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Association of Recent ST-Segment Elevation Myocardial Infarction with Diabetes, Insulin Resistance and Metabolic Liver Diseases

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Zusammenfassung

Insulinresistenz (IR) und nicht-alkoholische Fettlebererkrankung (NAFLD) sind häufig bei Menschen mit Typ-2-Diabetes (T2D) und Herz-Kreislauf-Erkrankungen (CVD) und verschlechtern deren Prognose. Eine Zunahme der Leberfibrose gilt als stärkster Risikofaktor für eine erhöhte Sterblichkeit bei Menschen mit NAFLD, die zugrundeliegenden Mechanismen der erhöhten Morbidität und Mortalität an CVD sind aber noch unklar. Nicht-invasive Tests, wie der Fettleberindex (FLI), NAFLD-Fibrose Score (NFS) und Fibrose-4 (FIB-4) Score, zählen dabei zu etablierten Tests zur Erfassung des NAFLD Risikos. Die primäre Hypothese dieser Studie ist, dass Menschen nach rezentem ST-Hebungsinfarkt (STEMI) eine ausgeprägtere IR sowie ein höheres NAFLD-Risiko aufweisen als Menschen ohne STEMI. Die sekundäre Hypothese ist, dass Menschen mit rezentem STEMI ein hohes Risiko für die Entwicklung eines Prädiabetes (*impaired glucose metabolism*, IGM) oder T2D sowie einer IR und NAFLD haben. Die Hypothesen wurden in der Studie „*Diabetes und ST-Hebungsinfarkt* (*DISTEMI*)“ geprüft, die Probanden 6-12 Wochen nach STEMI (V1) (MI+; n=49, 61,0±8,8 Jahre, BMI 27,4±3,0 kg/m^2, HbA1c 6,0±1,0%, 30,6% T2D) untersucht, und mit Probanden der *Deutschen Diabetes Studie* (*DDS/GDS*) ohne Herzinfarkt (MI-; n=49, 62,1±7,5 Jahre, BMI 27,6±3,5 kg/m^2, HbA1c 5,8±0,8%, 30,6% T2D) verglichen. MI+ Probanden wurden ein Jahr nach STEMI mit identen Tests nachuntersucht (V2; n=42). Die ^{1}H-Magnetresonanz-tomographie diente der Erfassung der LVEF und der hyperinsulinämisch-euglykämischen Clamp-Test der der Ganzkörper-Insulinsensitivität (M-Wert). Das NAFLD Risiko wurde mittels validierter Tests (FLI, NFS, FIB-4) beurteilt. Bei V1 hatten MI+ eine geringere LVEF (47±13 vs. 57±7%, p<0,001) und M-Werte (7,1±2,6 vs. 8,4±2,5 mg*kg^{-1}*min^{-1}, p<0,001) als MI-. In MI+ hatten 53,3% eine LVEF ≥50%, 20,0% eine LVEF 41-49% und 26,7% eine LVEF ≤40%. In MI- lag der Anteil derselben LVEF-Kategorien bei 85,7% zu 14,3% zu 0%. MI+ hatten vergleichbare FLI (52±24 vs. 52±25, p=0,95) und FIB-4 (1,37±1,05 vs. 1,36±0,48, p=0,96), aber niedrigere NFS (-1,26±1,46 vs. -0,75±1,08, p=0,03) als MI-. Im Vergleich zu V1 zeigten Probanden ohne T2D eine schlechtere Glykämie bei V2, gemessen am HbA1c (normale Glukosetoleranz (NGT): 5,4±0,3 vs. 5,6±0,2%, p=0,03; IGM: 5,7±0,2 vs. 6,0±0,2%, p<0,001). Jeder zehnte Proband mit NGT oder IGM bei V1 entwickelte einen neuen T2D und jeder vierte mit NGT einen neuen IGM bei V2. Die LVEF und M-Werte blieben bei allen MI+ Probanden unverändert. Im Vergleich zu V1 zeigten Probanden ohne T2D auch ein hohes Risiko für eine Progression der Leberfibrose bei V2, bemessen am NFS (NGT: -1,65±1,10 vs. -0,97±0,90, p=0,03; IGM: -1,63±1,54 vs. -1,11±1,49, p=0,046) und FIB-4 (IGM: 1,05±0,42 vs. 1,31±0,75, p=0,02). Zusammenfassend weisen Menschen nach rezentem STEMI eine größere IR, nicht jedoch ein höheres NAFLD Risiko auf als Menschen ohne Herzinfarkt. Ein Jahr nach STEMI zeigen die Betroffenen zwar keine Verschlechterung der Insulinsensitivität oder der Herzleistung, aber dennoch ein erhöhtes Risiko für die Entwicklung eines IGM oder T2D sowie einer NAFLD Progression, was langfristig zur Verschlechterung der kardialen Prognose beitragen könnte.

Summary

Insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) are common in individuals with type 2 diabetes (T2D) and cardiovascular disease (CVD), and predictive of a worse outcome. There is evidence that increasing liver fibrosis is the strongest predictor for mortality in individuals with NAFLD. However, the underlying mechanisms of increased morbidity and mortality from CVD are still unclear. Non-invasive tests, such as the Liver Fibrosis Index (FLI), the NAFLD-Fibrosis Score (NFS) and Fibrosis-4 (FIB-4) Score, serve as established methods to assess the risk of NAFLD. The primary hypothesis of this study is that individuals, who suffer from recent ST-segment elevation myocardial infarction (STEMI) feature a higher degree of IR and higher risk of NAFLD than individuals without MI. The second hypothesis is that individuals with recent STEMI are at high risk for development of impaired glucose metabolism (IGM) or T2D, as well as IR and NAFLD. Those hypotheses were tested in the study "*Diabetes and ST-segment elevation myocardial infarction (DISTEMI)"*, which investigated participants 6-12 weeks after STEMI (V1) (MI+; n=49, 61.0±8.8 years, BMI 27.4±3.0 kg/m^2, HbA1c 6.0±1.0%, 30.6% T2D), and compared them to participants of the *German Diabetes Study* (*GDS*/*DDS*) without myocardial infarction (MI-; n=49, 62.1±7.5 years, BMI 27.6±3.5 kg/m^2, HbA1c 5.8±0.8%, 30.6% T2D). MI+ participants were re-examined one year after STEMI using identical tests (V2; n=42). LVEF was measured with ^{1}H-magnetic resonance imaging, respectively. Whole-body insulin sensitivity (M-value) was assessed by hyperinsulinemic-euglycemic clamp tests. The risk of NAFLD was assessed using validated tests (FLI, NFS, FIB-4). At V1, MI+ had impaired LVEF (47±13 vs. 57±7%, p<0.001) and lower M-values (7.1±2.6 vs. 8.4±2.5 mg*kg^{-1}*min^{-1}, p<0.001) than MI-. In MI+, 53.3% had LVEF ≥50%, 20.0% had LVEF 41-49% and 26.7% had LVEF ≤40%. In MI- the proportion of the same LVEF categories was 85.7% vs. 14.3% vs. 0%. MI+ had comparable FLI (52±24 vs. 52±25 a.u., p=0.95) and FIB-4 (1.37±1.05 vs. 1.36±0.48 a.u., p=0.96), but lower NFS (-1.26±1.46 vs. -0.75±1.08 a.u., p=0.03) compared to MI-. In comparison to V1, participants without T2D had worse glycemia at V2, assessed by HbA1c (normal glucose tolerance (NGT): 5.4±0.3 vs. 5.6±0.2%, p=0.03; IGM: 5.7±0.2 vs. 6.0±0.2%, p<0.001). Every tenth participant with NGT or IGM at V1 newly developed T2D, and every fourth participant with NGT further newly developed IGM at V2. LVEF and M-values remained unchanged among all participants within the first year after STEMI. In contrast to V1, participants without T2D also showed higher estimates of liver fibrosis at V2, including NFS (NGT: -1.65±1.10 vs. -0.97±0.90 a.u., p=0.03; IGM: -1.63±1.54 vs. -1.11±1.49 a.u., p=0.046) and FIB-4 (IGM: 1.05±0.42 vs. 1.31±0.75 a.u., p=0.02). In conclusion, individuals with recent STEMI had higher IR early after the event, but did not show a higher risk of NAFLD compared to event-free individuals. One year after STEMI, those affected did not show impairment of insulin sensitivity or cardiac function, but were still at increased risk of developing IGM or T2D as well as NAFLD progression, which may contribute to a worsening of the cardiac outcome in the long term.

List of abbreviations

ADA	American Diabetes Association
AHA	American Heart Association
Adipo-IR	Adipose tissue insulin resistance (index)
ALT	Alanin-Aminotransferase
ANOVA	Analysis of variance
AP	Angina pectoris
AST	Aspartat-Aminotransferase
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
BW	Body weight
CP	C-Peptide
CRC	Clinical Research Center
CVD	Cardiovascular disease
DDG	Deutsche Diabetes Gesellschaft / German Diabetes Society
DM	Diabetes mellitus
DISTEMI	Diabetes and ST-Segment Elevation Myocardial Infarction (study)
ECG	Electrocardiogram / Electrocardiography
EDV	End-diastolic volume
ESV	End-systolic volume
EF	Ejection fraction
GAD(A)	Glutamic acid decarboxylase (antibodies)
GDC	German Diabetes Center
GDM	Gestational diabetes mellitus
GDS	German Diabetes Study
GGT	Gamma (γ)-glutamyltransferase
GIR	Glucose infusion rate
FPG	Fasting plasma glucose
FIB-4	Fibrosis-4 (Score)
FFA	Free fatty acids
FLI	Fatty Liver Index
HbA1c	Hemoglobin A1c
HCL	Hepatocellular lipid content
HDL-C	High-density lipoprotein cholesterol
HEC	Hyperinsulinemic-euglycemic clamp-test
^{1}H	Proton
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFrecovEF	Heart failure with recovered ejection fraction
HHU	Heinrich-Heine-University
HOMA	Homeostatic model assessment
HOMA2-B	Homeostasis model assessment 2 of beta-cell function
HOMA2-IR	Homeostasis model assessment 2 of insulin resistance
hsCRP	High-sensitive C-reactive protein
IAA	Insulin autoantibodies
ICA	Islet cell antibodies

IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry
IFG	Impaired fasting glucose
IGM	Impaired glucose metabolism
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IR	Insulin resistance
IVGTT	Intravenous glucose tolerance test
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LV	Left ventricular / left ventricle
MACE	Major adverse cardiovascular event
MetS	Metabolic syndrome
MODY	Maturity onset diabetes of the young
MI	Myocardial infarction
MR	Magnetic resonance
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
M-value	Whole-body insulin sensitivity
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFS	Non-alcoholic fatty liver disease - Fibrosis Score
NGT	Normal glucose tolerance
NHLBI	National Heart, Lung, and Blood Institute
NP	Natriuretic peptide
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
PA	Physical activity
(P)PCI	(Primary) Percutaneous coronary intervention
PG	Plasma glucose
SAID	Severe autoimmune diabetes
SC	Space correction
SD	Standard deviation
SIDD	Severe insulin-deficient diabetes
SIRD	Severe insulin-resistant diabetes
STEMI	ST-segment elevation myocardial infarction
SYSTEMI	Systemic organ communication in STEMI
TC	Total cholesterol
Th	Therapy
TG	Triglycerides
T1D	Type 1 diabetes
T2D	Type 2 diabetes
US	Ultrasound
USA	United States of America
WC	Waist circumference
WHR	Waist-to-hip ratio
WHO	World Health Organization

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1. Introduction

1.1 Cardiovascular disease (CVD)

Cardiovascular disease (CVD) consisting of ischemic heart disease (IHD), myocardial infarction (MI) and heart failure (HF), among others, are the main drivers of the global rise of mortality and morbidity in older adults [1, 2]. The total number of CVD cases and CVD-related deaths increased globally from 271 million to 523 million and 12.1 million to 18.6 million between 1990 and 2019 [2]. In the United States of America (USA), the prevalence of CVD in adults aged 20 years and older is estimated to be 49.2% overall, based on data from 2015 to 2018 [3]. In the USA, prevalence for MI and HF is further estimated to increase by 30.1% and 33.3% between 2025 and 2060, accounting for 12.3 million cases in 2025 and estimated to increase by 16.0 million until 2060 [4]. In 2020, coronary artery disease (42.1%), including MI, angina pectoris (AP) and sudden cardiac death, was the leading cause of death in the USA [5]. Stroke, complications related to high blood pressure (BP) and HF accounted for further 17.0%, 11.0% and 9.6% of all deaths [5]. In Germany, it was estimated that in 2020 34% of all deaths were due to CVD, of which 13% were attributed to MI [6]. The incidence of ST-segment elevation MI (STEMI) markedly decreased between 1999 and 2008 (47.0% to 22.9%), while the mortality did not decrease compared to individuals with Non-STEMI (NSTEMI) [7]. However, the 1-year all-cause mortality among STEMI cases decreased between 1995/96 and 2013/14 from 22.1% to 14.1% [8]. Prolonged survival and lower risk of recurrent ischemic events have been attributed to new and established evidence-based treatments in individuals with STEMI during the last 20 years [8]. Therefore, CVD represents the highest component of health expenditure worldwide [9]. The European Heart Network estimated that in 2015, CVD cost the European economy €210 billion, of which 53% (€111 billion) was due to healthcare costs [9]. Germany currently spends more than US$ 6000 per capita and more than 11% of the gross domestic product on healthcare [9]. Due to aging of population, increases in life expectancy, growth of population and increasing prevalence of cardiometabolic risk factors including diabetes mellitus (DM), CVD has become a strong and growing socio-economic burden. Thus, current guidelines increasingly focus on prevention efforts (e.g. treatment of established risk factors) to prevent new onset of CVD with subsequent targeted management [10-12].

1.1.1 Definition and classification of cardiovascular disease

CVD is a collective term for disorders affecting the heart and blood vessels, associated with atherosclerosis, increased risk of blood clots and damage to arteries in the brain, kidneys, eyes and heart. Atherosclerosis is defined as a chronic inflammatory condition with immune competent cells producing mainly pro-inflammatory mediators. In particular, oxidized forms of

low density lipoprotein-cholesterol (LDL-C) are the drivers for inflammation and immune stimulation, causing cell death at higher concentrations [13]. If not treated in time, the rupture of atherosclerotic plaques causes thromboembolic blood clots, which may occlude one or more arteries initiating the clinical presentation of CVD, which in turn, worsens the prognosis.

The acute coronary syndrome, otherwise called unstable chronic heart disease, is a collective term of disorders consisting of acute MI and unstable AP. These clinical syndromes are diagnosed by symptoms of myocardial ischemia due to coronary insufficiency, 12-lead-electrocardiogram (ECG) and/or biomarkers sensitive for myocardial necrosis. Unstable AP is diagnosed in individuals with suspected acute coronary syndrome but with presence of normal values of cardiac biomarkers. In contrast, acute MI is defined according to current guidelines [14] as “acute myocardial injury with clinical evidence of acute myocardial ischemia and newly detected dynamic rise and/or fall of cardiac troponin value and with at least one of the following criteria:

- Symptoms of myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography or autopsy”.

Individuals, who develop new ST-segment elevations in two contiguous leads or (presumably) new left bundle branch blocks (LBBB) with ischemic repolarization patterns, are designated as a STEMI, while individuals without those ECG detections, are designated NSTEMI [14].

According to the Fourth Universal Definition of Myocardial Infarction [14], MI can be classified into five different types, based on the pathogenesis and etiology, which come along with different prognosis and treatment strategies: **Type 1 MI** is due to atherosclerotic plaque rupture or erosion, or less frequently fissuring or dissection of coronary arteries, resulting in an obstructive thrombosis of one or more coronary arteries leading to distal coronary embolization with myocyte necrosis [14]. **Type 2 MI** is caused by a condition without an acute atherothrombotic event, contributing to an imbalance of oxygen supply and/or demand with subsequently ischemic myocardial injury with necrosis [14]. It may occur in individuals with stable coronary artery disease suffering from an acute stressor (i.e. hypoxia, tachycardia, severe anemia) and presenting with clinical manifestations of myocardial ischemia [14]. **Type 3 MI** comprises “cardiac death in individuals with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cardiac troponin values become available or abnormal” [14]. **Type 4a and 5 MI** are related to coronary revascularization procedures (4a: percutaneous coronary intervention (PCI), type 5: coronary artery bypass grafting) and occur

up to 48 hours after the index procedure [14]. **Type 4b and 4c MI** comprise individuals presenting with stent thrombosis (4b) or restenosis (4c), and clinical criteria of type 1 MI [14].

1.1.2 Clinical presentation of myocardial infarction

The clinical onset of acute MI can be fulminant with typical as well as atypical ischemic symptoms or even silent without its perception. Chest pain is the most frequent symptom often described as chest pressure, tightness, or a squeezing sensation [8]. This symptom can be classified into three different categories:

1. Typical angina: a) substernal chest pain (dull aching chest pressure, pain, or discomfort unchanged with respiration), b) usually precipitated by exertion, and c) often gets relieved with rest or nitroglycerin [15];
2. Atypical angina: absence of at least one of the three criteria characterizing typical angina [15];
3. Non-cardiac chest pain: presence or absence of any of the angina symptoms [15].

In individuals with stable symptoms, pain may occur in several areas outside the chest region, most commonly the arms (43-50%), back (26-30%) and shoulders (26-32%), in particular the right shoulder and upper arm [15]. Women are more likely to present themselves without chest pain and/or with dry mouth, nausea, emesis, jaw/teeth, throat/neck and right shoulder/upper arm pain compared to men, who are more likely to present with chest pain and diaphoresis [15]. Angina symptoms are overall predictors of MI and CVD-related death [16]. Individuals with angina are slightly younger, more often female and of higher weight, and present more often with hypertension, higher levels of LDL-C and symptoms of HF compared to individuals without angina [16]. In particular, younger age, female sex and presentation without chest pain are predictors of mortality in individuals with MI [17, 18].

1.1.3 Diagnosis criteria of myocardial infarction

Electrocardiography is the first diagnostic test for detecting MI in clinical practice. Presence or absence of new ischemic ECG changes is necessary to differentiate between STEMI and NSTEMI. ST-segment elevation is localized to the ECG lead of the affected myocardium (i.e. ECG lead II, III and aVF relate to the posterior wall of the heart). However, ST deviation occurs also in non-cardiac conditions including acute pericarditis, left ventricular (LV) hypertrophy, LBBB, and early repolarization [14]. Consequently, ECG by itself is often insufficient to diagnose acute MI. Early signs of acute MI in ECG are changes in T wave and ST-segment:

- Increased hyperacute T wave amplitude: They may precede the ST-segment elevation, but are rarely seen because they occur transiently and mostly prior to the arrival at the hospital [14].
- New or presumed new ST-segment elevation: In the absence of LV hypertrophy or LBBB, commonly defined as “new ST-segment elevation at the J point in at least 2 contiguous leads with the cut-point: ≥1 mm in all leads other than leads V_2-V_3, where the following cut-points apply: ≥2 mm in men ≥40 years, ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age” [14].

Further ECG signs associated with acute MI are cardiac arrhythmias, atrioventricular conduction delays and loss of precordial R wave amplitude [14]. Moreover, ECG interpretation can be more difficult in individuals with pacemakers.

The current gold standard for non-invasive assessment of myocardial function, structure, perfusion and viability is multiparametric proton (^{1}H) based cardiovascular magnetic resonance (MR). In particular, myocardial infarct size, microvascular obstruction and intramyocardial hemorrhage are important prognostic measures, useful for early triage and discharge of suspected MI [19, 20]. Mean myocardial infarct size among STEMI cases was 17.9% of LV mass, assessed early after PCI [21], whereas in a pig model infarct size was 22±6% [22].

