
38. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, Kereiakes DJ, Waksman R, Mauri L, Meredith IT, Finn AV, Kim HS, Kubica J, Suryapranata H, Aprami TM, Di Pasquale G, von Birgelen C, Kedhi E. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ*. 2013;347:f6530.
39. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P; Acute Dialysis Quality Initiative (ADQI) Consensus Group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur Heart J*. 2010;31:703–711. doi: 10.1093/eurheartj/ehp507.
40. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stähle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972. doi: 10.1056/NEJMoa0804626.
41. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansal S, King S 3rd, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384. doi: 10.1056/NEJMoa1211585.

42. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014;35:2541–2619.
43. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767. doi: 10.1161/CIR.0000000000000095.
44. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymaszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538–545. doi: 10.1016/j.jacc.2007.09.054.
45. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121:2645–2653. doi: 10.1161/CIRCULATIONAHA.109.899211.
46. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718–1727. doi: 10.1056/NEJMoa1100452.
47. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177–2185. doi: 10.1161/CIRCULATIONAHA.112.000646.
48. Verma S, Farkouh ME, Yanagawa B, Fitchett DH, Ahsan MR, Ruel M, Sud S, Gupta M, Singh S, Gupta N, Cheema AN, Leiter LA, Fedak PW, Teoh H, Latter DA, Fuster V, Friedrich JO. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2013;1:317–328. doi: 10.1016/S2213-8587(13)70089-5.
49. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, Hachamovitch R. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging*. 2013;6:363–372. doi: 10.1161/CIRCIMAGING.112.000138.

### CLINICAL PERSPECTIVE

Previous data have shown improved survival by revascularization with coronary artery bypass grafting compared with medical treatment for patients with coronary artery disease, but single studies in the setting of coronary artery disease with heart failure with reduced ejection fraction have been underpowered to draw definite conclusions, ultimately contributing to the uncertainty of current recommendations on the optimal strategy for patients with coronary artery disease and heart failure with reduced ejection fraction. The present meta-analysis indicates that revascularization strategies are superior to medical treatment in improving survival in patients with ischemic heart disease with reduced ejection fraction. Between the 2 revascularization strategies, coronary artery bypass grafting seems more favorable compared with percutaneous coronary intervention in this particular clinical setting. This large-scale article supports that in patients with HFrEF and coronary artery disease, there is a mortality benefit of revascularizations over medical therapy. These findings may inform an update of international guidelines with higher class and evidence of recommendations assigned to surgical revascularization in these high-risk patients.



#### **4.2.4 Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke: A Meta-analysis**

Lin Y, Schulze V, Brockmeyer M, Parco C, Karathanos A, Heinen Y, Gliem M, Hartung HP, Antoch G, Jander S, Turowski B, Perings S, Kelm M, **Wolff G**.

JAMA Neurol. 2019;76(7):850-4.

Pubmed PMID: 30958530

DOI: [10.1001/jamaneurol.2019.0525](https://doi.org/10.1001/jamaneurol.2019.0525)

In der Behandlung des akuten ischämischen Schlaganfalls wurde in randomisierten Studien seit 2015 gezeigt, dass die interventionelle endovaskuläre Therapie durch Thrombektomie die funktionellen Ergebnisse der Patienten im Vergleich zur rein intravenösen Lyse verbessern kann (29). Daraufhin haben internationale Leitlinien die endovaskuläre Therapie bei geeigneten Patienten mit akutem ischämischen Schlaganfall empfohlen (99). Es blieb jedoch aus allen Studien aufgrund von deren Design und fehlender statistischer Power unklar, ob diese interventionelle Therapie nur die funktionellen Ergebnisse verbessert, oder ob auch die Mortalität der Patienten gesenkt wird.

Wir konnten in einer Meta-Analyse aller zehn leitlinienrelevanten randomisierten, kontrollierten Studien mit 2.313 Patienten, welche endovaskuläre Thrombektomie gegen die Standardtherapie (Lyse) verglichen haben, zeigen, dass die interventionelle Therapie die 90-Tage-Sterblichkeit um 3,7% gegenüber dem bisherigen Therapiestandard senkt (15,0% vs. 18,7%). Sensitivitätsanalysen bestätigten diese Ergebnisse, es ergab sich auch kein Unterschied im Risiko für intracranielle Blutungen.

Damit war diese Arbeit die erste, welche in der Gesamtheit der Datenlage leitlinienreferenzierter randomisierter, kontrollierter Studien einen Mortalitätsvorteil für die interventionelle Behandlung des Schlaganfalls zeigen konnte.

# Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke

## A Meta-analysis

Yingfeng Lin, MD; Volker Schulze, MD; Maximilian Brockmeyer, MD; Claudio Parco, MD; Athanasios Karathanos, MD; Yvonne Heinen, MD; Michael Gliem, MD; Hans-Peter Hartung, MD; Gerald Antoch, MD; Sebastian Jander, MD; Bernd Turowski, MD; Stefan Perings, MD; Malte Kelm, MD; Georg Wolff, MD

### Supplemental content

**IMPORTANCE** Although endovascular thrombectomy (EVT) in acute ischemic stroke is recommended by guidelines to improve functional recovery, thus far there are insufficient data on its association with mortality.

**OBJECTIVE** To identify guideline-relevant trials of EVT vs medical therapy reporting 90-day mortality and perform a meta-analysis.

**DATA SOURCES** All randomized clinical trials cited for recommendations on EVT vs medical therapy in the latest 2018 American Stroke Association/American Heart Association guidelines.

**STUDY SELECTION** Ten American Stroke Association/American Heart Association guideline-relevant randomized clinical trials of EVT vs medical therapy were selected for inclusion. Two EVT trials were excluded owing to infrequent use of EVT.

**DATA EXTRACTION AND SYNTHESIS** Data were abstracted by 2 independent investigators and double-checked by 4 others. Singular study data were integrated using the Cochran-Mantel-Haenszel method and a random-effects model to compute summary statistics of risk ratios (RR) with 95% CIs.

**MAIN OUTCOMES AND MEASURES** Risk of 90-day mortality and 90-day intracranial hemorrhage was analyzed; sensitivity analyses were performed in early-window EVT trials (which included patients from the onset of symptoms onward) vs late-window EVT trials (which included patients from 6 hours after onset of symptoms onward).

**RESULTS** In 10 trials with 2313 patients, EVT significantly reduced the risk for 90-day mortality by 3.7% compared with medical therapy (15.0% vs 18.7%; RR, 0.81; 95% CI, 0.68-0.98;  $P = .03$ ). Trends were similar in early-window (RR, 0.83; 95% CI, 0.67-1.01;  $P = .06$ ) and late-window trials only (RR, 0.76; 95% CI, 0.41-1.40;  $P = .38$ ). There was no difference in the risk for intracranial hemorrhage in EVT vs medical therapy (4.2% vs 4.0%; RR, 1.11; 95% CI, 0.71-1.72;  $P = .65$ ). Limitations of the studies include trial protocol heterogeneity and bias originating from prematurely terminated trials.

**CONCLUSIONS AND RELEVANCE** This meta-analysis of all evidence on EVT cited in the 2018 American Stroke Association/American Heart Association guidelines shows significant benefits for survival during the first 90 days after acute ischemic stroke compared with medical therapy alone.

**Author Affiliations:** Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany (Lin, Schulze, Brockmeyer, Parco, Karathanos, Heinen, Perings, Kelm, Wolff); Department of Neurology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany (Gliem, Hartung, Jander); Department of Diagnostic and Interventional Radiology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany (Antoch, Turowski); Cardiovascular Research Institute Düsseldorf, Düsseldorf, Germany (Kelm).

**Corresponding Author:** Georg Wolff, MD, Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Heinrich-Heine-University, Moorenstrasse 5, 40225 Düsseldorf, Germany (georg.wolff@med.uni-duesseldorf.de).

JAMA Neurol. 2019;76(7):850-854. doi:10.1001/jamaneurol.2019.0525  
Published online April 8, 2019.

Twenty years after intravenous thrombolysis (IT) was established as the first-line therapy for acute ischemic stroke (AIS), several randomized clinical trials (RCTs)<sup>1-6</sup> have proven benefits on functional recovery of endovascular thrombectomy (EVT) compared with medical therapy. The 2018 American Stroke Association/American Heart Association AIS guidelines<sup>7</sup> thus adopted class IA to IIB recommendations for EVT in different clinical scenarios.

Parallels of this development with the history of the management of myocardial infarction are striking: in myocardial infarction as in AIS, IT was first established to improve clinical outcomes and then was found to be inferior to interventional strategies of primary percutaneous coronary intervention.<sup>8</sup> However, unlike with the use of IT for myocardial infarction, mortality benefits of IT for AIS were not seen in short-term or long-term follow-up. In logic succession, all EVT trials focused on measures of functional recovery from AIS (Table)<sup>1-6,9-12</sup> and were underpowered to detect differences in mortality, just like subsequent meta-analyses.<sup>13,14</sup> Thus, it still remains unknown whether EVT also improves survival in AIS.

## Key Points

**Question** Is there a benefit for short-term survival with endovascular thrombectomy vs medical therapy in acute ischemic stroke?

**Findings** In this meta-analysis of all randomized clinical trials of endovascular thrombectomy vs medical therapy cited in the 2018 American Stroke Association/American Heart Association guidelines for acute ischemic stroke, endovascular thrombectomy significantly reduced the risk for 90-day mortality compared with medical therapy, without a difference in risk of intracranial hemorrhage.

**Meaning** There is considerable evidence of the benefits of endovascular thrombectomy for survival during the first 90 days after acute ischemic stroke.

## Methods

To approach this question, RCTs comparing EVT vs medical therapy for treatment of AIS were selected from all guideline-referenced RCTs on endovascular therapy in the 2018 American Stroke Association/American Heart Association guideline.<sup>7</sup>

Table. Study Characteristics of Included Trials

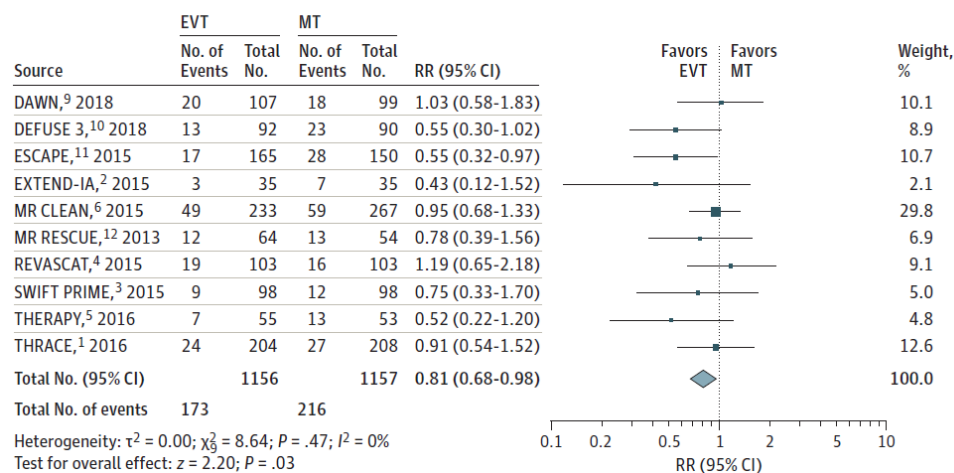
| Study                          | Journal                                | No. of Centers in Trial | No. of Patients (EVT/MT) | Randomization                         | Inclusion Criteria                                                                            | Device Used                           | IT Use (% per Group) | Primary End Point(s)                                       |
|--------------------------------|----------------------------------------|-------------------------|--------------------------|---------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------|----------------------|------------------------------------------------------------|
| DAWN, <sup>9</sup> 2018        | <i>New England Journal of Medicine</i> | 26                      | 107/99                   | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and M1) within 6-24 h, with NIHSS/imaging mismatch                       | 100% Trevo                            | 5/13                 | Utility-weighted mRS at 90 d; mRS score 0-2 at 90 d        |
| DEFUSE 3, <sup>10</sup> 2018   | <i>New England Journal of Medicine</i> | 38                      | 92/90                    | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and M1) within 6-16 h, with penumbra/infarct mismatch (CT perfusion/MRI) | 74% Stent retriever, 25% aspiration   | 11/9                 | mRS at 90 d                                                |
| ESCAPE, <sup>11</sup> 2015     | <i>New England Journal of Medicine</i> | 22                      | 165/150                  | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and M1) within 12 h                                                      | 77% Solitaire, 9% other               | 73/79                | mRS at 90 d                                                |
| EXTEND-IA, <sup>2</sup> 2015   | <i>New England Journal of Medicine</i> | 14                      | 35/35                    | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA, M1, and M2) within 4.5 h                                                | 100% Solitaire                        | 100/100              | Perfusion at 24 h; early improvement (NIHSS) at 24 h       |
| MR CLEAN, <sup>6</sup> 2015    | <i>New England Journal of Medicine</i> | 16                      | 233/267                  | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA, M1, M2, A1, and A2) within 4.5 h                                        | 81.5% Stent retriever                 | 87/91                | mRS at 90 d                                                |
| MR RESCUE, <sup>12</sup> 2013  | <i>New England Journal of Medicine</i> | 22                      | 64/54                    | Endovascular therapy + MT vs MT alone | Anterior stroke within 8 h                                                                    | 58% Merci, 22% Penumbra, 17% both     | 44/30                | Correlation of penumbral imaging (CT/MRI) with mRS at 90 d |
| REVASCAT, <sup>4</sup> 2015    | <i>New England Journal of Medicine</i> | 4                       | 103/103                  | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and M1) within 8 h                                                       | 95% Solitaire                         | 68/78                | mRS at 90 d                                                |
| SWIFT PRIME, <sup>3</sup> 2015 | <i>New England Journal of Medicine</i> | 39                      | 98/97                    | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and M1) within 6 h                                                       | 100% Solitaire                        | 100/100              | mRS at 90 d                                                |
| THERAPY, <sup>5</sup> 2016     | <i>Stroke</i>                          | 36                      | 55/53                    | Endovascular therapy + MT vs MT alone | Anterior stroke (ICA and MCA) and thrombus length ≥8 mm                                       | 100% Penumbra                         | 100/100              | mRS 0-2 at 90 d                                            |
| THRACE, <sup>1</sup> 2016      | <i>Lancet Neurology</i>                | 26                      | 204/208                  | Endovascular therapy + MT vs MT alone | Stroke (ICA, M1, and BA) within 4 h                                                           | 77% Solitaire, 15% Penumbra, 7% other | 100/100              | mRS 0-2 at 90 d                                            |

Abbreviations: A1, A1 segment of the anterior cerebral artery; A2, A2 segment of the anterior cerebral artery; BA, basilar artery; CT, computed tomography; DAWN, DAWN or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EVT, endovascular thrombectomy; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; ICA, internal carotid artery; IT, intravenous thrombolysis; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; MCA, middle cerebral artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular

Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; MRI, magnetic resonance imaging; mRS, modified ranking scale; MT, medical therapy; NIHSS, National Institutes of Health Stroke Scale; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; THRACE, Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke.



Figure 1. All-Cause Mortality in Randomized Clinical Trials of Endovascular Thrombectomy (EVT) vs Medical Therapy (MT) at 90 Days



Individual and summary risk ratios (RRs) with 95% CIs for all-cause mortality in randomized clinical trials of EVT vs MT at 90 days of follow-up. The size of the data markers indicates the study weight within the pooled meta-analysis. Detailed study weights are given in the respective column and correspond to the size of the data markers. Study weights were calculated according to the random-effects Cochran-Mantel-Haenszel model used. DAWN indicates DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in

Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; and THRACE, Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke.

Methods were applied according to Cochrane Collaboration and PRISMA recommendations: 2 independent investigators (Y.L. and G.W.) performed intention-to-treat data abstractions on study characteristics, risk of bias, and 90-day mortality and 90-day intracranial hemorrhage outcomes from published reports, which were double-checked accordingly by 4 of us (V.S., M.B., C.P., and A.K.). Risk ratios (RRs) and 95% CIs were used as summary statistics, and singular studies were integrated with the Cochran-Mantel-Haenszel method and a random-effects model. Statistical heterogeneity was quantified with the  $I^2$  statistic. A 2-tailed  $P < .05$  was considered statistically significant.

## Results

Included trial characteristics are shown in the Table<sup>1-6,9-12</sup>; 10 RCTs of EVT vs medical therapy referenced in the 2018 American Stroke Association/American Heart Association guideline<sup>7</sup> with a total of 2313 patients and a consistent follow-up of 90 days were included. Excluded trial characteristics are shown in eTable 1 in the Supplement; 5 trials were excluded for the wrong comparators, and trials were excluded for using EVT devices in only a minority of patients (mainly those with intra-arterial thrombolysis). Risk of bias of included trials was generally low (eTable 2 in the Supplement).

In the cumulative meta-analysis, EVT significantly reduced the risk for 90-day mortality by 3.7% compared with

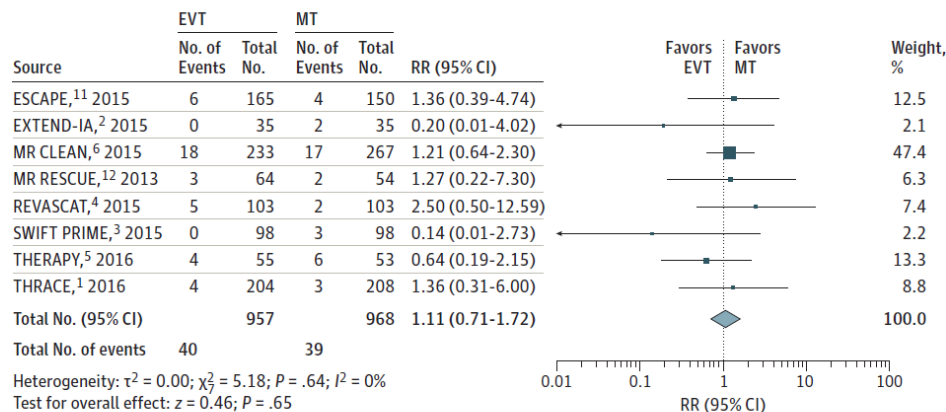
medical therapy (15.0% vs 18.7%; RR, 0.81; 95% CI, 0.68-0.98;  $P = .03$ ; Figure 1), with a number needed to treat of 27 to prevent 1 death from all causes. Trends were similar when analyzing early-window EVT vs IT (all trials except DAWN [DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo]<sup>9</sup> and DEFUSE 3 [Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke]<sup>10</sup>: RR, 0.83; 95% CI, 0.67-1.01;  $P = .06$ ) or late-window trials separately (DAWN<sup>9</sup> and DEFUSE 3<sup>10</sup>: RR, 0.76; 95% CI, 0.41-1.40;  $P = .38$ ).

In early-window EVT trials, nearly all patients received EVT in addition to IT (Table),<sup>1-6,9-12</sup> with a potential risk for symptomatic intracranial hemorrhage to confound mortality. The meta-analysis of intracranial hemorrhage events, however, showed no differences between EVT and medical therapy (4.2% vs 4.0%; RR, 1.11; 95% CI, 0.71-1.72;  $P = .65$ ) (Figure 2). Thus, the observed risk reduction for mortality probably does not originate from differences in adverse effects but from the functional benefits of EVT also translating to improved 90-day survival.

## Discussion

Previous works also observed mortality benefits between groups in favor of EVT; however, the differences were statistically insignificant (eg, 3.6%<sup>13</sup> and 2.6%,<sup>14</sup> with  $P$  values of approximately .15), similar to the present sensitivity analysis in early-window trials only. However, by including all trials of EVT

Figure 2. Symptomatic Intracranial Hemorrhage in Randomized Clinical Trials of Early-Window Endovascular Thrombectomy (EVT) vs Medical Therapy (MT) at 90 Days



Individual and summary risk ratios (RRs) with 95% CIs for symptomatic intracranial hemorrhage in randomized clinical trials of early-window EVT vs MT. The size of the data markers indicates the study weight within the pooled meta-analysis. Detailed study weights are given in the respective column and correspond to the size of the data markers. Study weights were calculated according to the random-effects Cochran-Mantel-Haenszel model used. ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of

Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; and THRACE, Mechanical Thrombectomy After Intravenous Alteplase vs Alteplase Alone After Stroke.

methods, this meta-analysis features the largest number of analyzed patients and events, to our knowledge, and achieves sufficient power to reach statistical significance.

### Limitations

Limitations include trial heterogeneity in study protocols (early-window and late-window) and EVT (eg, different modalities and generations of thrombectomy devices). Risk of bias additionally originates from analysis of secondary trial end points and incomplete recruitment in the prematurely terminated trials. Therefore, results must be interpreted with considerable caution. However, new EVT trials designed to show mortality differences in AIS might never be performed; thus, a meta-analysis of available data may be the only way to analyze short-term survival. Low statistical heterogeneity ( $I^2$  and  $\tau^2$  in Figure 1 and Figure 2) additionally indicates robust

effects. Long-term follow-ups of singular RCTs will be interesting with respect to mortality: the 2-year MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) study data have already shown a trend toward improved survival during the first 90 days after AIS with EVT.<sup>15</sup>

### Conclusions

Taken together, there is considerable evidence in guideline-referenced RCTs that EVT significantly benefits survival during the first 90 days after AIS compared with medical therapy alone. We cannot help but see the parallels: endovascular strategies may well turn out to be as successful in AIS as in myocardial infarction.

### ARTICLE INFORMATION

**Accepted for Publication:** January 10, 2019.

**Published Online:** April 8, 2019.  
doi:10.1001/jamaneurol.2019.0525

**Author Contributions:** Drs Lin and Wolff had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** Schulze, Parco, Karathanos, Hartung, Antoch, Perings, Kelm, Wolff.  
**Acquisition, analysis, or interpretation of data:** Lin, Brockmeyer, Karathanos, Heinen, Gliem, Hartung, Jander, Turowski, Wolff.

**Drafting of the manuscript:** Lin, Hartung, Wolff.  
**Critical revision of the manuscript for important intellectual content:** Schulze, Brockmeyer, Parco,

Karathanos, Heinen, Gliem, Hartung, Antoch, Jander, Turowski, Perings, Kelm, Wolff.

**Statistical analysis:** Lin, Schulze, Karathanos, Hartung, Wolff.

**Administrative, technical, or material support:** Schulze, Karathanos, Gliem, Hartung, Antoch, Wolff.

**Supervision:** Schulze, Heinen, Gliem, Jander, Turowski, Perings, Kelm, Wolff.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** Dr Wolff was supported by the Forschungskommission of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (No. 2018-32) for a Clinician Scientist Track. There was no direct funding for this project.

**Role of the Funder/Sponsor:** The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

### REFERENCES

- Bracard S, Ducrocq X, Mas JL, et al; THRACE Investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15(11):1138-1147. doi:10.1016/S1474-4422(16)30177-6
- Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND-IA Investigators. Endovascular therapy for

- ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018. doi:10.1056/NEJMoa1414792
3. Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061
  4. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306. doi:10.1056/NEJMoa1503780
  5. Mocco J, Zaidat OO, von Kummer R, et al; THERAPY Trial Investigators. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. *Stroke*. 2016;47(9):2331-2338. doi:10.1161/STROKEAHA.116.013372
  6. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587
  7. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110. doi:10.1161/STR.0000000000000158
  8. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393
  9. Nogueira RG, Jadhav AP, Haussen DC, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442
  10. Albers GW, Marks MP, Kemp S, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973
  11. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030. doi:10.1056/NEJMoa1414905
  12. Kidwell CS, Jahan R, Gornbein J, et al; MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368(10):914-923. doi:10.1056/NEJMoa1212793
  13. Goyal M, Menon BK, van Zwam WH, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X
  14. Román LS, Menon BK, Blasco J, et al; HERMES Collaborators. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol*. 2018;17(10):895-904. doi:10.1016/S1474-4422(18)30242-4
  15. van den Berg LA, Dijkgraaf MG, Berkhemer OA, et al; MR CLEAN Investigators. Two-year outcome after endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2017;376(14):1341-1349. doi:10.1056/NEJMoa1612136



#### **4.2.5 Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes**

**Wolff G**, Lin Y, Akbulut C, Brockmeyer M, Parco C, Hoss A, Sokolowski A, Westenfeld R, Kelm M, Roden M, Schlesinger S, Kuss O

ESC Heart Fail. 2022 Nov 7. doi: 10.1002/ehf2.14213. Online ahead of print.

Pubmed PMID: 36337026

DOI: [10.1002/ehf2.14213](https://doi.org/10.1002/ehf2.14213)

Neue Antidiabetika haben nicht nur in der Therapie des Diabetes mellitus, sondern auch in der Therapie der Herzinsuffizienz in randomisierten, kontrollierten Studien Vorteile für kardiovaskuläre Endpunkte gezeigt. Glucagon-like peptide-1 (GLP-1) Rezeptoragonisten und sodium glucose transporter 2 (SGLT2) Inhibitoren haben daher Leitlinienempfehlungen in der Diabetestherapie (100, 101), SGLT2 Inhibitoren auch in der Herzinsuffizienz (40) erhalten. Während relative Benefits im Vergleich zum Placebo in vielen Studien und Meta-Analysen gezeigt worden sind, werden absolute Behandlungseffekte – z.B. die sog. Number-needed-to-treat (NNT), die Anzahl der notwendigen Behandlungen zur Reduktion eines Ereignisses – selten betrachtet, sind aber für die Einschätzung der Behandlungseffekte von Bedeutung.

Wir haben in dieser Analyse unter Anwendung einer komplexen statistischen Methodik zunächst aus 16 randomisierten, kontrollierten Studien zu GLP-1 Rezeptoragonisten, SGLT2 Inhibitoren und Dipeptidyl-Peptidase-4 (DPP4) Inhibitoren mit Kaplan-Meier-Kurven zu kardiovaskulären Endpunkten graphische Daten extrahiert, modelliert und dann absolute Behandlungseffekte (NNT) über die Zeit analysiert. Schließlich wurden in einer random-effects Metaanalyse dieser Daten Meta-NNT über die Zeit errechnet. Es zeigten sich darin nur moderate Behandlungseffekte (Meta-NNT >100 über ca. 30 Monate) auf die Endpunkte *kardiovaskuläre Mortalität* und *Hospitalisierung aufgrund einer Herzinsuffizienz* sowohl für SGLT2 Inhibitoren als auch für GLP1 Rezeptoragonisten; DPP4 Inhibitoren zeigten keine signifikanten Effekte. In einer Sensitivitätsanalyse von Patienten mit Herzinsuffizienz mit reduzierter linksventrikulärer Pumpfunktion, welche primär in den Studien DAPA-HF (102) und EMPEROR-Reduced (103) eingeschlossen wurden, zeigte sich eine erheblich größere Effektivität von SGLT2 Inhibitoren, insbesondere auf den Endpunkt *Hospitalisierung aufgrund einer Herzinsuffizienz* (Meta-NNT von 25 über 16 Monate) – verglichen mit Patienten mit Diabetes mellitus ohne Herzinsuffizienz (Meta-NNT von 233 über 16 Monate).

Damit zeigten sich SGLT2 Inhibitoren in der Herzinsuffizienz mit reduzierter linksventrikulärer Pumpfunktion ähnlich effizient, wie die gängige Herzinsuffizienztherapie (104) mit Betablockern, Renin-Angiotensin-Aldosteron-Inhibitoren oder Mineralocorticoid-Rezeptor-Antagonisten.

# Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes

Georg Wolff<sup>1\*</sup> , Yingfeng Lin<sup>1</sup>, Cihan Akbulut<sup>2,3,4</sup>, Maximilian Brockmeyer<sup>1</sup>, Claudio Parco<sup>1</sup>, Alexander Hoss<sup>1</sup>, Alexander Sokolowski<sup>1</sup>, Ralf Westenfeld<sup>1</sup>, Malte Kelm<sup>1,5</sup>, Michael Roden<sup>2,5,6,7</sup>, Sabrina Schlesinger<sup>2,3</sup> and Oliver Kuss<sup>2,3,4</sup>

<sup>1</sup>Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225, Düsseldorf, Germany; <sup>2</sup>German Center for Diabetes Research, Partner Düsseldorf, München-Neuherberg, Germany; <sup>3</sup>Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany; <sup>4</sup>Centre for Health and Society, Faculty of Medicine, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; <sup>5</sup>Cardiovascular Research Institute Düsseldorf (CARID), Heinrich Heine University Düsseldorf, Düsseldorf, Germany; <sup>6</sup>Department of Endocrinology and Diabetology, Internal Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; and <sup>7</sup>Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany

## Abstract

**Aims** Absolute treatment effects—i.e. numbers needed to treat (NNTs)—of novel antidiabetic drugs for cardiovascular outcomes have not been comprehensively evaluated. We aimed to perform a meta-analysis of digitalized individual patient outcomes to display and compare absolute treatment effects.