1.1.4 Treatment in acute myocardial infarction

First-line therapy for the acute management of incident STEMI is rapid, complete and sustained reperfusion of the infarct-related coronary artery. Reperfusion therapy within 12 hours after new onset of symptoms is associated with a reduction of mortality in individuals with STEMI [23]. Reperfusion strategies include fibrinolysis and/or primary PCI (PPCI) such as balloon angioplasty, coronary stenting, or thrombectomy. Finally, in case of rapid performance, PPCI is the preferred strategy [23]. Based on data of the SWEDEHEART registry, the proportion of individuals with STEMI undergoing PPCI increased from 4.5% to 78.0% between 1995/96 and 2013/14 [8].

1.1.5 Risk factors for CVD

The INTERHEART study confirmed that lifestyle factors (e.g. physical inactivity, unhealthy diet, alcohol consumption, smoking) and psychological factors together with abdominal obesity, hypertension, dyslipidemia and DM account for >90% of the population’s attributable risk of acute MI in both sexes and at all ages worldwide [24]. In addition, aging, sex and ethnicity/race serve as non-modifiable risk factors for CVD [3, 7, 24].

Aging is an independent, non-modifiable risk factor for CVD [9] and MI-related mortality, the latter independent of infarct size [25]. High-income countries are characterized by a high proportion of older individuals. In Europe, population aged >65 years is predicted to exceed 30% by the end of the century [9]. Based on data from the 2005 to 2014, mean age at recent MI is 65.6 years for men and 72.0 years for women [3]. Among STEMI cases, mean age was 70 years based on data from 1995 to 2014 [8]. In Germany, individuals aged 65 years and older are particularly affected by CVD-related deaths [6].

In 2019, age-adjusted incidence and prevalence for CVD were lower for females compared to males [9]. It was shown that particularly the Y chromosome is associated with increased risk of coronary artery disease in European men [26]. According to a combined polygenic risk score published in 2022, comprising 540 genetic variants, the relative and absolute risks of incident coronary artery disease are stronger among males than females [27]. Among all registered Swedish STEMI cases, 31.5% were female in 2013/14 [8]. Explicitly young women with acute MI have more comorbidity and higher mortality than young men [17, 18, 28, 29], whereas men are affected more frequently by MI-related death than women [6].

Although CVD affects many racial or ethnic groups, incidence of MI is higher among black males independent of age [3]. It is estimated that by the year 2060, the prevalence of cardiovascular risk factors and disease will decrease among white individuals, while prevalence will increase in racial and ethnic minorities [4]. In addition, estimated prevalence of CVD is higher in middle-income compared to high-income countries [9].

Overweight and obesity, defined as body mass index (BMI) of ≥25 kg/m^2 and ≥30 kg/m^2, are associated with atherosclerosis and coagulation activation, adipose tissue inflammation, glucose intolerance and insulin resistance (IR) [30]. According to data from the World Health Organization (WHO) in 2021, obesity has nearly tripled worldwide between 1975 and 2016 [31] and affects 22.3% of Germany's adult population in 2016 [9]. Particularly abdominal obesity, determined by waist circumference (WC), is associated with DM, CVD [30, 32], and CVD-related mortality, the latter independently of BMI [33, 34]. Waist-to-hip ratio (WHR) further counts as strong predictor of future cardiovascular events and mortality [35-37]. A 0.01 increase in WHR thereby increases the relative risk of a CVD event by 5%, independent of sex [38].

Insufficient physical activity (PA) is one of the leading modifiable risk factors for CVD and all-cause mortality [39]. In Germany, prevalence of insufficient PA among adults aged 18 years and older is estimated to be 42.2% in 2016 [9]. The WHO recommended a weekly training of at least 150 min of moderate-intensity PA or 75 min of vigorous-intensity PA, or a corresponding combination of both [40]. Achieving those levels is proven to help prevent and

manage obesity, hypertension, CVD and DM [39] and comes along with positive affects by cardiovascular mortality and quality of life [41].

Unhealthy diet, specifically intake of fat and sugar, counts as additional predictor of CVD [9, 42]. Trans-fats but not saturated fats are associated with all-cause and cardiovascular mortality [9]. Risk of MI was further increased by 33% when carbohydrates with high-glycemic index replace saturated fat, whereas consumption of seven sugar-sweetened beverage servings weekly increases CVD mortality by 29% [42]. Consequently, nutritional strategies to prevent CVD recommend the consumption of a Mediterranean or plant-based diet [9, 42].

Regular heavy alcohol consumption and irregular “binge” drinking additionally increase CVD risk and CVD-related mortality, while moderate consumption is associated with lower cardiovascular risk and improvement of lipid status [42]. Risk of CVD death was even increased in female never-drinkers compared to moderate drinkers [42].

Passive smokers and light active smokers have the same relative risk of CVD [9]. Smoking induces oxidative stress, causes an instant and long-term rise in BP and heart rate, increases risk for blood clots and leads to impairment of vasomotoric function. Based on data from the European Society of Cardiology, smoking prevalence in member countries is 14.8% in females and 28.3% in males, aged 15 years and older [9]. However, the risk of MI conferred by smoking appears to be 25% higher in women than men [43]. Among deaths due to cardiovascular events, tobacco smoking accounts for 20% [44]. In contrast, smoking cessation can reduce the risk of CVD by 39% within 5 years and can further reduce the risk of death after MI [9]. In particular, cessation at an early age (40 years) is shown to reduce the risk of death by 90% [45].

Hypertension, defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, is the leading global risk factor for CVD and CVD-related deaths independent on age, race and sex [46]. In Germany, prevalence of elevated BP among adults aged 18 years or older, was 19.9% in 2015, whereas men are more likely to be affected compared to women [9]. Between 2025 and 2060, the number of individuals with hypertension is estimated to increase by 27.2% (127.8 million to 162.5 million individuals) [4]. The coexistence of coronary artery disease and hypertension accounts for 25-30% of all acute MI [24], worsens the clinical outcome and increases mortality in individuals with HF [47]. Furthermore, a BP difference of 20/10 mmHg is associated with a difference in cardiovascular risk by 50% [48]. According to the current guidelines, BP should be lowered if BP ≥140/90 mmHg and treated to a target <130/80 mmHg or <140/80 mmHg in elderly [49, 50]. Anti-hypertensive therapy starts with lifestyle modifications (i.e. salt reduction, healthy diet and drinks, moderation of alcohol consumption, weight reduction, smoking cessation, regular PA and stress reduction). However, major reductions in CVD and CVD-

related morbidity and mortality have been attributed to the use of anti-hypertensive drug treatment [51].

Dyslipidemia is a general term including elevated plasma triglyceride (TG), low high density lipoprotein cholesterol (HDL-C) and/or increased LDL-C concentrations. It is estimated, that the total number of individuals with dyslipidemia will increase by 27.5% between 2025 and 2060 (98.6 million to 125.7 million) [4]. In particular, elevated levels of LDL-C are strongly associated with increased incidence of cardiovascular events by promoting atherogenesis [13]. Lowering LDL-C reduces the risk of atherosclerotic CVD events proportional to the absolute reduction in LDL-C [13]. In particular, a meta-analysis showed a 22% CVD risk reduction with each 40 mg/dl (1.0 mmol/l) LDL-C reduction [52]. The evidence based goal of lipid-lowering therapy is to achieve an LDL-C reduction of ≥50% from baseline and a specific LDL-C goal according to the level of risk [53]. Individuals with MI, who are at very-high risk for additional atherosclerotic CVD, should achieve LDL-C levels <55 mg/dl (<1.4 mmol/l) according to the current guidelines [53]. To achieve this goal, statin treatment is the first line therapy after MI [53]. Its use increased from 14.1% to 93.6% between 1995/96 and 2013/14 [8].

1.1.6 CVD-related complications and comorbidities

The so called metabolic syndrome (MetS) mainly affects older individuals and is strongly associated with CVD [54-56] and type 2 diabetes mellitus (T2D) [57]. This syndrome, while currently controversially discussed, was defined by several metabolic and cardiovascular risk factors. Therefore, it received many different names over the last decades: Syndrome X (1988) [58], insulin resistance syndrome (1991) [59] or “the deadly quartet” (1989) [60]. The currently proposed criteria for diagnosing MetS are shown in Table 1.

Table 1. Criteria for clinical diagnosis of the metabolic syndrome based on statements of the American Heart Association / National Heart, Lung, and Blood Institute (2005), and the International Diabetes Federation (2006)

Clinical Measure	Categorical Cut-off points	
	AHA / NHLBI (2005)	**IDF (2006)**
	Any 3 of 5 constitute diagnosis of MetS	**Central obesity (ethnicity specific)* plus any 2 of the following 4**
Elevated waist circumference*	≥102 cm (man), ≥88 cm (woman)	Europids: ≥94 cm (man), ≥80 cm (woman); or BMI >30 kg/m^2
Elevated fasting triglycerides	≥150 mg/dl (1.7 mmol/l) or on drug treatment	
Reduced HDL-cholesterol	<40 mg/dl (1.03 mmol/l (man), <50 mg/dl (1.3 mmol/l) (woman) or on drug treatment	
Elevated blood pressure	≥130 mmHg (systolic) or ≥85 mmHg (diastolic) or on antihypertensive drug therapy	
Elevated fasting plasma glucose	≥100 mg/dl (5.6 mmol/l) or on drug treatment	≥100 mg/dl (5.6 mmol/l) or previously diagnosed T2D

Table Legend. Different clustering criteria for clinical diagnosis of the metabolic syndrome. AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; MetS: Metabolic syndrome; BMI, body mass index; HDL, high-density lipoprotein; T2D, type 2 diabetes. According to the consensus statements of the AHA and NHLBI [61] and the IDF [62].

The main difference between these definitions of MetS are the cut-off values for abdominal obesity. Values for elevated WC according to the International Diabetes Federation (IDF) are lower compared to the criteria of the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI). The WC criterion is further specific for ethnicity and obligatory for defining MetS. According to a consensus paper in 2009, MetS can be defined without the presence of elevated WC [63]. Following this statement, three out of five risk factors are sufficient for the diagnosis of MetS in both definitions.

DM is a major, independent risk factor for the development of CVD and HF, and associated with its higher morbidity and mortality [64-66]. The Framingham Heart study found a threefold increased risk for cardiovascular mortality in individuals with DM compared to individuals without DM [67, 68]. Furthermore, coexistence of DM makes females three times more likely to develop HF compared with men [64]. In 2009, 22.7% of individuals with STEMI and 35.0%

with NSTEMI also had DM in the USA [69]. According to data from the SWEDEHEART registry, the proportion of individuals with DM among STEMI cases was stable during the last 20 years, accounting for 20.5% cases in 2014 [8]. It was recently published, that among novel diabetes phenotypes, individuals with severe insulin-resistant diabetes (SIRD) have the greatest risk for CVD [70, 71].

IR predicts and promotes not only the development of DM and non-alcoholic fatty liver disease (NAFLD) [72, 73], but also atherosclerosis [74] and MI [75], and worsens the cardiovascular outcome (i.e. in-stent restenosis [76], LV dilation after STEMI [77]). IR as a dominant feature of DM is also common in individuals without DM. Within the first week after STEMI, IR in individuals without DM is associated with larger infarct size [78].

Ectopic fat deposition, specifically hepatic fat, i.e. NAFLD, serves as an independent predictor for clinically manifest coronary, cerebrovascular and peripheral vascular disease, as well as CVD-related death [79, 80]. The presence of NAFLD is strongly associated with cardiac arrhythmias and subclinical myocardial remodeling and dysfunction [79]. Severe myocardial dysfunction, with prominent LV reshaping and increased end-systolic (ESV) and end-diastolic volume (EDV) after MI was shown in a mouse model with NAFLD and IR [81]. In general, CVD are the most common cause of death in individuals with NAFLD [82, 83]. Particularly, increasing liver fibrosis represents the strongest predictor for mortality in individuals with NAFLD [84]. However, whether or not NAFLD counts as independent risk factor for CVD is still under debate [85].

1.1.7 Heart failure

LV remodeling is defined as “the hearts’ (mal-) adaptation to mechanical, neurohormonal and inherited changes by regulating ventricular size, shape and function” [20]. Whereas growth and training, among others, lead to physiological and reversible remodeling, LV remodeling following MI is considered adverse or pathological and increases the risk for HF and mortality [20]. Between 2025 and 2060, the prevalence for HF is estimated to increase by 33.3% [4]. Aging and female sex are known to be the strongest individual predictors, whereas comorbidities including T2D, hypertension or chronic obstructive pulmonary disease further increase the risk for HF [20, 64].

In 2021, a new universal definition and classification of HF was proposed by consensus statement as “a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion” [86]. Typical symptoms of HF include breathlessness, orthopnea, paroxysmal nocturnal dyspnea, ankle edema and reduced exercise tolerance up to inability to exercise [86]. More specific signs of HF include elevated

jugular venous pressure, third heart sound, hepatojugular reflux and cardiomegaly, among others [86]. The New York Heart Association (NYHA) Functional Classification system is based on symptom severity and specifies to which degree individuals with cardiac disease are limited during daily PA [86, 87].

Current classifications of HF are commonly used for risk stratification of HF and determination of clinical trial eligibility and candidacy for recommended treatments in clinical practice [86, 88]. Based on the current (2021) European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF [88], the following diagnostic tests are recommended for diagnosing HF : (1.) ECG with abnormalities (e.g. Q waves, LV hypertrophy, widened QRS complex), (2.) elevated levels of NPs (e.g. B-type NP ≥35 pg/ml, N-Terminal pro-B-type NP >125 pg/ml) and (3.) echocardiography, recommended as the key investigation for assessment of cardiac function (e.g. wall motion abnormalities, markers of diastolic dysfunction). If HF is confirmed, the HF phenotype can be defined based on LVEF measurements.

Individuals with LVEF less or equal 40% are diagnosed with HF with reduced EF (HFrEF), whereas individuals with LVEF from 41% up to 49% are diagnosed with HF with mildly reduced EF (HFmrEF) [88]. Both diagnosis additionally requires the presence of HF related symptoms (e.g. breathlessness, reduced exercise tolerance, fatigue, ankle swelling) and/or signs (e.g. hepatojugular reflux, third heart sound, elevated jugular venous pressure), whereas the presence of elevated NPs and other evidence of structural heart diseases are not mandatory if there is certainty regarding the LVEF measurements [88].

The diagnosis of HF with preserved EF (HFpEF) requires three criteria, firstly symptoms and signs of HF, secondly an LVEF greater or equal 50% and thirdly “objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised NPs” [88]. Individuals with HFpEF are older, more often female and suffering from additional comorbidities compared to individuals with HFrEF and HFmrEF [88]. The fourth phenotype is called HF with recovered EF (HFrecovEF). Individuals with prior HFrEF, who later improved to LVEF ≥50% belonging to this category. It is recommended that these individuals should continue treatment for HFrEF since they are not risk equivalent to individuals with HFpEF [88].

Based on data of the SWEDEHEART registry, the proportion of STEMI cases with in-hospital LVEF ≥50% increased from 28.4% to 47.7% between 1997/98 and 2013/14, whereas the proportion of those with LVEF 30-39% or <30% did not change [8]. Literature showed that the outcome is not necessarily related to EF [86, 89, 90]. However, EF categorization has proven to be clinically useful by showing that individualized therapies, specifically glucose-lowering treatment in individuals with DM, are more efficient in individuals belonging to a certain EF category [91].

1.2 Diabetes mellitus

DM is a chronic metabolic disease, which is characterized by hyperglycemia due to progressive dysfunction of insulin secretion or action or both [92]. The IDF has estimated that the global number of individuals with DM is expected to rise from 537 million to 783 million adults aged 20-79 years between 2021 and 2045, if no urgent action is taken [93]. It was further estimated, that in 2021, 541 million adults have impaired glucose tolerance (IGT) and therefore, are at increased risk of developing T2D [93]. In contrast, in 2021, 61 million European adults had DM; a number estimated to increase by 13% by 2045 [93]. It was also expected that in Europe, one in three (36%) individuals living with DM are undiagnosed [93]. In 2021, Germany was one of the top five countries for absolute number of individuals with DM, counting 6.2 million adults, and with a prevalence for individuals aged 20-79 years of 10.0% [93]. From 2015 to 2040, a relative increase in the number of T2D cases in Germany was estimated between 54% and 77% [94]. Individuals with DM are considered at high risk for developing chronic diabetes-related complications such as CVD or NAFLD, although rates of progression may differ among distinct DM types [95, 96]. According to IDF statistics, DM caused at least US$ 966 billion in health expenditure globally, with a portion of 19.6% accounting for the European Region [93]. A large amount of direct health costs accounts for the costs of treating complications [93]. In view of this socio-economic burden, the identification of those individuals, who may develop DM, diabetes-related complications and/or death, is of great importance and interest for our health care system. Thus, current guidelines focus on the management of established risk factors (i.e. hypertension, dyslipidemia) for recent onset T2D, in order to prevent migration into a deteriorated glucometabolic status with future risk of cardiovascular complications [49, 53, 97]. Since evidence found that DM prevalence in the USA remains stable and incidence decreases within recent years [98], those approaches may have increasing success and should be focused by physicians all over the world.

1.2.1 Definition of diabetes mellitus

According to the American Diabetes Association (ADA) [92] and the WHO [99], DM can be classified into four general categories [92]. An increase in blood glucose (BG) levels, called hyperglycemia, is the common and mandatory denominator for each type. Classical symptoms of hyperglycemia include polyuria, polydipsia, fatigue, weight loss, visual disturbances and susceptibility to infections. A severe hyperglycemia can progress from classic symptoms to ketoacidosis or non-ketoacidotic hyperosmolar syndrome with the risk of coma. Chronic hyperglycemia is associated with long-term damage and functional disorders of various tissues and organs (eyes, kidneys, nerves, heart and blood vessels) [100].

Well known diabetes-related symptoms like polyuria, polydipsia, weight loss and diabetic ketoacidosis are common in individuals with **Type 1 diabetes (T1D).** T1D due to immunologic (type 1a) or idiopathic (type 1b) causes, manifests as autoimmune-mediated β-cell destruction and presents with one or multiple autoantibodies (e.g. glutamic acid decarboxylase (GAD) antibodies, islet cell antibodies (ICA) and/or insulin autoantibodies (IAA)). The presence of two or more diabetes-related autoantibodies indicates a >80% risk of developing T1D within 15 years [92]. Multiple antibodies or GAD antibodies alone at diagnosis predict complete β-cell failure within 12 years after diagnosis [101]. The progression of T1D results in an absolute insulin deficiency with no to little serum levels of C-peptide (CP) [95]. Depending on the speed of insulin-producing beta-cell destruction, individuals with T1D depend on exogenous insulin immediately (typically in children) or in the further course of the disease, and usually require lifelong insulin therapy. However, literature found that antibody positive individuals with an insulin-free period of >6 months after DM diagnosis had better beta-cell function parameters compared to directly insulin dependent individuals, and further had higher insulin sensitivity compared to age- and sex-matched individuals with T2D [102].

Type 2 diabetes (T2D) is the most common type of diabetes, reflecting around 90-95% of all diabetes cases. The pathomechanism is based on peripheral IR and relatively impaired insulin secretion. The early stage of T2D is characterized by impaired first-phase insulin secretion causing postprandial hyperglycemia, followed by a deteriorating second-phase insulin response and persistent hyperglycemia in the fasting state. In the beginning, white adipose tissue dysfunction and unphysiological levels of circulating metabolites are affecting inter-organ cross-talk and insulin signaling, accelerated by the activation of inflammatory pathways in the further course of the disease [72]. Currently, several diabetes-related socioeconomic, demographic, environmental and genetic risk factors are known and drive the increasing prevalence of DM.

Diabetes mellitus due to other causes (in the German nomenclature also known as Type 3 DM) includes diseases of the exocrine pancreas (i.e. pancreatitis, post-surgical, cystic fibrosis), endocrine disorders (i.e. Cushing syndrome, acromegaly), drug-chemical causes (i.e. glucocorticoids), genetic defects in insulin secretion (i.e. types of maturity onset diabetes of the young (MODY)) and in the insulin effect (i.e. lipoatrophic diabetes), other genetic syndromes (i.e. Down-, Turner-, Klinefelter-syndromes), infections (i.e. congenital rubella) and rare forms of autoimmune-mediated diabetes (i.e. Stiff-Man-syndrome) [100].