**Methods and results** Individual patient time-to-event information from Kaplan–Meier plots of *cardiovascular mortality (CM)* and/or *hospitalization for heart failure (HHF)* endpoints from cardiovascular outcome trials (CVOTs) evaluating dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose transporter 2 (SGLT2) inhibitors vs. placebo were digitalized using WebPlotDigitizer 4.2 and the R code of Guyot *et al.*; Weibull regression models were generated, validated, and used to estimate NNT for individual trials; random-effects meta-analysis generated Meta-NNT with 95% confidence intervals. Sixteen CVOTs reported time-to-event information (14 in primary diabetes and 2 in primary heart failure populations). Thirteen studies including 96 860 patients were meta-analysed for *CM*: At the median follow-up of 30 months, Meta-NNTs were 178 (64 to ∞ to −223) for DPP-4 inhibitors, 261 (158 to 745) for GLP-1 receptor agonists, and 118 (68 to 435) for SGLT2 inhibitors. Ten studies including 96 128 patients were meta-analysed for *HHF*: At the median follow-up of 29 months, estimated Meta-NNTs were −644 (229 to ∞ to −134) for DPP-4 inhibitors, 441 (184 to ∞ to −1100) for GLP-1 receptor agonists, and 126 (91 to 208) for SGLT2 inhibitors. SGLT2 inhibitors were especially effective for *HHF* in primary heart failure populations [Meta-NNT 25 (19 to 39)] vs. primary diabetes populations [Meta-NNT 233 (167 to 385)] at 16 months of follow-up.

**Conclusions** We found only modest treatment benefits of GLP-1 receptor agonists and SGLT2 inhibitors for *CM* and *HHF* in primary type 2 diabetes mellitus populations. In primary heart failure populations, SGLT2 inhibitor benefits were substantial and comparable in efficacy to established heart failure medication.

**Keywords** SGLT2 inhibitor; GLP-1 receptor agonist; Number needed to treat; Absolute treatment effect; Meta-analysis; Heart failure

Received: 19 July 2022; Revised: 29 September 2022; Accepted: 6 October 2022

\*Correspondence to: Georg Wolff, MD, Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany. Tel: 0049-211-81-18801. Email: georg.wolff@med.uni-duesseldorf.de  
Georg Wolff and Yingfeng Lin contributed equally to this work.

## Introduction

Cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM) are among the leading causes of morbidity and mortality in Europe and worldwide.<sup>1–3</sup> Heart failure is a complex

secondary syndrome to both and an emerging cardiovascular epidemic, whose incidence and healthcare-related cost continue to rise.<sup>4,5</sup>

Novel antidiabetic drugs, mainly dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor

agonists, and sodium glucose transporter 2 (SGLT2) inhibitors,<sup>6</sup> have shown benefits for both diabetes-related outcomes and cardiovascular endpoints in major cardiovascular outcome trials (CVOTs).<sup>7</sup> Current guidelines for the treatment of T2DM have issued respective recommendations,<sup>8,9</sup> especially for SGLT2 inhibitors and GLP-1 receptor agonists. Recently, updated European guidelines for the treatment of heart failure with reduced ejection fraction (HFrEF) now also recommend SGLT2 inhibitors, dapagliflozin and empagliflozin, as an integral part of pharmacotherapy<sup>10</sup> because of their benefits for cardiovascular and heart failure endpoints<sup>11,12</sup>—regardless of T2DM. Recent findings even show benefits of SGLT2 inhibitors in heart failure with preserved ejection fraction<sup>13</sup>—different from any other tested drug class before.

As the U.S. Food and Drug Administration requires trialists to show non-inferiority on the hazard ratio (HR) scale, CVOTs almost exclusively report relative effect estimates to describe treatment differences and meta-analyses of these studies thus resorted to analysis of relative effects.<sup>14,15</sup> Absolute effect sizes—e.g. numbers needed to treat (NNTs)—are difficult to find in trial reports, even though guidelines recommend their use.<sup>16–18</sup> This is unfortunate, as absolute effects rather than relative measures are key to judging drug efficacy, perform cost/benefit calculations from both medical and health-economics perspectives, and actually explain benefits to patients. Meta-analyses of CVOTs should offer the highest class of evidence on the subject but are difficult to perform for absolute effects due to lack of data in trial reports. However, there are validated methods<sup>19–23</sup> to digitalize time-to-event information from published reports.

We here report a meta-analysis of absolute treatment effects expressed as NNTs in the large CVOTs of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, focusing on the outcomes of cardiovascular mortality and hospitalization for heart failure.

## Methods

### Study selection and data extraction

All major randomized controlled CVOTs indicated in *fig. 1* of Cefalu et al.<sup>6</sup> with comparisons of SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors to placebo were eligible for inclusion. Full texts and online supplements of the CVOTs published until September 2020 were downloaded and searched for original Kaplan–Meier plots reporting time-to-event information for outcomes of *cardiovascular mortality* and *hospitalization for heart failure*. Outcomes of individual patients were digitalized from Kaplan–Meier plots using WebPlotDigitizer, Version 4.2,<sup>19</sup> and the R code of Guyot et al.<sup>20</sup> Both methods have been shown to be reliable and

valid.<sup>21–23</sup> Additionally, original HRs with 95% confidence intervals (95% CIs) for both outcomes, as well as characteristics of the study and patients, were extracted from the original study reports. All data extractions were double checked; discrepancies were discussed and resolved in the group. CVOTs without placebo group or without reporting of Kaplan–Meier plots for either one of both relevant outcomes were excluded.

### Weibull fits and absolute treatment effect estimates

Parametric Weibull regression models were fitted for all studies and both outcomes separately, in order to estimate survival functions that are needed to calculate NNTs. Weibull models are parametric proportional hazards models<sup>24</sup> and thus yield Weibull HRs for treatment effects, which can be compared with the original HRs. From the respective Weibull models, we estimated monthly probability differences (treatment – control) for being free of the event of interest from Month 1 to the respective maximal observation time of each individual trial. These probability differences were then inverted to arrive at estimates for the monthly NNT, which are thus necessarily time dependent.<sup>25</sup>

### Numbers needed to treat notation

NNTs describe the number of patients that have to be treated for a certain time interval to prevent one additional outcome event in the treatment group: Positive NNT values indicate that the drug is beneficial compared with placebo (or *number needed to treat to benefit*); negative NNT values indicate placebo advantage (or *number needed to treat to harm*). Lower NNT values indicate more effective treatment, with the lowest possible value of NNT = 1 (or –1, respectively). A null effect of the treatment, corresponding to an HR of 1, is denoted by a value of infinity ( $\infty$ ) for the NNT. A 95% CI that does not include infinity ( $\infty$ ) [or –infinity ( $-\infty$ ), respectively] corresponds to a statistically significant absolute treatment effect (with a two-sided  $\alpha$  probability of 5%).

### Assessment of model validity

To assess the validity of the digitalized data, we compared HRs from the original papers to those from the Weibull models by calculating intra-class correlation coefficients. In addition, to assess the fit of the Weibull models graphically, we plotted Kaplan–Meier estimates from the digitalized data together with predicted survival curves from these models.



## Meta-analysis

To summarize NNTs overall and in the three drug classes, we used random-effects inverse-variance meta-analysis. Meta-analyses were performed separately for monthly time points. A sensitivity analysis of SGLT2 inhibitors in studies with primary T2DM vs. primary HFrEF populations for the endpoint of *hospitalization for heart failure* was performed. All computations were performed on the probability difference scale and only for displaying results in figures and graphs transformed to the NNT scale. We used SAS (SAS Institute Inc., Cary, NC, USA), Version 9.4, for data management and analysis.

## Results

### Study selection

A total of 16 major CVOTs reported original time-to-event information for at least one of the two outcomes and were included in the analysis: four trials on DPP-4 inhibitors (CARMELINA, EXAMINE, SAVOR-TIMI 53, and TECOS<sup>26–29</sup>), six trials on GLP-1 receptor agonists (EXSCCEL, HARMONY, LEADER, PIONEER 6, REWIND, and SUSTAIN 6<sup>30–35</sup>), and six trials on SGLT2 inhibitors (CANVAS, CREDENCE, DAPA-HF, EMPA-REG Outcome, EMPEROR-REDUCED, and VERTIS-CV<sup>11,12,36–39</sup>). The CAROLINA trial<sup>40</sup> was excluded for not having a placebo control; the results of FREEDOM-CVO and EMPEROR-PRESERVED<sup>13</sup> were not yet published in full text at the time of analysis. All endpoint definitions of individual trials are listed in Supporting Information, Table S1.

### Study characteristics

An overview of all trials and a description of the study populations are given in Table 1: A total of 131 753 patients with time-to-event information were analysed; follow-up times in the studies ranged between 15.5 and 65.5 months for *cardiovascular mortality* and between 14.3 and 46.4 months for *hospitalization for heart failure*. The overall median follow-up time was 30.6 months for *cardiovascular mortality* and 29.2 months for *hospitalization for heart failure*. All trials featured high to very high cardiovascular risk patient populations.<sup>41</sup> They were conducted in patients with T2DM, with the exception of EMPEROR-REDUCED<sup>12</sup> and DAPA-HF,<sup>11</sup> which primarily included patients with heart failure, about half of them with diabetes mellitus.

## Relative and absolute treatment effect estimates of individual trials

Thirteen studies with 4997 digitalized events from 96 860 observed patients gave information on *cardiovascular mortality* (Table 2). Ten studies with 4065 digitalized events from 96 128 observed patients reported data on *hospitalization for heart failure* (Table 3). For both outcomes, original study HRs, extracted HRs, and Weibull HRs with 95% CI are reported as relative effect measures. NNTs at 12, 24, 36, and 48 months are reported as absolute treatment effect estimates for individual trials (Tables 2 and 3). Additionally, monthly NNT point estimates with 95% CI for all three study drugs and both outcomes are graphically displayed in Figure 1.

Accuracy of data digitalization and Weibull model fits was assessed using scatterplots (Supporting Information, Figure S1) to compare the originally reported HRs to the Weibull HRs from digitalized data: Correspondence was excellent, with an intra-class correlation of 99.4% (95% CI: 98.7–100%) for *cardiovascular mortality* and 99.8% (99.5–100%) for *hospitalization for heart failure*. Supporting Information, Figure S2 depicts Kaplan–Meier estimates of both treatment groups based on the Weibull survival curves. Again, there is no relevant divergence that might compromise computation of NNTs.

### Meta-analysis of absolute treatment effects

Results of the random-effects inverse-variance meta-analysis from monthly pooled survival data from the Weibull models for individual study drugs and for both outcomes are depicted in Figure 2: At the overall median follow-up time of 30 months for *cardiovascular mortality*, estimated Meta-NNTs were 178 (95% CI: 64 to ∞ to –223) for DPP-4 inhibitors, 261 (95% CI: 158 to 745) for GLP-1 receptor agonists, and 118 (95% CI: 68 to 435) for SGLT2 inhibitors. At the overall median follow-up time of 29 months for *hospitalization for heart failure*, estimated Meta-NNTs were –644 (95% CI: 229 to ∞ to –134) for DPP-4 inhibitors, 441 (95% CI: 184 to ∞ to –1100) for GLP-1 receptor agonists, and 126 (95% CI: 91 to 208) for SGLT2 inhibitors.

Accuracy of estimates (smallest 95% CI) was highest for GLP-1 receptor agonists regarding *cardiovascular mortality*, with Meta-NNTs of 351 (95% CI: 214 to 981; CI length 767), 205 (95% CI: 125 to 576; CI length 452), and 141 (95% CI: 86 to 389; CI length 302) after 24/36/48 months of follow-up. Regarding *hospitalization for heart failure*, most accurate estimates were found for SGLT2 inhibitors, with Meta-NNTs of 135 (95% CI: 101 to 205; CI length 105), 102 (95% CI: 73 to 167; CI length 94), and 76 (95% CI: 55 to 125; CI length 70) after 24/36/48 months of follow-up.

Table 1 Characteristics of included studies

| Study                          | Journal and year | Study drug    | Number of patients (n) | Median duration of follow-up (years) | Mean age (years) | Male sex (%) | Mean BMI (kg/m <sup>2</sup> ) |
|--------------------------------|------------------|---------------|------------------------|--------------------------------------|------------------|--------------|-------------------------------|
| <b>DPP-4 inhibitors</b>        |                  |               |                        |                                      |                  |              |                               |
| CARMELINA <sup>27</sup>        | JAMA 2018        | Linagliptin   | 6991                   | 2.2                                  | 65.9             | 62.9         | 31.4                          |
| EXAMINE <sup>29</sup>          | NEJM 2013        | Alogliptin    | 5380                   | 1.5                                  | 61.0             | 67.8         | 28.7 <sup>a</sup>             |
| SAVOR-TIMI 53 <sup>28</sup>    | NEJM 2013        | Saxagliptin   | 16 492                 | 2.1                                  | 65.1             | 66.9         | 31.1                          |
| TECOS <sup>26</sup>            | NEJM 2015        | Sitagliptin   | 14 671                 | 3.0                                  | 65.5             | 70.7         | 30.2                          |
| <b>GLP-1 receptor agonists</b> |                  |               |                        |                                      |                  |              |                               |
| EXSCEL <sup>32</sup>           | NEJM 2017        | Exenatide     | 14 752                 | 3.2                                  | 62.0             | 62.0         | 31.8                          |
| HARMONY <sup>31</sup>          | Lancet 2018      | Albiglutide   | 9463                   | 1.6                                  | 64.2             | 69.4         | 32.3                          |
| LEADER <sup>35</sup>           | NEJM 2016        | Liraglutide   | 9340                   | 3.8                                  | 64.3             | 64.2         | 32.5                          |
| PIONEER 6 <sup>33</sup>        | NEJM 2019        | Semaglutide   | 3183                   | 1.3                                  | 66.0             | 68.4         | 32.3                          |
| REWIND <sup>30</sup>           | Lancet 2019      | Dulaglutide   | 9901                   | 5.4                                  | 66.2             | 53.7         | 32.3                          |
| SUSTAIN 6 <sup>34</sup>        | NEJM 2016        | Semaglutide   | 3297                   | 2.1                                  | 64.6             | 60.7         | 32.6                          |
| <b>SGLT2 inhibitors</b>        |                  |               |                        |                                      |                  |              |                               |
| CANVAS <sup>37</sup>           | NEJM 2017        | Canagliflozin | 10 142                 | 2.4                                  | 63.3             | 64.2         | 32.0                          |
| CREDENCE <sup>38</sup>         | NEJM 2019        | Canagliflozin | 4401                   | 2.6                                  | 63.0             | 66.1         | 31.3                          |
| DAPA-HF <sup>11</sup>          | NEJM 2019        | Dapagliflozin | 4744                   | 1.5                                  | 66.3             | 77.6         | 28.2                          |
| EMPA-REG <sup>39</sup>         | NEJM 2015        | Empagliflozin | 7020                   | 3.1                                  | 63.1             | 71.5         | 30.7                          |
| EMPEROR-REDUCED <sup>12</sup>  | NEJM 2020        | Empagliflozin | 3730                   | 1.3                                  | 66.8             | 76.0         | 27.9                          |
| VERTIS-CV <sup>36</sup>        | NEJM 2020        | Ertugliflozin | 8246                   | 3.0                                  | 64.4             | 70.0         | 31.9                          |

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; n.a., not available; SGLT2, sodium glucose transporter 2.

This table shows characteristics of randomized controlled trials included in the meta-analysis.

<sup>a</sup>Median instead of mean.

Table 1 (continued)

| Study                          | T2DM (%) | Mean HbA1c (%) | Mean diabetes duration (years) | Atherosclerotic cardiovascular disease (%) | Heart failure (%) | Hypertension (%) | Current smoker (%) | Mean eGFR (mL/min/1.73 m <sup>2</sup> ) |
|--------------------------------|----------|----------------|--------------------------------|--------------------------------------------|-------------------|------------------|--------------------|-----------------------------------------|
| <b>DPP-4 inhibitors</b>        |          |                |                                |                                            |                   |                  |                    |                                         |
| CARMELINA <sup>27</sup>        | 100      | 7.9            | 14.8                           | 58.5                                       | 26.8              | 91.0             | 10.2               | 54.6                                    |
| EXAMINE <sup>29</sup>          | 100      | 8.0            | 7.2 <sup>a</sup>               | 100                                        | 27.9              | 83.1             | 13.6               | 71.1 <sup>a</sup>                       |
| SAVOR-TIMI 53 <sup>28</sup>    | 100      | 8.0            | 10.7                           | 78.6                                       | 12.8              | 81.8             | n.a.               | 72.6                                    |
| TECOS <sup>26</sup>            | 100      | 7.2            | 11.6                           | 74.0                                       | 18.0              | n.a.             | 11.4               | 74.9                                    |
| <b>GLP-1 receptor agonists</b> |          |                |                                |                                            |                   |                  |                    |                                         |
| EXSCEL <sup>32</sup>           | 100      | 8.0            | 12.0                           | 73.1                                       | 16.2              | n.a.             | 11.7               | 76.3                                    |
| HARMONY <sup>31</sup>          | 100      | 8.7            | 14.2                           | 100                                        | 20.0              | 86.5             | 16.0               | 79.0                                    |
| LEADER <sup>35</sup>           | 100      | 8.7            | 12.9                           | 81.4                                       | 17.9              | 92.4             | n.a.               | n.a.                                    |

Table 1 (continued)

| Study                         | T2DM (%) | Mean HbA1c (%) | Mean diabetes duration (years) | Atherosclerotic cardiovascular disease (%) | Heart failure (%) | Hypertension (%) | Current smoker (%) | Mean eGFR (mL/min/1.73 m <sup>2</sup> ) |
|-------------------------------|----------|----------------|--------------------------------|--------------------------------------------|-------------------|------------------|--------------------|-----------------------------------------|
| PIONEER 6 <sup>33</sup>       | 100      | 8.2            | 14.9                           | 84.6                                       | n.a.              | 95.3             | 10.9               | 74.2                                    |
| REWIND <sup>30</sup>          | 100      | 7.4            | 10.6                           | 31.5                                       | 8.6               | 93.2             | 14.2               | 75.0                                    |
| SUSTAIN 6 <sup>34</sup>       | 100      | 8.7            | 13.9                           | 60.5                                       | 23.6              | 92.8             | n.a.               | n.a.                                    |
| <b>SGLT2 inhibitors</b>       |          |                |                                |                                            |                   |                  |                    |                                         |
| CANVAS <sup>37</sup>          | 100      | 8.2            | 13.5                           | 72.2                                       | 14.4              | 90.0             | 17.8               | 76.5                                    |
| CREDESCENCE <sup>38</sup>     | 100      | 8.3            | 15.8                           | 50.4                                       | 14.8              | 96.8             | 14.5               | 56.2                                    |
| DAPA-HF <sup>11</sup>         | 41.8     | 6.5            | n.a.                           | 56.4                                       | 100               | n.a.             | n.a.               | 65.8                                    |
| EMPA-REG <sup>39</sup>        | 100      | 8.1            | n.a.                           | 75.6                                       | 10.1              | 95.0             | n.a.               | 74.1                                    |
| EMPEROR-REDUCED <sup>12</sup> | 49.8     | n.a.           | n.a.                           | 51.7                                       | 100               | 72.3             | n.a.               | 62.0                                    |
| VERTIS-CV <sup>36</sup>       | 100      | 8.2            | 13.0                           | 75.9                                       | 23.7              | n.a.             | n.a.               | 76.0                                    |

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; n.a., not available; SGLT2, sodium glucose transporter 2.

This table shows characteristics of randomized controlled trials included in the meta-analysis.

\*Median instead of mean.

## Sensitivity analysis of sodium glucose transporter 2 inhibitors for *hospitalization for heart failure*

DAPA-HF<sup>11</sup> and EMPEROR-REDUCED<sup>12</sup> were conducted in primary HFrEF patient populations (Table 1). Their comparison to primary T2DM populations (Figure 3) showed remarkably higher efficacy of SGLT2 inhibitors for *hospitalization for heart failure* in HFrEF patients [Meta-NNT 25 (95% CI: 19 to 39) vs. Meta-NNT 233 (95% CI 167 to 385)] at 16 months of follow-up.

## Discussion

In this meta-analysis of absolute treatment effects of novel antidiabetic drugs in all available trials and in HFrEF subpopulations, we found that (i) GLP-1 receptor agonists and SGLT2 inhibitors were both effective to reduce *cardiovascular mortality*; (ii) the most effective drug class to reduce *hospitalization for heart failure* was SGLT2 inhibitors, with the highest efficacy in patients with HFrEF compared with primary T2DM populations; and (iii) DPP-4 inhibitors were not effective to reduce either endpoint.

GLP-1 receptor agonists and SGLT2 inhibitors have received Class I recommendations in T2DM<sup>8,9</sup> and heart failure<sup>10</sup> guidelines for their potential to reduce CVD events and mortality; however, relevant CVOTs predominantly reported relative measures of effect (HRs, odds ratios, and risk ratios). Those normalize treatment effects to the baseline risk of the placebo population. Although this results in relatively stable results across the whole risk spectrum, results can also be misleading: A statistically highly significant relative risk reduction of 50% may turn out to be clinically irrelevant, if the baseline risk is very low for an event in the placebo group. The higher the baseline risk of a population, the more impact on absolute risk reduction can be expected from an intervention such as a study drug. Guidelines thus recommend reporting of both relative and absolute effect measures.<sup>42</sup> The latter are key for assessment of treatment efficacy, comparison to other drug classes, cost/benefit calculations, and explanation of benefits to patients.

All trials included in this analysis were rigorously designed and well-conducted international studies with low risk of bias.<sup>14,15</sup> All trials included high to very high cardiovascular risk patient populations with long-term T2DM and a high prevalence of atherosclerotic CVD and chronic kidney disease (Table 1); DAPA-HF and EMPEROR-REDUCED were conducted in populations with HFrEF, of whom 40–50% had diabetes mellitus. Treatment effects in this high baseline risk population were large—and meta-analysis of almost 100 000 patients for each endpoint thus provides robust absolute treatment effect estimates.

In contrast, however, no single trial of any of the three drug classes showed a particularly high level of efficacy on



**Table 2** Effect estimates for the outcome of *cardiovascular mortality*

| Study                          | Number of digitalized events (n) | Number of patients (n) | Event proportion (%) | Median duration of follow-up (years) | Original HR [95% CI] | Extracted HR [95% CI] | Weibull HR [95% CI] |
|--------------------------------|----------------------------------|------------------------|----------------------|--------------------------------------|----------------------|-----------------------|---------------------|
| <b>DPP-4 inhibitors</b>        |                                  |                        |                      |                                      |                      |                       |                     |
| CARMELINA <sup>27</sup>        | 518                              | 6991                   | 7.4                  | 2.2                                  | 0.96 [0.81 to 1.14]  | 0.96 [0.81 to 1.14]   | 0.96 [0.80 to 1.13] |
| EXAMINE <sup>29</sup>          | 237                              | 5380                   | 4.4                  | 1.5                                  | 0.85 [0.66 to 1.10]  | 0.86 [0.66 to 1.11]   | 0.86 [0.64 to 1.08] |
| <b>GLP-1 receptor agonists</b> |                                  |                        |                      |                                      |                      |                       |                     |
| EXSCEL <sup>32</sup>           | 703                              | 14 752                 | 4.8                  | 3.2                                  | 0.88 [0.76 to 1.02]  | 0.88 [0.76 to 1.02]   | 0.88 [0.75 to 1.01] |
| HARMONY <sup>31</sup>          | 252                              | 9463                   | 2.7                  | 1.6                                  | 0.93 [0.73 to 1.19]  | 0.90 [0.70 to 1.15]   | 0.92 [0.69 to 1.15] |
| LEADER <sup>35</sup>           | 493                              | 9340                   | 5.3                  | 3.8                                  | 0.78 [0.66 to 0.93]  | 0.77 [0.65 to 0.93]   | 0.78 [0.64 to 0.92] |
| PIONEER 6 <sup>33</sup>        | 43                               | 3183                   | 1.4                  | 1.3                                  | 0.49 [0.27 to 0.92]  | 0.48 [0.25 to 0.90]   | 0.47 [0.17 to 0.76] |
| REWIND <sup>30</sup>           | 657                              | 9901                   | 6.6                  | 5.4                                  | 0.91 [0.78 to 1.06]  | 0.91 [0.78 to 1.06]   | 0.91 [0.77 to 1.05] |
| SUSTAIN 6 <sup>34</sup>        | 70                               | 3297                   | 2.1                  | 2.1                                  | 0.98 [0.65 to 1.48]  | 0.94 [0.59 to 1.51]   | 0.94 [0.50 to 1.38] |
| <b>SGLT2 inhibitors</b>        |                                  |                        |                      |                                      |                      |                       |                     |
| CANVAS <sup>37</sup>           | 471                              | 10 142                 | 4.6                  | 2.4                                  | 0.87 [0.72 to 1.06]  | 0.88 [0.73 to 1.06]   | 0.89 [0.73 to 1.06] |
| CREDENCE <sup>38</sup>         | 249                              | 4401                   | 5.7                  | 2.6                                  | 0.78 [0.61 to 1.00]  | 0.77 [0.60 to 0.99]   | 0.77 [0.58 to 0.96] |
| DAPA-HF <sup>11</sup>          | 498                              | 4744                   | 10.5                 | 1.5                                  | 0.82 [0.69 to 0.98]  | 0.82 [0.69 to 0.98]   | 0.82 [0.68 to 0.97] |
| EMPA-REG <sup>39</sup>         | 301                              | 7020                   | 4.3                  | 3.1                                  | 0.62 [0.49 to 0.77]  | 0.60 [0.48 to 0.75]   | 0.60 [0.46 to 0.74] |
| VERTIS-CV <sup>36</sup>        | 505                              | 8246                   | 6.1                  | 3.0                                  | 0.92 [0.77 to 1.11]  | 0.90 [0.75 to 1.09]   | 0.91 [0.74 to 1.07] |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.

This table shows effect estimates of individual studies for the outcome of *cardiovascular mortality*; depicted are raw event rates, originally reported hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull model, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

**Table 2** (continued)

| Study                          | NNT [95% CI]<br>12 months | NNT [95% CI]<br>24 months | NNT [95% CI]<br>36 months | NNT [95% CI]<br>48 months |
|--------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| <b>DPP-4 inhibitors</b>        |                           |                           |                           |                           |
| CARMELINA <sup>27</sup>        | 995 [180 to ∞ to –282]    | 444 [80 to ∞ to –126]     | 282 [51 to ∞ to –80]      | —                         |
| EXAMINE <sup>29</sup>          | 211 [80 to ∞ to –325]     | 123 [46 to ∞ to –190]     | —                         | —                         |
| <b>GLP-1 receptor agonists</b> |                           |                           |                           |                           |
| EXSCEL <sup>32</sup>           | 760 [349 to ∞ to –4279]   | 327 [151 to ∞ to –1886]   | 202 [93 to ∞ to –1168]    | 144 [66 to ∞ to –834]     |
| HARMONY <sup>31</sup>          | 754 [192 to ∞ to –391]    | 358 [91 to ∞ to –186]     | —                         | —                         |
| LEADER <sup>35</sup>           | 396 [230 to 1437]         | 173 [101 to 602]          | 107 [63 to 370]           | 77 [45 to 264]            |
| PIONEER 6 <sup>33</sup>        | 138 [76 to 774]           | —                         | —                         | —                         |
| REWIND <sup>30</sup>           | 1662 [627 to ∞ to –2548]  | 634 [239 to ∞ to –980]    | 363 [137 to ∞ to –563]    | 246 [93 to ∞ to –382]     |
| SUSTAIN 6 <sup>34</sup>        | 1424 [159 to ∞ to –205]   | —                         | —                         | —                         |
| <b>SGLT2 inhibitors</b>        |                           |                           |                           |                           |
| CANVAS <sup>37</sup>           | 806 [309 to –1318]        | 379 [145 to ∞ to –620]    | 246 [94 to ∞ to –401]     | 181 [69 to ∞ to –295]     |
| CREDENCE <sup>38</sup>         | 262 [133 to 8805]         | 103 [53 to 2449]          | 61 [31 to 1395]           | —                         |
| DAPA-HF <sup>11</sup>          | 82 [43 to 826]            | 39 [21 to 389]            | —                         | —                         |
| EMPA-REG <sup>39</sup>         | 175 [116 to 353]          | 74 [50 to 143]            | 45 [30 to 86]             | 32 [22 to 61]             |
| VERTIS-CV <sup>36</sup>        | 787 [272 to ∞ to –878]    | 338 [117 to ∞ to –379]    | 208 [72 to ∞ to –233]     | 149 [51 to ∞ to –167]     |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.