Gestational diabetes mellitus (GDM) represents the fourth type of diabetes and is defined as new onset of glucose tolerance disorder during pregnancy. An overt diabetes diagnosis prior to pregnancy must be ruled out beforehand. The pathomechanism is based on already pre-conceptually reduced insulin sensitivity, which is intensified during the 20th week of pregnancy by physiological hormone-related IR. Women with GDM feature more distinct IR

and impaired insulin secretion, which persists after delivery even if women reverse to normal glucose tolerance [103]. Thus, GDM represents a specific prediabetic condition with mostly the same diabetes-related risk factors (e.g. overweight/obesity, reduced PA) and due to this, a high risk for development of T2D within the following two decades [104].

Novel approaches to DM classification are trying to overcome the above mentioned four DM types. In 2018, a refined classification of individuals with newly diagnosed DM identifying five clusters of individuals with significant different metabolic characteristics, disease progression and risk of diabetes-related complications, was published [71]. The underlying cluster analysis was based on six variables: GAD antibodies, age at diagnosis, BMI, hemoglobin A1c (HbA1c) and homeostasis model assessment (HOMA) 2 estimates of beta-cell function (HOMA2-B) and insulin resistance (HOMA2-IR). Whereas severe autoimmune diabetes (SAID, cluster 1) overlapped with T1D, individuals with severe insulin-deficient diabetes (SIDD, cluster 2) and severe insulin-resistant diabetes (SIRD, cluster 3) represent two new, severe forms of DM previously masked within T2D.

1.2.2 Diagnostic criteria of diabetes mellitus and prediabetes

The current ADA guidelines define cut-off values for diagnosing DM and prediabetes, based on fasting plasma glucose (FPG), 2-hour plasma glucose (PG) during 75-g oral glucose tolerance test (OGTT), random PG and/or HbA1c criteria [92, 105]. DM was defined by FPG ≥126 mg/dl (≥7.0 mmol/l), 2-h-PG or random PG ≥200 mg/dl (≥11.1 mmol/l) with classic symptoms of hyperglycemia, and/or HbA1c ≥6.5% (≥48 mmol/mol) [92, 105]. The HbA1c cut-off value 6.5% (48 mmol/mol) is based on the increase in the risk of diabetic retinopathy, which is the most specific diabetes-related complication [106]. Individuals, who have values above the normal range but do not meet the diagnostic criteria of diabetes are diagnosed with impaired glucose metabolism (IGM), also termed prediabetes. The current ADA criteria define two different entities counting to this disturbed glucose metabolism including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG was defined as FPG levels of 100-125 mg/dl (5.6-6.9 mmol/l) and IGT as 2h-PG levels of 140-199 mg/dl (7.8-11.0 mmol/l) [92, 105]. HbA1c values of 5.7-6.4% (39-47 mmol/mol) were defined as the third criterion for diagnosing prediabetes [92, 105]. As these HbA1c values indicate an increased risk of DM, a diagnosis using FPG and OGTT is recommended. In addition, if no clear hyperglycemia was detected, two tests with abnormal results are required from the same blood sample or in two separate test samples [92]. An overview of the described criteria is shown in Table 2.

Table 2. Criteria for diagnosing prediabetes and diabetes

Diagnostic criteria	Prediabetes	Diabetes mellitus
FPG (mg/dl) *	100-125 (5.6-6.9 mmol/l) **(IFG)**	≥126 (7.0 mmol/l)
2-hours PG (mg/dl) during OGTT **	140-199 (7.8-11.0 mmol/l) **(IGT)**	≥200 (11.1 mmol/l)
Random PG (mg/dl)		≥200 (11.1 mmol/l) and classical symptoms of hyperglycemia or hyperglycemic crisis
HbA1c (%)	5.7-6.4 (39-47 mmol/mol)	≥6.5 (48 mmol/mol)

*Table Legend. Criteria for diagnosing prediabetes including impaired fasting glucose and/or impaired glucose tolerance and/or elevated values of HbA1c, and diagnosing diabetes mellitus. HbA1c: glycated hemoglobin A1c, FPG: fasting plasma glucose, PG: plasma glucose, OGTT: oral glucose tolerance test, IFG, impaired fasting glucose; IGT, impaired glucose tolerance; *: No caloric intake for at least 8 hours ("fasting"), **: The test should be performed as described by the World Health Organization, using a glucose load containing in equivalent of max. 75 g anhydrous glucose dissolved in water. Adapted from the American Diabetes Association "Standards of Care in Diabetes" [92].*

The cut-off values for diagnosing DM do not differ between the guidelines of WHO and ADA. By using the HbA1c as a parameter for diagnosing diabetes, the WHO postulates, that it must be assumed that "stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values" by the International Federation of Clinical Chemistry (IFCC) as well as "no conditions are present, which preclude its accurate measurement" [107]. The worldwide standardization of HbA1c should use the IFCC reference system. According to the IFCC standard, HbA1c values are given in mmol/mol [108]. The conversion of the percentage HbA1c value is as follows [109]:

$$\text{HbA1c (\%)} = (0.09148 * \text{HbA1c in mmol/mol}) + 2.152$$

HbA1c can be influenced by several factors i.e. age, ethnicity and disorders like disturbance of erythropoiesis (i.e. iron/vitamin B12 deficiency, chronic liver diseases), altered hemoglobin (i.e. hemoglobinopathies), glycation (i.e. alcoholism, chronic renal failure), erythrocyte destruction (i.e. splenectomy, splenomegaly) and conditions interfering with assays (i.e. hyperbilirubinemia, large doses of Aspirin, hypertriglyceridemia); in the latter cases, HbA1c is not suitable as a diagnostic criterion [92, 110].

Treatment goals for glycemia, BP, and dyslipidemia in older adults with diabetes are defined and revised annually by the ADA. According to the current guideline, HbA1c targets dependent on the personal characteristics and health status, for example the number of coexisting chronic illnesses (i.e. hypertension, myocardial infarction, stroke, depression). Older individuals, who are otherwise healthy (few coexisting chronic illnesses, intact cognitive and functional status) should have glycemic goals such as HbA1c <7.0-7.5% (53-58 mmol/mol) compared to those, who have a complex/intermediate heath status (i.e. at least three coexisting chronic illnesses) and should have less stringent goals such as HbA1c <8.0% (64 mmol/mol) [50].

The literature showed that, after the WHO recommended HbA1c as a measure for diagnosing DM, individuals with BG in the diabetic range but HbA1c levels less than 6.5% (48 mmol/mol), remained undiagnosed and untreated [111]. Furthermore, a meta-analysis showed increased all-cause mortality at high as well as low HbA1c levels in individuals with T2D [112]. Specifically, HbA1c levels <6% (<42 mmol/mol) were associated with an increased risk of mortality compared to those with 7.0-7.9% (53-63 mmol/mol) [113]. Since the HbA1c reflects the average BG level for the last two to three months, the HbA1c is limited by addressing fluctuations in BG, which may lead to hypoglycemic acute events or postprandial hyperglycemia with its effects on developing macro- and microvascular complications. Within the recent years, self-monitoring of BG levels has been increasingly replaced by continuous glucose monitoring with interstitial glucose measurements at 5-minute-intervals [114]. Evidence showed, that this effective new, personalized technique leads to improvements in hypoglycemica, “time in range” (time, spent in the target glucose range), glycemic variability and user compliance [114]. In 2019, clinical targets for continuous glucose monitoring were recommended by international consensus [115]. Those targets may further improve the outcome in individuals with DM.

1.2.3 Risk factors for diabetes mellitus

Many studies have identified several factors strongly associated with an increased risk of developing T2D. These risk factors can be categorized into non-modifiable and modifiable factors. Age counts as one important non-modifiable risk factor. According to IDF statistics, estimates show a typically increasing prevalence of DM by age [93]. Adults aged 20-24 years show the lowest prevalence for DM (2.2%), compared to adults aged 75-79 years, who show the highest prevalence of 24% in 2021 [93].

Geographic and ethnic differences also seem to play an important non-modifiable role in the development of DM. Prevalence of DM is greater in middle-income countries compared to high-income countries [9]. In 2021, the Middle East and North Africa region have the highest age-adjusted prevalence of DM worldwide (18.1%); in contrast, the age-adjusted prevalence

for DM in Europe is estimated to be 7.0% [93]. According to the countries or territories with the largest numbers of adults with DM, China (140.9 millions), India (74.2 millions), Pakistan (33.0 millions) and the USA (32.2 millions) are globally the top four countries [93]. According to the Centers for Disease Control and Prevention (www.cdc.gov/diabetes/data/statistics-report/diagnosed-diabetes.html, last accessed on 4th August 2022), in 2018-2019, the prevalence of diagnosed DM in the USA was highest among American Indians/Alaska Natives (14.5%) and non-Hispanic Blacks (12.1%); in contrast, DM prevalence among non-Hispanic Whites was 7.4%.

T2D also has a strong genetic component with the mode of inheritance being more influenced by the maternal environment [116]. The heritability of T2D is estimated to range from 30 to 70%, with the highest heritability for T2D seen in adults aged 35-60 years at disease onset [117]. It was shown that for a child of a parent with T2D, the probability of illness is up to 40% [118]. During the last years, genome-wide association studies have implicated around 250 genomic regions as predisposing for T2D [119]. However, each risk allele increases less than 15% the risk of developing T2D [120]. Thus, the predictive value of those genes is very limited compared to the classic risk factors such as elevated FBG. However, the development of T2D is strongly based on both, environmental as well as genetic factors. Epigenetic traits are considered reversible modifications. They can randomly arise in response to environmental factors or certain genetic mutations. A translational approach showed that epigenetic modification such as DNA methylation in islets of Langerhans can precede new onset of DM [121]. Since DNA methylation can be inherited mitotically and meiotically, the risk for T2D can be increased over more than one generation.

In 2021, globally 17.7 million more men than women are living with DM [93]. Even the prevalence among men is higher than in women (10.8% vs. 10.2%) [93]. European men are usually diagnosed with DM 3-4 years earlier and at a BMI 1-3 kg/m^2 lower than women, who in turn are affected by a sharp increase in the risk of DM-associated CVD after menopause due to a decrease in estrogen, which counts as protective factor against DM [122].

As overweight and obesity are the major modifiable risk factors of T2D in both sexes, sex differences in body composition and fat deposition clearly contribute to the sex-dimorphic DM risk. It is estimated that 90% of individuals with T2D are obese, however among individuals with obesity only 20-25% develop T2D [123]. Females tend to be more overweight/obese than men, in particular, after the age of 45 years [122]. Increasing age with the loss of estrogen production lead to an increase of abdominal fat, shifting to “visceral adiposity”, and a more prominent increase of WC in women than men [124]. In particular, higher WHR does not only predict cardiovascular events and mortality but also new onset of T2D [36].

Increased food intake and decreased PA are the main drivers for developing overweight/obesity. Unhealthy diet including refined carbohydrates; particularly food with high-glycemic index, saturated fats, red/processed meat and sugar sweetened beverages, is strongly associated with increased risk for T2D [42]. In turn, diets rich in whole grains, fruits, vegetables, coffee and moderate alcohol consumption, reduce diabetes risk and improve glycemic control and blood lipids in individuals with DM [42, 122, 125, 126]. Reduced PA is further associated with 42% higher risk of DM [127]. Achieving the WHO-recommended PA levels is associated with 26% lower incidence of T2D [127]. In contrast, a program of increased PA and moderate weight loss could decrease the risk for developing T2D by 58% [41]. However, among the new DM subtypes, in particular individuals with SIRD show reduced physical fitness despite similar PA levels [70]. In addition, active and passive smoking are associated with higher risk of developing T2D and diabetes-related complications [128].

Furthermore, hypertension is affecting 20-60% of individuals with DM [129]. The prevalence of hypertension depends on history of glycemic control, diabetes type and duration, among others. In individuals with DM, antihypertensive therapy reduces atherosclerotic CVD events, HF, and microvascular complications [130]. According to current guidelines, BP in individuals with DM should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg or <140/90 mmHg in elderly [49, 50].

Dyslipidemia is also common among individuals with DM, particularly in those with HbA1c values ≥7.0% (≥ 53 mmol/mol) [131]. The main cause of diabetic dyslipidemia is the increased release of free fatty acids (FFA) from insulin-resistant adipocytes. Hyperinsulinemia is further associated with low HDL-C levels [132]. Individuals with DM have to achieve individualized LDL-C targets, as presented in Table 3. Those targets depend on age, disease duration and related complications or presence of additional risk factors, recommended by current guidelines [53].

Table 3. Targets for LDL-cholesterol levels across distinct categories of total cardiovascular disease risk according to current guidelines [53]

Risk category	Specific diagnosis criteria	LDL-C level
Ultra high risk (Class III)	• Documented atherosclerotic CVD with a 2nd vascular event within 2y (not necessarily of the same type) while taking maximally tolerated statin-based therapy	<40 mg/dl (<1.0 mmol/l)
Very high risk	• Documented atherosclerotic CVD i.e. MI • DM with target organ damage (microalbuminuria, retinopathy or neuropathy); or ≥3 major risk factors; or early onset of T1D of >20y duration • Severe CKD (eGFR <30 ml/min) • Calculated SCORE ≥10%	<55 mg/dl (<1.4 mmol/l)
High risk	• Markedly elevated single risk factor i.e. BP ≥180/110 mmHg, TC >310 mg/dl or LDL-C >190 mg/dl • Moderate CKD (eGFR 30-59 ml/min) • DM without target organ damage, with disease duration ≥10y or another additional risk factor • Calculated SCORE ≥5 and <10%	<70 mg/dl (<1.8 mmol/l)
Moderate risk	• Young age (T1D <35y; T2D <50y) with diabetes duration <10y without other risk factors • Calculated SCORE ≥1 and <5%	<100 mg/dl (<2.6 mmol/l)
Low risk	• Calculated SCORE <1%	<116 mg/dl (<3.0 mmol/l)

Table legend. Targets for LDL-cholesterol levels for the management of dyslipidemia. LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular diseases; y, years; MI, myocardial infarction; DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; BP, blood pressure; TC, total cholesterol. Adapted from the 2019 ESC/EAS guidelines [53].

1.2.4 Diabetes-related complications and comorbidities

Women with prior GDM and with polycystic ovary syndrome are at greater risk of developing T2D [92]. Even psychosocial stress at work is associated with a twofold higher risk of T2D in women, but not in men [133]. In individuals with T2D, comorbid depression also increases the risk of early onset and progression of diabetes-related complications, and is associated with its higher mortality [134].

IGM, commonly an asymptomatic condition, indicates a higher risk for the development of T2D [135]. Five years after diagnosis of IFG or IGT, the cumulative incidence of T2D progression is estimated to be 50% and 26% [136]. Lifestyle interventions with regards to diabetes prevention show a relative risk reduction of 40-70% [137]. Evidence further showed that IGM is associated with increased risk of all-cause mortality, CVD development and mortality as well as HF [138]. In 2021, a refined classification of individuals without DM identifying six distinct phenotypes with different risk of developing T2D, IR, CVD and mortality [139]. The study showed that particularly individuals in cluster 3 and 5 are at greater risk of developing new onset of T2D, whereas individuals in cluster 5 were identified as obese and insulin resistant with additionally greater risk for CVD [139]. However, cluster 6 was even more insulin resistant than cluster 5 and additionally at high risk for all-cause mortality [139]. Furthermore, cluster 6 was strongly connected to the previously mentioned SIRD cluster [139].Upper body obesity, specifically the increase in visceral fat, leads to an increase in FFA in the blood. Ultimately, high levels of FFA can mediate IR in muscle [140] and liver [141], disorders which lead to a greater risk for developing prediabetes and diabetes. High concentrations of FFA are a characteristic feature of T2D and further contribute to myocardial dysfunction, impairment of cardiac function and development of HF [142, 143].

Cardiac autonomic neuropathy, characterized by reduced heart rate variability, is strongly associated with obesity, IR and dyslipidemia, the latter particularly in individuals with T2D [144]. Those individuals are more likely to develop silent MI and show higher total mortality rates compared to individuals without cardiac autonomic neuropathy [145].

DM is a major risk factor for CVD, and associates with its higher mortality and morbidity [146]. The risk for new onset of MI within 10 years after DM onset is >20% and the risk of recurrent MI exceeds 40% [147]. DM further associates with a 16% increase in all-cause and an 18% increase in cardiovascular mortality, while HbA1c in a range of 6% to 6.9% is associated with lowest mortality, independent of age and prior CVD [148]. Evidence has further shown that fasting hyperglycemia in individuals with DM is associated with hepatic IR [149, 150], whereas elevated postprandial glucose levels are associated with peripheral IR [150]. Among the novel diabetes phenotypes, individuals with the SIRD subtype have the greatest risk for CVD [70, 71] and further show the greatest risk for fatty liver at disease onset and for hepatic fibrosis over the next 5 years [95].

NAFLD is extremely common in individuals with DM, since the prevalence of NAFLD in T2D is estimated to be >70% [79, 151]. The coexistence of DM and NAFLD increases the risk of developing more severe forms of NAFLD as well as cardiovascular complications, associating with a worse clinical outcome [73, 79].

1.3 Non-alcoholic fatty liver disease (NAFLD)

NAFLD are the most common liver diseases in industrially developed states. In 2019, the pooled global prevalence of NAFLD was 29.8%, with the highest prevalence in South America (35.7%), followed by North America (35.3%) [152]. From 1991 to 2019, Europe showed the second greatest increase of NAFLD of 1.1% per year [152]. While the USA had the fastest rising incidence in advanced disease and China was predicted to have the greatest overall number of individuals with NAFLD, Germany belongs to the countries with the greatest expected incidence increase in advanced liver fibrosis [153]. In Germany, approximately 18.4 million individuals are suffering from NAFLD, of which around 2.5 million are affected with non-alcoholic steatohepatitis (NASH) [154]. However, as a result of inconsistent diagnostic measures (NAFLD prevalence in Europe diagnosed by imaging vs. blood tests: 23.71% vs. 13.00% [155]), the number of those individuals actually affected can currently be estimated only roughly. Finally, the strong increase in prevalence and total number of cases may lead to an alarming socioeconomic and financial burden of the health care system. In line with the worldwide increases in NAFLD-related risk factors such as obesity and T2D, more efficient strategies for prevention, diagnosis, and treatment are needed.

1.3.1 Definition of NAFLD

NAFLD is characterized by macrovesicular accumulation of lipids, especially TG, in the cytoplasm of hepatocytes caused by other factors than significant alcohol consumption. Unhealthy lifestyle, such as decreased PA and increased dietary carbohydrate and saturated fat intake, and adipose tissue dysfunction with excessive lipolysis are the main drivers of this disease [73]. Liver steatosis is defined by specific histological signs or the presence of >5.56% steatotic hepatocytes in the liver tissue section, measured by ^{1}H-MR spectroscopy [156]. Secondary causes (i.e. chronic viral hepatitis, autoimmune hepatitis, Wilson's disease, amiodarone, tamoxifen) and significant alcohol consumption (≥30 g/day in men and ≥20 g/day in women) have to be excluded before diagnosis [157, 158].