This table shows effect estimates of individual studies for the outcome of *cardiovascular mortality*; depicted are raw event rates, originally reported hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull model, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

*cardiovascular mortality* (Table 2): DPP-4 inhibitors did not show any effects; GLP-1 receptor agonists showed the lowest 4 year NNT of 77 in the LEADER trial; and SGLT2 inhibitors reached the best efficacy in DAPA-HF (24 month NNT of 39) and EMPA-REG (48 month NNT of 32). In comparison, the Meta-NNT across all trials at the median follow-up time was 261 for GLP-1 receptor agonists and 118 for SGLT2 inhibitors. These effects of all three drug classes on *cardiovascular mortality* do not seem very impressive when compared on

an absolute scale: Metformin as the long-term standard of care in oral antidiabetic therapy has been estimated with a 10 year NNT of ~10–20 for major endpoints.<sup>43</sup> Typical heart failure medication (beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor agonists, sacubitril/valsartan, etc.) showed estimated 5 year NNTs for all-cause mortality of ~8–24.<sup>44,45</sup> These data put GLP-1 receptor agonists and SGLT2 inhibitors in similar efficacy categories as PCSK9 inhibitors or statins for *cardiovascular mortality*.<sup>46</sup>

**Table 3** Effect estimates for the outcome of *hospitalization for heart failure*

| Study                          | Number of digitalized events (n) | Number of patients (n) | Event proportion (%) | Median duration of follow-up (years) | Original HR [95% CI] | Extracted HR [95% CI] |
|--------------------------------|----------------------------------|------------------------|----------------------|--------------------------------------|----------------------|-----------------------|
| <b>DPP-4 inhibitors</b>        |                                  |                        |                      |                                      |                      |                       |
| CARMELINA <sup>27</sup>        | 431                              | 6991                   | 6.2                  | 2.2                                  | 0.90 [0.74 to 1.08]  | 0.90 [0.74 to 1.08]   |
| SAVOR-TIMI 53 <sup>28</sup>    | 517                              | 16 492                 | 3.1                  | 2.1                                  | 1.27 [1.07 to 1.51]  | 1.26 [1.06 to 1.50]   |
| TECOS <sup>26</sup>            | 439                              | 14 671                 | 3.0                  | 3.0                                  | 1.00 [0.83 to 1.20]  | 0.98 [0.81 to 1.18]   |
| <b>GLP-1 receptor agonists</b> |                                  |                        |                      |                                      |                      |                       |
| EXSCEL <sup>32</sup>           | 434                              | 14 752                 | 2.9                  | 3.2                                  | 0.94 [0.78 to 1.13]  | 0.94 [0.78 to 1.14]   |
| LEADER <sup>35</sup>           | 463                              | 9340                   | 5.0                  | 3.8                                  | 0.87 [0.73 to 1.05]  | 0.87 [0.72 to 1.04]   |
| <b>SGLT2 inhibitors</b>        |                                  |                        |                      |                                      |                      |                       |
| CANVAS <sup>37</sup>           | 243                              | 10 142                 | 2.4                  | 2.4                                  | 0.67 [0.52 to 0.87]  | 0.68 [0.53 to 0.88]   |
| DAPA-HF <sup>11</sup>          | 545                              | 4744                   | 11.5                 | 1.5                                  | 0.70 [0.59 to 0.83]  | 0.71 [0.60 to 0.84]   |
| EMPA-REG <sup>39</sup>         | 212                              | 7020                   | 3.0                  | 3.1                                  | 0.65 [0.50 to 0.85]  | 0.63 [0.48 to 0.83]   |
| EMPEROR-REDUCED <sup>12</sup>  | 552                              | 3730                   | 14.8                 | 1.3                                  | 0.69 [0.59 to 0.81]  | 0.69 [0.59 to 0.82]   |
| VERTIS-CV <sup>36</sup>        | 229                              | 8246                   | 2.8                  | 3.0                                  | 0.70 [0.54 to 0.90]  | 0.68 [0.52 to 0.88]   |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.

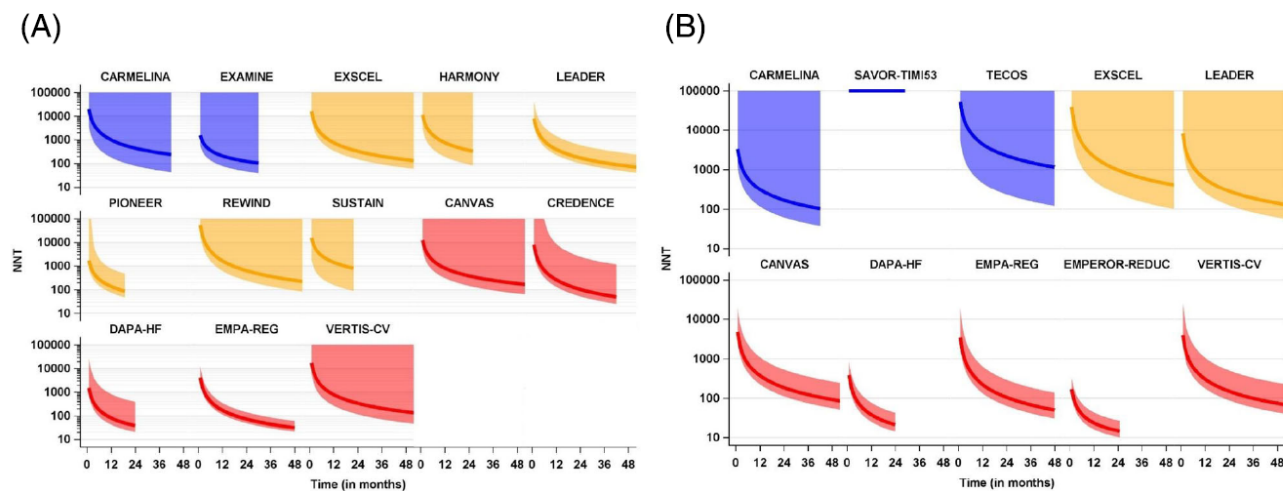
This table shows effect estimates of individual studies for the outcome of *hospitalization for heart failure*; depicted are raw event rates, original study hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull models, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.**Table 3** (continued)

| Study                          | Weibull HR [95% CI] | NNT [95% CI] 12 months   | NNT [95% CI] 24 months  | NNT [95% CI] 36 months  | NNT [95% CI] 48 months  |
|--------------------------------|---------------------|--------------------------|-------------------------|-------------------------|-------------------------|
| <b>DPP-4 inhibitors</b>        |                     |                          |                         |                         |                         |
| CARMELINA <sup>27</sup>        | 0.90 [0.73 to 1.07] | 317 [116 to ∞ to -440]   | 168 [62 to ∞ to -233]   | 117 [43 to ∞ to -163]   | —                       |
| SAVOR-TIMI 53 <sup>28</sup>    | 1.25 [1.03 to 1.47] | -267 [-1178 to -150]     | -144 [-629 to -81]      | —                       | —                       |
| TECOS <sup>26</sup>            | 0.98 [0.80 to 1.16] | 4463 [463 to ∞ to -584]  | 2257 [234 to ∞ to -296] | 1522 [158 to ∞ to -199] | 1154 [120 to ∞ to -151] |
| <b>GLP-1 receptor agonists</b> |                     |                          |                         |                         |                         |
| EXSCEL <sup>32</sup>           | 0.94 [0.76 to 1.12] | 2190 [536 to ∞ to -1052] | 983 [241 to ∞ to -473]  | 619 [152 to ∞ to -297]  | 447 [110 to ∞ to -215]  |
| LEADER <sup>35</sup>           | 0.87 [0.71 to 1.03] | 588 [257 to ∞ to -2006]  | 285 [125 to ∞ to -988]  | 188 [82 to ∞ to -654]   | 140 [61 to ∞ to -489]   |
| <b>SGLT2 inhibitors</b>        |                     |                          |                         |                         |                         |
| CANVAS <sup>37</sup>           | 0.67 [0.50 to 0.84] | 374 [225 to 1101]        | 185 [112 to 530]        | 123 [74 to 351]         | 92 [56 to 264]          |
| DAPA-HF <sup>11</sup>          | 0.71 [0.59 to 0.83] | 38 [26 to 77]            | 21 [14 to 43]           | —                       | —                       |
| EMPA-REG <sup>39</sup>         | 0.63 [0.46 to 0.81] | 223 [135 to 648]         | 105 [64 to 291]         | 68 [42 to 186]          | 50 [31 to 137]          |
| EMPEROR-REDUCED <sup>12</sup>  | 0.69 [0.58 to 0.81] | 24 [16 to 44]            | 15 [10 to 27]           | —                       | —                       |
| VERTIS-CV <sup>36</sup>        | 0.67 [0.50 to 0.85] | 305 [178 to 1076]        | 150 [88 to 502]         | 99 [58 to 328]          | 74 [44 to 245]          |

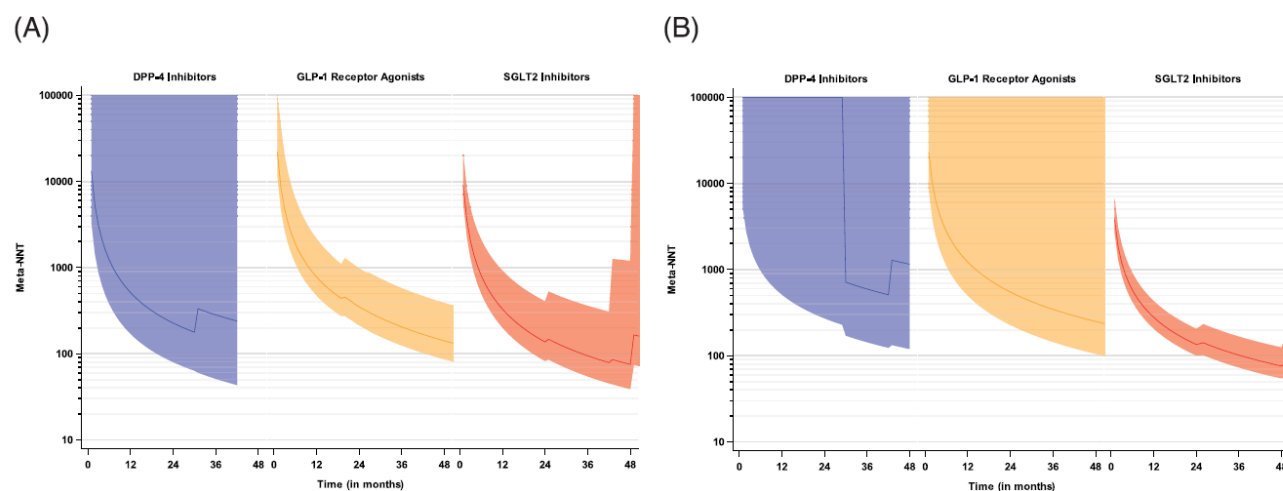
DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.

This table shows effect estimates of individual studies for the outcome of *hospitalization for heart failure*; depicted are raw event rates, original study hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull models, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

**Figure 1** Numbers needed to treat (NNTs) over study follow-up time for individual studies, for the outcome of (A) *cardiovascular mortality* and (B) *hospitalization for heart failure*. Blue: dipeptidyl peptidase-4 inhibitors, yellow: glucagon-like peptide-1 receptor agonists, red: sodium glucose transporter 2 inhibitors with their pointwise 95% confidence intervals. Estimates and confidence intervals are truncated from above at 100 000.



**Figure 2** Random-effects inverse-variance meta-analysis of numbers needed to treat (Meta-NNT, with 95% confidence interval) over study follow-up time for the outcomes of (A) *cardiovascular mortality* and (B) *hospitalization for heart failure*. Data were pooled from all studies according to study drug. Estimates and confidence intervals are truncated from above at 100 000. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.

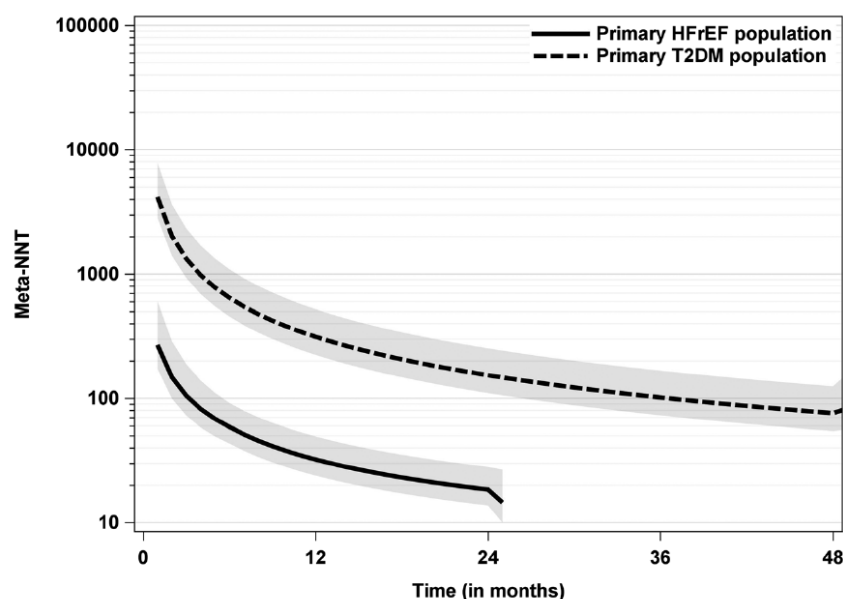


Regarding *hospitalization for heart failure*, GLP-1 receptor agonists and DPP-4 inhibitors showed no effects on this endpoint, either in single trials or in meta-analysis. SGLT2 inhibitors showed considerable effects (Meta-NNT at median follow-up of 126), which were especially large in the HFrEF trials DAPA-HF (24 month NNT of 21) and EMPEROR-REDUCED (24 month NNT of 15) and thus compa-

rable with other established guideline-recommended heart failure medication.<sup>44,45</sup> This is a substantial difference between primary HFrEF populations and primary T2DM populations (Figure 3), even though population characteristics other than ejection fraction were similar (Table 1). SGLT2 inhibitors are thus very effective for the endpoint of *hospitalization for heart failure*, especially in HFrEF patient populations, with



**Figure 3** Sensitivity analysis of numbers needed to treat (Meta-NNT, with 95% confidence interval) with sodium glucose transporter 2 inhibitors to reduce *hospitalization for heart failure*, stratified for studies with primary type 2 diabetes mellitus (T2DM) or primary heart failure with reduced ejection fraction (HFrEF) populations. Estimates and confidence intervals are truncated from above at 100 000.



smaller effects in non-HFrEF patients (Figure 3). This is confirmed by recent findings from EMPEROR-PRESERVED,<sup>13</sup> which found a 26 month NNT of ~31 for *hospitalization for heart failure* and of ~111 for *cardiovascular mortality*—again with 50% of the population also suffering from diabetes mellitus. Unfortunately, other trials in HFpEF are not yet available, which rendered further meta-analysis of HFpEF futile. Further research on the underlying mechanism for these surprisingly strong effects in heart failure is ongoing.<sup>47</sup> In addition, these results make SGLT2 inhibitors promising tools to reduce expenditures in heart failure care, where hospitalizations are the main driver of cost.<sup>48</sup>

Davies *et al.* previously performed an analysis of NNT for the class of GLP-1 receptor agonists,<sup>49</sup> however, not for the other two drug classes. Ludwig *et al.* reported NNTs for two drug classes<sup>25</sup> at median follow-up time points; however, they did not use original data but relied on formulas for summary data. Both groups used other software tools for data digitalization and different statistical models to arrive at NNT estimates as compared with our approach<sup>25,49</sup>—however with very similar results. Palmer *et al.* recently published a very large network meta-analysis<sup>50</sup> of GLP-1 receptor agonists and SGLT2 inhibitors including 764 trials with absolute treatment effect estimates, however did not use digitalization of time-to-event data, and thus offered no time-sensitive analysis. Hence, our work is the first to present absolute treatment effects in all three drug classes and offer time-sensitive meta-analysis of individual patient outcomes of *cardiovascular mortality* and *hospitalization for heart failure* in the large CVOTs.

## Limitations

Trials were selected based on a common definition of CVOTs in diabetes mellitus<sup>6</sup>; however, there was no systematic literature review performed. Trial and population heterogeneity introduces unavoidable bias into this analysis, as in any other meta-analysis. This work relies on digitalized individual patient outcomes and fitted Weibull models rather than the original patient data, which renders analysis of endpoint associations with patient characteristics or other outcomes [e.g. haemoglobin A1c (HbA1c) and adverse events] impossible. However, this inherent main limitation is unavoidable, as no pooled primary data are available to perform such an analysis in a different way. To account for this and ensure validity of our methods, we performed sensitivity analyses on different levels and found that the full Weibull survival curves (from which the NNTs are directly derived) give excellent fits to the digitalized survival data; they additionally allow computation of HR and thus a comparison to the extracted data. The original studies used Cox models with proportional hazards assumptions, which—of course—might also be wrong.<sup>51</sup> And a parametric model additionally allows for directly estimating survival probabilities and NNTs.

As the full individual patient data were not available, it was impossible to adjust for the parallel competing risk of all-cause mortality. Although this would probably be less of a problem with the outcome of *cardiovascular mortality* (because most deaths in the CVOTs would be cardiovascular deaths), this might be an issue for *hospitalization for heart failure*: A patient who dies in the course of the trial is no lon-

ger at risk for this endpoint. We expect the risks for dying and *hospitalization for heart failure* to be positively correlated, and thus, we expect treatment effects rather being estimated as too small than overestimated.

## Conclusions

In this meta-analysis of digitalized individual patient outcomes from CVOTs of novel antidiabetic drugs, we report absolute treatment benefits of GLP-1 receptor agonists and SGLT2 inhibitors on *cardiovascular mortality* and *hospitalization for heart failure*. Although the magnitude of effect of both drugs was rather small in primary T2DM populations, SGLT2 inhibitors showed high efficacy to prevent *hospitalization for heart failure* in patients with reduced ejection fraction, where they were comparable in effect to established heart failure medication.

## Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

## Conflicts of interest

All authors declare that there was no financial or other support from any industry or third party for the submitted work.

Unrelated to this work, OK received honoraria for biostatistical education from Berlin-Chemie. MR received personal

fees from Allergan, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Fishawack Group, Gilead Sciences, Intercept Pharma, Inventiva, Novartis, Novo Nordisk, Pfizer, ProSciento, Sanofi US, and Target RWE and investigator-initiated research support from Boehringer-Ingelheim, Nutricia/Danone, and Sanofi-Aventis.

## Funding

There was no direct funding for this project. GW was personally supported by the *Forschungskommission* of the Medical Faculty of the Heinrich Heine University Düsseldorf (No. 2018-32 for a Clinician Scientist Track).

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Individual Trial Endpoint Definitions.

**Figure S1.** Scatterplots to compare the hazard ratios (HRs) from the original publications (x-axis, with 95% CI) with the hazard ratios from the fitted Weibull model of the extracted data (y-axis, with 95% CI), both for outcomes of a) *Cardiovascular Mortality* and b) *Hospitalization for Heart Failure*.

**Figure S2.** Kaplan–Meier plots of the Weibull model fit from extracted data, for the placebo groups (red, with 95% CI) in comparison to the treatment groups (blue, with 95% CI), both for outcomes of a) *Cardiovascular Mortality* and b) *Hospitalization for Heart Failure*.

## References

1. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, de Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P, European Society of Cardiology, Mimoso J, Artan G, Aurel D, Chettibi M, Hammoudi N, Sisakian H, Pepoyan S, Metzler B, Siostrzonek P, Weidinger F, Jahangirov T, Aliyev F, Rustamova Y, Manak N, Mrochak A, Lancellotti P, Pasquet A, Claeys M, Kušljugić Z, Dizdarević Hudić L, Smajić E, Tokmakova MP, Gatzov PM, Milicic D, Bergovec M, Christou C, Moustra HH, Christodoulides T, Linhart A, Taborsky M, Hansen HS, Holmvang L, Kristensen SD, Abdelhamid M, Shokry K, Kampus P, Viigimaa M, Ryödi E, Niemelä M, Rissanen TT, le Heuzey JY, Gilard M, Aladashvili A, Gamkrelidze A, Kereselidze M, Zeiher A, Katus H, Bestehorn K, Tsioufis C, Goudevenos J, Csanádi Z, Becker D, Tóth K, Jóna Hrafnkelsdóttir Þ, Crowley J, Kearney P, Dalton B, Zahger D, Wolak A, Gabrielli D, Indolfi C, Urbinati S, Imantayeva G, Berkinbayev S, Bajraktari G, Ahmeti A, Berisha G, Erkin M, Saamay A, Erglis A, Bajare I, Jegere S, Mohammed M, Sarkis A, Saadeh G, Zvirblyte R, Sakalyte G, Slapikas R, Ellafi K, el Ghamari F, Banu C, Beissel J, Felice T, Buttigieg SC, Xuereb RG, Popovici M, Boskovic A, Rabrenovic M, Ztot S, Abir-Khalil S, van Rossum AC, Mulder BJM, Elsendoorn MW, Srbinska-Kostovska E, Kostov J, Marjan B, Steigen T, Mjølstad OC, Ponikowski P, Witkowski A, Jankowski P, Gil VM, Mimoso J, Baptista S, Vinereanu D, Chioncel O, Popescu BA, Shlyakhto E, Oganov R, Foscoli M, Zavatta M, Dikic AD, Beleslin B, Radovanovic MR, Hlivák P, Hatala R, Kaliská G, Kenda M, Fras Z, Anguita M, Cequier Á, Muñiz J, James S, Johansson B, Platonov P, Zellweger MJ, Pedrazzini GB, Carballo D, Shebli HE, Kabbani S, Abid L, Addad F, Bozkurt E, Kayıkcioglu M, Erol MK, Kovalenko V, Nesukay E, Wragg A, Ludman P, Ray S, Kurbanov R, Boateng D, Daval G, de Benito Rubio V, Sebastiao D, de Courtelary PT, Bardinnet I. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *Eur Heart J*. 2019; **41**: 12–85.
2. WHO. Cardiovascular diseases—key facts [Online source]. 2021. Available from: <https://www.who.int/news->



- room/fact-sheets/detail/cardiovascular-diseases-cvds). Accessed Dec 17, 2021
- WHO. The top 10 causes of death [Online source]. 2020. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. Accessed Dec 17, 2021
  - Braunwald E. Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997; **337**: 1360–1369.
  - Roger VL. Epidemiology of heart failure. *Circ Res*. 2021; **128**: 1421–1434.
  - Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, Green JB, Buse JB, Inzucchi SE, Leiter LA, Raz I, Rosenstock J, Riddle MC. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* editors' expert forum. *Diabetes Care*. 2018; **41**: 14–31.
  - U.S. Food and Drug Administration. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes [Internet]. 2008.
  - ADA. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. *Diabetes Care*. 2021; **44**: S111–S24.
  - Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group, Piepoli MF, Birkeland KI, Adamopoulos S, Ajjan R, Avogaro A, Baigent C, Brodmann M, Bueno H, Ceconi C, Chioncel O, Coats A, Collet JP, Collins P, Cosyns B, di Mario C, Fisher M, Fitzsimons D, Halvorsen S, Hansen D, Hoes A, Holt RIG, Home P, Katus HA, Khunti K, Komajda M, Lambrinou E, Landmesser U, Lewis BS, Linde C, Lorusso R, Mach F, Mueller C, Neumann FJ, Persson F, Petersen SE, Petronio AS, Richter DJ, Rosano GMC, Rossing P, Rydén L, Shlyakhto E, Simpson IA, Touyz RM, Wijns W, Wilhelm M, Williams B, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, Windecker S, Aboyans V, Baigent C, Collet JP, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee DE, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen SE, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Zelveian PH, Scherr D, Jahangirov T, Lazareva I, Shivalkar B, Naser N, Gruet I, Milicic D, Petrou PM, Linhart A, Hildebrandt P, Hasan-Ali H, Marandi T, Lehto S, Mansourati J, Kurashvili R, Siasos G, Lengyel C, Thrainsdottir IS, Aronson D, di Lenarda A, Raissova A, Ibrahim P, Abilova S, Trusinskis K, Saade G, Benlamin H, Petrulioniene Z, Banu C, Magri CJ, David L, Boskovic A, Alami M, Liem AH, Bosevski M, Svingen GFT, Janion M, Gavina C, Vinereanu D, Nedogoda S, Mancini T, Illic MD, Fabryova L, Frasz Z, Jiménez-Navarro MF, Norhammar A, Lehmann R, Mourali MS, Ural D, Nesukay E, Chowdhury TA. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2019; **41**: 255–323.
  - McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
  - McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; **381**: 1995–2008.
  - Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiere E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020; **383**: 1413–1424.
  - Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-la Rocca HP, Choi DJ, Chopra V, Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021; **385**: 1451–1461.
  - Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019; **7**: 776–785.
  - Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019; **393**: 31–39.
  - Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010; **340**: c332.
  - Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ. GRADE guidelines: 12. Preparing summary of findings tables—binary outcomes. *J Clin Epidemiol*. 2013; **66**: 158–172.
  - Sciences TaoM. Sources of evidence for assessing the safety, efficacy and effectiveness of medicines [Online source]. 2017. Available from: <https://acmedsci.acuk/file-download/86466482>. Accessed Oct 10, 2020
  - Rohatgi A. WebPlotDigitizer [Online source]. 2019. Available from: <https://automerisio/WebPlotDigitizer/>. Accessed Oct 10, 2020
  - Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012; **12**: 9.
  - Drevon D, Fursa SR, Malcolm AL. Inter-coder reliability and validity of WebPlotDigitizer in extracting graphed data. *Behav Modif*. 2017; **41**: 323–339.
  - Moeyert M, Maggin D, Verkuilen J. Reliability, validity, and usability of data extraction programs for single-case research designs. *Behav Modif*. 2016; **40**: 874–900.
  - Saluja R, Cheng S, Delos Santos KA, Chan KKW. Estimating hazard ratios from published Kaplan-Meier survival curves: a methods validation study. *Res Synth Methods*. 2019; **10**: 465–475.
  - Collett D. *Modelling Survival Data in Medical Research*, 3rd ed. Chapman and Hall/CRC; 2015. p 548.
  - Ludwig L, Darmon P, Guerci B. Computing and interpreting the Number Needed to Treat for Cardiovascular Outcomes Trials: perspective on GLP-1 RA and SGLT-2i therapies. *Cardiovasc Diabetol*. 2020; **19**: 65.
  - Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, van de Werf F, Peterson ED, Holman RR. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015; **373**: 232–242.



27. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK, for the CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019; **321**: 69–79.
28. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederick R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013; **369**: 1317–1326.
29. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F, EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013; **369**: 1327–1335.
30. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanis F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WHH, Temelkova-Kurktschiev T, Abella M, Alebuena A, Almagro S, Amoroso E, Anadon P, Andreu E, Aristimuño G, Arzadun M, Barbieri M, Barcudi R, Bartolacci I, Bolobanich G, Bordonava A, Bustamante Labarta M, Bustos B, Caccavo A, Camino A, Cantero M, Carignano M, Cartasegna L, Cipullo M, Commendatore V, Conosciuto V, Costamagna O, Crespo C, Cuello J, Cuneo C, Cusimano S, Dean S, Ditturo C, Dominguez A, Farah M, Fernandez A, Fernandez F, Ferrari A, Flammia P, Fuentealba J, Gallardo KB, Garcia C, Garcia Duran R, Garrido M, Gavicola R, Gerbaudo C, Gilli G, Giotto AP, Godoy Bolzán P, Gomez Vilamajo O, Guerlloy F, Guridi C, Gutierrez Garrido N, Hasbani E, Hermida S, Hominal M, Hrabar A, Ingaramo A, Izzicupo A, Krynski M, Lagrutta M, Lanchiotti P, Langhe M, Leonard V, Llanos J, Lopez Santi R, Lowenstein J, Luquez C, Mackinnon I, Mana M, Manzur S, Marino J, Martella C, Martinez R, Matias R, Matkovich J, Meritano M, Montaña O, Mulazzi M, Ochoa J, Paterlini G, Pelagagge M, Peralta Lopez ME, Prado A, Pruyas L, Racca M, Ricotti C, Rodriguez C, Romero Vidomlansky M, Ronderos R, Sadowski AL, Sala J, Sánchez A, Santoro A, Schiavi L, Sein M, Sernia V, Serra L, Sicer M, Smith T, Soso L, Sposetti G, Steinacher A, Stival J, Tedesco J, Tonin H, Tortolo M, Ulla M, Vallejos J, Vico M, Virgillito L, Visco V, Vogel D, Waisman F, Zaidman C, Zucchiatti N, Badshah I, Cohen N, Colman P, Colquhoun D, Davis T, Fourlanos S, Fulcher G, Hamlyn J, Haywood C, Hocking S, Hutchinson M, Jeffries W, Kyl M, Lo C, Mah PM, Makepeace A, Marope D, Nanayakkar N, Nankervis A, Palmer N, Palolus B, Pillai S, Price S, Price S, Proietto J, Reutens A, Rodrigo N, Sheikh A, Smith G, So M, Soldatos G, Stuckey B, Sumithran P, Teede H, Vora P, Williams L, Abib E, Adão Poço C, Alves EF, Andreatta Bernardi Barea J, Avezum Oliveira L, Castro DLC, Correa da Cruz I, Costa M, Cruz I, Cunha S, da Silva MAV, de Carvalho Camara Bona R, de Paula B, Eliaschewitz F, Fazolli G, Ferreira Filho CA, Fortes J, França C, Franco DR, Genestreti PR, Giorgeto F, Gonçalves RM, Grossman ME, Henrique Marcelino AC, Hernandez M, Horta A, Jaeger C, Kaneblair M, Kauffman Rutenberg C, Kerr Saraiva JF, Lemos MA, Maia L, Manenti ER, Marques M, Melissa Valerio C, Moreira R, Mothé F, Mouco OM, Moura P, Moura Jorge JC, Nakashima C, Nakazone M, Napoli T, Nunes C, Nunes Salles JE, Oliveira K, Oliveira M, Pantano GS, Petri F, Piazza L, Pires AC, Pizzato P, Prata S, Precoma D, Rech R, Reis G, Reis H, Resende E, Ribas Fortes J, Rodovalho S, Rossi dos Santos F, Salles JE, Sampaio CR, Santos T, Santos dos Santos V, Silva e Quadros T, Silveira D, Siqueira KN, Teixeira M, Uehara M, Valerio C, Vianna H, Vidotti MH, Visconti GL, Zanella MT, Andreeva V, Borisov R, Botushanov N, Dimitrov G, Dimova K, Dragoychev T, Grigorova V, Gushterova V, Ivanov I, Kocelova T, Kurktschiev D, Miletieva M, Nenkov-Gugusheva N, Pancheva R, Pavlova M, Raev D, Spasova V, Stoikov A, Troev D, Yanev T, Yoncheva-Mihaylova M, Abitbol A, Ajala B, Alguwaihes A, Ardilouze JL, Aris-Jilwan N, Arnaout A, Aronson R, Aslam N, Babin S, Bailargeon JP, Bailey A, Bajaj H, Beauchesne C, Beca S, Belanger A, Bell A, Bellabarba D, Berard L, Berenbaum B, Bergeron V, Berlingieri J, Bernier F, Bishara P, Blank D, Blumer I, Brault S, Breton D, Carpentier A, Cha J, Chandra P, Chiasson JL, Conway JR, Couture G, Couture N, Dagenais G, Datta D, D'Ignazio G, Dumas R, Fay D, Frechette A, Frenette L, Fung D, Gagnon N, Galter M, Garon J, Gauthier JS, Geadah C, Gilbert J, Girard R, Goldenberg R, Grossman LD, Gupta N, Halle JP, Hivert MF, Houde G, Houlden R, Hramiak I, Jablonski T, Jain AJ, Khandwala H, Khosla M, Lachance C, Laflamme E, Langlois MF, Larivee L, Liutkus J, Lochnan H, Malik S, McDonald C, Mehta P, Mihailidis J, Milot A, Narula P, Nault P, Nayar A, Niskier W, Ouellet G, Palardy J, Patel M, Paul T, Pedersen S, Perron P, Pesant MH, Poirier P, Poulin MC, Punthakee Z, Rehman W, Ross S, Sagar P, Saliba N, Sandler S, Schiffrin A, Schlosser R, Seth-Sharma A, Sherman M, Sionit D, Sivakumar T, Soto J, St-Amour E, Steen O, Sussman J, Telner A, Tobe S, Twum-Barima DY, van Zanten A, VanRossum N, Vecchiarelli J, Ward R, Wessengel J, Weisnagel S, Wilderman I, Woo V, Yakubovich N, Yale JF, Yared Z, Acevedo M, Aguirre ML, Aizman A, Barroso MS, Cobos L, Danin Vargas A, Descalzi B, Godoy G, Grumberg E, Lahsen RM, Larenas G, Ortiz E, Paredes J, Potthoff S, Retamal E, Rojas L, Salgado M, Santibanez C, Solis C, Stokins B, Accini J, Acebedo J, Agudelo Baena LM, Alarcon S, Angel J, Arcos E, Aroca Martinez M, Atuesta L, Balaguera J, Ballestas D, Barrera SI, Barrios Reyes R, Bayona A, Bermudez A, Bernal DZ, Blanquicett M, Bravo V, Bueno W, Burbano Delgado A, Cadena A, Cadena A, Caicedo S, Celemin C, Consuegra R, Contreras Pimienta C, Corredor KJ, Cure C, de la Hoz Rueda LD, Delgado E, Diaz S, Diego M, Donado A, Encinales Sanabria W, Escobar J, Escorcia G, Forero L, Fuentes L, Garcia M, Garcia Lozada H, Garcia Ortiz L, Giraldo A, Gomez Gonzalez L, Granada J, Gutierrez C, Henao N, Hernandez E, Herrera Uejbe OM, Higuera Cobos JD, Ibarra Gómez J, Jaimes EH, Jaramillo M, Jaramillo N, Jaramillo Gomez C, Jaramillo Sanchez M, Jarava Durán I, Lopez Ceballos C, Madrid C, María Amastha E, Mercado J, Molina DI, Molina Soto J, Montoya C, Morales A, Muñoz C, Orozco LA, Osorio O, Palmera Sanchez JM, Peña A, Perez J, Perez Agudelo J, Pérez Amador G, Pertuz C, Posada I, Puerta C, Quintero A, Quiroz D, Rendon C, Reyes A, Reyes A, Ripoll D, Rivera C, Rocha M, Rodriguez JF, Rodriguez Villanueva KA, Rodriguez Zabala JE, Rojas S, Romero M, Rosero R, Rosillo Cardenas AR, Rueda L, Sanchez G, Sanchez T, Sotomayor Herazo A, Suarez M, Torres M, Trujillo F, Urina M, van Strahlen L, Velandia C, Velasquez Guzman C, Velazquez E, Vidal Prada T, Yopez Alvaran JP, Zarate D, Andelova J, Benesova R, Buzova B, Cech V, Chodova I, Choura M, Dufka A, Gamova A, Gorgol J, Hala T, Havlova H, Hlavkova D, Horanska P, Ilcisin-Valova J, Jenickova P, Jerabek O, Kantorova I, Kolomaznikova K, Kopeckova I, Kopeckova M, Linhart K, Linhart T, Malecha J, Malicherova E, Neubauerova D, Oznerova M, Partys R, Pederzoliova E, Petrusova M, Prymkova V, Racicka E, Reissova I, Roderova E, Stanek L, Striova A, Svarcova D, Svoboda P, Szeghy Malicharova E, Urge J, Vesely L, Wasserburger B, Wasserburgerova H, Zahumensky E, Zamrazil V, Alawi H, Anastasiadis E, Axthelm E, Bieler T, Buhrig C, Degtyareva E, Dellanna F, Derwahl KM,

- Diessel S, Dogiami B, Dorn-Weitzel K, Ernst M, Faulmann G, Fetscher B, Forst T, Freyer-Lahres G, Funke K, Ganz X, Gleixner C, Hanefeld C, Heinrichs S, Helleberg S, Henkel E, Hetzel GR, Hoffmann C, Jacob F, Jacob S, John F, Jonczyk A, Kamke W, Klein C, Kleinhardt M, Kleophas W, Kosch C, Kreutzmann K, Kühn A, Lee-Barkey YH, Lier A, Maatouk S, Minnich J, Mitry M, Muessig I, Nicula D, Niemann M, Nothroff J, Ott P, Pfuetzner A, Pfützner A, Pistrosch F, Pohl W, Prochazkova Z, Retkowska M, Rosin H, Sachsenheimer D, Samer H, Sanuri M, Schaefer A, Schaper F, Schulze ED, Schulze M, Schumann M, Segiet T, Sowa V, Stahl HD, Steinfeldt F, Teige M, Trieb B, Tschoepe D, Uebel P, Warken B, Weigmann I, Weyland K, Wilhelm K, Balo T, Balsay M, Bende I, Bezzegh K, Birkus Z, Buday B, Csomai M, Deak L, Dezzo E, Faludi P, Faluvegi M, Fazekas I, Feher A, Fejer C, Finta E, Fulcz A, Gaal Z, Gurzo M, Hati K, Herczeg G, Jozsef I, Juhasz M, Keltai K, Koranyi L, Kulcsar E, Kun K, Laczko A, Literati-Nagy B, Mezo I, Miledler M, Moricz I, Nagy K, Nagybacsoni B, Nemeth C, Oze A, Pauer J, Peterfai E, Polocsanyi B, Poor F, Reiber I, Salamon C, Sebestyen J, Torok I, Tuu M, Varga A, Vass V, Ahn CM, Ahn C, ByungWon P, Chang HJ, Chang K, Choi EY, Choi HS, Chung JW, Hong BK, Hong YJ, Hyon MS, Jeong MH, Kang S, Kim BK, Kim JH, Kim JH, Kim KS, Kim KS, Kim MH, Kim PJ, Kim SK, Kim YS, Kim YK, Koh YS, Kwon HM, Lee BK, Lee BW, Lee JB, Lee MM, Lim YM, Min PK, Park JS, Park J, Park KH, Park S, Pyun WB, Rim SJ, Ryu DR, Seo HS, Seung KB, Shin DH, Sim DS, Yoon YW, Andersone I, Babicka K, Balcer I, Barons R, Capkovska I, Geldner K, Grigane I, Jegere B, Lagzdina I, Mora L, Pastare S, Ritenberga R, Romanova J, Sakniete I, Sidlovska N, Sokolova J, Steina S, Strizko I, Teterovska D, Vizina B, Barsiene L, Belozariene G, Daugintyte-Petrusiene L, Drungiliene N, Garsviene N, Grigiene A, Grizas V, Jociene V, Kalvaitiene D, Kaupiene J, Kavaliauskiene J, Kozloviene D, Lapteva I, Maneikiene B, Marcinkeviciene J, Markauskiene V, Meiluniene S, Norkus A, Norviliene R, Petrenko V, Radzeviciene R, Sakalyte G, Urbonas G, Urbutiene S, Vasiliauskas D, Velickiene D, Aguilar C, Alcocer M, Avalos-Ramirez JA, Banda-Elizondo R, Bricio-Ramirez R, Cardenas Mejia K, Cavazos F, Chapa J, Cienfuegos E, de la Peña A, de la Peña Topete G, de los Rios Ibarra MO, Elias D, Flores-Moreno C, Garcia Hernandez P, Gonzalez LG, Guerra Moya RL, Guerra-Lopez A, Hernandez Baylon R, Herrera Colorado C, Herrera-Marmolejo M, Islas-Palacios N, Lopez E, Lopez F, Lopez Alvarado A, Luna Ceballos RI, Morales Villegas E, Moreno-Virgen G, Parra Perez RL, Pascoe Gonzalez S, Peralta-Cantu I, Previn R, Ramirez R, Ramirez R, Ramos Zavala MG, Rodriguez M, Salgado-Sedano R, Sanchez-Aguilar AC, Santa Rosa Franco E, Sauque-Reyna L, Suarez Otero R, Torres I, Velarde-Hernandez E, Villagordoa J, Villeda-Espinoza E, Vital-Lopez J, Zavala-Bello CJ, Baker J, Barrington-Ward E, Brownless T, Carroll R, Carson S, Choe M, Corin A, Corley B, Cutfield R, Dalaman N, Dixon P, Drury P, Dyson K, Florkowski C, Ford M, Frengley W, Helm C, Katzen C, Kerr J, Khanolkar M, Kim D, Koops R, Krebs J, Leikis R, Low K, Luckey A, Luke R, Macaulay S, Marks R, McNamara C, Millar-Coote D, Miller S, Mottershead N, Reid J, Robertson N, Rosen I, Rowe D, Schmiedel O, Scott R, Sebastian J, Sheahan D, Stiebel V, Ternouth I, Tofield C, Venter D, Williams M, Williams M, Wu F, Young S, Arciszewska M, Bochenek A, Borkowski P, Borowy P, Chrzanoski T, Czerwinski E, Dwojak M, Grodzicka A, Janiec I, Jaruga J, Jazwinska-Tarnawska EK, Jedynasty K, Juzwiak-Czapiewska D, Karczewicz-Janowska J, Konieczny J, Konieczny M, Korol M, Kozina M, Krzyzagska E, Kucharczyk-Petryka E, Laz R, Majchrzak A, Mrozowska Z, Mularczyk M, Nowacka E, Peczynska J, Petryka R, Pietrzak R, Pisarczyk-Wiza D, Rozanska A, Ruzga Z, Rzeszotarska E, Sacha M, Sekulska M, Sidorowicz-Bialynicka A, Stasinska T, Strzelecka-Sosik A, Swierszcz T, Szymkowiak KM, Turowska O, Wisniewska K, Wiza M, Wozniak I, Zelazowska K, Ziolkowska-Gawron B, Zytkeiwicz-Jaruga D, Albota A, Alexandru C, Avram R, Bala C, Barbonta D, Barbu R, Braicu D, Calutiu N, Catrinioiu D, Cerghizan A, Ciorba A, Craciun A, Doros R, Duma L, Dumitrache A, Ferariu I, Ferician Moza A, Ghergan A, Ghise G, Graur M, Gribovski M, Mihai B, Mihalache L, Mihalcea M, Mindrescu N, Morosanu M, Morosoiu A, Mota M, Moza A, Naftomita V, Natea N, Nicodim S, Nita C, Onaca A, Onaca M, Pop C, Pop L, Popa A, Popescu A, Pruna L, Roman G, Rosu M, Sima A, Sipciu D, Sitterli-Natea CN, Szilagyi I, Tapurica M, Tase A, Tutescu AC, Vanghelie L, Verde I, Vlad A, Zarnescu M, Akhmetov R, Allenova I, Avdeeva I, Baturina O, Biserova I, Bokovin N, Bondar I, Burova N, Chufeneva G, Chumachek E, Demidova M, Demin A, Drobysheva V, Egorova I, Esenyana L, Gelig E, Gilyarevsky S, Golshmid M, Goncharov A, Gorbunova A, Gordeev I, Gorelysheva V, Goryunova T, Grebenshchikova I, Ilchenko R, Ivannikova M, Karabalieva S, Karpeeva J, Khaykina E, Kobalava Z, Kononenko I, Korolik O, Korshunova A, Kostenko V, Krasnopevtseva I, Krylova L, Kulkova P, Kuzmina I, Ledyayeva A, Levashov S, Lokhovinina N, Lvov V, Martirosyan N, Nedogoda S, Nilk R, Osmolovskaya Y, Panov A, Paramonova O, Pavlova E, Pekareva E, Petunina N, Ponamareva S, Reshedko G, Salasyuk A, Sepkhanian M, Serebrov A, Shabelnikova O, Skvortsov A, Smirnova O, Spiridonova O, Strogova S, Taratukhin E, Tereschenko S, Trukhina L, Tsarkova O, Tsoma V, Tumarov F, Tyan N, Tyurina T, Villevalde S, Yankovaya E, Zarutskaya L, Zenkova E, Badat A, Bester F, Blignaut S, Blom D, Booyesen S, Boyd W, Brice B, Brown S, Burgess L, Cawood R, Coetzee K, Conradie H, Cronje T, de Jong D, Ellis G, Emanuel S, Engelbrecht I, Foulkes S, Fourie D, Gibson G, Govender T, Hansa S, Hemus AC, Hendricks F, Heradien M, Holmgren C, Hoosain Z, Horak E, Howard J, Immink I, Janari E, Jivan D, Klusmann K, Labuschagne W, Lai YY, Latiff G, Lombaard J, Lottering H, Meeding R, Middlemost S, Mitha H, Mitha I, Mkhwanazi S, Moodley R, Murray A, Musungaie D, Osman Y, Peacey K, Pillay-Ramaya L, Pretorius C, Prozesky H, Sarvan M, Scholtz E, Sebesteny A, Skinner B, Skriker M, Smit M, Stapelberg AM, Swanepoel N, Urbach D, van Aswegen D, van Zyl F, van Zyl L, Venter E, Wadvalla S, Wing J, Wolmarans K, Abreu C, Aguilá P, Aguilera E, Alonso N, Alvarez C, Cajas P, Castro JC, Codinachs R, Contreras J, Coves MJ, Fajardo C, Ferrer JC, Font N, Garcia M, Gil MA, Gomez F, Gomez LA, Gonzalbez J, Grieria JL, Masmiquel L, Mauricio D, Narejos Perez S, Nicolau JA, Noheda Contreras O, Olivan J, Olivares J, Ortega E, Pellitero S, Pertusa S, Rius F, Rodriguez I, Sánchez-Juan C, Santos D, Soldevila B, Subias D, Terns M, Trescoli C, Vilaplana J, Villanueva A, Albo J, Antus K, Axelsson M, Bergström L, Binsell-Gerdin E, Boman K, Botond F, Dotevall A, Graipe A, Jarret C, Kaminska J, Kempe A, Korhonen M, Linderfalk C, Liu B, Ljungstrom K, Ljungström K, Malmqvist L, Mellbin L, Moee T, Nicol P, Norrby A, Ohlsson A, Rosengren A, Saaf J, Salmonsson S, Strandberg O, Svensson KA, Tengmark BO, Tsatsaris G, Ulvenstam A, Vasko P, Chang CT, Chang HM, Chen JF, Chen TP, Chung MM, Fu CP, Hsia TL, Hua SC, Kuo MC, Lee CL, Lee IT, Liang KW, Lin SY, Lu CH, Ma WY, Pei D, Shen FC, Su CC, Su SW, Tai TS, Tsai WN, Tsai YT, Tung SC, Wang JS, Yu HI, al-Qaissi A, Arutchelvam V, Atkin S, Au S, Aye MM, Bain S, Bejnariu C, Bell P, Bhatnagar D, Bilous R, Black N, Brennan U, Brett B, Bujanova J, Chow E, Collier A, Combe A, Courtney C, Courtney H, Crothers J, Eavis P, Elliott J, Febraro S, Finlayson J, Gandhi R, Gillings S, Hamling J, Harper R, Harris T, Hassan K, Heller S, Jane A, Javed Z, Johnson T, Jones S, Kennedy A, Kerr D, Kilgallon B, Konya J, Lindsay J, Lomova-Williams L, Looker H, MacFarlane D, Macrury S, Malik I, McCrimmon R, McKeith D, McKnight J, Mishra B, Mukhtar R, Mulligan C, O'Kane M, Olateju T, Orpen I, Richardson T, Rooney D, Ross SB, Sathyapalan T, Siddaramaiah N, Sit LE, Stephens J, Turtle F, Wakil A,



- Walkinshaw E, Ali A, Anderson R, Arakaki R, Aref O, Ariani MK, Arkin D, Banarer S, Barchini G, Bhan A, Branch K, Brautigam D, Brietzke S, Brinas M, Brito Y, Carter C, Casagni K, Casula S, Chakko S, Charatz S, Childress D, Chow L, Chustecka M, Clarke S, Cohen L, Collins B, Colon Vega G, Comulada-Rivera A, Cortes-Maisonet G, Davis M, de Souza J, Desouza C, Dinnan M, Duffy-Hidalgo B, Dunn B, Dunn J, Elman M, Felicetta J, Finkelstein S, Fitz-Patrick D, Florez H, Forker A, Fowler W, Fredrickson S, Freedman Z, Gailey Narron B, Gailey-Ferree K, Gardner M, Gastelum C, Giddings S, Gillespie E, Gimness MP, Goldstein G, Gomes M, Gomez N, Gorman T, Goswami K, Graves A, Hacking S, Hall C, Hanson L, Harman S, Heber D, Henry R, Hiner J, Hirsch I, Hollander P, Hooker T, Horowitz B, Hoste L, Huang L, Huynh M, Hyman D, Idriss S, Iranmanesh A, Karounos D, Kashyap M, Katz L, Kaye W, Khaitey Y, Khardori R, Kitchen T, Klein A, Kniffem W, Kosiborod M, Kreglinger N, Kruger D, Kumar A, Laboy I, Larrabee P, Larrick L, Lawson D, Ledet M, Lenhard J, Levy J, Li G, Li Z, Lieb D, Limcolio A, Lions-Patterson J, Lorber D, Lorch D, Lorrello M, Lu P, Lucas KJ, Ma SL, MacAdams M, Magee M, Magno A, Mahakala AR, Marks J, McCall A, McClanahan W Jr, McClary C, Melendez L, Melish J, Michaud D, Miller C, Miller N, Mora P, Moten M, Mudaliar C, Myrick G, Narayan P, Nassif M, Neri K, Newton T, Niblack P, Nicol P, Nyenwe E, Odugbesan AO, Okorochoa Y, Ortiz Carrasquillo R, Osei K, Palermo C, Patel H, Patel K, Pau C, Perley M, Plevin S, Plummer E, Powell R, Qintar M, Rawls R, Reyes-Castano J, Reynolds L, Richards R, Rosenstock J, Rowe C, Saleh J, Sam S, Sanchez A, Sander D, Sanderson B, Savin V, Seaquist E, Shah J, Shi S, Shivaswamy V, Shlotzhauer T, Shore D, Skukowski B, Soe K, Solheim V, Soufer J, Steinberg H, Steinsapir J, Tarkington P, Thayer D, Thomson S, Thrasher J, Tibaldi J, Tjaden J, Tores O, Trencle D, Trikudanathan S, Ullal J, Uwaifo G, Vo A, Vu K, Walia D, Weiland K, Whitehouse F, Wiegmann T, Wyne K, Wynne A, Yuen K, Zaretzky J, Zebreck J, Zieve F, Zigrang W. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *The Lancet*. 2019; **394**: 121–130.
31. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, del Prato S, del Prato S, McMurray JJV, D'Agostino RB, Granger CB, Hernandez AF, Janmohamed S, Leiter LA, Califf RM, Holman R, DeMets D, Riddle M, Goodman S, McGuire D, Alexander K, Devore A, Melloni C, Patel C, Kong D, Bloomfield G, Roe M, Tricoci P, Harrison R, Lopes R, Mathews R, Mehta R, Schuyler Jones W, Vemulapalli S, Povsic T, Eapen Z, Dombrowski K, Kolls B, Jordan D, Ambrosy A, Greene S, Mandawat A, Shavadia J, Cooper L, Sharma A, Guimaraes P, Friedman D, Wilson M, Endsley P, Gentry T, Collier J, Perez K, James K, Roush J, Pope C, Howell C, Johnson M, Bailey M, Cole J, Akers T, Vandyne B, Thomas B, Rich J, Bartone S, Beaulieu G, Brown K, Chau T, Christian T, Coker R, Greene D, Haddock T, Jenkins W, Haque G, Marquess M, Pesarchick J, Rethaford R, Stone A, al Kawas F, Anderson M, Enns R, Sinay I, Mathieu C, Yordanov V, Hramiak I, Haluzik M, Galatius S, Guerci B, Nauck M, Migdalis I, Tan CBK, Kocsis G, Giaccari A, Lee MK, Muñoz EGC, Corneli J, Birkeland K, Pinto M, Tirador L, Olesinska-Mader M, Shestakova M, Distiller L, Lopez-Sendon J, Eliasson B, Chiang CE, Srimahachota S, Mankovsky B, Bethel MA, Dungan K, Kosiborod M, Alvarisqueta A, Baldovino J, Besada D, Calella P, Cantero MC, Castaño P, Chertkoff A, Cuadrado J, de Loreda L, Dominguez A, Español MV, Finkelstein H, Frechtel G, Fretes J, Garrido Santos N, Gonzalez J, Litvak M, Loureiro J, Maffei L, Maldonado N, Mohr Gasparini D, Orio S, Perez Manghi F, Rodriguez Papini N, Sala J, Schygiel P, Sposetti G, Ulla M, Verra F, Zabalua S, Zaidman C, Crenier L, Debroye C, Duyck F, Scheen A, van Gaal L, Vercammen C, Damyanova V, Dimitrov S, Kovacheva S, Lozanov L, Margaritov V, Mihaylova-Shumkova R, Nikolaeva A, Stoyanova Z, Akhras R, Beaudry Y, Bedard J, Berlingieri J, Chehayev R, Cheung S, Conway J, Cusson J, Della Siega A, Dumas R, Dzongowski P, Ferguson M, Gaudet D, Grondin F, Gupta A, Gupta M, Halperin F, Houle PA, Jones M, Kouz S, Kovacs C, Landry D, Lonn E, O'Mahony W, Peterson S, Reich D, Rosenbloom A, St-Maurice F, Tugwell B, Vizel S, Woo V, Brychta T, Cech V, Dvorakova E, Edelsberger T, Halciakova K, Krizova J, Lastuvka J, Piperek M, Prymkova V, Raclavská L, Silhova E, Urbanek R, Vrkoc J, Andersen U, Brønnum-Schou J, Hove J, Jensen JS, Kober L, Kristiansen OP, Lund P, Melchior T, Nyvad O, Schou M, Boye A, Cadinet D, Gouet D, Henry P, Kessler L, Lalau JD, Petit C, Thuan JF, Voinot C, Vouillarmet J, Axthelm C, Berger D, Bieler T, Birkenfeld A, Bott J, Busch K, Caca K, Chevts J, Donaubauer T, Erlinger R, Funke K, Grosskopf J, Hagenow A, Hamann M, Hartard M, Heymer P, Huppertz W, Illies G, Jacob S, Jung T, Kahrmann G, Kast P, Kellerer M, Kempe HP, Khariousov A, Klausmann G, Klein C, Kleinecke-Pohl U, Kleinertz K, Koch T, Kosch C, Lorra B, Luedemann J, Luttermann M, Maxeiner S, Milek K, Moelle A, Neumann G, Nischik R, Oehrig-Pohl E, Plassmann G, Pohlmeier L, Proepper F, Regner S, Rieker W, Rose L, Samer H, Sauter J, Schaper F, Schiffer C, Schmidt J, Scholz BM, Schulze J, Segner A, Seufert J, Sigal H, Steindorf J, Stockhausen J, Stuebner P, Taeschner H, Tews D, Tschoepe D, Wilhelm K, Zeller-Stefan H, Avramidis I, Bousboulas S, Bristianou M, Dimitriadis G, Elisaf M, Kotsa K, Melidonis A, Mitrakou A, Pagkalos E, Papanas N, Pappas A, Sampanis C, Tentolouris N, Tsapas A, Tzatzagou G, Ozaki R, Hajdú C, Harcsa E, Konyves L, Muci J, Pauker Z, Petró G, Plés Z, Revesz K, Sándor V, Vass V, Avogaro A, Boemi M, Bonadonna R, Consoli A, de Cosmo S, di Bartolo P, Dotta F, Frontoni S, Trevisan R, Ahn CW, Baik SH, Cha BS, Chung CH, Jang HC, Kim CJ, Kim HS, Kim IJ, Lee EY, Lee HW, Lee KW, Moon KW, Namgung J, Park KS, Yoo SJ, Yli J, Llamas EAB, Cervantes-Escárcega JU, Flota-Cervera LF, González-González JG, Pascoe-Gonzalez S, Pelayo-Orozco ES, Ramirez-Diaz SP, Saldana-Mendoza A, Jerjes-Diaz CS, Torres-Colores JJ, Vidrio-Velázquez M, Villagordoa-Mesa J, Beijerbacht HP, Groutars RGEJ, Hoek BA, Hoogslag PAM, Kooy A, Kragten JA, Lieverse AG, Swart HP, Viergever EP, Ahlqvist J, Cooper J, Gulseth H, Guttormsen G, Wium C, Arbañil H, Calderon J, Camacho L, Espinoza AD, Garrido E, Luna A, Manrique H, Revoredo FM, Gonzales RV, Rincon LZ, Zubiate C, Ebo G, Morales-Palomares E, Arciszewska M, Banach M, Bijata-Bronisz R, Dereziński T, Gadziński W, Gajek J, Klodawska K, Krzyżagorska E, Madej A, Miekus P, Opiela J, Romanczuk P, Siegel A, Skokowska E, Stankiewicz A, Stasinska T, Trznadel-Morawska I, Witek R, Aksentyev S, Bondar I, Demidova I, Dreval A, Ershova O, Galstyan G, Garganeva A, Izmozherova N, Karetnikova V, Kharakhulakh M, Khokhlov A, Kobalava Z, Koshelskaya O, Kosmacheva E, Kostin V, Koziolova N, Kuzin A, Lesnov V, Lysenko T, Markov V, Mayorov A, Moiseev S, Myasoedova S, Petunina N, Rebrov A, Ruyatkina L, Samoylova J, Sazonova O, Shilkina N, Sokolova N, Vasilevskaya O, Verbovaya N, Vishneva E, Vorobyev S, Vorokhobina N, Zanozina O, Zhdanova E, Zykova I, Burgess L, Coetzee JM, Dawood S, Lombard L, Makotoko E, Moodley R, Oosthuysen W, Sarvan M, Calvo Gómez C, Cano Rodríguez I, Castro Conde A, Cequier Fillat A, Cuatrecasas Cambra G, de Álvaro Moreno F, de Teresa Parreño L, Delgado Lista J, Domínguez Escribano JR, Durán García S, Elvira González J, Fernández Rodríguez JM, Goday Arno A, Gomez Huelgas R, González Juanatey JR, Hernandez Mijares A, Jiménez Díaz VA, Jodar Gimeno E, Lucas Morante N, Marazuela M, Martell Claros T, Mauricio Puente D, Mena Ribas E, Merino Torres JF, Mezquita Raya P,