NAFLD can be classified into two distinct conditions with different prognosis [158]: Non-alcoholic fatty liver is the most common type, characterized by simple steatosis with little or no inflammation or liver cell damage. Typically, this type is reversible and usually shows an indolent, non-progressive course of disease with good prognosis. In turn, NASH is defined histologically by the presence of liver steatosis with lobular inflammation, hepatocellular ballooning and necrosis. NASH can progress into complications such as hepatic fibrosis, cryptogenic cirrhosis, end-stage liver failure and hepatocellular carcinoma. Among individuals with histological NASH, approximately 41% experience fibrosis progression [155]. Hepatic

fibrosis is caused by excessive accumulation of extracellular matrix proteins, which results in the induction of hepatocyte necroinflammation and the differentiation of hepatic stellate cells into myofibroblasts. It can occur as a complication of NASH, but also due to excessive alcohol consumption, viral hepatitis (B, C, D) or autoimmune hepatitis, among others. In early stages, hepatic fibrosis can be reversible. Individuals, in whom hepatic fibrosis progresses to cirrhosis, may also develop complications such as portal hypertension or hepatocellular carcinoma. In case of cirrhosis, healing by medication is no longer possible and due to liver failure, liver transplantation is the only option to cure and survive. Thus, in the USA, NASH-related cirrhosis is the second most frequent indication for liver transplantation among adults [155].

1.3.2 Diagnosis of NAFLD

Various blood tests, scores and imaging methods such as ultrasound (US), computertomography, ^{1}H-MR imaging (MRI), spectroscopy (MRS) and elastography (MRE) can be used for identifying and staging of NAFLD. According to the Clinical Practice Guidelines in 2016 [158], the non-invasive, widely available abdominal US should be the first-line diagnostic method for detection of steatosis. This technique is cheaper than the other mentioned methods, however US depends on the investigator´s experience, is subjectively interpretable and has low sensitivity in individuals with BMI >40 kg/m^2 and for the detection of steatosis when the hepatocellular lipid (HCL) content is less than 20% [158]. Nevertheless, a quantitative estimation of HCL can only be achieved by ^{1}H-MRS, but this technique is expensive, time consuming and not recommended in the clinical setting. Non-invasive tests can be used to provide validated results, whenever imaging methods and liver biopsy are not available. Those tests have the advantages to be cost-effective, readily available and can be used for follow-up monitoring. On the other hand, they have low specificity and cannot sufficiently reflect the pathophysiologic liver status. The Fatty Liver Index (FLI) is one of the best validated tests for detecting liver steatosis in the general population and recommended by international guidelines for NAFLD screening [158]. Evidence showed that HCL content and IR correlated positively with FLI [95, 159]. However, even if FLI is of clinical and practical relevance, it cannot substitute the current gold standard technique for detection and staging of NASH, fibrosis and cirrhosis. Liver biopsy is the only procedure that reliably differentiates non-alcoholic fatty liver from NASH by characteristic histological features [158].

The NAFLD-Fibrosis Score (NFS), the Fibrosis-4 (FIB-4) Score, US-based transient elastography and MRE are clinically useful methods to assess liver fibrosis non-invasively. Transient elastography can be used for identification of cases at low risk of advanced fibrosis and cirrhosis, but has a limited ability to differentiate between histological grades of NAFLD [158]. This method gives a first indication whether NAFLD is present or not, but it is highly

operator- and interpretation-dependent and inter-individually different results are possible. In clinical practice, a combination of non-invasive tests can be used for monitoring of fibrosis progression. This includes, among others, the NFS and FIB-4 score with established cut-offs for diagnosing liver fibrosis, validated among individuals with diagnosed NAFLD [160, 161]. Those two tests offer the best non-invasively diagnostic performance for detecting advanced fibrosis [162]. At last, ^{1}H-MRE has been proven to be highly predictive for detection and evaluation of tissue stiffness, which is associated with grades of liver fibrosis [163-165]. In contrast to US-based transient elastography, MRE is accurate and effective even in individuals with obesity [166] and has a higher diagnostic accuracy in detection of each stage of fibrosis in individuals with NAFLD [167]. Furthermore, it can be used when liver biopsy cannot be performed and is therefore of high clinical value.

1.3.3 Risk factors and comorbidities of NAFLD

Evidence found several non-modifiable (i.e. sex, age, genetics) and modifiable (i.e. nutrition, reduced PA) risk factors for the development of NAFLD. Firstly, NAFLD prevalence and incidence are estimated to be higher in men than in premenopausal women while tend to become more common in women after menopause [168, 169]. Secondly, younger individuals aged 15-49 years, account for nearly 50% of the total number of cases worldwide and further accounted for the greatest global increase in NAFLD prevalence between 1990 and 2017 [170]. In the USA, adults aged 60-74 years, show a NAFLD prevalence of 40.3% [171]. In this age group, NAFLD is associated with an increased risk of all-cause and cardiovascular mortality [171]. Advanced age is also associated with disease severity and fibrosis progression [172]. Thirdly, family history of NASH or cryptogenic cirrhosis increase the risk of developing NAFLD [173]. Previous studies found a possible genetic link between NAFLD and DM by specific gene polymorphisms. It was shown, that the TM6SF2 rs58542926 single nucleotide polymorphism in the patatin-like phospholipase domain-containing 3 gene, usually related to increased risk of NAFLD and liver fibrosis progression [174, 175], also associates with the novel diabetes phenotype “SIRD” [71].

The most common modifiable metabolic comorbidities, associated with NAFLD, include obesity, T2D, hyperlipidemia/dyslipidemia, hypertension and the MetS. A meta-analysis in 2016 [155] had specified the prevalence of these risk factors among individuals with NAFLD or NASH as shown in Table 4:

Table 4. Prevalence of risk factors among individuals with NAFLD and NASH

Risk factor	With NAFLD (%)	With NASH (%)
Obesity	51.34	81.83
Hyperlipidemia / dyslipidemia	69.16	72.13
Hypertrigylceridemia	40.74	83.33
Hypertension	39.34	67.97
Metabolic syndrome	42.54	70.65
Type 2 diabetes	22.51	43.63

Table legend. Prevalence of risk factors among adults aged 18 years or older with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Meta-analysis of cross-sectional, longitudinal or descriptive studies published between 1989 and 2015. Data are presented in percentages (%). Adapted from Younossi et al. [155].

Obesity is a major risk factor for the presence (incidence) and progression of NAFLD, since individuals with obesity have a 3.5 fold increased risk of developing NAFLD [176]. Hypertriglyceridemia rather than hypercholesterolemia may further increase the risk of NAFLD [177]. Serum alanine aminotransferase (ALT) and/or serum ɣ-glutamyltransferase (GGT) are surrogate markers of NAFLD. Both markers are also independently associated with an increased incidence of T2D [178, 179] and CVD [178]. GGT is further a marker for oxidative stress, whereas ALT levels are already associated with obesity as well as whole body and hepatic IR [180]. Consequently, both parameters are not reliable indictors for screening and diagnosis of NAFLD and should not be used as sole diagnostic criterion.

NAFLD is closely linked with hepatic and peripheral IR, a (patho-) physiological phenomenon occurring as transient adaptation to oxidative stress, chronic hyperglycemia and elevated circulating lipids, amino acids, cytokines and FFA, resulting in the inhibition of insulin signaling [73]. IR was found in about 60% of all individuals with NAFLD and in almost 100% with NASH [172]. Liver steatosis is further associated with impaired mitochondrial activity and insulin sensitivity in muscle cells [181].

NAFLD is also associated with a twofold higher risk of developing T2D [73]. Personal history of DM and even family history of DM in individuals without DM increases the risk for NASH and fibrosis[182, 183] as well as all-cause and CVD-related mortality in individuals with NAFLD [184]. Among the novel diabetes phenotypes, individuals assigned to the SIRD subtype exhibit the highest degree of HCL and have the greatest risk for liver steatosis at disease onset and liver fibrosis progression after 5 years [175]. In particular, increasing liver fibrosis is known to be the strongest predictor for mortality in individuals with NAFLD [84, 155].

Literature additionally showed that individuals with advanced liver disease are at higher risk for CVD events [185]. Thus, NAFLD is not only tightly associated with T2D [73, 83], but also with CVD [79, 80, 82, 83, 185], which may be mainly due to the overlapping cardiometabolic risk factors (i.e. obesity, dyslipidemia, hypertension). Taken together, there is strong evidence that CVD are the most common cause of death in individuals with NAFLD [82, 83].

1.4 The global burden of cardiovascular diseases, diabetes and NAFLD

It has been noted that over the last decades the prevalences of CVD and CVD-related deaths have been increasing [1-3], which can be attributed to aging of the population, increasing of life expectancy, population growth but also increasing prevalence of cardiometabolic risk factors such as DM and altered lifestyle. Individuals generally present with high heterogeneity of metabolic features such as IR and ectopic fat deposition, specifically NAFLD. DM and NAFLD represent major risk factors for CVD and HF, and are additionally associated with higher mortality and morbidity [64, 65, 68, 79]. These features represent primary factors in the diagnostic and therapeutic decision, since it has been shown that distinct treatment procedures (i.e. lifestyle changes, choice of medication) have positive impact on the prognosis. Furthermore, in the last years advances have been made in identifying novel diabetes phenotypes with susceptibility to development of DM and diabetes-related complications such as CVD and NAFLD [71, 95, 139]. These studies pave the road to precise, individualized prevention and therapy and fundamentally inspired the *DISTEMI* study as well as the current analyses.

2. Hypotheses

Against the complex background of disturbed inter-organ crosstalk in the context of CVD, DM and NAFLD, the present work tested the following hypotheses:

1. Individuals after recent STEMI have (i) lower LVEF, (ii) higher degree of IR and (iii) higher estimates of NAFLD compared to event-free individuals of similar gender, BMI and HbA1c.
2. Individuals with recent STEMI are at high risk for development of recent onset IGM and T2D, and progression of IR, HF and NAFLD within the first year after STEMI.

These hypotheses were tested in a study cohort of participants of the "**DI**abetes and **ST**-segment **E**levation **M**yocardial **I**nfarction" (*DISTEMI*) Study and the **G**erman **D**iabetes **S**tudy (*GDS*), both conducted at the German Diabetes Center (GDC) in Düsseldorf.

The hypotheses were tested in a cross-sectional approach in a cohort of 49 participants with STEMI (*DISTEMI* cohort) compared to a cohort of 49 participants without myocardial infarction (*GDS* subcohort). Furthermore, in a longitudinal approach, 42 of 49 participants of the *DISTEMI* study were followed up for one year.

3. Material and Methods

3.1 Diabetes and ST-segment elevation myocardial infarction (*DISTEMI*) Study

The *DISTEMI* study is a monocentric, ongoing prospective observational cohort study describing the impact of metabolic features such as insulin resistance on the course of STEMI. The overarching aim of the study is to characterize in detail the functional and metabolic phenotype in order to

(1) assess the impact of IR and ectopic fat distribution i.e. NAFLD on cardiac outcomes (i.e. myocardial infarct size, contractile function)
(2) investigate the risk for progression of HF, IR and NAFLD after recent STEMI
(3) improve risk assessment algorithms for the design of individualized interventional strategies and subsequent targeted management in line with the concept of precision medicine.

The *DISTEMI* study is approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University (HHU) of Düsseldorf (reference number: 2018-213-KFmgU, registry ID: 2018104839) and registered at Clinicaltrials.gov (registration number: NCT05046483). All procedures conformed to the World's Medical Association Declaration of Helsinki, current (2013) version. All participants gave written informed consent prior to inclusion into the trial. The *DISTEMI* study is funded by a Research Network SFB 1116 of the German Research Foundation [186]. The funding sources have no role in study design, data collection, data analysis, data interpretation, or data publication.

3.1.1 Study design and population

The study comprises deep functional and metabolic phenotyping as well as tissue-specific in vivo and ex vivo studies, with a special focus on the liver. Investigations take place six till twelve weeks (baseline, visit 1, V1) and one year after STEMI (follow-up, visit 2, V2) at the Clinical Research Center (CRC), Institute for Clinical Diabetology, GDC, Leibniz Institute for Diabetes Research at HHU Düsseldorf. The timeline of events and investigations within the first year post-STEMI is shown in Figure 1.

Figure 1. Timeline after myocardial infarction in the population of the "DIabetes and ST-segment elevation Myocardial Infarction" (*DISTEMI*) study

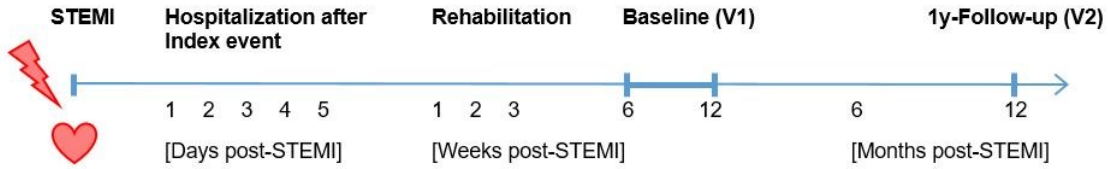


Figure Legend: Events and investigations within the first year after recent ST-segment elevation myocardial infarction for participants of the DISTEMI study. Numbers refer to times (days, weeks, months) after the index event. DISTEMI, participants with and without Diabetes and STEMI; STEMI, ST-segment elevation myocardial infarction; V1, visit 1; V2, visit 2; y, year.

The main inclusion criterion for participating in the *DISTEMI* study was the condition after recent STEMI, while individuals with NSTEMI and recurrent MI, among others, were not included. A summary of the inclusion and exclusion criteria for participating in the *DISTEMI* study is shown in Table 5.

Table 5. Key inclusion and exclusion criteria of the "Dlabetes and ST-segment elevation Myocardial Infarction" (*DISTEMI*) study

Inclusion criteria	- Condition after new onset of STEMI - Age from ≥18 to ≤80 years - Individuals with DM diagnosis according to ADA and DDG criteria (i.e. HbA1c ≥6.5% or pathological OGTT) - Healthy individuals with normal glucose tolerance status (i.e. HbA1c <5.7% and normal OGTT) - Individuals with prediabetes (i.e. HbA1c 5.7-6.4% and/or IFG and/or IGT) - Consent-able, hemodynamically stable individuals, without sedation (e.g. opiates) or other interfering medications (e.g. catecholamines)
Exclusion criteria	- Poor glycemic control (HbA1c ≥9.0% (≥75 mmol/mol)) - Diabetes mellitus due to other causes (e.g. pancreatogenic) - Gestational diabetes, Pregnancy - Acute infections / fever, Infectious disease - Immunosuppressive therapy - Acute and chronic heart, renal or liver failure (e.g. NYHA class ≥2, serum creatinine ≥1.6 mg/dl, AST and/or ALT above twice the reference range) - Peripheral artery occlusive disease stage IV - Severe chronic psychiatric illness or addiction - Active malignant diseases - Participation in an intervention trial

Table Legend: Specific inclusion and exclusion criteria for participation in the DISTEMI study. STEMI, ST-segment elevation myocardial infarction; DM, diabetes mellitus; ADA, American Diabetes Association; DDG, Deutsche Diabetes Gesellschaft / German Diabetes Society; HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NYHA, New York Heart Association; AST, aspartate-aminotransferase; ALT, alanine-aminotransferase.

3.1.2 Cohort of *DISTEMI*

In the period from November 10th, 2018 until February 18th, 2021, 343 individuals suffering from recent STEMI were hospitalized at the University hospital of the HHU Düsseldorf. Within a few years, the Department of Cardiology, Pulmonology, and Vascular Medicine under the direction of Univ.-Prof. Dr. Malte Kelm, successfully implemented an allcomer cohort of participants with STEMI, who undergo comprehensive cardiac phenotyping (*SYSTEMI* study – systemic organ communication in STEMI) within the first week and six months after STEMI.

A subcohort of these participants underwent detailed metabolic phenotyping by participating in the *DISTEMI* study.

Until begin of May 2021, 66 suitable candidates, prescreened at the University Hospital Düsseldorf, were recruited for participation in the *DISTEMI* study. Of these, 49 participants completed the first visit. Thus, the baseline inclusion rate was 14.3%. One year after the event, 42 participants also completed the second visit. Consequently, the drop-out rate at follow-up was 14.3%. The state of recruitment is shown in Figure 2. The main exclusion criterion for participating in the *DISTEMI* study is the presence of additional severe diseases (e.g. chronic renal failure, severe depression, dementia, stroke). Detailed information about the participants' characteristics is provided in the Results section and in Table 9 and 10.

Figure 2. Recruitment of participants with and without diabetes mellitus after recent ST-segment elevation myocardial infarction (STEMI) for participation in the *"Diabetes and STEMI" (DISTEMI)* study at the German Diabetes Center in Düsseldorf

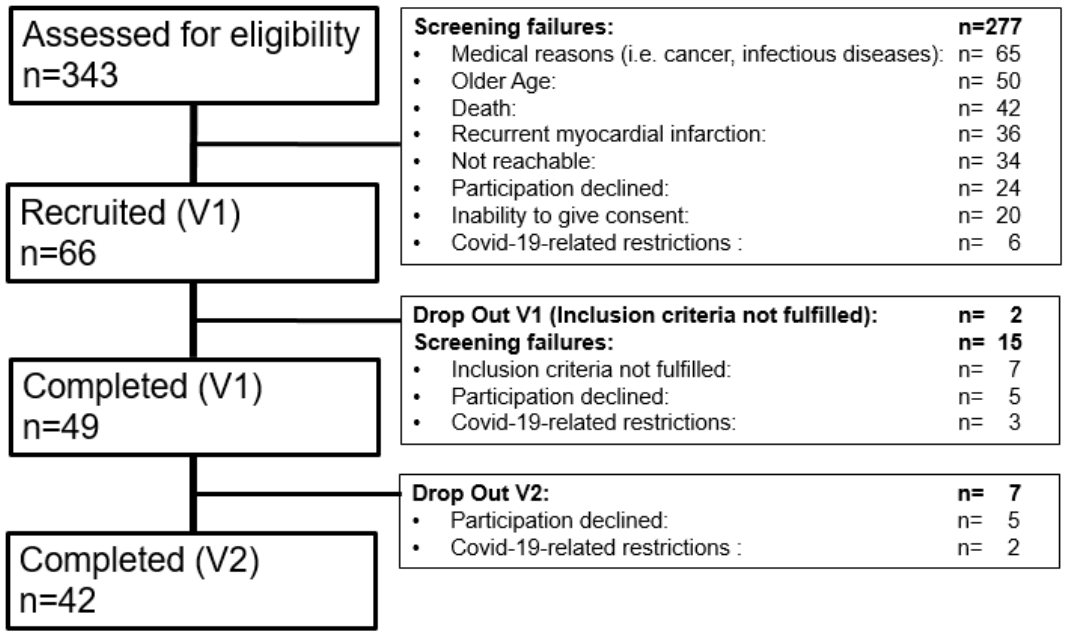


Figure Legend: Recruitment of participants with and without diabetes mellitus (DI) after recent ST-segment elevation myocardial infarction (STEMI) in the period from November 10th, 2018 until February 18th, 2021, hospitalized at the University Hospital of the Heinrich-Heine-University Düsseldorf, recruited and screened for participation in the DISTEMI study at the German Diabetes Center in Düsseldorf. V1, visit 1 / baseline; V2, visit 2 / 1-year follow-up.

3.2 German Diabetes Study (*GDS*)

The *German Diabetes Study* (*GDS*) is a multicentric, ongoing prospective observational cohort study conducted at the GDC for more than 15 years. The *GDS* aims to identify diabetes subphenotypes and prognostic factors and mechanisms underlying the development of diabetes-related complications and comorbidities [95, 187]. The *GDS* is approved by the ethics committee of the Medical Faculty of the HHU of Düsseldorf (reference number: 4508), registered at Clinicaltrials.gov (registration number: NCT01055093) and performed according to the Declaration of Helsinki, current (2013) version. Written informed consent was obtained from all study participants prior to inclusion into the trial. The *GDS* was initiated and financed by the GDC (which is funded by the German Federal Ministry of Health and the Ministry of Culture and Science of the state of North Rhine-Westphalia), the German Diabetes Association, the German Federal Ministry of Education and Research (to the German Center for Diabetes Research), the Research Network SFB 1116 of the German Research Foundation, and the Schmutzler Stiftung.