- Nubiola Calonge A, Ordoñez Sánchez X, Pascual Izuel JM, Perea Castilla V, Pérez Pérez A, Perez Soto I, Quesada Charneco M, Quesada Simón A, Redón Mas J, Rego Iraeta A, Rodríguez Alvarez M, Rodríguez Rodríguez I, Sabán Ruiz J, Soto González A, Tinahones Madueno F, Trescoli Serrano C, Ulied Armifiñana A, Bachus E, Berndtsson Blom K, Eliasson K, Koskinen P, Larnefeldt H, Lif-Tiberg C, Linderfalk C, Lund G, Lundman P, Moris L, Olsson Å, Salmonsson S, Sanmartin Berglund J, Sjöberg F, Söderberg S, Torstensson I, Chen JF, Tien KJ, Tseng ST, Tu ST, Wang CY, Wang JH, Phrommintikul A, Yamwong S, Jintapakorn W, Hutayanon P, Sansanayudh N, Bazhan L, Fushetey I, Grachova M, Katerenchuk V, Korpachev V, Kravchun N, Larin O, Mykhalchysyn G, Myshanych H, Oleksyk O, Orlenko V, Pashkovska N, Pertseva N, Petrosyan O, Smirnov I, Vlasenko M, Zlova T, Aye M, Baksi A, Balasubramani M, Beboso R, Blagden M, Bundy C, Cookson T, Copland A, Emslie-Smith A, Green F, Gunstone A, Issa B, Jackson-Voyzey E, Johnson A, Maclean M, McKnight J, Muzulu S, O'Connell I, Oyesile B, Patterson C, Pearson E, Philip S, Smith P, Sukumaran U, Abbas J, Aggarwala G, Akhter F, Andersen J, Anglade M, Argoud G, Ariani M, Ashdji R, Bakhtari L, Banerjee S, Bartlett A, Baum H, Bays H, Beasley R, Belfort de Aguiar R, Benjamin S, Bhagwat R, Bhargava A, Bode B, Bratcher C, Briskin T, Brockmyre A, Broughton R, Brown J, Budhraj M, Cannon K, Carr J, Cathcart H, Cavale A, Chaykin L, Cheung D, Childress R, Cohen A, Condit J, Cooksey E, Cornett GM, Dauber I, Davila W, de Armas L, Dean J, Detweiler R, Diaz E, di Giovanna M, Dor I, Drummond W, Eagerton D, Earl J, Eaton C, Ellison H, Farris N, Fiel T, Firek A, First B, Forgosh L, French W, Gandy W, Garcia R, Gill S, Gordon M, Guice M, Gummadi S, Hackenjos J, Hairston K, Hanson L, Harrison L, Hartman I, Heitner J, Hejeebu S, Hermany P, Hernandez-Cassis C, Hidalgo H, Higgins A, Ibrahim H, Jacobs S, Johnson D, Joshi P, Kaster S, Kellum D, Kim C, Kim E, Kirby W, Knouse A, Kulback S, Kumar M, Kuruvanka T, Labroo A, Lasswell W, Lentz J, Lenzmeier T, Lewis D, Li Z, Lillestol M, Little R, Lorraine R, McKeown-Biagas C, McNeill R, Mehta A, Miller A, Moran J, Morawski E, Nadar V, O'Connor T, Odio A, Parker R, Patel R, Phillips L, Raad G, Rahman A, Raikhel M, Raisinghani A, Rajan R, Rasouli N, Rauzi F, Rohr K, Roseman H, Rovner S, Saba F, Sachson R, Schabauer A, Schneider R, Schuchard T, Sensenbrenner J, Shlesinger Y, Singh N, Sivalingam K, Stonesifer L, Storey D, Suh D, Tahir M, Tan A, Tan M, Taylor A, Thakkar M, Tripathy D, Uwaifo G, Vedere A, Venugopal C, Vo A, Welch M, Welker J, White A, Willis J, Wynne A, Yazdani S, Green JB, Rosenberg A, Price L, Sigmon K, Lokhngina Y, Xing W, Overton R, Stewart M, Stead J, Lindsay A, Patel V, Ross J, Soffer J, Daga S, Sowell M, Patel P, Garvey L, Ackert J, Abraham S, Sabol MB, Altobelli D, Ha JY, Kulkarni M, Somerville M, Noronha D, Casson E, Zang E, Sandhu C, Kumar R, Chen D, Taft L, Patel R, Ye J, Shannon J, Wilson T, Babi C, Miller D, Jones NP, Thorpe K, Russell R, Bull G, Heregthy B, Fernandez-Salazar E, Longley T, Donaldson J, Jarosz M, Murphy K, Adams P, Smith P, James R, Richards J, Sedani S, Althouse D, Watson D, Lorimer J, Lauder S, Schultheis R, Womer T, Wraight E, Li W, Price-Olsen E, Watson A, Kelly A, McLaughlin P, Fleming J, Schubert J, Schleiden D, Harris T, Prakash R, Breneman J, Deshpande S, Saswadkar A, Kumari A, Shitut A, Raorane A, Karmalkar A, Mhambrey A, Bhosale A, Vaphare A, Patil AP, Khandelwal C, Shaik F, Nadar M, Karka M, Kadgaonkar N, Gupta N, Aher N, Potnis O, Naicker P, Shinde R, Sharma R, Godse R, Solanki S, Sahu S, Dumbre S, Kumar S, Patil S, Mandal T. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *The Lancet*. 2018; **392**: 1519–1529.
32. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017; **377**: 1228–1239.
  33. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliasschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019; **381**: 841–851.
  34. Marso SP, Bain SC, Consoli A, Eliasschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016; **375**: 1834–1844.
  35. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016; **375**: 311–322.
  36. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020; **383**: 1425–1435.
  37. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erond N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017; **377**: 644–657.
  38. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; **380**: 2295–2306.
  39. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; **373**: 2117–2128.
  40. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, Pfarr E, Keller A, Mattheus M, Baanstra D, Meinicke T, George JT, von Eynatten M, McGuire DK, Marx N, for the CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019; **322**: 1155–1166.
  41. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsiofis KP, van Dis I, van Gelder I, Wanner C, Williams B, ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2021; **42**: 3227–3337.
  42. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010; **340**: c869.
  43. Gerstein HC. Metformin reduced diabetes-related end points and all-cause mortality in overweight patients with type 2 diabetes. *ACP J Club*. 1999; **130**: 3.

44. Srivastava PK, Claggett BL, Solomon SD, McMurray JJV, Packer M, Zile MR, Desai AS, Rouleau JL, Swedberg K, Fonarow GC. Estimated 5-year number needed to treat to prevent cardiovascular death or heart failure hospitalization with angiotensin receptor-neprilysin inhibition vs standard therapy for patients with heart failure with reduced ejection fraction: an analysis of data from the PARADIGM-HF trial. *JAMA Cardiol.* 2018; **3**: 1226–1231.
45. Ferreira JP, Docherty KF, Stienen S, Jhund PS, Claggett BL, Solomon SD, Petrie MC, Gregson J, Pocock SJ, Zannad F, McMurray J. Estimating the lifetime benefits of treatments for heart failure. *JACC: Heart Failure.* 2020; **8**: 984–995.
46. Lee EY, Yoon K-H. How to interpret recent CV outcome trials and future: PCSK9 inhibitors. *J Lipid Atheroscler.* 2018; **7**: 1–11.
47. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol.* 2020; **17**: 761–772.
48. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, di Tanna GL. A systematic review of medical costs associated with heart failure in the USA (2014–2020). *Pharmacoeconomics.* 2020; **38**: 1219–1236.
49. Davies MJ, Kloecker DE, Webb DR, Khunti K, Zaccardi F. Number needed to treat in cardiovascular outcome trials of glucagon-like peptide-1 receptor agonists: a systematic review with temporal analysis. *Diabetes Obes Metab.* 2020; **22**: 1670–1677.
50. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ.* 2021; **372**: m4573.
51. Gregson J, Sharples L, Stone GW, Burman C-F, Öhrn F, Pocock S. Nonproportional hazards for time-to-event outcomes in clinical trials: JACC Review Topic of the Week. *J Am Coll Cardiol.* 2019; **74**: 2102–2112.

## 5 Diskussion

Die wesentlichen Erkenntnisse dieser Habilitationsschrift sind:

- a) Moderne Risikomodelle für die Vorhersage von patientenindividuellem Risiko koronarer Herzkatheteruntersuchungen zeigten eine gute bis sehr gute Diskrimination von Hoch- und Niedrigrisikopatienten in allen klinischen Settings und für verschiedene Endpunkte, teilweise besser als leitlinienempfohlene Alternativen. Die Kalibration der Modelle – also die Vorhersage einer Ereigniswahrscheinlichkeit – war jedoch häufig ungenau.
- b) Risikoprädiktion für interventionelle TAVI-Eingriffe bei hochgradiger Aortenklappenstenose hatte große Limitationen: Die Diskrimination von patientenindividuellem Risiko und auch die Kalibration der Modelle waren ungenügend – sowohl für TAVI-spezifische Scores, als auch für ursprünglich in chirurgischen Kollektiven entwickelte Modelle.
- c) Methoden künstlicher Intelligenz in der patientenindividuellen Risikovorhersage können unter Einbezug von Daten des Krankheitsverlaufs die Genauigkeit konventioneller Vorhersagemodelle deutlich verbessern.
- d) Meta-analytische Methoden zur populationsbasierten Risiko-/Nutzenabwägung eignen sich gut zur Analyse interventioneller und operativer Therapien in verschiedenen klinischen Settings, sowie zur vergleichenden Evaluation adjunktiver medikamentöser Therapien und absoluter und relativer Effektgrößen.

### 5.1 Patientenindividuelles Risikoassessment in koronarvaskulären

#### Herzkatheteruntersuchungen und in TAVI-Eingriffen

Für die patientenindividuelle Risikovorhersage in kardiovaskulären Erkrankungen existieren eine Vielzahl von statistischen Modellen (105). Die Nutzung eines Modells außerhalb einer validierten Population oder unter divergierenden klinischen Bedingungen – beispielsweise bedingt durch medizinischen Fortschritt oder demographische Veränderungen – kann die Vorhersagekraft jedoch reduzieren (69, 70), wenn die relative Gewichtung von Risikofaktoren in einem Modell sich verändert oder neue Risikofaktoren relevanten Einfluss bekommen. Daher ist eine zeitliche, geographische und inhaltliche Validierung von Risikomodelle entscheidend (106), um eine gute Vorhersagekraft innerhalb einer Patientenpopulation zu gewährleisten – aber nur sehr wenige der verfügbaren Risikomodelle werden tatsächlich extern validiert (107), weshalb die Nutzung in anderen Populationen entsprechenden Limitationen unterliegt. Insbesondere im akuten Koronarsyndrom jedoch, wo Scoring-abhängiges Risikomanagement von Leitlinien empfohlen wird (35), kann die Güte des Risikoassessment direkten Einfluss auf klinisches Management und damit auf die Qualität der



Patientenversorgung haben. Aus diesem Grund ist eine Überprüfung der angewandten Modelle im jeweiligen Kontext von entscheidender Bedeutung.

Die leitlinienempfohlenen Risikomodelle des GRACE-Registers (55-57) für die Vorhersage von Mortalität im akuten Koronarsyndrom und das Mehran-Risikomodell (58) für die Vorhersage von kontrastmittelinduziertem akutem Nierenversagen wurden im Düsseldorfer Setting koronarvaskulärer Herzkatheteruntersuchungen auf ihre Leistungsfähigkeit überprüft und mit den moderneren NCDR- und ACTION-Risikomodellen (60-64, 87, 88) verglichen (Tabelle 1). Hintergrund dieser Vergleichsauswahl war, dass die moderneren Modelle in sehr großen und vergleichsweise zeitgemäßen Patientenkollektiven entwickelt wurden und wir davon Vorteile für ihre Vorhersageleistung hypothesisierten:

Tabelle 1: Übersicht über die verglichenen koronaren Risikomodelle

| <b>Score</b>                                                                                                                      | <b>Jahr der Publikation</b>          | <b>Patienteneinschluss</b> |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------|
| <i>Global Registry of Acute Coronary Events</i> (GRACE) (55-57)                                                                   | 2003/2006 (GRACE)<br>2014 (GRACE II) | 1999-2001<br>2002-2007     |
| <i>Mehran Scores</i> (58, 59)                                                                                                     | 2004                                 | 1998-2004                  |
| <i>National Cardiovascular Data / CathPCI Registry</i> (NCDR) Modelle für Mortalität, Blutungen und akutes Nierenversagen (60-64) | 2010-2014                            | 2004-2011                  |
| <i>Acute Coronary Treatment and Intervention Outcomes Network</i> (87, 88)                                                        | 2016                                 | 2012-2013                  |

Tabelle 1: Übersicht über die verglichenen koronaren Risikomodelle zur Vorhersage des patientenindividuellen Risikos; inkl. Jahre der Publikation der Modelle und des Patienteneinschlusses im entsprechenden Register, sowie Referenzen. Eigene Tabelle.

Wichtigste Maßzahlen für die Vorhersageleistung aller Modelle waren a) die *Diskrimination* von Niedrig- und Hoch-Risiko-Patienten, und b) die *Kalibration* von vorhergesagten und tatsächlichen Ereignissen – also die Genauigkeit der Vorhersage von Ereignis-Wahrscheinlichkeiten (108).

Wir konnten in Düsseldorfer Patienten zunächst sehr gute und mit den ursprünglichen Entwicklungskohorten vergleichbare Diskriminationsleistungen für alle NCDR-Modelle nachweisen, unabhängig vom klinischen Setting (109). Dies stellte die bisher umfangreichste externe Validierungsstudie dieser Modelle dar: Zuvor waren das Mortalitätsmodell in portugiesischen Patienten mit STEMI (110), das Blutungsmodell in verschiedenen amerikanischen Populationen (111) und das Modell für die Vorhersage von Nierenversagen in einer japanischen Patientenkohorte (112) mit ähnlichen Ergebnissen untersucht worden. Die Kalibration aller drei Modelle war jedoch insbesondere im Vergleich zur guten Diskriminationsleistung eher inakkurat.

In weiterführenden Untersuchungen im Setting des akuten Koronarsyndroms konnten wir zeigen (113), dass sowohl das NCDR-Risikomodell (82) als auch das ACTION-Modell (87, 88) für Mortalität in ihrer Diskriminationsleistung dem leitlinienempfohlenen Goldstandard des GRACE-Scores gleichwertig (ACTION) bzw. überlegen (NCDR) waren. Für das ACTION-Modell war dies die erste externe Validierungsstudie. Die Kalibrationsleistungen sowohl des GRACE- als auch des NCDR-Modells waren mangelhaft, während das ACTION-Modell sehr akkurat kalibriert war (113). Weiterhin zeigten wir einen Vorteil des moderneren NCDR-Modells gegenüber dem leitlinienempfohlenen Mehran-Modell in der Diskrimination von patientenindividuellem Risiko für kontrastmittelinduziertes Nierenversagen (114) – mit erneut mäßiger Kalibration beider Modelle.

In allen Untersuchungen zeigte sich deutlich, dass die Kalibration der Risikomodelle im Vergleich zur Risikodiskrimination der volatilere Parameter bei externer Validierung war, wohl aufgrund des Einflusses von Abweichungen in der Gewichtung von Faktoren im Modell: Eine Vorhersage von Ereigniswahrscheinlichkeiten hat damit klare Limitationen, wie auch bereits andere Validierungsstudien gezeigt haben (70, 110, 112).

Im Gegensatz zu den positiven Ergebnissen in koronarvaskulären Herzkatheteruntersuchungen war der Vergleich von drei konventionell-chirurgischen Risikomodellen (logistischer EuroSCORE I (90, 115), EuroSCORE II (89) und *Society of Thoracic Surgeons Predicted Risk of Mortality model* (91) mit drei TAVI-spezifischen Risikomodellen (FRANCE-2, OBSERVANT und GAVS-2 (92-94)) ernüchternd (116): Keines der Modelle erreichte auch nur annähernd gute Diskriminations- und Kalibrationsleistungen zur Vorhersage von 30-Tage-Mortalität nach TAVI-Eingriffen. Diese Ergebnisse bestätigten englische (117) und niederländische Studien (118) mit ähnlichem Design: Offensichtlich ist die Auswahl der Risikofaktoren für TAVI-Eingriffe in den Modellen noch nicht hinreichend gut – möglicherweise geschuldet den im Vergleich zu koronarvaskulären Modellen geringeren Stichprobengrößen und der noch größeren technischen und demographischen Dynamik der Prozedur im letzten Jahrzehnt.

## 5.2 Risikoadjustiertes Risikomanagement

In der interventionellen Kardiologie ist das GRACE-Risikomodell führend in seiner externen Validierung (119-123), insbesondere auch prospektiv im Hinblick auf prognostische Relevanz des Timings invasiver Maßnahmen (19) im akuten Koronarsyndrom. Trotz der Empfehlungen zur Nutzung von Risikomodellen in kardiovaskulären Leitlinien (35-38) ist die Evidenz jedoch rar, dass der Einsatz die Qualität der Patientenversorgung verbessert (124). Eingebettet in das australische *Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events (CONCORDANCE)* Register (125) von Patienten mit akutem Koronarsyndrom

hat die AGRIS Studie (67, 126) bisher als einzige randomisiert-kontrollierte Untersuchung dezidiert Risikomanagement mithilfe des GRACE Modells im ACS untersucht, wurde jedoch frühzeitig abgebrochen: Der routinemäßige Einsatz des Modells führte zu mehr früh-invasiven Behandlungsstrategien im akuten Koronarsyndrom, insbesondere bei Niedrig-Risiko-Patienten, hatte jedoch keinen Einfluss auf klinische Outcomes nach 12 Monaten (67). Eine Begründung der Autoren war (67), dass die Leitlinienadhärenz der beteiligten Krankenhäuser bereits so gut war, dass Unterschiede im Timing nur in derjenigen Gruppe gefunden wurden, welche die größte Variation in der ärztlichen Risikowahrnehmung aufwies – im Niedrig-Risiko-Bereich.

Neben der Untersuchung des Timings von invasivem Management im ACS sind weitere Maßnahmen zum Risikomanagement denkbar, welche das Potenzial haben, klinische Outcomes zu verbessern: Die höhere Erfahrung des Operateurs beeinflusst Outcomes positiv (127); intensiviertes Monitoring kann helfen, adverse Ereignisse frühzeitiger zu erkennen (128, 129); radialer anstatt von femoralem Zugangsweg und der Nutzen von arteriellen Gefäßverschlusssystemen beeinflussen Outcomes (130-135) über eine Reduktion des Blutungsrisikos; und nicht zuletzt können präventive Maßnahmen möglicherweise akute kontrastmittelinduzierte Nierenversagen verhindern (136) und damit Outcomes verbessern (137).

Ob diese Maßnahmen positive Wirkung haben, wenn sie risikoadjustiert eingesetzt werden, ist bisher unklar. Auf Basis der Studienergebnisse 4.1.1 bis 4.1.3 wurde in Düsseldorf eine Standard-Operating-Procedure für das risikoadjustierte Management von Patienten mit koronaren Herzkatheteruntersuchungen eingeführt, in welcher risikoabhängige Sicherheitsmaßnahmen dezidiert untersucht wurden (NCT03671356 auf <https://www.clinicaltrials.gov>). Die Auswertung der Ergebnisse ist zum Zeitpunkt der Anfertigung dieser Schrift noch nicht abgeschlossen.

### 5.3 Optimierung von Risikomodellen unter Anwendung von künstlicher Intelligenz

Wir haben in Studien 4.1.1 bis 4.1.4 gezeigt, dass der Einsatz von fast allen getesteten Risikomodellen zur patientenindividuellen Risikovorhersage außerhalb der ursprünglichen Entwicklungspopulationen mit einem Verlust von Genauigkeit in der Kalibration einherging. Eine Rekalibrierung von Risikomodellen wird daher sehr wichtig, um klinische Entscheidungen von einem solchen Modell abhängig machen zu können (138-140): Idealerweise würden Modelle während Ihrer Anwendung in einer bestimmten Population bzw. einem bestimmten klinischen Setting einem kontinuierlichem Monitoring unterzogen, um Abweichungen und deren Ursachen frühzeitig zu erkennen (138, 140, 141). Eine Rekalibrierung kann sowohl eine



Neuberechnung der vorhandenen Koeffizienten für Prädiktoren im Modell, oder aber auch den Einschluss neuer Prädiktoren in das Modell beinhalten (139, 140, 142).

Algorithmen mit Nutzung künstlicher Intelligenz – in unserer Studie 4.1.5 *Machine learning* – sind in der Lage, sehr große Datenmengen automatisiert zu verarbeiten. Sie versprechen im Kontext der Risikoprädiktion (143), relevante Einflussfaktoren automatisiert zu erkennen, in Modelle zu inkorporieren und damit die Vorhersagekraft gegenüber konventionellen Modellen zu verbessern (144) – wie auch im präsentierten intensivmedizinischen Anwendungsbeispiel (145). *Machine learning* Algorithmen haben jedoch – so vielversprechend ihre Anwendung sein mag – eine Reihe an Limitationen durch Intransparenz (146, 147): Modell-Overfitting, Umgang mit fehlenden Daten, inadäquate Stichprobengrößen können zu fehlerhaften Ergebnissen führen, insbesondere im Rahmen von sog. *automation bias* – wenn Anwender die Vigilanz für die eingegebenen Informationen und deren Prozessierung verlieren (148). Diese Algorithmen müssen daher ebenfalls rigoros und unter Berücksichtigung klinisch-epidemiologischer Grundsätze evaluiert werden, um für zuverlässige patientenindividuelle Risikovorhersage geeignet zu sein.

#### 5.4 Meta-Analyse als Methodik zur populationsbasierten Risiko-/Nutzenabwägung

Im Kapitel 4.2 werden in dieser Habilitationsschrift Studien präsentiert, welche mithilfe von meta-analytischen Verfahren populationsbasierte Risiko-/Nutzen-Abwägungen verschiedener adjunktiver und interventioneller Therapien untersucht haben. Eine Meta-Analyse ist dabei ein quantitatives, epidemiologisches Studiendesign, welches systematisch die gesamte Evidenz verschiedener – oftmals in ihren Ergebnissen konträrer – Studien zu einer bestimmten klinischen Fragestellung evaluiert und integriert (75). Meta-Analysen sind integraler Bestandteil der evidenzbasierten Medizin, insbesondere, um Fragestellungen zu beantworten, welche aus den Ergebnissen einzelner Studien nicht beantwortbar wären. Entscheidend für ihre Ergebnisqualität ist – wie oftmals – die Qualität ihrer methodischen Durchführung (149, 150) – wofür hier besondere Beispiele gewählt wurden:

Die Studien 4.2.1 und 4.2.2 haben einen systematischen Suchprozess entlang der Leitfäden der *Cochrane Collaboration* (79) und des *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Statement (80) zugrunde gelegt, um im klinischen Setting des akuten Koronarsyndroms adjunktive Therapien der plasmatischen Antikoagulation (151) und der Thrombozytenaggregationshemmung (152) zu untersuchen. Kennzeichnend für die Evidenz in diesem Feld ist, dass durch eine beständige Weiterentwicklung von konkurrierenden pharmakologischen Therapieoptionen über zwei Jahrzehnte (153) direkte

Vergleiche aus RCTs oftmals nicht verfügbar und die jeweils beste Therapiestrategien unklar waren.

Mithilfe einer Netzwerk-Methodik zur Analyse direkter und indirekter Vergleiche (76) konnten wir zeigen (151), dass die Auswahl von Heparinen zur plasmatischen Gerinnungshemmung im akuten Koronarsyndrom ischämische Ereignisse reduzierte, jedoch gegenüber Bivalirudin zu mehr Blutungen führte. Aktuelle europäische Leitlinien empfehlen primär unfractioniertes Heparin, Bivalirudin wird als Alternative mit Klasse IIa/b Empfehlungen gesehen (35, 36). Die kürzlich publizierte BRIGHT-4 Studie kam in chinesischen Patienten mit STEMI zu Vorteilen für Bivalirudin (154) – es bleibt abzuwarten, ob dies auch in Europa die Behandlungsstrategien ändern wird. GPI sind starke intravenöse Thrombozytenhemmer, welche von früheren Leitlinien als Routinetherapie im STEMI empfohlen wurden (155, 156). Mit dem Erscheinen moderner oraler Thrombozytenaggregationshemmer wurden GPI-Empfehlungen von der Routinetherapie zur Therapie ausgewählter Patienten mit hoher Thrombuslast reduziert (36, 157). In einer differenzierten Analyse der gesamten Evidenz zur Routinetherapie im STEMI konnten wir zeigen, dass GPI-Therapie mit signifikant geringerer Mortalität bei mehr Blutungsereignissen assoziiert war (152) – allerdings mit der Limitation, dass Studien mit moderner oraler Thrombozytenaggregationshemmung weitestgehend inexistent sind.

In Studien 4.2.3 und 4.2.4 wurden Revaskularisierungsstrategien in der Herzinsuffizienz aufgrund einer koronaren Herzerkrankung (158) und im akuten Schlaganfall (159) analysiert. Kennzeichnend war hier in beiden Feldern, dass die vorhandenen Studien zu kleine Fallzahlen besaßen, um relevante klinische Endpunkte vollständig analysieren zu können. Wir konnten nach einem systematischen Suchprozess mit Identifikation von 21 Studien und in über 16.000 Patienten zeigen, dass Revaskularisierungsstrategien in der Herzinsuffizienz aufgrund einer koronaren Herzerkrankung zu besserem Überleben führten, als alleinige konservative Therapie (158). Die Ergebnisse dieser Arbeit waren von großer Bedeutung für dieses Forschungsfeld und wurden in mehreren internationalen Leitlinien zur Revaskularisierung und Therapie der Herzinsuffizienz zitiert (37, 38, 40). Während die Befunde der Analyse durch die STICHES-Studie für operative Revaskularisierung bestätigt wurden (160), hat die REVIVED-BCIS2 Studie kürzlich für die perkutane Koronarintervention keinen relevanten Vorteil in diesem Kollektiv gezeigt und damit die Ergebnisse unserer Analyse teilweise korrigiert (161). In der Analyse von zehn leitlinienrelevanten Studien zur mechanischen Thrombektomie im akuten ischämischen Schlaganfall konnten wir durch Kumulation statistischer Power erstmals zeigen, dass diese interventionelle Technik nicht nur funktionelle Ergebnisse für die Patienten verbessert, sondern gleichfalls die Mortalität nach 90 Tagen signifikant reduziert (159). Dieser Nachweis konnte bisher noch von keiner einzelnen Studie geführt werden (162) und ist insofern ein Alleinstellungsmerkmal dieser Arbeit in diesem Feld.

In Studie 4.2.5 wurden neben relativen Effektgrößen neuer antidiabetischer Therapien auf kardiovaskuläre Endpunkte im Vergleich von Verum- und Placebogruppe auch absolute Behandlungseffekte (absolute Risikoreduktion, number-needed-to-treat (NNT)) in einer Meta-Analyse untersucht: Dazu wurden aus Kaplan-Meier-Kurven von insgesamt 16 RCTs Daten mithilfe von WebPlotDigitizer extrahiert und anschließend in Weibull-Modellen rekonstruiert (77, 163). In einer Meta-Analyse von NNT zeigte sich schließlich, dass der Einfluss aller betrachteten Medikationen auf kardiovaskuläre Mortalität gering bis nicht vorhanden war, jedoch SGLT2 Inhibitoren insbesondere in Patienten mit Herzinsuffizienz große Effekte auf den Endpunkt „Hospitalisierung aufgrund einer Herzinsuffizienz“ hatten (164). Diese Arbeit stellt die bisher umfangreichste Publikation zu absoluten Behandlungseffekten dieser Pharmakotherapie dar. Ihre Befunde gehen einher mit Leitlinienempfehlungen zu SGLT2 Inhibitoren in der Therapie der Herzinsuffizienz (40) und werden von kürzlich publizierten Studien EMPEROR-Preserved und DELIVER in Patienten mit Herzinsuffizienz mit erhaltener Pumpfunktion bestätigt (165, 166).



## 6 Zusammenfassung

Risikoadjustierte Strategien sind in der kardiovaskulären Medizin für behandelnde Ärzte alltägliche Herausforderungen, welche unter Prinzipien der evidenzbasierten Medizin durch eine Vielzahl an Studienergebnissen und Leitlinien unterstützt werden.

Für patientenindividuelle Nutzen-/Risiko-Abwägungen können statistische Risikomodelle zur Vorhersage der Wahrscheinlichkeit eines Eintretens adverser Ereignisse im Rahmen eines Eingriffes oder einer Behandlung genutzt werden. Wir konnten zeigen, dass in koronaren Herzkatheteruntersuchungen die modernen Modelle zur Vorhersage von Mortalität, Blutungen und akuten Nierenversagen aus dem amerikanischen National Cardiovascular Data Registry (NCDR) nicht nur sehr akkurat in Düsseldorfer Patienten funktionieren, sondern dass diese auch zur Vorhersage von Mortalität im akuten Koronarsyndrom und zur Vorhersage von kontrastmittelinduziertem, akutem Nierenversagen den leitlinienempfohlenen Goldstandards GRACE (Mortalität) und Mehran (Nierenversagen) überlegen waren. Einzig die Kalibration dieser Modelle war oftmals verbesserungswürdig. Wir konnten in einer intensivmedizinischen Studie zeigen, dass Methoden künstlicher Intelligenz (Machine learning) geeignet sein können, um die Genauigkeit der Risikoprädiktion von etablierten Risikomodellen zu optimieren.

Für populationsbasierte Nutzen-/Risiko-Abwägungen stellen Meta-Analyseverfahren randomisierter, kontrollierter Studien den höchsten Evidenzgrad dar: Diese sind geeignet, Fragestellungen zu beantworten, welche aufgrund von methodischen Limitationen einzelner Studien ansonsten unbeantwortet blieben. Wir konnten zeigen, dass systematische Reviews und Meta-Analysen mit differenzierter Methodik (inkl. Analyse indirekter Evidenz durch Netzwerke) sowohl in der Beurteilung adjunktiver Antikoagulation und Thrombozytenaggregationshemmung im akuten Koronarsyndrom, als auch in der integrativen Analyse von Revaskularisierungstherapien in der Herzinsuffizienz und im akuten Schlaganfall entscheidende neue Erkenntnisse bringen können, welche teilweise in kardiovaskulären Leitlinien zitiert wurden. Weiterhin kann der meta-analytische Vergleich relativer und absoluter Behandlungseffekte die Bedeutung einer Therapie in ausgewählten Patientenkollektiven herausstellen.

Die Ergebnisse dieser Arbeit helfen dabei, risikoadjustierte Behandlungsstrategien in interventioneller Kardiologie und Intensivmedizin zu verstehen, für den individuellen Patienten die beste populationsbasierte Studienevidenz zur Behandlung auszuwählen und diese vor dem Hintergrund seines individuellen Risikos für adverse Ereignisse einzusetzen. Weiterführende Arbeiten können in Zukunft helfen, sowohl die individuelle Risikoprädiktion (mithilfe von künstlicher Intelligenz), als auch die Methodik zur Meta-Analytik klinischer Studien weiter zu verbessern – mit dem Ziel, einer patientenindividuellen Präzisionsmedizin näher zu kommen.

## 7 Literaturverzeichnis

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, et al. European Society of Cardiology: cardiovascular disease statistics 2021. *European Heart Journal*. 2022;43(8):716-99.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics—2021 Update. *Circulation*. 2021;143(8):e254-e743.
3. World Health Organization (WHO). Cardiovascular diseases - Key facts. Online source. 2021;[https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)).
4. Statistisches Bundesamt. Todesursachenstatistik 2020. Online abgerufen am 17.11.2022. 2021;[https://www.destatis.de/DE/Presse/Pressemitteilungen/2021/11/PD21\\_505\\_23211.html](https://www.destatis.de/DE/Presse/Pressemitteilungen/2021/11/PD21_505_23211.html).
5. Deutsche Herzstiftung e.V. Herzbericht 2021. 2021.
6. Zahn R, Schiele R, Schneider S, Gitt Anselm K, Wienbergen H, Seidl K, et al. Primary angioplasty versus intravenous thrombolysis in acute myocardial infarction: can we define subgroups of patients benefiting most from primary angioplasty? *Journal of the American College of Cardiology*. 2001;37(7):1827-35.
7. Zijlstra F, Hoorntje JCA, de Boer M-J, Reijnders S, Miedema K, Ottervanger JP, et al. Long-Term Benefit of Primary Angioplasty as Compared with Thrombolytic Therapy for Acute Myocardial Infarction. *New England Journal of Medicine*. 1999;341(19):1413-9.
8. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. *New England Journal of Medicine*. 2001;345(7):494-502.
9. Schüpke S, Neumann F-J, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*. 2019;381(16):1524-34.
10. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*. 2009;361(11):1045-57.
11. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*. 2007;357(20):2001-15.
12. Rodriguez F, Harrington RA. Management of Antithrombotic Therapy after Acute Coronary Syndromes. *New England Journal of Medicine*. 2021;384(5):452-60.
13. Stefanini GG, Holmes DR. Drug-Eluting Coronary-Artery Stents. *New England Journal of Medicine*. 2013;368(3):254-65.
14. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet*. 1999;354(9180):708-15.
15. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344(25):1879-87.
16. Fox KAA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TRD, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. *The Lancet*. 2002;360(9335):743-51.
17. Puymirat E, Taldir G, Aissaoui N, Lemesle G, Lorgis L, Cuisset T, et al. Use of invasive strategy in non-ST-segment elevation myocardial infarction is a major determinant of improved long-term survival: FAST-MI (French Registry of Acute Coronary Syndrome). *JACC Cardiovasc Interv*. 2012;5(9):893-902.
18. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, et al. Early Versus Standard Care Invasive Examination and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *Circulation*. 2018;138(24):2741-50.
19. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, et al. Early versus Delayed Invasive Intervention in Acute Coronary Syndromes. *New England Journal of Medicine*. 2009;360(21):2165-75.
20. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. *New England Journal of Medicine*. 2020;382(17):1608-18.
21. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *New England Journal of Medicine*. 2020;382(15):1395-407.
22. Winter M-P, Bartko P, Hofer F, Zbiral M, Burger A, Ghanim B, et al. Evolution of outcome and complications in TAVR: a meta-analysis of observational and randomized studies. *Scientific Reports*. 2020;10(1):15568.
23. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *New England Journal of Medicine*. 2019;380(18):1706-15.
24. Mehra MR, Uriel N, Naka Y, Cleveland JC, Yuzefpolskaya M, Salerno CT, et al. A Fully Magnetically Levitated Left Ventricular Assist Device — Final Report. *New England Journal of Medicine*. 2019;380(17):1618-27.
25. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. *New England Journal of Medicine*. 2001;345(20):1435-43.
26. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med*. 2016;374(16):1511-20.
27. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *New England Journal of Medicine*. 2017;377(25):2419-32.
28. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. *New England Journal of Medicine*. 2012;367(14):1287-96.

29. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *New England Journal of Medicine*. 2014;372(1):11-20.
30. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *New England Journal of Medicine*. 2020;383(25):2451-60.
31. Jung C, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, et al. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. *Crit Care*. 2021;25(1):344.
32. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *Bmj*. 1996;312(7023):71-2.
33. Karanickolas PJ, Kunz R, Guyatt GH. Point: Evidence-Based Medicine Has a Sound Scientific Base. *CHEST*. 2008;133(5):1067-71.
34. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-77.
35. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2020;42(14):1289-367.
36. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2017;39(2):119-77.
37. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(3):e18-e114.
38. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165.
39. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032.
40. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-726.
41. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*. 2021;43(7):561-632.
42. Foot DK, Lewis RP, Pearson TA, Beller GA. Demographics and cardiology, 1950-2050. *J Am Coll Cardiol*. 2000;35(5 Suppl B):66b-80b.
43. Grotti S, Bolognese L. Interventional cardiology is changing: demographic, clinical and economic considerations. *J Cardiovasc Med (Hagerstown)*. 2017;18 Suppl 1:e67-e70.
44. Hooker W. *Physician and Patient*. New York: Baker and Scribner. 1847;219.
45. Loeffer I. Why the Hippocratic ideals are dead. *BMJ*. 2002;324(7351):1463.
46. Saar A, Marandi T, Ainla T, Fischer K, Blöndal M, Eha J. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *International Journal of Cardiology*. 2018;272:26-32.
47. Block PC, Peterson ED, Krone R, Kesler K, Hannan E, O'Connor GT, et al. Identification of variables needed to risk adjust outcomes of coronary interventions: evidence-based guidelines for efficient data collection. *J Am Coll Cardiol*. 1998;32(1):275-82.
48. Moscucci M, O'Connor GT, Ellis SG, Malenka DJ, Sievers J, Bates ER, et al. Validation of risk adjustment models for in-hospital percutaneous transluminal coronary angioplasty mortality on an independent data set. *J Am Coll Cardiol*. 1999;34(3):692-7.
49. Bouch DC, Thompson JP. Severity scoring systems in the critically ill. *Continuing Education in Anaesthesia Critical Care & Pain*. 2008;8(5):181-5.
50. Knaus WA. APACHE 1978-2001: The Development of a Quality Assurance System Based on Prognosis: Milestones and Personal Reflections. *Archives of Surgery*. 2002;137(1):37-41.
51. Chew DP, Juergens C, French J, Parsonage W, Horsfall M, Brieger D, et al. An examination of clinical intuition in risk assessment among acute coronary syndromes patients: observations from a prospective multi-center international observational registry. *Int J Cardiol*. 2014;171(2):209-16.
52. Ranasinghe I, Alprandi-Costa B, Chow V, Elliott JM, Waites J, Counsell JT, et al. Risk stratification in the setting of non-ST elevation acute coronary syndromes 1999-2007. *Am J Cardiol*. 2011;108(5):617-24.
53. Bing R, Goodman SG, Yan AT, Fox K, Gale CP, Hyun K, et al. Use of clinical risk stratification in non-ST elevation acute coronary syndromes: an analysis from the CONCORDANCE registry. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2018;4(4):309-17.
54. Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, et al. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. *Circulation: Cardiovascular Quality and Outcomes*. 2013;6(3):299-308.
55. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091.



56. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014;4(2):e004425.
57. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345-53.
58. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44(7):1393-9.
59. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55(23):2556-66.
60. Brennan JM, Curtis JP, Dai D, Fitzgerald S, Khandelwal AK, Spertus JA, et al. Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2013;6(8):790-9.
61. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2010;55(18):1923-32.
62. Rao SV, McCoy LA, Spertus JA, Krone RJ, Singh M, Fitzgerald S, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI Registry. *JACC Cardiovasc Interv*. 2013;6(9):897-904.
63. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc*. 2014;3(6):e001380.
64. Weintraub WS, Grau-Sepulveda MV, Weiss JM, DeLong ER, Peterson ED, O'Brien SM, et al. Prediction of long-term mortality after percutaneous coronary intervention in older adults: results from the National Cardiovascular Data Registry. *Circulation*. 2012;125(12):1501-10.
65. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31(10):1345-55.
66. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-10.
67. Chew DP, Hyun K, Morton E, Horsfall M, Hillis GS, Chow CK, et al. Objective Risk Assessment vs Standard Care for Acute Coronary Syndromes: A Randomized Clinical Trial. *JAMA Cardiology*. 2021;6(3):304-13.
68. Antoniou S, Colicchia M, Guttman OP, Rathod KS, Wright P, Fhadil S, et al. Risk scoring to guide antiplatelet therapy post-percutaneous coronary intervention for acute coronary syndrome results in improved clinical outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2018;4(4):283-9.
69. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162(4):266-75.
70. Matheny ME, Ohno-Machado L, Resnic FS. Discrimination and calibration of mortality risk prediction models in interventional cardiology. *J Biomed Inform*. 2005;38(5):367-75.
71. Fanaroff AC, Califf RM, Windecker S, Smith SC, Jr, Lopes RD. Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018. *JAMA*. 2019;321(11):1069-80.
72. van Dijk WB, Grobbee DE, de Vries MC, Groenwold RHH, van der Graaf R, Schuit E. A systematic breakdown of the levels of evidence supporting the European Society of Cardiology guidelines. *Eur J Prev Cardiol*. 2019;26(18):1944-52.
73. Piepoli MF, Ceconi C. Levels of evidence in the European Society of Cardiology Guidelines: Gaps in knowledge? *European Journal of Preventive Cardiology*. 2020;26(18):1941-3.
74. Glass GV. Primary, Secondary, and Meta-Analysis of Research. *Educational Researcher*. 1976;5(10):3-8.
75. Haidich AB. Meta-analysis in medical research. *Hippokratia*. 2010;14(Suppl 1):29-37.
76. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *Bmj*. 2005;331(7521):897-900.
77. Guyot P, Ades AE, Ouwers MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology*. 2012;12(1):9.
78. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318(26):1728-33.
79. Higgins J, Thomas J, J C, M C, T L, MJ P, et al. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 6.3 (updated February 2022). Available from [www.trainingcochrane.org/handbook](http://www.trainingcochrane.org/handbook). 2022.
80. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
81. Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study designs in the health sciences. *Jama*. 2005;293(19):2362-6.
82. Brennan JM, Curtis JP, Dai D, Fitzgerald S, Khandelwal AK, Spertus JA, et al. Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2013;6(8):790-9.

83. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2010;55(18):1923-32.
84. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999-3054.
85. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2016;37(3):267-315.
86. Pieper KS, Gore JM, Fitzgerald G, Granger CB, Goldberg RJ, Steg G, et al. Validity of a risk-prediction tool for hospital mortality: the Global Registry of Acute Coronary Events. *Am Heart J*. 2009;157(6):1097-105.
87. Chin CT, Chen AY, Wang TY, Alexander KP, Mathews R, Rumsfeld JS, et al. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: The Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry®-Get with the Guidelines (GWTG)<sup>TM</sup> acute myocardial infarction mortality model and risk score. *American Heart Journal*. 2011;161(1):113-22.e2.
88. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, et al. Predicting In-Hospital Mortality in Patients With Acute Myocardial Infarction. *Journal of the American College of Cardiology*. 2016;68(6):626-35.
89. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4):734-44; discussion 44-5.
90. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J*. 2003;24(9):881-2.
91. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. *Ann Thorac Surg*. 2009;88(1 Suppl):S23-42.
92. Capodanno D, Barbanti M, Tamburino C, D'Errigo P, Ranucci M, Santoro G, et al. A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol*. 2014;113(11):1851-8.
93. Jung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, et al. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart*. 2014;100(13):1016-23.
94. Schiller W, Barnewold L, Kazmaier T, Beckmann A, Masseli F, Welz A, et al. The German Aortic Valve Score II. *Eur J Cardiothorac Surg*. 2017;52(5):881-7.
95. Jung C, Flaatten H, Fjølner J, Bruno RR, Wernly B, Artigas A, et al. The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. *Crit Care*. 2021;25(1):149.
96. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes. *Circulation*. 2014;130(25):e344-e426.
97. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-425.
98. Steg PG, James SK, Atar D, Badano LP, Blömlstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-619.
99. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e99.
100. Association AD. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. *Diabetes Care*. 2020;44(Supplement\_1):S111-S24.
101. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *European Heart Journal*. 2019;41(2):255-323.
102. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.
103. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020;383(15):1413-24.
104. Ferreira JP, Docherty KF, Stienen S, Jhund PS, Claggett BL, Solomon SD, et al. Estimating the Lifetime Benefits of Treatments for Heart Failure. *JACC Heart Fail*. 2020;8(12):984-95.
105. Tufts PACE Clinical Predictive Model Registry. . Accessed April 27, 2020.
106. Moons KGM, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart*. 2012;98(9):691.
107. Adibi A, Sadatsafavi M, Ioannidis JPA. Validation and Utility Testing of Clinical Prediction Models: Time to Change the Approach. *JAMA*. 2020.
108. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21(1):128-38.

109. Wolff G, Lin Y, Quade J, Bader S, Kosejian L, Brockmeyer M, et al. Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center. *Clin Res Cardiol.* 2020;109(2):235-45.
110. Timoteo AT, Monteiro AV, Portugal G, Teixeira P, Aidos H, Ferreira ML, et al. Validation of two US risk scores for percutaneous coronary intervention in a single-center Portuguese population of patients with acute coronary syndrome. *Rev Port Cardiol.* 2016;35(2):73-8.
111. Dobies DR, Barber KR, Cohoon AL. Validity of a PCI Bleeding Risk Score in patient subsets stratified for body mass index. *Open Heart.* 2015;2(1):e000088.
112. Inohara T, Kohsaka S, Miyata H, Ueda I, Maekawa Y, Fukuda K, et al. Performance and Validation of the U.S. NCDR Acute Kidney Injury Prediction Model in Japan. *J Am Coll Cardiol.* 2016;67(14):1715-22.
113. Parco C, Brockmeyer M, Kosejian L, Quade J, Trostler J, Bader S, et al. Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort. *Int J Cardiol.* 2021;329:28-35.
114. Parco C, Brockmeyer M, Kosejian L, Quade J, Trostler J, Bader S, et al. National Cardiovascular Data Registry-Acute Kidney Injury (NCDR) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort. *J Nephrol.* 2021;34(5):1491-500.
115. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16(1):9-13.
116. Wolff G, Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K, et al. Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients. *Clin Res Cardiol.* 2021;110(3):368-76.
117. Martin GP, Sperrin M, Ludman PF, de Belder MA, Gale CP, Toff WD, et al. Inadequacy of existing clinical prediction models for predicting mortality after transcatheter aortic valve implantation. *American heart journal.* 2017;184:97-105.
118. Al-Farra H, Abu-Hanna A, de Mol BAJM, ter Burg WJ, Houterman S, Henriques JPS, et al. External validation of existing prediction models of 30-day mortality after Transcatheter Aortic Valve Implantation (TAVI) in the Netherlands Heart Registration. *International journal of cardiology.* 2020.
119. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP, et al. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *American Heart Journal.* 2009;158(3):392-9.
120. Prabhudesai AR, Srilakshmi MA, Santosh MJ, Shetty GG, Varghese K, Patil CB, et al. Validation of the GRACE score for prognosis in Indian patients with acute coronary syndromes. *Indian Heart Journal.* 2012;64(3):263-9.
121. Komiya K, Nakamura M, Tanabe K, Niikura H, Fujimoto H, Oikawa K, et al. In-hospital mortality analysis of Japanese patients with acute coronary syndrome using the Tokyo CCU Network database: Applicability of the GRACE risk score. *Journal of Cardiology.* 2018;71(3):251-8.
122. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS. *European Heart Journal.* 2005;26(9):865-72.
123. Wenzl FA, Kraler S, Ambler G, Weston C, Herzog SA, Räber L, et al. Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. *The Lancet.* 2022;400(10354):744-56.
124. Chew DP, Bhatt DL. Predicting Risk in ACS: Taking the Long-Term View\*. *Journal of the American College of Cardiology.* 2017;70(15):1858-60.
125. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). *Heart Lung Circ.* 2013;22(7):533-41.
126. Chew DP, Astley CM, Luker H, Alprandi-Costa B, Hillis G, Chow CK, et al. A cluster randomized trial of objective risk assessment versus standard care for acute coronary syndromes: Rationale and design of the Australian GRACE Risk score Intervention Study (AGRIS). *Am Heart J.* 2015;170(5):995-1004.e1.
127. Xu B, Redfors B, Yang Y, Qiao S, Wu Y, Chen J, et al. Impact of Operator Experience and Volume on Outcomes After Left Main Coronary Artery Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2016;9(20):2086-93.
128. Ranhoff AH, Rozzini R, Sabatini T, Cassinadri A, Boffelli S, Ferri M, et al. Subintensive care unit for the elderly: a new model of care for critically ill frail elderly medical patients. *Intern Emerg Med.* 2006;1(3):197-203.
129. Taenzer AH, Pyke JB, McGrath SP, Blike GT. Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before-and-after concurrence study. *Anesthesiology.* 2010;112(2):282-7.
130. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet.* 2015;385(9986):2465-76.
131. Baklanov DV, Kim S, Marso SP, Subherwal S, Rao SV. Comparison of bivalirudin and radial access across a spectrum of preprocedural risk of bleeding in percutaneous coronary intervention: analysis from the national cardiovascular data registry. *Circ Cardiovasc Interv.* 2013;6(4):347-53.
132. Farooq V, Goedhart D, Ludman P, de Belder MA, Harcombe A, El-Omar M, et al. Relationship Between Femoral Vascular Closure Devices and Short-Term Mortality From 271 845 Percutaneous Coronary Intervention Procedures Performed in the United Kingdom Between 2006 and 2011: A Propensity Score-Corrected Analysis From the British Cardiovascular Intervention Society. *Circ Cardiovasc Interv.* 2016;9(6).



133. Wimmer NJ, Secemsky EA, Mauri L, Roe MT, Saha-Chaudhuri P, Dai D, et al. Effectiveness of Arterial Closure Devices for Preventing Complications With Percutaneous Coronary Intervention: An Instrumental Variable Analysis. *Circ Cardiovasc Interv.* 2016;9(4):e003464.
134. Jiang J, Zou J, Ma H, Jiao Y, Yang H, Zhang X, et al. Network Meta-analysis of Randomized Trials on the Safety of Vascular Closure Devices for Femoral Arterial Puncture Site Haemostasis. *Sci Rep.* 2015;5:13761.
135. Rao SV, Stone GW. Arterial access and arteriotomy site closure devices. *Nat Rev Cardiol.* 2016;13(11):641-50.
136. Navarese EP, Gurbel PA, Andreotti F, Kolodziejczak MM, Palmer SC, Dias S, et al. Prevention of contrast-induced acute kidney injury in patients undergoing cardiovascular procedures-a systematic review and network meta-analysis. *PLoS One.* 2017;12(2):e0168726.
137. Kooiman J, Seth M, Nallamothu BK, Heung M, Humes D, Gurm HS. Association between acute kidney injury and in-hospital mortality in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv.* 2015;8(6):e002212.
138. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW, Bossuyt P, et al. Calibration: the Achilles heel of predictive analytics. *BMC Medicine.* 2019;17(1):230.
139. Su T-L, Jaki T, Hickey GL, Buchan I, Sperrin M. A review of statistical updating methods for clinical prediction models. *Statistical Methods in Medical Research.* 2018;27(1):185-97.
140. Steyerberg E. Clinical prediction models. A Practical Approach to Development. 2009.
141. Hickey GL, Grant SW, Caiado C, Kendall S, Dunning J, Poullis M, et al. Dynamic Prediction Modeling Approaches for Cardiac Surgery. *Circulation: Cardiovascular Quality and Outcomes.* 2013;6(6):649-58.
142. Edlinger M, Wanitschek M, Dörler J, Ulmer H, Alber HF, Steyerberg EW. External validation and extension of a diagnostic model for obstructive coronary artery disease: a cross-sectional predictive evaluation in 4888 patients of the Austrian Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort. *BMJ Open.* 2017;7(4):e014467.
143. Sundström J, Schön TB. Machine Learning in Risk Prediction. *Hypertension.* 2020;75(5):1165-6.
144. Wu X, Yuan X, Wang W, Liu K, Qin Y, Sun X, et al. Value of a Machine Learning Approach for Predicting Clinical Outcomes in Young Patients With Hypertension. *Hypertension.* 2020;75(5):1271-8.
145. Jung C, Mamandipoor B, Fjolner J, Bruno RR, Wernly B, Artigas A, et al. Disease-Course Adapting Machine Learning Prognostication Models in Elderly Patients Critically Ill With COVID-19: Multicenter Cohort Study With External Validation. *JMIR Med Inform.* 2022;10(3):e32949.
146. Andaur Navarro CL, Damen JAA, Takada T, Nijman SWJ, Dhiman P, Ma J, et al. Risk of bias in studies on prediction models developed using supervised machine learning techniques: systematic review. *BMJ.* 2021;375:n2281.
147. Lauritsen SM, Thieson B, Jørgensen MJ, Riis AH, Espelund US, Weile JB, et al. The Framing of machine learning risk prediction models illustrated by evaluation of sepsis in general wards. *npj Digital Medicine.* 2021;4(1):158.
148. Lyell D, Coiera E. Automation bias and verification complexity: a systematic review. *J Am Med Inform Assoc.* 2017;24(2):423-31.
149. Berlin JA, Golub RM. Meta-analysis as Evidence: Building a Better Pyramid. *JAMA.* 2014;312(6):603-6.
150. Mahmood S, Nona P, Villablanca P, Nunez-Gil I, Ramakrishna H. The Meta-Analysis in Evidence-Based Medicine: High-Quality Research When Properly Performed. *Journal of Cardiothoracic and Vascular Anesthesia.* 2021;35(9):2556-8.
151. Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, Wolff G, Dias S, et al. Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients. *Thromb Haemost.* 2015;114(5):933-44.
152. Karathanos A, Lin Y, Dannenberg L, Parco C, Schulze V, Brockmeyer M, et al. Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis. *Can J Cardiol.* 2019;35(11):1576-88.
153. Bhatt DL, Hulot J-S, Moliterno DJ, Harrington RA. Antiplatelet and Anticoagulation Therapy for Acute Coronary Syndromes. *Circulation Research.* 2014;114(12):1929-43.
154. Li Y, Liang Z, Qin L, Wang M, Wang X, Zhang H, et al. Bivalirudin plus a high-dose infusion versus heparin monotherapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a randomised trial. *The Lancet.* 2022;400(10366):1847-57.
155. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KAA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal.* 2003;24(1):28-66.
156. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation.* 2004;110(5):588-636.
157. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *Circulation.* 2016;133(11):1135-47.
158. Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, et al. Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. *Circ Heart Fail.* 2017;10(1).

159. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA*. 2019;322(12):1155-66.
160. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *New England Journal of Medicine*. 2016;374(16):1511-20.
161. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *New England Journal of Medicine*. 2022;387(15):1351-60.
162. van den Berg LA, Dijkgraaf MGW, Berkhemer OA, Fransen PSS, Beumer D, Lingsma HF, et al. Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke. *New England Journal of Medicine*. 2017;376(14):1341-9.
163. Rohatgi A. WebPlotDigitizer <https://automerisio/WebPlotDigitizer/>. 2019;Online Source.
164. Wolff G, Lin Y, Akbulut C, Brockmeyer M, Parco C, Hoss A, et al. Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes. *ESC Heart Fail*. 2022.
165. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine*. 2021;385(16):1451-61.
166. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine*. 2022;387(12):1089-98.