3.2.1 Study design and population of *GDS*

Individuals, aged 18-69 years, with recent onset (<12 months) of T1D or T2D and healthy controls without family history of DM are included in the *GDS* and are followed for at least 20 years at 5 years-intervals and annual telephone interviews in between [95]. Exclusion criteria are the same as for the *DISTEMI* study, as described in Table 5. Intensive phenotyping includes assessment of insulin secretion, insulin sensitivity, whole-body fat distribution, tissue specific lipid deposition and analyses of micro- and macrovascular morphology and function, among others [95] .

3.2.2 Subcohort of *GDS*

The control cohort of individuals without MI (MI-) consists of participants of the *GDS*. The main inclusion criterion for participating in the control cohort is the non-existence of any previous MI. Participants of the *GDS* underwent the same examinations, as participants of the *DISTEMI* cohort. The methods and the required materials for both cohorts are described in 3.3. For the analyses of the current study, a total of 49 *GDS* participants, for whom M-value and MR examinations were available, were included. Detailed information about the participants' characteristics is provided in the Results section and in Table 9.

3.3 Methods applied in the *DISTEMI* and *GDS* cohort

Data collection was performed in the CRC at the GDC according to a standard protocol at baseline and follow-up. All participants were comprehensively characterized by detailed anamnesis, which includes PA, nutrition and consumption habits, social status and aspects of quality of life, depression and congestive function, by physical examination and determination of multiple clinical-chemical parameters. OGTT enabled identification and monitoring of the glucometabolic spectrum. Insulin sensitivity was assessed by the hyperinsulinemic-euglycemic clamp test and estimates of HOMA. Cardiac variables were assessed by ^{1}H-MRI at the GDC. Estimates of NAFLD including the fatty liver index, fibrosis 4 score and NAFLD fibrosis score were calculated from routine laboratory variables and anthropometric parameters.

3.3.1 Oral glucose tolerance test (OGTT)

All participants, except those with T2D from the *GDS*, underwent a 75-g OGTT after an overnight fasting of at least 10 hours. Furthermore, the OGTT is not performed if FBG is greater than 250 mg/dl. Participants, who take diabetes medication, had stopped their oral antidiabetic drugs three days prior to the study day and/or applyed the last insulin injection no later than the evening before the study day. After drinking a glucose load equivalent of 75 g anhydrous glucose dissolved in 300 ml water (ACCU-CHEK® Dextrose O.G-T., Roche Diagnostics, Mannheim, Germany or NRF 13.8 Glucose-Solution 250 mg/ml for OGTT, University Hospital Düsseldorf - Central pharmacy, Düsseldorf, Germany) within 5 minutes [188], blood samples were collected in fixed time intervals over the next three hours (0, +10, +20, +30 min. followed by 30-min.-intervals until +180 min.). At every time point, BG, insulin and CP levels were measured.

3.3.2 Classification of the glucose tolerance status

The glucose tolerance status was classified according to the criteria of the ADA [92] and German Diabetes Society [189] based on FPG, 2h-PG during 75-g OGTT, random PG and/or HbA1c criteria. T2D was defined by the absence of diabetes-specific (auto-)antibodies, and levels of FPG ≥126 mg/dl (≥7.0 mmol/l), 2h-PG or random PG ≥200 mg/dl (≥11.1 mmol/l) and/or HbA1c ≥6.5% (≥48 mmol/mol) [92, 189]. IGM was defined by IFG and/or IGT and/or HbA1c 5.7-6.4% [92, 189]. IFG was defined as FPG levels 100-125 mg/dl (5.6-6.9 mmol/l) and IGT as 2h-PG levels 140-199 mg/dl (7.8-11.0 mmol/l) [92, 189]. Participants with levels of FPG <100 mg/dl (<5.6 mmol/l), 2h-PG <140 mg/dl (<7.8 mmol/l) and HbA1c <5.7% (<39 mmol/mol) were classified as normal glucose tolerant (NGT).

3.3.3 Anthropometric measurements

Body height (in cm) and body weight (BW, in kg) were measured by a scale with stadiometer (SECA 764; SECA, Hamburg, Germany). WC was assessed manually using a non-stretchable tape according to WHO guidelines [190]. WHR was calculated by dividing WC at its narrowest point by hip circumference at the widest point. The BMI was calculated as BW in kilograms divided by height in meters squared, as recommended by the WHO [191]. The BP was measured in supine position following 10-min rest on both arms and both legs.

3.3.4 Laboratory measurements

Routine laboratory variables (e.g. PG, HbA1c, cholesterol levels) were analyzed in a centralized laboratory (GDC, Düsseldorf, Germany), as previously described [187]. Following standard operating procedures, all participants underwent an identical protocol for blood sampling. Participants were under at least 10-hours fasted condition. After inserting a venous catheter in the antecubital vein of the right or left arm, blood samples were taken and collected in tubes. After centrifugation, the serum and plasma samples were directly analyzed or frozen and stored at -80°C until further analysis. Glycated HbA1c was measured by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories, Feldkirchen, Germany). PG concentrations were measured locally using a hexokinase method (Cobas C311; Roche Diagnostics, Mannheim, Germany). Serum concentrations of insulin and CP were analyzed chemoluminimetrically, FFA microfluorimetrically and cholesterol levels (total blood cholesterol (TC), LDL-C, HDL-C, and TG) by using an autoanalyzer (Cobas C311; Roche Diagnostics). FLI, NFS and FIB-4 scores were calculated from routine laboratory parameters and used to describe NAFLD [162].

3.3.5 Assessment of insulin resistance

Estimates of HOMA, calculated from CP and FPG, were used to assess IR during fasting (HOMA2-IR) [192]. The calculation was performed using the HOMA2-IR online calculator downloaded from https://www.dtu.ox.ac.uk.

Estimates of adipose-tissue insulin sensitivity (Adipo-IR) were calculated as the product of fasting concentrations of insulin and FFA [193].

3.3.6 Intravenous glucose tolerance test (IVGTT) and Hyperinsulinemic-euglycemic clamp (HEC) test

The modified Botnia clamp test was performed to measure insulin secretion and endogenous insulin sensitivity. This test consists of an intravenous glucose tolerance test (IVGTT), for testing of beta-cell function, followed by a hyperinsulinemic-euglycemic clamp (HEC) test [187, 194], with frequent measurements of BG, CP and insulin. For the measurement of tissue specific insulin sensitivity in human individuals, the glucose clamp technique, developed by DeFronzo et al. in 1979 [195], and widely accepted as the gold standard method, was used.

All participants were under fasted condition for at least 10 hours and instructed to refrain from PA three days prior to the study day. Oral diabetes medication had to be stopped three days prior to the study day. The last insulin injection, if needed, was applied no later than the evening before the study day. The test was started by inserting venous catheters in the antecubital vein of each arm for blood sampling (right side) and infusion of saline, insulin and glucose (left side). A primed intravenous infusion of saline was started at minute -120'. After a 10-min-bolus [ml/h; 0.06 * BW (in kg) * fasting BG (mg/dl)] a constant infusion rate [ml/h; 0.54 * BW (in kg)] remained unchanged until the end of the HEC. During the IVGTT, the first and second phase of insulin and CP secretion were detected by taking multiple blood samples after a standardized glucose bolus. The IVGTT was started at min 0' by injecting an intravenous 30% glucose bolus of 1 ml/kg BW, within 30 seconds into the venous catheter on the left side. For the first 10 minutes' blood samples were taken every 2 minutes ("first phase") and thereafter every 10 minutes up to 60 minutes ("second phase") after the glucose bolus. Thereafter, the HEC was started by applying an intravenous 10-min-bolus [10 mIU * kg BW^{-1} * min^{-1}] of short-acting human insulin (Insuman rapid 100 U/ml; Sanofi, Frankfurt, Germany), followed by constant infusion [1.5 mIU * kg $(BW)^{-1}$ * min^{-1}] until the end of the HEC. During the 180-minutes HEC, a continuous insulin infusion was used to achieve hyperinsulinemic BG levels in order to increase glucose uptake in muscles cells and adipose tissue and to suppress glucose production in the liver. The BG level was kept constant in euglycemic range by a variable 20% glucose infusion rate (GIR), in order to achieve a steady state for at least over the last 30 minutes of the HEC. To this end, BG levels were measured every 5 minutes and blood samples for measuring insulin and CP levels were taken in fixed time intervals.

Whole-body insulin sensitivity (M-value, expressed as $mg*kg^{-1}*min^{-1}$) was assessed from mean GIR with space correction (SC) during steady state conditions of the HEC [187]. Whole body insulin sensitivity is mainly reflected by skeletal muscle [196], which is responsible for ~80% of insulin-stimulated glucose uptake [197]. The M-value was calculated as follows:

M-value without SC:	M	= (GIR, ml/h * 200, mg/ml) / (BW, kg * 60, min/h)
SC:	SC	= (BG (end - start), mg/dl * 1.9, dl/kg) / (time (end - start), min)
M-value with SC:	M_{SC}	= M - SC

M-values less than 4.7 $mg*kg^{-1}*min^{-1}$ were considered the cut-off for diagnosing insulin resistance, according to Bergman et al. [198]. A collection of mean M-values of whole-body insulin sensitivity under various metabolic conditions is shown in Table 6 [95, 199, 200].

Table 6. Representative M values from hyperinsulinemic-euglycemic clamp tests under various metabolic conditions

Metabolic characteristics	*M ($mg*kg^{-1}*min^{-1}$)*	*References*
Athletes	10.0 ± 0.8	Yki-Jarvinen & Koivisto 1983
Healthy with normal weight	7.1 ± 2.1	Ferrannini et al. 1997
Healthy with obesity	5.5 ± 2.0	Ferrannini et al. 1997
Impaired glucose tolerance with overweight	5.4 ± 0.9	Bavenholm et al. 2001
Elderly (aged 69 years)	3.8 ± 0.5	Fink et al. 1983
Type 2 diabetes with		
• moderate glycemic control	4.7 ± 1.4	Bavenholm et al. 2001
• poor glycemic control	2.7 ± 0.4	Doberne et al. 1982
Newly diagnosed (duration <12 months)		Simon et al. 2019
• Type 1 diabetes	7.8 [6.0 - 9.8]	
• Type 2 diabetes	6.6 [5.0 - 8.5]	
Newly diagnosed (duration <12 months)		Zaharia et al. 2019
• Severe autoimmune diabetes	8.4 ± 3.2	
• Severe insulin-resistant diabetes	4.3 ± 2.0	
• Severe insulin-deficient diabetes	5.5 ± 2.4	
• Mild age-related diabetes	7.5 ± 2.5	
• Mild obesity-related diabetes	6.6 ± 2.6	

Table Legend: Assessment of insulin sensitivity based on M-values calculated from the hyperinsulinemic-euglycemic clamp-test under various metabolic conditions (i.e. normal weight, obesity, impaired glucose metabolism, novel diabetes endotypes). Data are presented as mean ± standard deviation or as the median (25^{th} and 75^{th} percentiles)). Adapted from M. Roden [199], Simon et al. [200] and Zaharia et al. [95].

3.3.7 Assessment of heart failure

HF was defined and classified according to the European Society of Cardiology guidelines [88] and the American College of Cardiology / AHA Clinical Data Standards [11], both published in 2021. The four established phenotypes of HF are presented in Table 7.

Table 7. Ejection fraction categories for clinical diagnosis of heart failure based on current guidelines [11, 88]

Definition	Left ventricular ejection fraction (%)
HF with preserved EF (HFpEF)	≥50
HF with mildly reduced EF (HFmrEF)	>40 and <50
HF with reduced EF (HFrEF)	≤40
HF with recovered EF (HFrecovEF)	≤40 in the past with improvement to ≥50

Table legend. Four phenotypes of heart failure, defined by different ejection fraction ranges. HF, heart failure; EF, ejection fraction. Adapted from the 2021 European Society of Cardiology Guidelines [88] and a report of the American College of Cardiology / American Heart Association Task Force on Clinical Data Standards in 2021 [11].

Each diagnosis of HF additionally requires the presence of HF related symptoms (e.g. breathlessness, fatigue, ankle swelling) and/or signs (e.g. hepatojugular reflux, third heart sound), whereas only the diagnosis of HFpEF also mandatory requires the presence of elevated NPs and other evidence of structural heart diseases (e.g. ECG and/or echocardiography with abnormalities) [88].

3.3.8 ^{1}H-magnetic resonance imaging

MR measurements at the GDC were performed after an overnight fasting in a 3.0 Tesla whole-body MR scanner (Achieva dStream X-series, Philips Healthcare, Best, The Netherlands), a non-invasive technique without ionizing radiation. All participants had to give informed consent prior to the MR measurements. No contrast agent or sedative was applied before or during the measurement. Specific exclusion criteria, as presented in Table 8, were checked previously.

Table 8. Specific exclusion criteria for magnetic resonance measurements at the German Diabetes Center

Specific exclusion criteria for MR measurements
- Pregnancy
- Cardiac pacemaker
- Non-MR-compatible metallic and magnetic implants (e.g. mechanical heart valves, joint prostheses, middle and inner ear implants)
- Waist circumference >135 cm
- Claustrophobia

Table legend: Specific criteria for exclusion from magnetic resonance measurements at the German Diabetes Center in the population of the DISTEMI (DIabetes and ST-segment elevation myocardial infarction) study and the German Diabetes Study (GDS). MR, magnetic resonance.

Participants of both cohorts underwent cardiac ^{1}H-MRI for the determination of cardiac functional variables. The 4-chamber plane was planned by acquiring a series of sensitivity encoding balanced turbo field echo cine MR scans. For the characterization of LV structure and function, a short axis multislice balanced turbo field echo cine MR scan (repetition time/echo time = 2.9/1.5 ms, 10 mm of slice thickness, matrix size 320×320 mm^2 and temporal resolution of ~30 ms between the phases) was set to cover the volume from the base to the apex. LV volumes were determined at end systole and end diastole and manually segmented on ImageJ software [201]. Stroke volume, LVEF and cardiac output were calculated as follows:

Stroke volume [ml]	= EDV - ESV
LVEF [%]	= (stroke volume / EDV) x 100
Cardiac output [ml/min]	= stroke volume x HR

3.3.9 Assessment of NAFLD

Firstly, the FLI, a surrogate parameter of liver steatosis, previously validated against the US-based method [159], was calculated as follows:

$$FLI = e^{y} / (1 + e^{y}) \times 100$$

$$y = 0.953 * \ln(TG, mg/dl) + 0.139 * BMI, kg/m^2 + 0.718 * \ln(GGT, U/l) + 0.053 * WC - 15.745$$

Liver steatosis was ruled out by values <30 and was ruled in by values ≥60, according to Bedogni et al. [202].

Secondly, the NFS, previously validated in individuals with NAFLD [160], was used to assess liver fibrosis. The score was calculated as follows:

NFS = -1.675 + (0.037 * age, years + (0.094 * BMI, kg/m^2 + (1.13 * IFG/diabetes (yes=1, no=0)) + (0.99 * AST/ALT ratio) – (0.013 * platelet count, x10^9/l) – (0.66 * albumin, g/dl)

Advanced liver fibrosis was ruled out by values <-1.455 and was ruled in by values >0.676, according to Angulo et al. [160].

Thirdly, the FIB-4 score was used to identify/exclude advanced fibrosis (stage 3 or 4 fibrosis), previously validated in individuals with NAFLD [161]. The score was calculated as follows:

FIB-4 score = (Age * AST) / (Platelets * √(ALT))

According to McPherson et al. [161], values >2.67 indicate an increased risk for advanced liver fibrosis.

3.3.10 Statistics

In the current analyses, data are presented as means with standard deviation (SD) for continuous variables and percentages (%) or absolute numbers (n) for categorical variables. Participations of both cohorts (*DISTEMI* and *GDS*) were stratified into three subgroups according to their degree of glucose tolerance (NGT, IGM or T2D). Matching was performed for sex, BMI and HbA1c. Participants with T2D were further matched for diabetes duration.

To account for multiple group comparisons, one-way analysis of variance (ANOVA) with Tukey-Kramer correction was used. Comparisons between baseline and follow-up within the *DISTEMI* cohort were calculated by using paired t-test. All reported P values were nominal and two-sided with a 95% confidence interval. Statistically differences or correlations were considered significant with P values of less than 5%.

Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, North Carolina, USA). Chi-square analysis were performed using online calculator from https://www.socscistatistics.com/tests/chisquare/. Figures were drawn using GraphPad PRISM (version 9.0.1; GraphPad Software, San Diego, California, USA) and using https://www.sankeymatic.com.

4. Results

4.1 Participants' characteristics at baseline

4.1.1 Anthropometric and clinical characteristics of the study population at baseline

For the baseline analysis, a total of 49 participants of the *DISTEMI* study (MI+) and likewise 49 participants of the *GDS* (MI-) were included. Inclusion rate from the larger *SYSTEMI* cohort at the University Hospital of the HHU Düsseldorf was 14.3%. Anthropometric and clinical data at baseline are shown in Table 9.

Table 9. Participants' characteristics at baseline

Variable	*DISTEMI* cohort (MI+)			*GDS* subcohort (MI-)		
	NGT	IGM	T2D	NGT	IGM	T2D
Number (n, % female)	15 (33)	19 (21)	15 (20)	15 (33)	19 (21)	15 (20)
Diabetes duration (mo)	--	--	51±83	--	--	52±52
Age (years)	63.3±9.6	57.6±8.1[h]	62.8±8.0	62.3±8.1	63.7±6.5[h]	60.0±7.9
BMI (kg/m^2)	26.5±3.0	27.5±3.5	28.3±2.0	26.1±2.8	28.5±2.9	28.0±4.3
WC (cm)	94±12	102±9[h]	98±8	95±8	95±7[h]	101±9
WHR (a.u.)	0.91±0.08	0.94±0.07	0.98±0.08	0.92±0.09	0.97±0.06	0.97±0.05
HbA1c (%)	5.4±0.2[a,b]	5.7±0.2[a,c]	7.1±1.3[b,c]	5.2±0.3[d,e]	5.6±0.4[d,f]	6.5±1.0[e,f]
HbA1c (mmol/mol)	36±3[a,b]	39±3[a,c]	54±15[b,c]	34±3[d,e]	38±4[d,f]	48±11[e,f]
Adipo-IR (a.u.)	26±15[a]	38±21	83±72[a]	26±21	30±27	75±95
Fasting FFA (µmol/l)	380±130	391±117	500±193	406±133	389±158	432±162
Fasting TG (mg/dl)	93±46	103±42	126±86	130±121	120±45	127±71
TC (mg/dl)	134±31[g]	131±25[h]	120±24[i]	217±46[g]	205±32[h]	183±31[i]
LDL-C (mg/dl)	72±24[g]	73±17[h]	62±17[i]	141±45[g]	137±31[h]	117±26[i]
HDL-C (mg/dl)	53±13	49±15	44±13	70±31	56±14	50±15
AST (U/l)	26±7	28±8	30±18	26±16	23±7	23±5
ALT (U/l)	30±13	40±22[h]	33±23	33±40	26±13[h]	29±14
GGT (U/l)	52±71	38±31	71±73[i]	25±19	38±41	28±16[i]
Creatinin (mg/dl)	0.88±0.18	0.95±0.20[c]	0.83±0.20[c,i]	0.88±0.16	0.96±0.13	0.93±0.19[i]
Hemoglobin (g/dl)	13.3±1.6[g]	13.7±1.4	13.3±1.3[i]	14.4±1.1[d,g]	13.9±0.8[d]	14.4±1.0[i]
hsCRP (mg/dl)	0.2±0.3	0.3±0.5	0.4±0.4	0.1±0.1	0.2±0.2	0.2±0.3
EDV (ml)	123±42	128±30	149±59	103±29	114±25	100±20
ESV (ml)	64±30	66±28	97±67	43±18	49±13	44±14
Stroke volume (ml)	59±19	62±16	52±16	60±15	64±16	56±10
Cardiac output (l/min)	3.0±0.9	3.3±0.7	3.2±1.0	3.3±1.0	3.5±0.8	3.3±0.9
Smoker, ever (n, %)	8 (50)	15 (79)	13 (87)	7 (47)	12 (63)	9 (60)
Smoker, current (n, %)	3 (20)	6 (32)	2 (13)	3 (20)	2 (11)	5 (33)
Hypertension* (n, %)	14 (93)	17 (89)	13 (87)	7 (47)	11 (58)	13 (87)
Lipid-lowering th (n, %)	12 (80)	19 (100)	15 (100)	0 (0)	2 (11)	2 (13)
Antihyperglycemic th** (n, %)	--	--	10 (67)	--	--	10 (67)

Table legend: Data are presented as mean±SD, percentages (%) or absolute numbers (n). Data are analyzed by ANOVA General Linear Models with Tukey-Kramer adjustment for sex, age and BMI between participants within the same cohort and paired t-test between matched participants (MI+ vs. MI-). MI, myocardial infarction; GDS, German Diabetes Study; NGT, normal glucose tolerance; IGM, impaired glucose metabolism including impaired fasting glucose, impaired glucose tolerance and/or HbA1c 5.7-6.4%; T2D, type 2 diabetes; mo, months; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip-ratio; Adipo-IR, adipose tissue insulin resistance; FFA, free fatty acids; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ALT, alanin-aminotransferase; AST, aspartat-aminotransferase; GGT, gamma-glutamyltransferase*; hsCRP, high sensitive C-reactive protein; EDV, end-diastolic volume; ESV, end-systolic volume; a.u., arbitrary unit; *, blood pressure systolic ≥140 mmHg and/or diastolic ≥90 mmHg and/or under anti-hypertensive therapy; th, therapy; **, oral antidiabetic drugs and/or glucagon-like peptide-1 analoga and/or insulin therapy. a, p<0.05: MI+, NGT vs. IGM; b, p<0.05: MI+, NGT vs. T2D; c, p<0.05: MI+, IGM vs. T2D; d, p<0.05: MI-, NGT vs. IGM; e, p<0.05: MI-, NGT vs. T2D, f, p<0.05: MI-, IGM vs. T2D; g, p<0.05: NGT, MI+ vs. MI-; h, p<0.05: IGM, MI+ vs. MI-; i, p<0.05: T2D, MI+ vs. MI-.*

4.1.2 Cardiometabolic risk factors at baseline

In MI+, mean age was 61.0±8.8 years at V1. Age in MI+ was comparable between participants with different degrees of glucose tolerance, as listed in Table 9. Age was also comparable between MI+ and MI- within total cohort comparison (p=0.30) and also between MI+ and MI- among participants with NGT (p=0.18) and T2D (p=0.30). In IGM, participants with MI+ were younger compared to MI- (p<0.001). The proportion of women in MI+ was further 24.5%. Within the entire MI+ cohort, 30.6% had NGT, 38.8% had IGM and 30.6% had T2D.