## 8 Verzeichnis eigener Publikationen und Kongressbeiträge

### 8.1 Originalarbeiten

#### Original-Publikationen als Erstautor (\* geteilte Erstautorenschaft):

| Jahr:        | Autoren timer, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Impact-Faktor (IF) des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------|
| 2017         | <b>Wolff G</b> , Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP. Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. Circ Heart Fail. 2017;10(1):e003255.                                                                                                                                                                             | 5,7 (2017)                                            | 5,7                         |
| 2017         | <b>Wolff G</b> , Lin Y, Karathanos A, Brockmeyer M, Wolters S, Nowak B, Furnkranz A, Makimoto H, Kelm M, Schulze V. Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials. Clin Res Cardiol. 2017;106(7):501-13.                                                                                                                                                                                                                                        | 4,5 (2017)                                            | 4,5                         |
| 2018         | <b>Wolff G</b> , Navarese EP, Brockmeyer M, Lin Y, Karathanos A, Kolodziejczak M, Kubica J, Polzin A, Zeus T, Westenfeld R, Andreotti F, Kelm M, Schulze V. Perioperative aspirin therapy in non-cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. Int J Cardiol. 2018;258:59-67.                                                                                                                                                                                                                                                                | 3,5 (2018)                                            | 3,5                         |
| 2019         | Dannenberg L*, <b>Wolff G*</b> , Naguib D, Pohl M, Zako S, Helten C, Mourikis P, Levkau B, Hohlfeld T, Zeus T, Kelm M, Schulze V, Polzin A. Safety and efficacy of Tirofiban in STEMI-patients. Int J Cardiol. 2019;274:35-9.                                                                                                                                                                                                                                                                                                                                                          | 3,2 (2019)                                            | 3,2                         |
| 2020         | Leo F, Krenz T, <b>Wolff G</b> , Weidenbach M, Heiss C, Kelm M, Isakson B, Cortese-Krott MM. Assessment of tissue perfusion and vascular function in mice by scanning laser Doppler perfusion imaging. Biochem Pharmacol. 2020:113893.                                                                                                                                                                                                                                                                                                                                                 | 5,9 (2020)                                            | 5,9                         |
| 2020         | <b>Wolff G</b> , Lin Y, Quade J, Bader S, Kosejian L, Brockmeyer M, Karathanos A, Parco C, Krieger T, Heinen Y, Perings S, Albert A, Icks A, Kelm M, Schulze V. Validation of National Cardiovascular Data Registry risk models for mortality, bleeding and acute kidney injury in interventional cardiology at a German Heart Center. Clin Res Cardiol. 2020;109(2):235-45.                                                                                                                                                                                                           | 5,5 (2020)                                            | 5,5                         |
| 2021         | <b>Wolff G</b> , Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K, Maier O, Sedaghat A, Polzin A, Sugiura A, Jung C, Grube E, Westenfeld R, Icks A, Zeus T, Sinning JM, Baldus S, Nickenig G, Kelm M, Veulemans V. Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients. Clin Res Cardiol 2021 Mar;110(3):368-376. doi: 10.1007/s00392-020-01731-9. Epub 2020 Aug 26.                                                                                                                                     | 6,1 (2021)                                            | 6,1                         |
| 2022         | <b>Wolff G</b> , Wernly B, Flaatten H, Fjølner J, Bruno RR, Artigas A, Pinto BB, Schefold JC, Kelm M, Binneboessel S, Baldia P, Beil M, Sivri S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Flamm M, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Boumendil A, De Lange DW, Guidet B, Leaver S, Jung C; COVIP Study Group. Sex-specific treatment characteristics and 30-day mortality outcomes of critically ill COVID-19 patients over 70 years of age-results from the prospective COVIP study. Can J Anaesth. 2022 Aug 9:1-9. doi: 10.1007/s12630-022-02304-2.s | 6,7 (2021)                                            | 6,7                         |
| 2022         | <b>Wolff G*</b> , Lin Y, Akbulut C, Brockmeyer M, Parco C, Hoss A, Sokolowski A, Westenfeld R, Kelm M, Roden M, Schlesinger S, Kuss O. Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes. ESC Heart Fail. 2022 Nov 7. doi: 10.1002/ehf2.14213. Online ahead of print.                                                                                                                                                                                                                                                                      | 3,6 (2021)                                            | 3,6                         |
| <b>Summe</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>44,7</b>                                           | <b>44,7</b>                 |

## Original-Publikationen als Letztautor:

| Jahr:        | Autoren timer, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                                                                                                                                                                                               | Impact-Faktor des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 2018         | Schulze V, Lin Y, Karathanos A, Brockmeyer M, Zeus T, Polzin A, Perings S, Kelm M, <b>Wolff G</b> . Patent foramen ovale closure or medical therapy for cryptogenic ischemic stroke: an updated meta-analysis of randomized controlled trials. Clin Res Cardiol. 2018;107(9):745-55.                                                                                                                                                                                    | 4,9 (2018)                                       | 4,9                         |
| 2019         | Karathanos A, Lin Y, Dannenberg L, Parco C, Schulze V, Brockmeyer M, Jung C, Heinen Y, Perings S, Zeymer U, Kelm M, Polzin A, <b>Wolff G</b> . Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis. Can J Cardiol. 2019;35(11):1576-1588.                                                                                                                                                                    | 5,2 (2019)                                       | 5,2                         |
| 2019         | Lin Y, Schulze V, Brockmeyer M, Parco C, Karathanos A, Heinen Y, Gliem M, Hartung HP, Antoch G, Jander S, Turowski B, Perings S, Kelm M, <b>Wolff G</b> . Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke: A Meta-analysis. JAMA Neurol. 2019;76(7):850-4.                                                                                                                                                                            | 13,6 (2019)                                      | 13,6                        |
| 2020         | Brockmeyer M, Lin Y, Parco C, Karathanos A, Krieger T, Schulze V, Heinen Y, Bejinaru A, Muller P, Makimoto H, Kelm M, <b>Wolff G</b> . Uninterrupted anticoagulation during catheter ablation for atrial fibrillation: no difference in major bleeding and stroke between direct oral anticoagulants and vitamin K antagonists in an updated meta-analysis of randomised controlled trials. Acta Cardiol. 2020:1-8.                                                     | 1,7 (2020)                                       | 1,7                         |
| 2021         | Parco C, Brockmeyer M, Kosejian L, Quade J, Tröstler J, Bader S, Lin Y, Karathanos A, Krieger T, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, <b>Wolff G</b> . Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort. Int J Cardiol 2021 Apr 15;329:28-35. doi: 10.1016/j.ijcard.2020.12.085. Epub 2021 Jan 4.                                                            | 4,0 (2021)                                       | 4,0                         |
| 2021         | Parco C, Brockmeyer M, Kosejian L, Quade J, Tröstler J, Bader S, Lin Y, Sokolowski A, Hoss A, Heinen Y, Schulze V, Icks A, Jung C, Kelm M, <b>Wolff G</b> . National Cardiovascular Data Registry-Acute Kidney Injury (NCDRI) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort. J Nephrol. 2021 Oct;34(5):1491-1500. doi: 10.1007/s40620-021-01124-9. Epub 2021 Aug 7. | 4,4 (2021)                                       | 4,4                         |
| 2022         | Lin Y, Parco C, Karathanos A, Krieger T, Schulze V, Chernyak N, Icks A, Kelm M, Brockmeyer M, <b>Wolff G</b> . Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: a systematic review and meta-analysis. BMJ Open. 2022 Feb 24;12(2):e048893. doi: 10.1136/bmjopen-2021-048893.                                                                                                                | 3,0 (2021)                                       | 3,0                         |
| 2022         | Kuss O, Akbulut C, Schlesinger S, Georgiev A, Kelm M, Roden M, <b>Wolff G</b> . Absolute treatment effects for the primary outcome and all-cause mortality in the cardiovascular outcome trials of new antidiabetic drugs: a meta-analysis of digitalized individual patient data. Acta Diabetol. 2022 Jul 25. doi: 10.1007/s00592-022-01917-9                                                                                                                          | 4,1 (2021)                                       | 4,1                         |
| 2022         | Brockmeyer M, Wies E, Joerges J, Sommer J, Borgmann SO, Chernyak N, Lin Y, Parco C, Schulze V, Heinen Y, Kelm M, Icks A, Perings S, <b>Wolff G</b> . Knowledge of HbA1c and LDL-C treatment goals, subjective level of disease-related information and information needs in patients with atherosclerotic cardiovascular disease. Clin Cardiol. 2022 Nov 30. doi: 10.1002/clc.23948. Online ahead of print.                                                             | 3,3 (2021)                                       | 3,3                         |
| <b>Summe</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <b>44,2</b>                                      | <b>44,2</b>                 |



**Original-Publikationen als korrespondierender Autor (ohne diejenigen, wo gleichzeitig Erst- oder Letztautor):**

| Jahr:        | Autorennamen, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                                                 | Impact-Faktor des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 2019         | Brockmeyer M, <b>Wolff G</b> , Krieger T, Lin Y, Karathanos A, Afzal S, Zeus T, Westenfeld R, Polzin A, Heinen Y, Perings S, Kelm M, Schulze V. Kidney function stratified outcomes of percutaneous left atrial appendage occlusion in patients with atrial fibrillation and high bleeding risk. Acta Cardiol. 2019;1-9. | 1,2 (2019)                                       | 1,2                         |
| <b>Summe</b> |                                                                                                                                                                                                                                                                                                                          | <b>1,2</b>                                       | <b>1,2</b>                  |

**Original-Publikationen als Ko-Autor:**

| Jahr: | Autorennamen, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                                                                                                                                                                                      | Impact-Faktor des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 2015  | Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, <b>Wolff G</b> , Dias S, Claessen B, Brouwer M, Tarantini G, Iliceto S, Brockmeyer M, Kowalewski M, Lin Y, Eikelboom J, Musumeci G, Lee L, Lip GY, Valgimigli M, Berti S, Kelm M. Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients. Thromb Haemost. 2015;114(5):933-44. | 5,3 (2015)                                       | 2,65                        |
| 2016  | Hellhammer K, Zeus T, Verde PE, Veulemans V, Kahlstadt L, <b>Wolff G</b> , Erkens R, Westenfeld R, Navarese EP, Merx MW, Rassaf T, Kelm M. Red cell distribution width in anemic patients undergoing transcatheter aortic valve implantation. World J Cardiol. 2016;8(2):220-30.                                                                                                                                                                              | -                                                | -                           |
| 2018  | Cortese-Krott MM, Mergia E, Kramer CM, Luckstadt W, Yang J, <b>Wolff G</b> , Panknin C, Bracht T, Sitek B, Pernow J, Stasch JP, Feelisch M, Koesling D, Kelm M. Identification of a soluble guanylate cyclase in RBCs: preserved activity in patients with coronary artery disease. Redox Biol. 2018;14:328-37.                                                                                                                                               | 7,8 (2018)                                       | 3,9                         |
| 2019  | Dannenberger L, Mourikis P, Naguib D, Zako S, Helten C, M'Pembale R, Trojovský K, Konsek D, <b>Wolff G</b> , Brockmeyer M, Schulze V, Levkau B, Hohfeld T, Zeus T, Kelm M, Polzin A. Antiplatelet effects of aspirin and clopidogrel after left atrial appendage (LAA) occluder implantation. Int J Cardiol. 2019;275:95-100.                                                                                                                                 | 3,2 (2019)                                       | 1,6                         |
| 2019  | Veulemans V, Polzin A, Maier O, Klein K, <b>Wolff G</b> , Hellhammer K, Afzal S, Piayda K, Jung C, Westenfeld R, Blehm A, Lichtenberg A, Kelm M, Zeus T. Prediction of One-Year Mortality Based upon A New Staged Mortality Risk Model in Patients with Aortic Stenosis Undergoing Transcatheter Valve Replacement. J Clin Med. 2019;8(10).                                                                                                                   | 3,3 (2019)                                       | 1,65                        |
| 2020  | Bruno RR, Lin Y, <b>Wolff G</b> , Polzin A, Veulemans V, Klein K, Westenfeld R, Zeus T, Kelm M, Jung C. Virtual reality assisted conscious sedation during transcatheter aortic valve implantation - a randomized pilot study. EuroIntervention. 2020 Jun 30:EIJ-D-20-00269                                                                                                                                                                                   | 6,5 (2020)                                       | 3,25                        |
| 2020  | Jung C, Bruno RR, Wernly B, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Fernandes AM, Artigas A, Pinto BB, Schefold J, <b>Wolff G</b> , Kelm M, De Lange DW, Guidet B, Flaatten H, Fjølner J; COVIP study group. Inhibitors of the Renin-Angiotensin-Aldosterone System and Covid-19 in critically ill elderly patients. Eur Heart J Cardiovasc Pharmacother 2020 Jul 9;pvaa083. doi: 10.1093/ehjcvp/pvaa083. Online ahead of print.  | 6,6 (2020)                                       | 3,3                         |
| 2020  | Bruno RR, Wernly B, Beil M, Muessig JM, Rahmel T, Graf T, Meybohm P, Schaller SJ, Allgäuer S, Franz M, Westphal JG,                                                                                                                                                                                                                                                                                                                                           | 3,4 (2020)                                       | 1,7                         |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |      |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|
|      | Barth E, Ebelt H, Fuest K, Horacek M, Schuster M, Dubler S, Schering S, <b>Wolff G</b> , Steiner S, Rabe C, Dieck T, Lauten A, Sacher AL, Brenner T, Bloos F, Jánosi RA, Simon P, Utzolino S, Kelm M, De Lange DW, Guidet B, Flaatten H, Jung C. Therapy limitation in octogenarians in German intensive care units is associated with a longer length of stay and increased 30 days mortality: A prospective multicenter study. J Crit Care 2020 Aug 1;60:58-63.doi: 10.1016/j.jcrc.2020.07.024. Online ahead of print.            |             |      |
| 2021 | Afzal S, Piayda K, Hellhammer K, Veulemans V, <b>Wolff G</b> , Heidari H, Stüwe D, Kanschik D, Polzin A, Kelm M, Zeus T. Real-time echocardiography-fluoroscopy fusion imaging for left atrial appendage closure: prime time for fusion imaging? Acta Cardiol. 2021 Jan 13:1-9.                                                                                                                                                                                                                                                     | 1,7 (2021)  | 0,85 |
| 2021 | Dannenberg L, Afzal S, Czychy N, M'Pembale R, Zako S, Helten C, Mourikis P, Zikeli D, Ahlbrecht S, Trojovský K, Benkhoff M, Barcik M, <b>Wolff G</b> , Zeus T, Kelm M, Polzin A. Risk prediction of bleeding and MACCE by PRECISE-DAPT score post-PCI. Int J Cardiol Heart Vasc. 2021 Mar 13;33:100750                                                                                                                                                                                                                              | 0,6 (2021)  | 0,3  |
| 2021 | Jung C, Flaatten H, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, <b>Wolff G</b> , Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, Boumendil A, De Lange DW, Guidet B; COVIP study group. The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. Crit Care. 2021 Apr 19;25(1):149                                                       | 19,3 (2021) | 9,65 |
| 2021 | Jung C, Wernly B, Fjølner J, Bruno RR, Dudzinski D, Artigas A, Pinto BB, Schefold JC, <b>Wolff G</b> , Kelm M, Beil M, Sigal S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, Boumendil A, De Lange DW, Guidet B, Flaatten H. Steroid use in elderly critically ill COVID-19 patients. Eur Respir J. 2021 Jun 25:2100979.                                                                                                             | 33,8 (2021) | 16,9 |
| 2021 | Busch L, Heinen Y, Stern M, <b>Wolff G</b> , Özaslan G, Tzetou K, Sansone R, Heiss C, Kelm M. Angioplasty of Flow-Limiting Stenosis Reduces Aortic and Brachial Blood Pressure in Patients With Peripheral Artery Disease. J Am Heart Assoc. 2021 Jul 6:e019724. doi: 10.1161/JAHA.120.019724.                                                                                                                                                                                                                                      | 6,1 (2021)  | 3,05 |
| 2021 | Bruno RR, Wernly B, Mamandipoor B, Rezar R, Binneboessel S, Baldia PH, <b>Wolff G</b> , Kelm M, Guidet B, De Lange DW, Dankl D, Koköfer A, Danninger T, Szczeklik W, Sigal S, van Heerden PV, Beil M, Fjølner J, Leaver S, Flaatten H, Osmani V, Jung C. ICU-Mortality in Old and Very Old Patients Suffering From Sepsis and Septic Shock. Front Med (Lausanne). 2021 Jul 9;8:697884. doi: 10.3389/fmed.2021.697884. eCollection 2021.                                                                                             | 5,1 (2021)  | 2,55 |
| 2021 | Schweitzer J, Horn P, Voss F, Kivel M, <b>Wolff G</b> , Jung C, Zeus T, Kelm M, Westenfeld R. Incidence of Acute Kidney Injury Is Lower in High-Risk Patients Undergoing Percutaneous Coronary Intervention Supported with Impella Compared to ECMO. J Cardiovasc Transl Res. 2021 Jul 29. doi: 10.1007/s12265-021-10141-9. Online ahead of print.                                                                                                                                                                                  | 3,2 (2021)  | 1,6  |
| 2021 | Bruno RR, Wernly B, Hornemann J, Flaatten H, Fjølner J, Artigas A, Bollen Pinto B, Schefold JC, <b>Wolff G</b> , Baldia PH, Binneboessel S, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Kondili E, Wollborn J, Marsh B, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Jung C; COVIP study group. Early evaluation of organ failure using MELD-XI in critically ill elderly COVID-19 patients. Clin Hemorheol Microcirc. 2021;79(1):109-120. doi: 10.3233/CH-219202 | 2,4 (2021)  | 1,2  |
| 2021 | Jung C, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, <b>Wolff G</b> , Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Joannidis M, Oeyen S,                                                                                                                                                                                                                                                                                                                                             | 19,3 (2021) | 9,65 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |      |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|
|      | Zafeiridis T, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Flaatten H; , COVIP Study Group. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. Crit Care. 2021 Sep 23;25(1):344. doi: 10.1186/s13054-021-03739-7.                                                                                                                                                                                                                                                                    |             |      |
| 2021 | Vornholz L, Nienhaus F, Gliem M, Alter C, Henning C, Lang A, Ezzahoini H, <b>Wolff G</b> , Clasen L, Rassaf T, Flögel U, Kelm M, Gerdes N, Jander S, Bönner F. Acute Heart Failure After Reperused Ischemic Stroke: Association With Systemic and Cardiac Inflammatory Responses. Front Physiol. 2021 Dec 21;12:782760. doi: 10.3389/fphys.2021.782760.                                                                                                                                                                                                           | 4,8 (2021)  | 2,4  |
| 2022 | Jung C, Mamandipoor B, Fjølner J, Bruno R, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, <b>Wolff G</b> , Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Czuczwar M, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, De Lange DW, Guidet B, Flaatten H, Osmani V. Disease-course adapting machine learning prognostication models in critically ill elderly COVID-19 patients: a multi-centre cohort study with external validation. JMIR Med Inform. 2022 Mar 31;10(3):e32949. doi: 10.2196/32949. | 3,2 (2021)  | 1,6  |
| 2022 | Bruno RR, Wernly B, <b>Wolff G</b> , Fjølner J, Artigas A, Bollen Pinto B, Schefold JC, Kindgen-Milles D, Baldia PH, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Topeli A, Elhadi M, Joannidis M, Oeyen S, Kondili E, Marsh B, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Flaatten H, Jung C; COVIP study group. Association of chronic heart failure with mortality in old intensive care patients suffering from Covid-19. ESC Heart Fail. 2022 Mar 10. doi: 10.1002/ehf2.13854. Online ahead of print.                     | 3,6 (2021)  | 1,8  |
| 2022 | Bruno RR, Wernly B, Flaatten H, Fjølner J, Artigas A, Baldia PH, Binneboessel S, Bollen Pinto B, Schefold JC, <b>Wolff G</b> , Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Kondili E, Marsh B, Wollborn J, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Jung C; COVIP study group. The association of the Activities of Daily Living and the outcome of old intensive care patients suffering from COVID-19. Ann Intensive Care. 2022 Mar 18;12(1):26. doi: 10.1186/s13613-022-00996-9.         | 10,3 (2021) | 5,15 |
| 2022 | Wernly B, Rezar R, Flaatten H, Beil M, Fjølner J, Bruno RR, Artigas A, Pinto BB, Schefold JC, Kelm M, Sigal S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, <b>Wolff G</b> , Marsh B, Andersen FH, Moreno R, Leaver S, Wernly S, Boumendil A, De Lange DW, Guidet B, Jung C; COVIP study group. Variations in end-of-life care practices in older critically ill patients with COVID-19 in Europe. J Intern Med. 2022 Apr 5. doi: 10.1111/joim.13492. Online ahead of print.                                                                      | 13,1 (2021) | 6,55 |
| 2022 | Wischmann P, Bruno RR, Wernly B, <b>Wolff G</b> , Afzal S, Rezar R, Cramer M, Heramvand N, Kelm M, Jung C. Relevance of pre-existing anaemia for patients admitted for acute coronary syndrome to an intensive care unit: a retrospective cohort analysis of 7418 patients. Eur Heart J Open. 2022 Jun 15;2(4):oeac040. doi: 10.1093/ehjopen/oeac040                                                                                                                                                                                                              | -           | -    |
| 2022 | Cortese-Krott MM, Suvorava T, Leo F, Heuser SK, LoBue A, Li J, Becher S, Schneckmann R, Srivastava T, Erkens R, <b>Wolff G</b> , Schmitt JP, Grandoch M, Lundberg JO, Pernow J, Isakson BE, Weitzberg E, Kelm M. Red blood cell eNOS is cardioprotective in acute myocardial infarction. Redox Biol. 2022 Aug;54:102370. doi: 10.1016/j.redox.2022.102370.                                                                                                                                                                                                        | 10,8 (2021) | 5,4  |
| 2022 | Heinen Y, <b>Wolff G</b> , Klein K, Brockmeyer M, Parco C, Perings S, Zeus T, Kelm M, Icks A, Jung C. Process Standardization in High-Risk Coronary Interventions is Associated With Quality of Care Measures. J Invasive Cardiol. 2022 Oct;34(10):E743-E749.                                                                                                                                                                                                                                                                                                     | 1,7 (2021)  | 0,85 |
| 2022 | Jung C, Fujita B, Feldt K, Wernly B, Bruno RR, <b>Wolff G</b> , Zeus T, Polzin A, Lichtenberg A, Beyersdorf F, Bauer T, Bekeredjian                                                                                                                                                                                                                                                                                                                                                                                                                               | 1,7 (2021)  | 0,85 |

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |              |              |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|
|              | R, Bleiziffer S, Beckmann A, Frerker C, Möllmann H, Walther T, Gummert J, Zeiher A, Hamm C, Meduri CU, Settergren M, Kelm M, Ensminger S. A Novel Model to Predict 1-Year Mortality in Elective Transfemoral Aortic Valve Replacement: The TAVR-Risk Score. J Invasive Cardiol. 2022 Nov;34(11):E776-E783. Epub 2022 Oct 13.                                                                                                                                                                                                                                                           |              |              |
| 2022         | Wernly B, Flaatten H, Beil M, Fjølner J, Bruno RR, Artigas A, Pinto BB, Schefold JC, Kelm M, Sigal S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Rezar R, Oeyen S, Wolff G, Marsh B, Andersen FH, Moreno R, Wernly S, Leaver S, Boumendil A, De Lange DW, Guidet B, Perings S, Jung C. A retrospective cohort study comparing differences in 30-day mortality among critically ill patients aged ≥ 70 years treated in European tax-based healthcare systems (THS) versus social health insurance systems. Sci Rep. 2022 Oct 19;12(1):17460. doi: 10.1038/s41598-022-21580-y. | 5,0 (2021)   | 2,5          |
| 2022         | Binneboessel S, Bruno RR, Wernly B, Masyuk M, Flaatten H, Fjølner J, Wolff G, Kelm M, Beil M, Svirid S, Szczeklik W, Leaver S, De Lange DW, Guidet B, Jung C; COVIP study group. Cytokine absorption in critically ill old COVID-19 patients with renal failure: A retrospective analysis of 503 intensive care unit patients. Clin Hemorheol Microcirc. 2022 Oct 15. doi: 10.3233/CH-221579. Online ahead of print.                                                                                                                                                                   | 2,4 (2021)   | 1,2          |
| 2022         | Baldia PH, Wernly B, Flaatten H, Fjølner J, Artigas A, Pinto BB, Schefold JC, Kelm M, Beil M, Bruno RR, Binneboessel S, <b>Wolff G</b> , Erkens R, Sigal S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Marsh B, Andersen FH, Moreno R, Leaver S, De Lange DW, Guidet B, Jung C; COVIP study group. The association of prior paracetamol intake with outcome of very old intensive care patients with COVID-19: results from an international prospective multicentre trial. BMC Geriatr. 2022 Dec 27;22(1):1000. doi: 10.1186/s12877-022-03709-w.                    | 4,1 (2021)   | 2,05         |
| 2022         | Binneboessel S, Masyuk M, Piayda K, Bruno RR, Wernly B, Jirak P, <b>Wolff G</b> , Gerdes N, Baldia PH, Kelm M, Nienhaus F, Lang A, Winkels H, Geerling G, Guthoff R, Kaya S, Flossmann G, Riemer T, Baertschi M, Jung C. Rational and design of the REMOTE trial: An exploratory, pilot study to analyze REtinal Microcirculation in weightlessness. Clin Hemorheol Microcirc. 2023 Jan 20. doi: 10.3233/CH-221691. Online ahead of print.                                                                                                                                             | 2,4 (2021)   | 1,2          |
| <b>Summe</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>190,7</b> | <b>95,35</b> |

## 8.2 Übersichtsartikel

| Jahr: | Autorennamen, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                            | Impact-Faktor des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 2016  | Navarese EP, Kolodziejczak M, Dimitroulis D, <b>Wolff G</b> , Busch HL, Devito F, Sionis A, Ciccone MM. From proprotein convertase subtilisin/kexin type 9 to its inhibition: state-of-the-art and clinical implications. Eur Heart J Cardiovasc Pharmacother. 2016;2(1):44-53.                     | -                                                | -                           |
| 2019  | Polzin A, Dannenberg L, <b>Wolff G</b> , Helten C, Achilles A, Hohlfeld T, Zeus T, Kelm M, Massberg S, Petzold T. Non-vitamin K oral anticoagulants (NOAC) and the risk of myocardial infarction: Differences between factor IIa and factor Xa inhibition? Pharmacol Ther. 2019;195:1-4.            | 10,6 (2019)                                      | 5,3                         |
| 2020  | Polzin A, Dannenberg L, Thienel M, Orban M, <b>Wolff G</b> , Hohlfeld T, Zeus T, Kelm M, Petzold T. Noncanonical Effects of Oral Thrombin and Factor Xa Inhibitors in Platelet Activation and Arterial Thrombosis. Thromb Haemost. 2020 Sep 17. doi: 10.1055/s-0040-1716750. Online ahead of print. | 5,7 (2020)                                       | 2,85                        |
| 2020  | Jung C, Bruno RR, Wernly B, <b>Wolff G</b> , Beil M, Kelm M. Frailty as a Prognostic Indicator in Intensive Care. Dtsch Arztebl Int. 2020 Oct 2;117(40):668-673.                                                                                                                                    | 5,6 (2020)                                       | 2,8                         |



|              |                                                                                                                                                                                                                                                                                                          |             |              |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|
| 2021         | Jung C, <b>Wolff G</b> , Wernly B, Bruno RR, Franz M, Schulze PC, Silva JNA, Silva JR, Bhatt DL, Kelm M. Virtual and Augmented Reality in Cardiovascular Care: State-of-the-Art and Future Perspectives. JACC Cardiovasc Imaging. 2021 Oct 7:S1936-878X(21)00684-7. doi: 10.1016/j.jcmg.2021.08.017      | 16,1 (2021) | 8,05         |
| 2022         | Bruno RR, <b>Wolff G</b> , Kelm M, Jung C. Pharmacological treatment of cardiogenic shock - A state of the art review. Pharmacol Ther. 2022 Jun 10:108230. doi: 10.1016/j.pharmthera.2022.108230. Online ahead of print.                                                                                 | 13,4 (2021) | 6,7          |
| 2022         | Bruno RR, Wolff G, Wernly B, Masyuk M, Piayda K, Leaver S, Erkens R, Oehler D, Afzal S, Heidari H, Kelm M, Jung C. Virtual and augmented reality in critical care medicine: the patient's, clinician's, and researcher's perspective. Crit Care. 2022 Oct 25;26(1):326. doi: 10.1186/s13054-022-04202-x. | 19,3 (2021) | 9,65         |
| <b>Summe</b> |                                                                                                                                                                                                                                                                                                          | <b>70,7</b> | <b>35,35</b> |

### 8.3 Fallberichte und Kommentare

| Jahr: | Autorenennamen, Titel, Zeitschriftentitel [Kurzbezeichnung], Jahrgang, Seiten [von – bis]:                                                                                                                                                                                                                                            | Impact-Faktor des Journals zum Publikationsjahr: | Gewichteter persönlicher IF |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|
| 2018  | Polzin A, Dannenberg L, Wolff G, Zeus T, Kelm M, Petzold T. Increased risk of myocardial infarction with dabigatran etexilate: Fact or fiction? A critical meta-analysis from integrating randomized controlled trials and real-world studies: Wine or spritzer? Int J Cardiol. 2018 Nov 1;270:82. doi: 10.1016/j.ijcard.2018.07.020. | 3,5 (2018)                                       | 1,75                        |
| 2019  | <b>Wolff G</b> , Kelm M, Westenfeld R, Horn P. Low-Dose Thrombolysis for the Management of Left Atrial Thrombus Formation During Percutaneous Mitral Valve Repair. JACC Cardiovasc Interv. 2019;12(2):e9-e10.                                                                                                                         | 8,4 (2019)                                       | 8,4                         |
| 2019  | Bruno RR, Nia AM, <b>Wolff G</b> , Erkens R, Kelm M, Westenfeld R, Jung C. Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. Int J Cardiol Heart Vasc. 2019;23:100377.                                                                                                   | 0,5 (2019)                                       | 0,25                        |
| 2019  | Veulemans V, <b>Wolff G</b> , Afzal S, Zeus T. Addressing limitations of partial oral treatment of left-sided infectious endocarditis (POET) criteria for prosthetic valve endocarditis: a note of caution. Eur Heart J. 2019 Oct 14;40(39):3276                                                                                      | 22,7 (2019)                                      | 11,85                       |
| 2019  | <b>Wolff G</b> , Westenfeld R, Kelm M, Jung C. No focus for Staphylococcus aureus bacteremia? Don't swallow it! An educational report of a rare sepsis presentation. Arch Med Sci. 2019 Jul 22;16(6):1491-1492. doi: 10.5114/aoms.2019.86769.                                                                                         | 2,8 (2019)                                       | 2,8                         |
| 2020  | <b>Wolff G</b> , Bruno RR, Reiter M, Kantzow B, Kelm M, Jung C. Virtual reality device training for extracorporeal membrane oxygenation. Crit Care. 2020 Jul 2;24(1):390                                                                                                                                                              | 9,1 (2020)                                       | 9,1                         |
| 2020  | Bruno RR, <b>Wolff G</b> , Wernly B, Kelm M, Jung C. Frailty Assessment in Patients Undergoing Aortic Valve Replacement: Be Quick and Be Sure. JACC Cardiovasc Interv 2020 Aug 24;13(16):1965-1967. doi: 10.1016/j.jcin.2020.06.006.                                                                                                  | 11,2 (2020)                                      | 5,6                         |