In T2D, HbA1c levels and diabetes duration were similar between MI+ and MI-, as listed in Table 9. In MI+/T2D, 60.0% (n=9) had excellent glycemic control, defined by HbA1c <7.0% (53 mmol/mol) according to the current ADA guideline [50]. In contrast, in MI-/T2D 73.3% (n=11) had excellent glycemic control.

In MI+, prevalence of new onset of T2D within the last 12 months was 46.7% (n=7). In T2D, 33.3% (n=5) in both cohorts were under lifestyle modification. Among participants with T2D treated with antihyperglycemic drugs, Metformin was used in 90% (MI+) and 80% (MI-). Sodium glucose cotransporter-2 inhibitors were used in 20% in MI+ and 10% in MI-.

After analyzing the cardiovascular risk factors, WHR was similar between MI+ and MI- within total cohort comparison [p=0.22], and also between both cohorts among participants with NGT [p=0.47], IGM [p=0.13] and T2D [p=0.82] (Table 9).

MI+ had lower levels of TC [p<0.001], LDL-C [p<0.001] and HDL-C [p=0.004], but similar fasting TG levels [p=0.21], compared to MI- within total cohort comparison. Levels of TC and LDL-C were also lower in MI+ compared to MI- among participants with NGT, IGM and T2D, however levels of HDL-C were similar between both cohorts in relation to NGT, IGM and T2D, as listed in Table 9. In both cohorts, LDL-C levels were similar between participants with NGT, IGM and T2D. According to current guidelines [53], individuals with MI had to achieve LDL-C levels of at least less than 55 mg/dl (<1.4 mmol/l). In MI+, 16.3% (n=8) reached this target at V1, of whom everyone was under lipid-lowering therapy. Overall, in MI+, 93.9% (n=46/49) were under lipid-lowering therapy. In MI-, 23.5% (n=8/34) among those without T2D reached the target for individuals at low cardiovascular risk, defined as LDL-C levels <116 mg/dl (<3.0 mmol/l) according to current guidelines [53]. In MI-/T2D, 40.0% (n=6/15) had LCL-C levels <116 mg/dl, of whom, 13.3% (n=2) were treated with lipid-lowering drugs (e.g. statins).

Furthermore, MI+ were more likely to reach the BP target, defined as systolic <140 mmHg and/or diastolic <90 mmHg, compared to MI- (73.5 vs. 49.0%, p=0.01). MI+ were also more likely to be under anti-hypertensive treatment compared to MI- (79.6 vs. 30.6%, p<0.001). Only in T2D, prevalence of anti-hypertensive treatment was similar between MI+ and MI- (80.0 vs. 60%, p=0.23).

4.1.3 Insulin resistance at baseline

MI+ had greater insulin resistance compared to MI-, by showing 15.5% lower M-values [7.1±2.6 vs. 8.4±2.5 mg*kg^{-1}*min^{-1}, p<0.001] and 35.3% higher estimates of HOMA2-IR [2.3±1.3 vs. 1.7±0.7 a.u., p=0.005], on average, in total cohort comparison.

In MI+, mean M-values were 13.6% lower in NGT [8.9±1.9 vs. 10.3±2.2 mg*kg^{-1}*min^{-1}, p=0.049] and 36.4% lower in T2D [4.2±1.5 vs. 6.6±2.2 mg*kg^{-1}*min^{-1}, p=0.002], but similar in IGM [7.6±2.2 vs. 8.3±2.0 mg*kg^{-1}*min^{-1}, p=0.24], compared to MI- with similar glucose tolerance (Fig. 3A). In T2D, MI+ were more likely to present with M-values less than 4.7 mg*kg^{-1}*min^{-1}, defined as cut-off for IR according to Bergman et al. [198], compared to MI- (60.0 vs. 6.7%, p=0.004). In both cohorts, participants with NGT showed higher M-values compared to participants with T2D [both: p<0.001].

In MI+, estimates of HOMA2-IR were, on average, 55% higher in T2D [3.1±1.7 vs. 2.0±0.9 a.u., p=0.04], but similar in NGT [1.7±0.9 vs. 1.5±0.7 a.u., p=0.41] and IGM [2.1±0.8 vs. 1.6±0.6 a.u., p=0.08], compared to MI- with similar glucose tolerance (Fig. 3B).

Estimates of Adipo-IR were also similar between MI+ and MI- within total cohort comparison [48±47 vs. 43±61 a.u., p=0.49], and among participants with NGT [p=0.69], IGM [p=0.12] and T2D [p=0.83] (Table 9). Only in MI+, participants with T2D had higher Adipo-IR estimates compared to participants with NGT [83±72 vs. 26±15 a.u., p=0.03].

Figure 3. Comparison of insulin sensitivity between participants with and without myocardial infarction under insulin-stimulated and fasted condition

(A) Whole-body insulin sensitivity (M-value) **(B) Fasting insulin sensitivity (HOMA2-IR)**

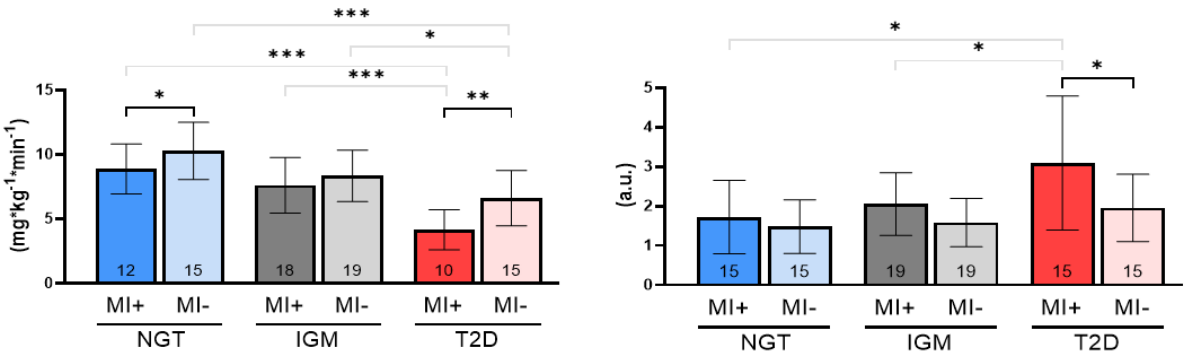


*Figure legends: Bar graphs of insulin sensitivity in participants with recent ST-segment elevation myocardial infarction (MI+) compared to participants without myocardial infarction (MI-). Assessment of whole-body insulin sensitivity (A), by calculation of the M-value, and homeostasis model assessment of insulin resistance during fasting (B). MI: myocardial infarction, NGT: normal glucose tolerance (blue bars), IGM: impaired glucose metabolism (grey bars), T2D: type 2 diabetes (red bars); a.u., arbitrary unit. Data are shown as mean ± SD. *p<0.05, **p<0.01, ***p<0.001.*

4.1.4 Cardiac variables at baseline

MI+ had lower LVEF [47±13 vs. 57±7%, p<0.001], higher EDV [130±43 vs. 106±25 ml, p=0.02] and ESV [72±42 vs. 46±15 ml, p=0.004], but similar stroke volume [58±17 vs. 60±14 ml, p=0.52] compared to MI-.

In MI+ compared to MI-, LVEF was lower among participants with NGT [49±10 vs. 59±8%, p=0.01] and T2D [39±17 vs. 57±8%, p=0.045], but did not differ among participants with IGM [50±12 vs. 57±6%, p=0.12] (Fig. 4A). In MI+, 53.3% had LVEF ≥50%, 20.0% had LVEF >40% and <50%, and 26.7% presented with LVEF ≤40%, the latter defined as cut-off for diagnosing HFrEF [11].

In MI+, participants with LVEF less than 50% presented with symptoms of HF (e.g. fatigue, tiredness). Thus, in MI+, the prevalence of HFrEF was 23.1% in NGT (n=3/13), 20.0% in IGM (n=2/10) and 42.9% in T2D (n=3/7) and was further comparable between NGT and T2D [p=0.36], NGT and IGM [p=0.86] and IGM and T2D [p=0.31]. In contrast, in MI- every participant had LVEF greater than 40% and presented without signs and symptoms of HF. In MI-, 85.7% had LVEF ≥50% and 14.3% had LVEF >40 and <50%.

EDV, ESV, stroke volume and cardiac output were further comparable between MI+ and MI- among participants with NGT, IGM and T2D, as presented in Table 9. At last, in MI+, mean infarct size was 17±13% of LV myocardial mass. The infarct size was further similar between participants with NGT and T2D [16±13 vs. 21±14%, p=0.81], NGT and IGM [16±13 vs. 15±12%, p=1.0] and IGM and T2D [15±12 vs. 21±14%, p=0.83] (Fig. 4B).

Figure 4. Comparison of cardiac function between participants with and without myocardial infarction and comparison of infarct size after recent myocardial infarction

(A) Left ventricular ejection fraction (LVEF) **(B) Myocardial infarct size**

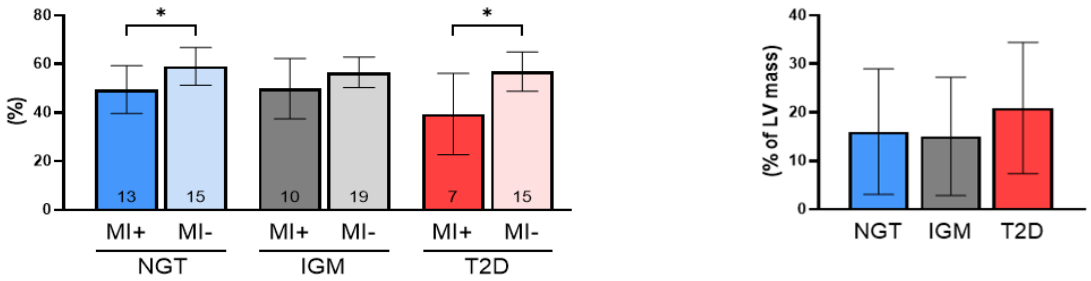


*Figure legends: Bar graphs of cardiac function (A) in participants with recent ST-segment elevation myocardial infarction (MI+) compared to participants without myocardial infarction (MI-). Bar graphs of myocardial infarct size (B) between distinct degrees of glucose tolerance. MI, myocardial infarction; NGT, normal glucose tolerance (blue bars); IGM, impaired glucose metabolism (grey bars); T2D, type 2 diabetes (red bars). Data are shown as mean ± SD. *p<0.05.*

4.1.5 Risk of NAFLD at baseline

MI+ had similar FLI [52±24 vs. 52±25 a.u., p=0.95] and FIB-4 scores [1.37±1.05 vs. 1.36±0.48 a.u., p=0.96], but lower NFS [-1.26±1.46 vs. -0.75±1.08 a.u., p=0.03] than MI- in total cohort comparison.

FLI were also comparable between MI+ and MI- among participants with NGT [44±26 vs. 41±26 a.u., p=0.75], IGM [49±23 vs. 60±22 a.u., p=0.12] and T2D [62±23 vs. 52±25 a.u., p=0.31] (Fig. 5A).

In MI+, 46.8% (n=22/49) had FLI ≥60, which is defined as cut-off for diagnosing liver steatosis [202]. In detail, 35.7% in NGT, 38.9% in IGM and 66.7% in T2D exceeded this cut-off. In contrast, in MI-, the cut-off was exceeded in 40.8% (n=20/49) within the entire cohort, 26.7% in NGT, 52.6% in IGM and 40.0% in T2D. Based on FLI, MI+ and MI- were further at the same risk for liver steatosis [p=0.68].

In MI+, participants with IGM had lower NFS compared to MI- [-1.62±1.49 vs. -0.35±0.84 a.u., p=0.003], whereas NFS were similar between MI+ and MI- among participants with NGT [-1.78±1.02 vs. -1.59±1.16 a.u., p=0.53] and T2D [-0.28±1.37 vs. -0.40±0.81 a.u., p=0.77] (Fig. 5B).

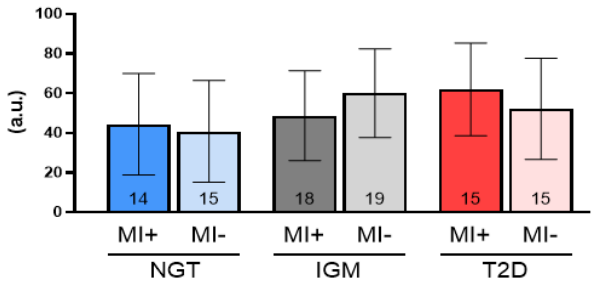
In MI+, 10.2% (n=5/49) had NFS greater 0.676, which is defined as cut-off, where advanced fibrosis is ruled in [160]. In contrast, in MI-, 6.1% (n=3/49) within the entire cohort exceeded this cut-off. The risk for advanced fibrosis, based on NFS, was further similar between MI+ and MI- [p=0.46]. In addition, in both cohorts, participants with NGT presented with lower NFS than participants with T2D [MI+: p=0.02, MI-: p<0.001].

At last, FIB-4 scores were lower in MI+ compared to MI- in participants with IGM [1.05±0.41 vs. 1.35±0.51 a.u., p=0.04], but similar between MI+ and MI- among participants with NGT [1.34±0.71 vs. 1.44±0.54 a.u., p=0.63] and T2D [1.81±1.63 vs. 1.29±0.39 a.u., p=0.22] (Fig. 5C).

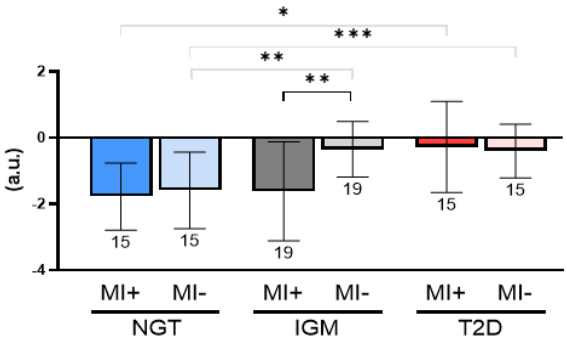
In MI+, 6.1% (n=3/49) presented with FIB-4 scores greater 2.67, which is defined as cut-off for diagnosing advanced fibrosis [161]. In contrast, in MI-, 4.1% (n=2/49) exceeded this cut-off. Risk for advanced fibrosis based on FIB-4 scores, was further comparable between MI+ and MI- [p=0.65].

Figure 5. Comparison of NAFLD estimates between participants with and without myocardial infarction

(A) Fatty liver index (FLI)



(B) NAFLD-Fibrosis Score (NFS)



(C) Fibrosis-4 (FIB-4) Score

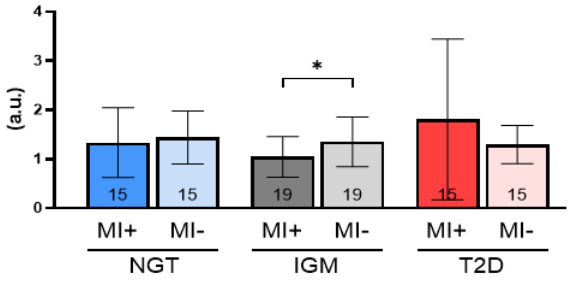


*Figure legends: Bar graphs for the comparison of risk for NAFLD, in particular liver steatosis, calculated by Fatty Liver Index (FLI) (A), and liver fibrosis, calculated by the Non-alcoholic fatty liver disease Fibrosis Score (NFS) (B) and Fibrosis-4 (FIB-4) Score (C), between participants with recent STEMI (MI+) compared to participants without myocardial infarction (MI-). MI, myocardial infarction; NGT, normal glucose tolerance (blue bars); IGM, impaired glucose metabolism (grey bars); T2D, type 2 diabetes (red bars); a.u., arbitrary unit. Data are shown as mean ± SD. *p<0.05; **p<0.01; ***p<0.001.*

4.2 *DISTEMI* participants' characteristics at baseline and follow-up

4.2.1 Anthropometric and clinical characteristics of the *DISTEMI* cohort

One year after STEMI, 42 participants of the *DISTEMI* study had also completed the second visit (V2). Therefore, the drop-out rate at V2 was 14.3%. Drop-out reasons are listed in Figure 2. The anthropometric and clinical data of those participants, who completed both visits, are shown in Table 10.

Table 10. *DISTEMI* participants' characteristics at baseline and 1-y follow-up

Variable	Baseline (V1)			1-y follow-up (V2)		
	NGT	IGM	T2D	NGT	IGM	T2D
Number (n, % female)	12 (33)	18 (22)	12 (17)	12 (33)	18 (22)	12 (17)
Diabetes duration (mo)	--	--	63±89	--	--	74±89
Age (years)	64.7±9.6	57.2±8.1	64.2±7.6	65.5±9.6	58.0±8.1	65.1±7.5
BMI (kg/m^2)	26.7±3.3	27.7±3.5	28.4±2.1	26.3±3.1	27.7±3.8	28.3±3.1
WC (cm)	94±9[a]	95±7	101±9	90±8[a]	94±10	98±9
WHR (a.u.)	0.91±0.08	0.94±0.08	0.98±0.08	0.97±0.25	0.94±0.04	0.97±0.09
HbA1c (%)	5.4±0.3[a]	5.7±0.2[b]	7.3±1.4	5.6±0.2[a]	6.0±0.2[b]	7.3±0.9
HbA1c (mmol/mol)	36±3[a]	39±3[b]	56±15	38±2[a]	42±2[b]	56±10
Adipo-IR (a.u.)	23±13	39±22	85±77	23±14	37±26	65±40
Fasting FFA (µmol/l)	404±120	393±121	518±196	363±181	347±144	528±295
Fasting TG (mg/dl)	79±32[a]	106±42	112±53	64±20[a]	105±60	115±73
TC (mg/dl)	134±34	130±25	114±16	129±17	130±29	123±41
LDL-C (mg/dl)	72±27	73±18	60±17	65±12	72±26	63±30
HDL-C (mg/dl)	55±13[a]	47±14	43±13[c]	60±11[a]	48±15	48±16[c]
AST (U/l)	26±7	28±9	29±20	26±7	29±12	23±12
ALT (U/l)	29±14	40±23	31±26[c]	29±11	36±27	22±18[c]
GGT (U/l)	36±26[a]	38±32[b]	55±59	25±13[a]	24±13[b]	46±41
Creatinin (mg/dl)	0.88±0.20	0.95±0.21	0.85±0.18[c]	0.88±0.14	0.94±0.21	0.95±0.23[c]
Hemoglobin (g/dl)	13.1±1.2	13.7±1.4	13.2±1.4	13.3±1.3	13.8±1.1	12.8±1.6
hsCRP (mg/dl)	0.2±0.2	0.3±0.5	0.3±0.2	0.3±0.9	0.2±0.1	0.2±0.3
EDV (ml)	129±36	130±30	128±25	123±35	133±35	140±33
ESV (ml)	67±28	68±28	74±32	68±26	66±31	89±39
Stroke volume (ml)	62±16	62±17	54±17	54±21	67±22	51±17
Cardiac output (l/min)	3.1±0.9	3.3±0.8	3.3±1.1	2.5±1.0	3.5±1.4	3.0±0.9
Smoker, current (n, %)	1 (8)	6 (33)	2 (17)	2 (17)	7 (41)	3 (25)
Hypertension* (n, %)	11 (92)	16 (89)	10 (83)	10 (83)	17 (94)	10 (83)
Lipid-lowering th (n, %)	10 (83)	18 (100)	12 (100)	11 (92)	16 (89)	11 (92)
Antihyperglycemic th** (n, %)	--	--	10 (83)	--	--	10 (83)

*Table legend: Data are presented as mean ± SD, percentages (%) or absolute numbers (n). Data are analyzed by paired t-test within the same glucometabolic status. NGT, normal glucose tolerance; IGM, impaired glucose metabolism ("prediabetes") including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or HbA1c 5.7-6.4 %; T2D, type 2 diabetes; V1, 6-12 weeks after ST-segment elevation myocardial infarction; V2, 1-year after ST-segment elevation myocardial infarction; mo, months; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip-ratio; Adipo-IR, adipose tissue insulin resistance; FFA, free fatty acids; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanin-aminotransferase; AST, aspartat-aminotransferase; GGT, gamma-glutamyltransferase; hsCRP, high sensitive C-Reactive Protein; EDV, end-diastolic volume; ESV, end-systolic volume; a.u., arbitrary unit; *, blood pressure systolic ≥140 mmHg and/or diastolic ≥90 mmHg and/or under anti-hypertensive therapy; th, therapy; **, oral antidiabetic drugs and/or glucagon-like peptide-1 analoga and/or insulin therapy. a, p<0.05: V1 vs. V2, NGT; b, p<0.05: V1 vs. V2, IGM; c, p<0.05: V1 vs. V2, T2D.*

4.2.2 Cardiometabolic risk factors one year after STEMI

First of all, one year after STEMI, all *DISTEMI* participants presented without a newly developed major adverse cardiovascular event (MACE) including all-cause death, recurrent MI and hospitalization for HF.

One year after MI, glycemia assessed by HbA1c became worse in participants with baseline NGT [p=0.03] and IGM [p<0.001], as listed in Table 10. In contrast, glycemic control in participants with T2D was similar between V1 and V2 [p=0.88].

In T2D, 41.7% (n=5/12) had excellent glycemic control on both visits by achieving HbA1c levels <7.0% (<53 mmol/mol). At V2, two participants newly achieved this cut-off and one participant´s glycemic control worsened and exceeded the cut-off, even if antihyperglycemic therapy remained unchanged in all three cases.

In NGT, 25% (n=3/12) newly developed IGM at V2. Among participants with NGT and IGM at V1, 10.0% (n=3/30) developed new onset of T2D, diagnosed by 75 g-OGTT at V2. Thus, prevalence of migration into a deteriorated glucometabolic status (IGM or T2D) one year after STEMI was 20.0%. The migration pattern within the glucometabolic spectrum one year after STEMI is shown in Figure 6.

Figure 6. Migration pattern across the glucometabolic spectrum one year after ST-segment elevation myocardial infarction (STEMI) in the population of the *DISTEMI* study

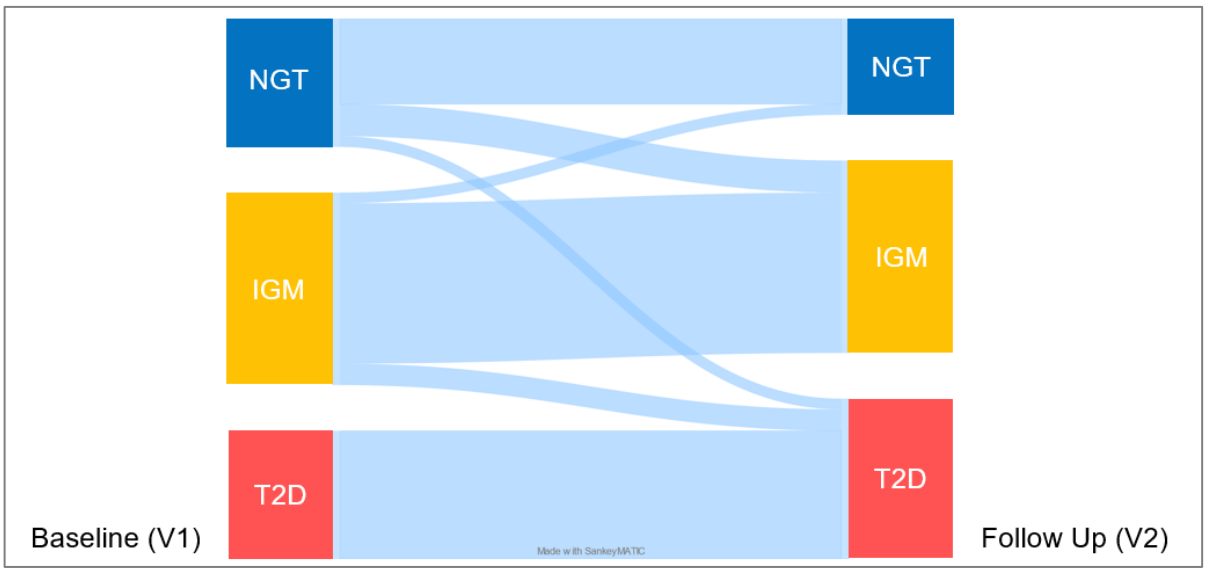


Figure legend. Migration pattern as Sankey plot across the glucometabolic spectrum one year after STEMI in the population of the DISTEMI study (participants with and without diabetes after recent STEMI). V1, 6-12 weeks after STEMI; V2, 1-year after STEMI; STEMI, ST-segment elevation myocardial infarction; NGT; normal glucose tolerance (blue); IGM, impaired glucose metabolism; T2D, type 2 diabetes (red).

Overall, BMI [27.6±3.1 vs. 27.5±3.5 kg/m^2, p=0.53] and WHR [0.94±0.08 vs. 0.96±0.14 a.u., p=0.34] were comparable between V1 and V2. As listed in Table 10, BMI and WHR were also comparable between V1 and V2 among participants with NGT, IGM and T2D, as listed in Table 10.

Similarly, levels of TC [126±26 vs. 128±30 mg/dl, p=0.78] and LDL-C [69±21 vs. 67±24 mg/dl, p=0.77] did not differ between V1 and V2 within total cohort comparison. TC and LDL-C were also comparable between both visits among participants with NGT, IGM and T2D (Table 10).

HDL-C was higher at V2 compared to V1 among all STEMI cases [V1 vs. V2: 48±14 vs. 52±15, p=0.003]. Higher HDL-C values at V2 were also seen among participants with baseline NGT [p=0.008] and T2D [p=0.002], whereas values did not differ among participants with IGM [p=0.61].

One year after STEMI, 26.2% (n=11/42) showed excellent lipid status with LDL-C levels <55 mg/dl (<1.4 mmol/l). Only 11.9% (n=5/42) achieved this target on both visits. Among all STEMI cases, 66.7% (n=28/42) showed LDL-C levels <70 mg/dl (<1.8 mmol/l) at V2.

The largest increase of achieving the target of LDL-C <55 mg/dl (<1.4 mmol/l) was seen among participants with T2D (V1 vs. V2: 25.0 vs. 41.7%). One participant with T2D, who achieved the target at V1 and lost it at V2, also discontinued lipid-lowering medication between both visits. In contrast, every participant, who was below this cut-off at V1 and/or V2, was under lipid-lowering therapy.

At V2, 28.6% (n=12/42) showed increased BP with systolic ≥140 mmHg and/or diastolic ≥90 mmHg. In contrast, in this analysis, prevalence of arterial hypertension at V1 was 23.8% (n=10/42). Two participants had stopped anti-hypertensive treatment during study participation, of whom one participant showed increased BP at V2. Furthermore, two participants, who exceeded the cut-off at V1 and also did not take lipid-lowering medication, newly achieved the target under anti-hypertensive therapy at V2.

In this analysis, 28.6% (n=12/42) among all STEMI cases were smoking one year after STEMI. Furthermore, prevalence of smoking at V2 was higher in females than in males (60.0 vs. 18.8%; n=6/10 vs. 6/32). Participants, who were smoking at V1 were still smoking at V2. In addition, one participant in each subgroup relapsed and started smoking again. On both visits, the highest prevalence of smoking was seen among participants with IGM. In this subgroup, prevalence of smoking was 33.3% at V1 (n=6/18) and 38.9% at V2.

4.2.3 Insulin resistance one year after STEMI

Overall, MI+ showed similar M-values between V1 and V2 [7.1±2.7 vs. 7.5±2.7 mg*kg^{-1}*min^{-1}, p=0.10]. M-values likewise did not differ between V1 and V2 among participants with NGT [n=10, 9.0±2.0 vs. 8.5±2.2 mg*kg^{-1}*min^{-1}, p=0.37], IGM [n=16, 7.4±2.2 vs. 8.3±2.4 mg*kg^{-1}*min^{-1}, p=0.09] and T2D [n=8, 4.0±1.6 vs. 5.3±2.5 mg*kg^{-1}*min^{-1}, p=0.06] (Fig. 7A).

On both visits, participants with NGT and IGM showed M-values greater or equal 4.7 mg*kg^{-1}*min^{-1}. In contrast, among all T2D cases, 55.6% (n=5/9) presented with M-values less than 4.7 mg*kg^{-1}*min^{-1} at V2. This value represents the cut-off for diagnosing IR according to Bergman et al. [198]. In addition, one participant with T2D newly exceeded the cut-off at V2 under intensified antihyperglycemic treatment. One participant with T2D, who was below the cut-off at V2, was only measured at V2 because the HEC at V1 did not take place due to lockdown at the DDZ. One participant with IGM was also only measured once, due to new presence of a HEC related exclusion criterion at V2.

Among 42 STEMI cases, estimates of HOMA2-IR did not differ between V1 and V2 [2.2±1.3 vs. 2.2±1.2 a.u., p=0.89]. The estimates were also similar between both visits among participants with NGT [n=12, p=0.95], IGM (n=18, p=0.79] and T2D [n=12, p=0.97] (Fig. 7B).

Figure 7. Changes in insulin sensitivity in the population of the *DISTEMI* study within the first year after recent ST-segment elevation myocardial infarction

(A) Whole-body insulin sensitivity (M-value) **(B) Fasting insulin sensitivity (HOMA2-IR)**

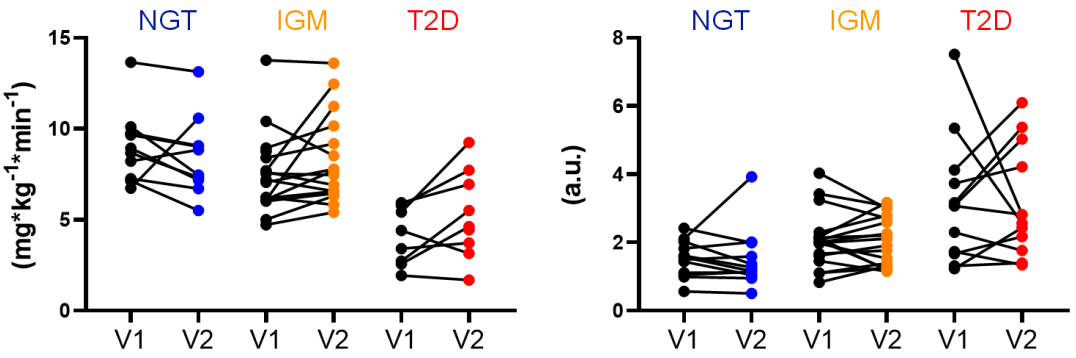


Figure legends: Changes in whole-body insulin sensitivity (A), by calculation of the M-value, and fasting insulin sensitivity, assessed by homeostasis model estimates of insulin resistance (B) one year after STEMI in the population of the DISTEMI study. V1, 6-12 weeks after STEMI; V2, 1-year after STEMI; STEMI, ST-segment elevation myocardial infarction; NGT, normal glucose tolerance (blue bullets); IGM, impaired glucose metabolism (orange bullets); T2D, type 2 diabetes (red bullets); a.u., arbitrary unit; HOMA2-IR, homeostasis model assessment 2 of insulin resistance.

Estimates of Adipo-IR were also similar between V1 and V2 within total cohort comparison [n=36, 47±49 vs. 39±32 a.u., p=0.28] and also between both visits among participants with NGT [n=10, p=0.92], IGM [n=16, p=0.47] and T2D [n=10, p=0.41], as listed in Table 10.

4.2.4 Cardiac variables one year after STEMI

In this analysis, 64.3% of all STEMI cases underwent cardiac MRI on both visits. One participant with IGM did not undergo MRI at V1, but was measured at V2. Additionally, one participant with T2D wasn't measured at V2 due to the newly presence of an exclusion criterion for MR measurements.

Among all STEMI cases, LVEF did not differ between V1 and V2 [n=27, 48±12 vs. 46±13%, p=0.13]. Even in the same subgroup, LVEF did not differ between both visits [NGT: 49±10 vs. 45±12%, p=0.08; IGM: 49±13 vs. 52±14%, p=0.13; T2D: 44±14 vs. 38±14%, p=0.054] (Fig. 8A).

At V2, 81,5% of all cases, who underwent cardiac MRI on both visits, still belong to the same EF category, established by current guidelines [11]. Five participants migrated into another EF category at V2, of whom everyone presented with LVEF greater than 40% at V1: Two of three participants, who showed LVEF ≥50% at V1, showed impaired LVEF with values between 41 and 49% at V2. The third participant newly developed LVEF ≤40% at V2. The other two participants presented with LVEF 41-49% at V1, of whom one participant newly showed LVEF ≥50% and the other participant newly presented with LVEF ≤40%. Both participants, who were only measured on one visit, also showed LVEF ≤40%. Furthermore, no participant showed LVEF ≤40% at V1 with improvement to ≥50% at V2. In this analysis, prevalence of HFrEF, based on established criteria for diagnosing HF according to current guidelines [11, 88], was 35.7% (n=10/28) at V2 and 28.6% (n=8/28) at V1. At V2, prevalence of HFrEF was further similar among females and males [57.1 vs. 28.6%, p=0.17] and among participants without and with T2D [50.0 vs. 31.8%, p=0.41]. Conclusively, prevalence of HFrEF, without those participants only measured once, was similar between V1 and V2 [p=0.55].

In this analysis, mean myocardial infarct size was likewise similar between participants with NGT, IGM and T2D [NGT vs. T2D: p=0.88; NGT vs. IGM: p=0.97; IGM vs. T2D: p=0.79]. Mean infarct size was 15.9±13.3% in NGT, 14.9±12.6% in IGM and 24.1±12.1% in T2D (Fig. 8B).

Among all cases, ESV [p=0.47], EDV [p=0.95] and stroke volume [p=0.54] were further comparable between V1 and V2. Even among the three subgroups (NGT, IGM and T2D), those parameters did not differ between V1 and V2 (Table 10).

Figure 8. Cardiac variables in the population of the *DISTEMI* study within the first year after recent ST-segment elevation myocardial infarction

(A) Left ventricular ejection fraction **(B) Myocardial infarct size**

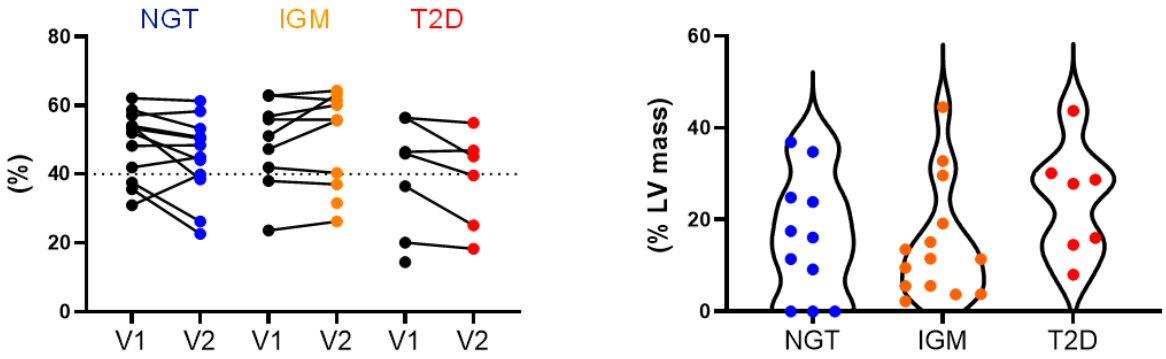


Figure legend: Changes in left ventricular ejection fraction (A) one year after STEMI as well as myocardial infarct size (B) in the population of the DISTEMI study (participants with and without diabetes after recent STEMI). V1, 6-12 weeks after STEMI; V2, 1-year after STEMI; STEMI, ST-segment elevation myocardial infarction; NGT, normal glucose tolerance (blue bullets); IGM, impaired glucose metabolism (orange bullets); T2D, type 2 diabetes (red bullets); dotted line in (A), established cut-off for diagnosing heart failure with reduced ejection fraction (LVEF ≤40%) [11]; *violin plots with points in (B).*

4.2.5 Risk of NAFLD one year after STEMI

Among 41 STEMI cases, mean FLI was lower at V2 compared to V1 [V1 vs. V2: 50±23 vs. 41±24 a.u., p=0.0009]. However, in relation to the degree of glucose tolerance, FLI was only lower among participants with NGT [40±24 vs. 28±17 a.u., p=0.008] and IGM [50±22 vs. 41±25 a.u., p=0.04], but not among participants with T2D [60±21 vs. 55±24 a.u., p=0.35] (Fig. 9A).

At V2, prevalence of liver steatosis, based on FLI greater or equal 60 [202], was 19.0% (n=8/42). In contrast, in this analysis, prevalence at V1 was 43.9% (n=18/41). Conclusively, prevalence of steatosis, based on established cut-off values of FLI, was lower at V2 compared to V1 (p=0.02).