**Gesamt-Summe gewichteter persönlicher IF:**  
(100% bei Erst- und Letztautorenschaft, 50% bei Ko-Autorenschaft)

**260,65**

## 8.4 Buchbeiträge / Zeitschriftenbeiträge ohne Pubmed-Listung

|       |                                                                                                                                                                        |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jahr: | Autorenennamen, Titel des Buchbeitrags, Herausgeber, Buchtitel, Verlag und Ort, Seitenangaben [von – bis] bzw. Autorenennamen, Buchtitel, Verlag und Ort, Seitenumfang |
| 2019  | G. Wolff, C. Jung. Demographische Herausforderung: Der alte Patient in der kardiovaskulären Intensivmedizin. Cardio News 04.2019   22. Jahrgang                        |
| 2020  | G. Wolff, A. Wolff, C. Jung. ARDS – neue Evidenz für ein altes Krankheitsbild. Cardio News 01.2020   23. Jahrgang                                                      |
| 2021  | G. Wolff, S. A. Potthoff, C. Jung. Timing der Nierenersatztherapie. Cardio News 06.2021   24. Jahrgang                                                                 |

## 8.5 Kongressbeiträge

### 8.5.1 Posterpräsentationen

|       |                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jahr: | Autorenennamen, Postertitel, Titel der wiss. Tagung und der Fachgesellschaft, Ort; ggfl. Verweis auf gedrucktes Abstract in wiss. Fachzeitschrift (Kurzbezeichnung, Jahrgang, Seiten [von – bis])                                                                                                                                                                                                                                     |
| 2017  | <b>G. Wolff</b> , Y. Lin, A. Karathanos, M. Brockmeyer, S. Wolters, B. Nowak, A. Fürnkranz, H. Makimoto, M. Kelm, V. Schulze. Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials. DGK Congress 2017. Clin Res Cardiol 106, Suppl. 1, April 2017.                                                    |
| 2017  | <b>G. Wolff</b> , D. Dimitroulis, F. Andreotti, M. Kolodziejczak, C. Jung, E. Navarese. Survival benefits of invasive vs. conservative strategies in heart failure patients with reduced ejection fraction and coronary artery disease. DGK Congress 2017. Clin Res Cardiol 106, Suppl. 1, April 2017                                                                                                                                 |
| 2017  | <b>G. Wolff</b> , E.P. Navarese, M. Brockmeyer, Y.F. Lin, A. Karathanos, M. Kolodziejczak, J. Kubica, T. Zeus, R. Westenfeld, F. Andreotti, M. Kelm, V. Schulze. Efficacy and safety of perioperative aspirin therapy in non-cardiac surgery: a systematic review and comprehensive meta-analysis of randomized controlled trials. ESC Congress 2017. European Heart Journal, Volume 38, Issue suppl. 1, 1 August 2017, ehx504.P4011. |
| 2018  | <b>G. Wolff</b> , J. Quade, L. Kosejian, S. Bader, Y. Lin, M. Brockmeyer, A. Karathanos, Y. Heinen, M. Kelm, V. Schulze. Comparison of NCDR-, GRACE- and CRUSADE-Scores for Mortality and Bleeding Risk Prediction in Acute Coronary Syndrome in a German Population. DGK Congress 2018. Clin Res Cardiol 107 Suppl 1, April 2018 - Beitrag P1787                                                                                     |
| 2018  | Y. Lin, <b>G. Wolff</b> , L. Kosejian, J. Quade, S. Bader, M. Brockmeyer, A. Karathanos, Y. Heinen, M. Kelm, V. Schulze. Validation of an NCDR-Score-based Risk Model for Cardiac Catheterization in a German Population. DGK Congress 2018. Clin Res Cardiol 107 Suppl 1, April 2018 - Beitrag P787.                                                                                                                                 |
| 2018  | <b>G. Wolff</b> , A. Karathanos, L. Dannenberg, Y. Lin, M. Brockmeyer, Y. Heinen, T. Zeus, M. Kelm, A. Polzin, V. Schulze. Glycoprotein IIb/IIIa inhibitor therapy in ST-segment elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. ESC Congress 2018. European Heart Journal (2018) 39 (Supplement), 750.                                                                       |
| 2018  | <b>G. Wolff</b> , Y. Lin, A. Karathanos, M. Brockmeyer, Y. Heinen, T. Zeus, A. Polzin, M. Kelm, V. Schulze. Interventional patent foramen ovale closure or medical therapy for cryptogenic ischemic stroke: an updated meta-analysis of randomized controlled trials. ESC Congress 2018. European Heart Journal (2018) 39 (Supplement), 741.                                                                                          |
| 2018  | C. Quast, R. Erkens, K. Piayda, <b>G. Wolff</b> , M. Kelm, M.M. Cortese-Krott. Lack of endothelial nitric oxide synthase leads to aortic valve stenosis in aging mice. ESC Congress 2018. European Heart Journal (2018) 39 (Supplement), 1069.                                                                                                                                                                                        |
| 2018  | <b>G. Wolff</b> , Y. Lin, J. Quade, S. Bader, L. Kosejian, A. Karathanos, M. Brockmeyer, Y. Heinen, M. Kelm, V. Schulze. Validation of an NCDR-score-based risk model for cardiac catheterization procedures in a european population. ESC Congress 2018. European Heart Journal (2018) 39 (Supplement), 1333.                                                                                                                        |
| 2019  | Y. Lin, A. Karathanos, M. Brockmeyer, C. Parco, Y. Heinen, S. Perings, A. Albert, V. Schulze, M. Kelm, <b>G. Wolff</b> . Perioperative Levosimendan in Patients with Low Cardiac Output Syndrome Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. DGK Congress 2019. Clin Res Cardiol 108, Suppl 1, April 2019 - Beitrag P1894.                                                     |
| 2019  | A. Karathanos, S. Bader, J. C. Quade, L. Kosejian, Y. Lin, M. Brockmeyer, Y. Heinen, A. Albert, S. Perings, A. Icks, M. Kelm, V. Schulze, <b>G. Wolff</b> . Comparison of Risk Prediction in Transradial vs. Transfemoral Cardiac Catheterization using the National Cardiovascular Data Registry Risk Models. DGK Congress 2019. Clin Res Cardiol 108, Suppl 1, April 2019 - Beitrag P1897.                                          |
| 2019  | C. Parco, J. Quade, Y. Lin, S. Bader, L. Kosejian, A. Karathanos, M. Brockmeyer, Y. Heinen, S. Perings, A. Albert, A. Icks, M. Kelm, V. Schulze, <b>G. Wolff</b> . Comparison of NCDR and Mehran Risk Models for Prediction of In-Hospital Acute Kidney Injury, Contrast Induced Nephropathy and                                                                                                                                      |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      | Dialysis in Non-ST-Segment-Elevation Myocardial Infarction. DGK Congress 2019. Clin Res Cardiol 108, Suppl 1, April 2019 - Beitrag P1901.                                                                                                                                                                                                                                                                                                        |
| 2019 | <b>G Wolff</b> , K Klein, C Parco, Y Lin, O Maier, A Karathanos, M Brockmeyer, T Zeus, A Polzin, R Westenfeld, C Jung, A Blehm, A Lichtenberg, M Kelm, V Veulemans. Comparative evaluation of risk model performance for prediction of 30-day mortality in transcatheter aortic valve replacement. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz748.0604.                                          |
| 2019 | V Veulemans, K Klein, O Maier, <b>G Wolff</b> , A Polzin, R Westenfeld, C Jung, A Blehm, A Lichtenberg, M Kelm, T Zeus. Differences in short-term outcome between balloon- and self-expandable TAVR devices relating to more than one generation. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz745.0593.                                                                                           |
| 2019 | V Veulemans, K Klein, O Maier, <b>G Wolff</b> , A Polzin, R Westenfeld, C Jung, A Blehm, A Lichtenberg, M Kelm, T Zeus. Differences in short-term outcome between early- and new-generation TAVR devices. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz745.0597.                                                                                                                                   |
| 2019 | Y Lin, C Parco, M Brockmeyer, A Karathanos, V Schulze, T Krieger, Y Heinen, S Perings, M Kelm, <b>G Wolff</b> . Cardiovascular outcomes of new anti-diabetic agents - A meta-analysis of randomized controlled trials. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz746.0867.                                                                                                                      |
| 2019 | M Brockmeyer, Y Lin, A Karathanos, C Parco, T Krieger, Y Heinen, A Albert, M Kelm, V Schulze, <b>G Wolff</b> . Preoperative levosimendan improves survival in patients with low cardiac output syndrome undergoing cardiac surgery: a meta-analysis of randomized controlled trials. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz748.1107.                                                        |
| 2019 | A Karathanos, YF Lin, L Dannenberg, C Parco, V Schulze, M Brockmeyer, T Krieger, C Jung, Y Heinen, S Perings, U Zeymer, M Kelm, A Polzin, <b>G Wolff</b> . Survival benefits of routine glycoprotein IIb/IIIa inhibitors during primary PCI in ST-segment elevation myocardial infarction: A meta-analysis of randomised controlled trials. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz747.0551. |
| 2020 | J. Tröstler, C. Parco, M. Brockmeyer, Y. Lin, T. Krieger, J. Quade, S. Bader, L. Kosejian, A. Karathanos, Y. Heinen, A. Icks, V. Schulze, M. Kelm, <b>G. Wolff</b> . Standardized risk-adjusted management after cardiac catheterization for non-ST-elevation myocardial infarction – associations with in-hospital clinical outcomes. Clin Res Cardiol 109, Suppl 1, April 2020 - Beitrag P1212                                                 |
| 2020 | <b>G. Wolff</b> , K. Klein, C. Parco, O. Maier, A. Polzin, C. Jung, R. Westenfeld, A. Mehdiani, A. Lichtenberg, A. Icks, M. Kelm, T. Zeus, V. Veulemans. Performance comparison of classical surgical and modern interventional transcatheter aortic valve replacement (TAVR) risk models for prediction of 30-day mortality in a German cohort of 1,569 patients. Clin Res Cardiol 109, Suppl 1, April 2020 - Beitrag P1946.                    |
| 2020 | C. Parco, L. Kosejian, J. Quade, S. Bader, Y. Lin, A. Karathanos, T. Krieger, M. Brockmeyer, A. Icks, S. Perings, M. Kelm, V. Schulze, <b>G. Wolff</b> . Comparative performance analysis of GRACE and ACTION risk models for prediction of in-hospital mortality in a German patient population with acute coronary syndrome. Clin Res Cardiol 109, Suppl 1, April 2020 - Beitrag P1964.                                                        |
| 2020 | Y. Lin, M. Brockmeyer, C. Parco, A. Karathanos, T. Krieger, V. Schulze, Y. Heinen, A. G. Bejinariu, P. Müller, H. Makimoto, M. Kelm, <b>G. Wolff</b> . Uninterrupted direct oral anticoagulants and vitamin K antagonists during ablation for atrial fibrillation: an updated meta-analysis. Clin Res Cardiol 109, Suppl 1, April 2020 - Beitrag V1728.                                                                                          |
| 2020 | C Parco, L Kosejian, J Quade, S Bader, Y Lin, A Karathanos, T Krieger, M Brockmeyer, A Icks, S Perings, M Kelm, V Schulze, <b>G Wolff</b> . ACTION and NCDR risk models outperform GRACE for prediction of in-hospital mortality in acute coronary syndrome – a retrospective analysis from a German Heart Center. European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.1599                                            |
| 2020 | M Brockmeyer, Y Lin, C Parco, A Karathanos, T Krieger, V Schulze, Y Heinen, A Bejinariu, P Mueller, H Makimoto, M Kelm, <b>G Wolff</b> . Uninterrupted direct oral anticoagulants and vitamin K antagonists during ablation for atrial fibrillation: an updated meta-analysis. European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.0569                                                                                |
| 2020 | A Karathanos, I Simon, M Brockmeyer, Y Lin, C Parco, T Krieger, V Schulze, K Hellhammer, M Kelm, T Zeus, <b>G Wolff</b> . Iron status, anemia and functional capacity in adults with congenital heart disease: a single center analysis. European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.2216                                                                                                                      |
| 2020 | J Troestler, C Parco, M Brockmeyer, Y Lin, T Krieger, J Quade, S Bader, L Kosejian, A Karathanos, Y Heinen, V Schulze, A Icks, M Kelm, <b>G Wolff</b> . Standardized risk management in catheterization procedures for non-ST-segment elevation myocardial infarction: associations with in-hospital clinical outcomes. European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.1762                                       |
| 2021 | M. Brockmeyer, E. Wies, Y. Lin, A. Karathanos, C. Parco, A. Sokolowski, A. Hoss, J. Sommer, S. Grobosch, V. Schulze, S. Perings, N. Chernyak, M. Kelm, A. Icks, <b>G. Wolff</b> . Associations of patient                                                                                                                                                                                                                                        |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      | disease-related knowledge and treatment goal attainment for LDL-C and HbA1c in very high-risk patients with cardiovascular disease and diabetes mellitus. Clin Res Cardiol (2021)                                                                                                                                                                                                                                   |
| 2021 | Y Lin, C Parco, A Karathanos, T Krieger, V Schulze, N Chernyak, A Icks, M Kelm, M Brockmeyer, <b>G Wolff</b> . Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: a systematic review and meta-analysis. European Heart Journal, Volume 42, Issue Supplement_1, October 2021, ehab724.2936                                                 |
| 2022 | <b>G Wolff</b> , Y Lin, C Akbulut, M Brockmeyer, C Parco, A Hoss, A Sokolowski, R Westenfeld, M Kelm, M Roden, S Schlesinger, O Kuss. Absolute treatment effects of novel oral antidiabetic drugs on cardiovascular mortality and hospitalization for heart failure: a meta-analysis of digitalized individual patient outcomes. European Heart Journal, Volume 43, Issue Supplement_2, October 2022, ehac544.2686. |
| 2022 | O Kuss, C Akbulut, S Schlesinger, A Georgiev, M Kelm, M Roden, <b>G Wolff</b> . Absolute treatment effects for the primary outcome and all-cause mortality in the cardiovascular outcome trials in type 2 diabetes: a meta-analysis of individual patient data. European Heart Journal, Volume 43, Issue Supplement_2, October 2022, ehac544.2685.                                                                  |

## 8.5.2 Vorträge

|       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jahr: | Autorenennamen, Titel des Vortrags, Titel der wiss. Tagung und der Fachgesellschaft, Ort; ggfl. Verweis auf gedrucktes Abstract in wiss. Fachzeitschrift (Kurzbezeichnung, Jahrgang, Seiten [von – bis])                                                                                                                                                                                                                                                                                    |
| 2014  | <b>G. Wolff</b> , G. Wapenhans, M. Weidenbach, T. Krenz, C. Rammos, C. Heiss, A. Gödecke, M. Kelm, M. M. Cortese-Krott. The role of endothelial nitric oxide synthase (eNOS) for age-related changes of vascular function and survival in mice. DGK Congress 2014. Clin Res Cardiol 103, Suppl 1, April 2014.                                                                                                                                                                               |
| 2017  | <b>G. Wolff</b> , Y. Lin, A. Karathanos, M. Brockmeyer, S. Wolters, B. Nowak, A. Fuernkranz, H. Makimoto, M. Kelm, V. Schulze. Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials. ESC Congress 2017. European Heart Journal (2017) 38 (Supplement), 619                                                                                                  |
| 2018  | <b>G. Wolff</b> ; E. Navarese; M. Brockmeyer; Y. Lin; A. Karathanos; M. Kołodziejczak; F. Andreotti; T. Zeus; R. Westenfeld; J. Kubica; M. Kelm; V. Schulze. Efficacy and Safety of Perioperative Aspirin Therapy in Non-Cardiac Surgery: A Systematic Review and Comprehensive Meta-Analysis of Randomized Controlled Trials. DGK Congress 2018. Clin Res Cardiol 107 Suppl 1, April 2018 - Beitrag V1135.                                                                                 |
| 2018  | A. Karathanos, V. Schulze, L. K. Dannenberg, Y. Lin, M. Brockmeyer, T. Zeus, M. Kelm, A. Polzin, <b>G. Wolff</b> . Glycoprotein IIb/IIIa Inhibitor Administration in ST-Segment Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. DGK Congress 2018. Clin Res Cardiol 107 Suppl 1, April 2018 - Beitrag V178.                                                                                                                         |
| 2018  | V. Schulze, Y. Lin, A. Karathanos, M. Brockmeyer, T. Zeus, A. Polzin, M. Kelm, <b>G. Wolff</b> . Patent Foramen Ovale Closure or Medical Therapy for Cryptogenic Ischemic Stroke: An Updated Meta-Analysis of Randomized Controlled Trials. DGK Congress 2018. Clin Res Cardiol 107 Suppl 1, April 2018 - Beitrag V7.                                                                                                                                                                       |
| 2019  | T. Krieger, M. Brockmeyer, <b>G. Wolff</b> , C. Parco, A. Karathanos, Y. Lin, T. Zeus, A. Polzin, Y. Heinen, S. Perings, M. Kelm, V. Schulze. Percutaneous Left Atrial Appendage Occlusion for Prevention of Thromboembolic Stroke: Procedural success, In-hospital and Follow-up Outcomes. DGK Congress 2019. Clin Res Cardiol 108, Suppl 1, April 2019 - Beitrag V678.                                                                                                                    |
| 2019  | Y Lin, V Schulze, M Brockmeyer, C Parco, A Karathanos, T Krieger, Y Heinen, M Gliem, HP Hartung, G Antoch, S Jander, B Turowski, S Perings, M Kelm, <b>G Wolff</b> . Endovascular thrombectomy as a means to improve survival in acute ischemic stroke - A meta-analysis. ESC Congress 2019. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz747.0087.                                                                                                              |
| 2021  | Y. Lin, C. Parco, A. Karathanos, T. Krieger, V. Schulze, N. Chernyak, A. Icks, M. Kelm, M. Brockmeyer, <b>G. Wolff</b> . Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: a systematic review and meta-analysis. Clin Res Cardiol (2021) <a href="https://doi.org/10.1007/s00392-021-01843-w">https://doi.org/10.1007/s00392-021-01843-w</a>                                                                     |
| 2021  | C. Parco, J. Tröstler, M. Brockmeyer, Y. Lin, T. Krieger, J. Quade, S. Bader, L. Kosejian, A. Karathanos, Y. Heinen, A. Icks, V. Schulze, M. Kelm, <b>G. Wolff</b> . Associations of standardized risk-adjusted peri-procedural management in catheterization procedures for non-ST-segment elevation myocardial infarction with in-hospital clinical outcomes. Clin Res Cardiol (2021) <a href="https://doi.org/10.1007/s00392-021-01843-w">https://doi.org/10.1007/s00392-021-01843-w</a> |
| 2021  | C. Parco, M. Brockmeyer, L. Kosejian, J. Quade, S. Bader, Y. Lin, A. Karathanos, T. Krieger, Y. Heinen, V. Schulze, A. Icks, C. Jung, M. Kelm, <b>G. Wolff</b> . Modern NCDR and ACTION risk models outperform the GRACE model for prediction of in-hospital mortality in acute coronary syndrome in a German cohort. Clin Res Cardiol (2021) <a href="https://doi.org/10.1007/s00392-021-01843-w">https://doi.org/10.1007/s00392-021-01843-w</a>                                           |



|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2022 | <b>G. Wolff</b> , Y. Lin, M. Brockmeyer, C. Parco, A. Hoss, A. Sokolowski, R. Westenfeld, M. Kelm, M. Roden, C. Akbulut, S. Schlesinger, O. Kuß. Absolute Treatment Effects of Novel Oral Antidiabetic Drugs on Cardiovascular Mortality and Hospitalization for Heart Failure – A Meta-Analysis of Digitalized Individual Patient Outcomes. Clin Res Cardiol (2022). <a href="https://doi.org/10.1007/s00392-022-02002-5">https://doi.org/10.1007/s00392-022-02002-5</a> |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 9 Lebenslauf

### Dr. med. Georg Ulrich Wolff

geboren am 20.08.1985 in Ostercappeln, Niedersachsen

Facharzt für Innere Medizin und Kardiologie

Zusatzbezeichnung Notfallmedizin, Intensivmedizin

Zusatzqualifikation Interventionelle Kardiologie, Herzinsuffizienz,  
Intensiv- und Notfallmedizin, Schlafmedizin



### Aktuelle Position

Oberarzt in der Klinik für Kardiologie, Pneumologie und Angiologie des Universitätsklinikums Düsseldorf

Abteilung für Koronarvaskuläre Kardiologie und internistische Intensivmedizin

Stellv. Leitender Arzt

Moorenstrasse 5, 40225 Düsseldorf, Germany

Tel.: +49 (0)211-81-18801

Fax: +49 (0)211-81-18812

eMail: [Georg.Wolff@med.uni-duesseldorf.de](mailto:Georg.Wolff@med.uni-duesseldorf.de)

 Orcid: 0000-0002-1734-6177

### Familie

Verheiratet mit Annika Caroline Wolff, 1 Sohn

### Ausbildung und beruflicher Werdegang

|             |                                                                                                                                                                         |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2005 – 2012 | Medizinstudium, Heinrich-Heine-Universität, Düsseldorf                                                                                                                  |
| 2012 – 2019 | Assistenzarzt in Facharztweiterbildung, Abteilung für Kardiologie, Pneumologie und Angiologie, Universitätsklinikum Düsseldorf                                          |
| 2015        | Promotion zum Dr. med. mit : “Die Bedeutung der Ekto-5'-Nukleotidase (CD73) für die ischämische Präkonditionierung des Mäuseherzens in vivo“ ( <i>magna cum laude</i> ) |
| 2018        | Zusatzbezeichnung Notfallmedizin (Ärztekammer Nordrhein)                                                                                                                |
| 2018        | Europäisches Examen in allgemeiner Kardiologie                                                                                                                          |
| 2019        | Facharzt für Innere Medizin und Kardiologie (Ärztekammer Nordrhein)                                                                                                     |
| 2020        | Zusatzqualifikation Herzinsuffizienz (Deutsche Gesellschaft für Kardiologie)                                                                                            |
| 2020        | Zusatzbezeichnung internistische Intensivmedizin (Ärztekammer Nordrhein)                                                                                                |
| 2020        | Zusatzqualifikation Interventionelle Kardiologie (Deutsche Gesellschaft für Kardiologie)                                                                                |
| 2021        | Zusatzqualifikation Intensiv- und Notfallmedizin (Deutsche Gesellschaft für Kardiologie)                                                                                |
| 2022        | Zusatzqualifikation Kardiovaskuläre Schlafmedizin (Deutsche Gesellschaft für Kardiologie)                                                                               |

## **Drittmittel, Stipendien und Auszeichnungen**

|             |                                                                                                                  |
|-------------|------------------------------------------------------------------------------------------------------------------|
| 2018        | Deutsche Gesellschaft für Kardiologie – Hans-Blöhrer Young Investigator Award (2. Platz)                         |
| 2018        | European Society of Cardiology “Educational Grant”                                                               |
| 2018 – 2021 | Forschungs-Stipendium “Clinician Scientist Track”, Medizinische Fakultät, Heinrich-Heine-Universität, Düsseldorf |

## **Mitgliedschaften in Fachgesellschaften**

Deutsche Gesellschaft für Kardiologie (DGK)

- Arbeitsgruppe Kardiovaskuläre Intensiv- und Notfallmedizin (AG3)
- Arbeitsgruppe Interventionelle Kardiologie (AGIK, AG6)
- Arbeitsgruppe „Young DGK“ (S3)
- Arbeitsgruppe Magnetresonananzverfahren (AG21)

European Society of Cardiology (ESC)

- European Association of Percutaneous Cardiovascular Interventions (EAPCI)
- Association of Acute Cardiovascular Care (ACVC)
- Heart Failure Association (HFA)

Deutsche Gesellschaft für Internistische Intensiv- und Notfallmedizin

Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)

European Society of Intensive Care Medicine (ESICM)

Deutsche Gesellschaft für Innere Medizin (DGIM)

## **Mitarbeit in Gremien der Medizinischen Fakultät**

2021 Vertreter der akad. Mitarbeiter/-innen in Strukturkommission für Professur (W3) für Molekulare Kardiologie

2022 Vertreter der akad. Mitarbeiter/-innen in Berufungskommission für Professur (W3) für Mol. Kardiologie

## **Studienarzt in klinischen Studien**

ASAP-TOO

AMULET-IDE

PROTECT KIDNEY

Realism HF

ExPAND G4

RESHAPE HF

REDUCE LAP HF II

REDUCE LAP HF III

RIP-HIGH

RESILIENCE

VRAP-HEART

ANDROMEDA Shock II

CLEVER-ACS

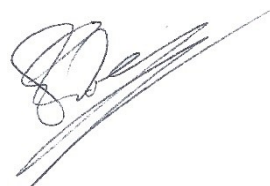
DanGer Shock

ECLS Shock

## **Reviewer für Pubmed-gelistete Journale/Zeitschriften**

New England Journal of Medicine  
European Heart Journal  
JACC Cardiovascular Interventions  
BMC Medicine  
Scientific Reports  
Clinical Research in Cardiology  
Cochrane Heart Group  
ESC Heart Failure  
Life Sciences  
Clinical Epidemiology  
JACC: Case Reports  
European Journal of Clinical Epidemiology  
European Journal of Medical Research  
Journal of Cardiovascular Pharmacology and Therapeutics  
BMJ Open  
Clinical Cardiology  
Journal of Clinical Medicine  
Catheterization and Cardiovascular Interventions  
Archives of Medical Science  
Therapeutics and Clinical Risk Management  
Frontiers in Medicine

Düsseldorf, 31.01.2023



Dr. Georg Wolff



## 10 Danksagung

Ich möchte an erster Stelle Herrn Prof. Dr. Malte Kelm für seine jahrzehntelange Unterstützung danken: Er hat mich im PJ begeistert für die Kardiologie, mich beständig weiter ausgebildet und – bisweilen kopfschüttelnd – begleitet durch verschiedene Mentoren- und Arbeitsgruppenwechsel mit zeitweise inhaltlicher Wankelmütigkeit. Er hat trotzdem nie aufgehört, an und mit mir zu arbeiten, mich als Arzt und Wissenschaftler zu entwickeln und zu fördern – auch wenn ich dies nicht zu jedem Zeitpunkt verstanden habe. Dafür meinen allerherzlichsten Dank!

Ich danke besonders Herrn Prof. Dr. Dr. Christian Jung für sein Geleit in den letzten Jahren – klinisch, wie wissenschaftlich: Unsere vertrauensvolle Art der Zusammenarbeit hat mich in besonderem Maße gepackt, motiviert und inhaltlich entwickelt. Ich habe in vielerlei Hinsicht davon profitiert und bin stolz darauf, was für ein gutes Team wir geworden sind – Danke!

Ich danke Herrn Dr. Volker Schulze: Er war zunächst mein klinischer Mentor, später nahm er mich in seine Arbeitsgruppe auf und gab mir die Möglichkeit, mich dort wissenschaftlich frei zu entfalten – mit dem Ergebnis, dass ich diese später an seiner statt weiterführen durfte. Danke!

Ich danke allen Mitgliedern meiner Arbeitsgruppe: Unsere im Kern seit vielen Jahren gemeinsame klinische und wissenschaftliche Entwicklung und unser Erfolg ist fest in unserer freundschaftlichen Zusammenarbeit verwurzelt – und welch besonderes Gut dies ist, ist mir wohl bewusst. Ich wünsche Euch allen das Beste und hoffe, noch lange mit Euch arbeiten zu dürfen. Danke!

Ich danke Herrn PD Dr. Westenfeld und Herrn PD Dr. Zeus für ihr Mentoring meiner klinischen Ausbildung und vielerlei Unterstützung im letzten Jahrzehnt. Danke!

Ich danke Herrn Prof. Dr. Navarese für die Begeisterung für die evidenzbasierte Medizin und Meta-Analytik, sowie Frau Prof. Dr. Dr. Icks für die Einführung in die kardiovaskuläre Versorgungsforschung. Danke!

Ein besonderer Dank gilt meiner Familie, insbesondere meiner wunderbaren Annika: Ohne endlose Geduld, Unterstützung und auch Entbehrung wäre dies nicht möglich gewesen. Ich weiß dies über alle Maßen zu schätzen – Danke von Herzen!