Among all 42 STEMI cases, mean NFS was higher at V2 compared to V1 [V1 vs. V2:-1.20±1.51 vs. -0.63±1.41 a.u., p=0.003]. In relation to the distinct degrees of glucose tolerance, NFS were also higher among participants with NGT [-1.65±1.10 vs. -0.97±0.90 a.u., p=0.03] and IGM [-1.63±1.54 vs. -1.11±1.49 a.u., p=0.046], but similar in participants with T2D [-0.10±1.35 vs. 0.43±1.21 a.u., p=0.054] (Fig. 9B).

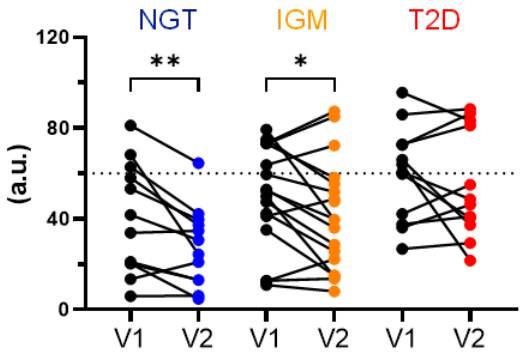
In the current analysis, prevalence of advanced liver fibrosis, diagnosed according to Angulo et al. by NFS >0.676 [160], was 11.9% (n=5/42) at V1 and 14.3% (n=6/42) at V2. Overall, prevalence was stable during study participation (p=0.75). In T2D, in particular, prevalence of advanced liver fibrosis, based on NFS, was 33.3% (n=4/12) at V2. In NGT, no participant ever exceeded the cut-off of 0.676. In contrast, in T2D, two participants newly exceeded this cut-off, whereas one participant newly underwent it at V2. Two participants with IGM and two participants with T2D exceeded this cut-off on both visits.

Within total cohort comparison (n=42), mean FIB-4 score was higher at V2 compared to V1 [V1 vs. V2: 1.39±1.10 vs. 1.56±1.16 a.u., p=0.02]. At V2, participants with IGM had higher FIB-4 [V1 vs. V2: 1.05±0.42 vs. 1.31±0.75 a.u., p=0.02], whereas FIB-4 were similar in NGT [1.41±0.78 vs. 1.55±0.62 a.u., p=0.06] and in T2D [1.89±1.79 vs. 1.96±1.87 a.u., p=0.70] compared to V1 (Fig. 9C).

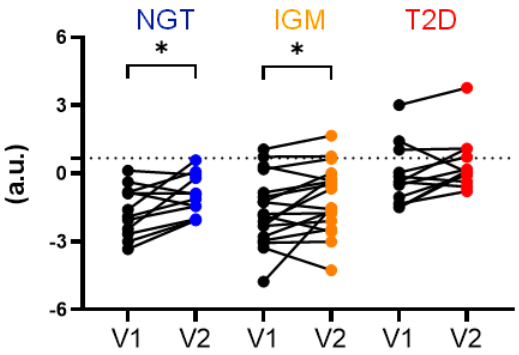
At V2, five participants showed FIB-4 scores greater 2.67, representing the cut-off for diagnosing advanced liver fibrosis according to McPherson et al. [161], of whom 60% exceeded the cut-off on both visits. Two participants with IGM newly exceeded the cut-off at V2. Overall, among all STEMI cases, prevalence for advanced fibrosis, based on FIB-4 scores, was stable within the first year after STEMI (V1 vs. V2: 7.1 vs. 11.9%, n=3/42 vs. 5/42).

Figure 9. Changes in estimates of NAFLD in the population of the *DISTEMI* study within the first year after recent ST-segment elevation myocardial infarction

(A) Fatty Liver Index (FLI)



(B) NAFLD-Fibrosis Score (NFS)



(C) Fibrosis-4 (FIB-4) Score

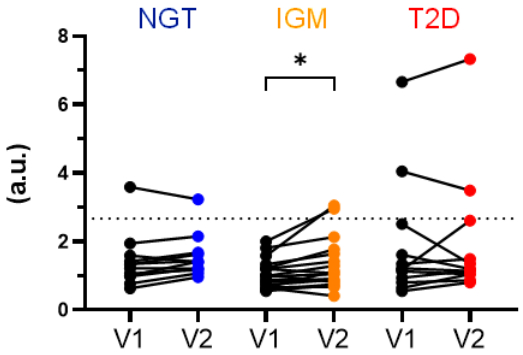


Figure legends: Changes in estimates of non-alcoholic fatty liver disease (NAFLD), specifically Fatty Liver Index (FLI) (A), NAFLD-Fibrosis Score (NFS) (B) and Fibrosis-4 (FIB-4) Score (C), one year after STEMI in the population of the DISTEMI study (participants with and without diabetes after recent STEMI). V1; 6-12 weeks after STEMI; V2, 1-year after STEMI; STEMI, ST-segment elevation myocardial infarction; NGT, normal glucose tolerance (blue bullets); IGM, impaired glucose metabolism (orange bullets); T2D, type 2 diabetes (red bullets); dotted line in (A), cut-off for diagnosing liver steatosis according to Bedogni et al. [202]; dotted line in (B), cut-off for diagnosing advanced liver fibrosis according to Angulo et al. [160]; dotted line in (C), cut-off for diagnosing advanced liver fibrosis according to McPherson et al. [161].

5. Discussion

The DISTEMI study was designed to test the hypothesis that individuals after recent STEMI have lower LVEF, higher degree of IR and higher estimates of NAFLD compared to individuals without MI. It was further hypothesized that individuals with recent STEMI are at high risk for development of new onset of IGM and DM, and progression of IR, HF and NAFLD within the first year after STEMI. To this end, participants of the *DISTEMI* study were compared to event-free participants of the *GDS* and the *DISTEMI* population was further followed up for one year.

Firstly, the analyses at V1 showed that participants with NGT and T2D after recent STEMI presented with impaired LVEF as well as impaired whole-body insulin sensitivity compared to event-free participants of similar age, BMI, gender, glycemia and diabetes duration. Participants with T2D after recent STEMI additionally showed greater IR under fasting conditions compared to participants with T2D but without STEMI. These findings are in line with the previously described first hypothesis and emphasize the need for a cardio-protective therapeutic approach aiming to improve the cardiovascular outcome in individuals with and without T2D.

Secondly, findings undermined the hypothesis that individuals after recent STEMI have higher estimates of NAFLD compared to individuals without MI. The analyses showed that estimates of NAFLD were mostly similar between participants with and without STEMI, even among participants with the same degree of glucose tolerance. Interestingly, in IGM, the NFS and FIB-4 score, were even lower in participants with recent STEMI compared to event-free *GDS* participants.

Thirdly, findings support the hypothesis that individuals are at high risk for migration into a deteriorated glucometabolic status within the first year after recent STEMI. The analyses showed that among participants without T2D at V1, 10% newly developed T2D at V2, diagnosed by 75-g OGTT and/or HbA1c criteria. In addition, every forth participant with NGT at V1, newly developed IGM at V2. These findings are supported by the finding that glycemia worsens in participants with NGT and IGM within the first year post-STEMI. Thus, the results emphasize the importance of an intensified follow-up after recent STEMI using established diagnostic criteria such as OGTT and HbA1c in order to identify individuals at increased risk for new onset of T2D and further diabetes-related complications and associated comorbidities.

However, findings rejected the hypothesis that individuals after STEMI are at high risk of IR progression, since analyses showed, that degrees of whole-body, fasting and adipose-tissue insulin sensitivity were comparable between V1 and V2 among participants with recent STEMI.

Furthermore, findings did not confirm the hypothesis that individuals after STEMI are at risk of HF progression, since analyses at V2 revealed that cardiac function remained stable within the first year after STEMI. It was additionally shown that risk of HFrEF was similar between both visits, independent of the degree of glucose tolerance.

At last, findings supported the hypothesis that individuals after recent STEMI are at high risk for NFALD progression within the first year post-STEMI, since analyses showed that participants without DM had higher liver fibrosis estimates (NFS and FIB-4 scores) at V2 compared to V1. These findings suggest that risk of NAFLD, in particular risk of liver fibrosis, increases among participants with NGT and IGM within the first year after the acute event. This approach is highly important, as it characterizes those individuals as candidates for application of preventive strategies aiming to impede the development of advanced liver fibrosis.

In conclusion, the *DISTEMI* study indicates that improved cardiometabolic phenotyping after STEMI would contribute to a more precise identification of individuals at high risk for additionally cardiometabolic disorders, aiming to prevent a worsening of the outcome after recent STEMI.

5.1 Risk factors in individuals with recent STEMI

STEMI is a heterogeneous disease, with some individuals being at greater risk due to genetic [26, 27, 203] and/or lifestyle-associated predisposition [37, 39, 42, 43, 46, 51]. Over the last decades, numerous studies have analyzed risk factors of CVD and their impact on the course of MI which led to guidelines implementing preventive strategies and evidence-based treatments to reduce the prevalence of CVD and CVD-related death [12, 23, 49, 53, 92, 97]. To prove the hypotheses, that the metabolic phenotype (i.e. IR, NAFLD) of individuals with recent STEMI differs from event-free individuals, and further aggravate in the first year after STEMI, the current study cohort consists of 49 participants of the *DISTEMI* study, who presented with new onset of STEMI, compared to an event-free control cohort of 49 participants of the *GDS*.

The *DISTEMI* study shows that men are more frequently affected by STEMI than women (75.5% vs. 24.5%), largely corresponding to findings previously described in literature [8, 9, 26, 27]. Furthermore, several studies [3, 8] have shown that MI mainly affects older individuals, especially those aged 65 years and older. Based on data of the SWEDEHEART registry [8], mean age among STEMI cases in 2013/14 was 69 years. The results showed that mean age in the population of the *DISTEMI* study was 61±9 years. This trend for younger ages in the *DISTEMI* cohort may be due to the fact that age from ≥18 to ≤80 years was specified as inclusion criterion for participation in the study. According to literature, women with MI tend to

be older [3] and have more comorbidities [18, 204]. Therefore, the specific exclusion criteria in the *DISTEMI* study, as listed in Table 5, may be further responsible for a lower proportion of women within the *DISTEMI* cohort.

In accordance with the observations by Szummer et al. [8], participants of the *DISTEMI* cohort were commonly overweight with a mean BMI of 27.4±3.0 mg/kg^2. Several studies showed that obesity is not only a well-known risk factor for T2D [36] and NAFLD [155, 176], but also for CVD development and mortality [9, 30, 34]. In contrast, other studies found that obesity may be associated with improved survival in individuals with established CVD, termed the obesity paradox [205]. Up to date, experts are debating over this concept and since results of the obesity paradox are inconsistent, obesity prevention and therapy remains in the focus of several guidelines [12, 88, 92, 158].

Smoking is known to be one of the main causes of CVD [43], with women being at higher risk for MI than men [206]. The results at V1 identified 36 participants after recent STEMI as former smokers, which corresponds to a smoker prevalence of 73.5%, of whom 69.4% (n=25) had quit smoking sometime in the past. Several studies [9, 45] found that smoking cessation can reduce the risk of CVD and CVD-related death. Interestingly, the results at V2 showed that participants did not quit smoking during study participation. The smoking prevalence at V2 was even higher at V2 compared to V1, estimated to be 28.6% among all STEMI cases, with women being more affected by smoking than men (60.0 vs. 18.8%). Whereas evidence from previous studies [9, 45] showed that cardiovascular risk reduction occurs years after smoking cessation, the impact of smoking on the development of metabolic features within the *DISTEMI* cohort cannot be determined with certainty since the *DISTEMI* study is not designed for such a long-lasting follow-up.

By analyzing the medication within the *DISTEMI* cohort, the results showed that nearly every participant was under statin treatment (93.9% at V1 and 90.5% at V2). This finding is similar to Szummer et al. [8], indicating that individuals with recent STEMI are highly compliant for taking long-term medication following the acute event. However, the results at V2 showed that only 26.2% had excellent lipid status with LDL-C levels <55 mg/dl (<1.4 mmol/l) one year after STEMI, of whom only every second participant also achieved the target at V1. Studies showed that genetics [207] and lifestyle modification such as diet [208], have strong impact on lipid status improvement. Thus, the lower numbers of STEMI cases achieving the LDL-C target may not only be explained by the chosen lipid-lowering treatment and its dosage, but also by modifiable and non-modifiable factors, which should be analyzed in more detail in future approaches. In contrast, the percentage of statin use within the event-free *GDS* subcohort was low, particularly in participants with T2D, which corresponds to previously published analyses of the *GDS* population [187].

Ning et al. [209] found that increased 2h-PG is associated with IR and increased risk for incident CVD and CVD mortality. The DECODE study group [210] additionally showed, that individuals with DM and IGT, but not individuals with IFG are at increased risk for CVD mortality. Therefore, the OGTT, implemented within the *DISTEMI* study, is indispensable since this test is the only way to identify individuals with IGT. Yet it should be emphasized, that the subgroup with IGM in the population of the *DISTEMI* study, consists of participants with IFG and/or IGT and/or HbA1c 5.7-6.4%. Thus, the findings did not allow for conclusions for individual subdegrees of IGM, which may be exposed to individual risk of STEMI-related outcomes, metabolic outcomes and related extra-cardiac comorbidities.

Previous studies [211, 212] showed that increasing HbA1c is associated with increasing risk for DM, CVD and CVD mortality in individuals without DM. However, further studies reported contradicting statements about the impact of IGM on clinical outcomes after STEMI. While one study [213] reported no association between IGM and adverse prognosis after STEMI, another study [214] found that IGM could have a similar impact as T2D on major clinical outcomes after STEMI. Established outcome parameters include recurrent MI, hospitalization for stroke or HF as well as CV death [8]. Fortunately, analyses at V2 showed that no *DISTEMI* participant developed such a prognosis-related complication during study participation.

Values of HbA1c, typically reflect the average BG level for the last two to three months, are commonly used as criterion for diagnosing DM and monitoring of glycemic control [92, 107]. In the population of the *DISTEMI* study, the HbA1c at V1 could be influenced by several factors such as the inflammatory condition during acute MI and nutrition habits before/during hospitalization and during rehabilitation. In contrast, the HbA1c at V2 might represent a state of metabolic stability. Interestingly, glycemia, assessed by HbA1c, was impaired in participants without T2D at V2 compared to V1. In addition, migration into a deteriorated glucometabolic status within the first year after STEMI was further common in the *DISTEMI* cohort, since IGM occurred in one of four participants with NGT and additionally every tenth participant with NGT or IGM at V1 developed new onset of T2D at V2. In this context, screening strategies can be highly useful to better identify individuals at risk and to introduce adequate prevention and individualized therapy in line with the concept of precision medicine.

Furthermore, impaired PA is known to increase the risk for development of T2D [30, 127] and CVD and CVD mortality [30, 33, 34]. The WHO consistently recommended regular PA as an important part of life style modification in the prevention of overweight and obesity [40]. Achieving the recommended PA levels is highly important since studies showed that PA is beneficial of preventing the development and progression of obesity, T2D and CVD [3, 39, 215]. In the *DISTEMI* cohort, PA may be reduced due to demobilization during hospitalization and reduced cardiac capacity following the acute event, which may further predict the development of new onset of IGM and T2D, and worsening of glycemic control specifically in

individuals with T2D. In contrast, rehabilitation may increase PA by building up muscles, which may further lead to an increase of insulin sensitivity, particularly whole-body insulin sensitivity, which is mainly reflected by skeletal muscle [196]. Therefore, rehabilitation following recent CVD and implementation of PA within everyday life after the acute event is highly important to improve physical fitness and stabilize cardiac function. This approach should be focused particularly in individuals with T2D since literature [70] showed that physical fitness, assessed from spiroergometry, differs between individuals with distinct diabetes phenotypes, even despite similar PA.

Evidence from previous studies show that DM strongly predict CVD and CVD mortality [10]. The results at V1 showed that early after STEMI, 30.6% of the *DISTEMI* cohort had T2D. Thus, the proportion of T2D was even higher within the DISTEMI population than previously reported in the literature [8, 69]. This contrasting finding may be due to the fact, that the *DISTEMI* cohort consists only of 49 participants, whereas the data of Szummer et al. [8] are based on the SWEDEHEART registry 1995-2014 including 105,674 STEMI cases and the data of Roe et al. [69] are based on 11,125 STEMI cases in 2009. Yet it should be mentioned that the *DISTEMI* study is still ongoing and recruitment is planned for ten years.

Furthermore, the analyses showed that at V1 three of five participants (60%) with T2D after STEMI had HbA1c levels less than 7%, which corresponds to excellent glycemic control according to established HbA1c cut-offs for individuals with T2D [50]. Interestingly, nearly every second participant (46.7%) with T2D after STEMI was newly diagnosed within the last twelve months. This finding underlines that T2D and CVD are frequently linked, however, the underlying mechanism are not yet very well understood.

As CVD is the number one cause of morbidity and mortality in individuals with DM, it has become apparent in previous studies [70, 71, 216] that individuals with DM are not risk equivalent. Up to date, risk stratification and subsequent targeted management of cardiovascular risk factors and cardiovascular complications are strongly recommended in line with the concept of precision medicine [217]. Thus, future approaches of the *DISTEMI* study should focus on deep cardiometabolic phenotyping aiming to allocate individuals with STEMI to a specific cardiometabolic phenotype (cluster), which present with greater risk for developing IR, T2D, NAFLD, additional cardiovascular complications or increased cardiovascular mortality. In conclusion, this approach will help to understand the link between STEMI, T2D and NAFLD, aiming to improve the outcome after recent STEMI within the following years and to reduce the global socio-economic burden of CVD.

5.2 Insulin resistance in individuals with recent STEMI

IR is one of the most common metabolic disorders mainly affecting target organs of insulin such as skeletal muscle, adipose tissue and liver. IR and hyperglycemia contribute to the pathogenesis of a pro-thrombotic state [218] and are further associated with ectopic fat storage [73]. Thus, IR is not only a feature of T2D, but also of CVD [70, 71] and NAFLD [95], with worsening of the prognosis directly or due to indirect effects on the development of related complications [78, 79, 84].

The *DISTEMI* study was assessing the degree of IR twice within the first year after STEMI and further comparing dysglycemic with individuals without MI, aiming to investigate the impact of IR on the course of STEMI. In contrast to previous studies, the *DISTEMI* study cohort includes individuals with different degrees of glucose tolerance. With regard to the elucidation of the interaction between IR and STEMI, the specific aims of the current analyses were to explore (i) if individuals with recent STEMI are more likely to be insulin resistant compared to individuals without an cardiac event, and (ii) if individuals with STEMI are at increased risk for worsening of IR within the first year post-STEMI.

The HEC test is well-established as the gold standard method for the assessment of insulin sensitivity [219]. The steady state is determined by the whole-body glucose update at rest under a constant insulin infusion, from which the M-value can be calculated as a measure of whole-body insulin sensitivity [195]. This procedure is widely accepted for insulin sensitivity assessment in situations of metabolic stability but its use in individuals with an unstable metabolic situation, such as acute STEMI, has been discussed controversially. However, Moura et al. [220] found that despite the metabolic instability in individuals with acute MI, associations between values of IR were very close to those values observed in individuals at metabolically stable conditions. Therefore, the HEC test can be regarded as useful, sensitive technique for the assessment of insulin sensitivity even in the early period of the *DISTEMI* study. However, the HEC is a time-consuming and labor-intensive method and not easy to implement in high-risk individuals like those with acute STEMI. Consequently, studies are more likely to use simplified surrogate indices such as HOMA estimates, which are more readily and easily assessing insulin sensitivity, and are proven to correlate very well with values of IR assessed by the HEC [78, 220]. Whereas estimates of HOMA-IR serve as an index of fasting hepatic insulin sensitivity [192], and estimates of Adipo-IR are representing adipose tissue inulin sensitivity [193], the M-value mainly reflects glucose uptake in insulin-stimulated skeletal muscle [196]. Therefore, assessment of those variables adds a high diagnostic value in the clinical setting, representing IR in different affected tissues.

Roden and Shulman [72] described, that adipose tissue dysfunction resulting in lipid overflow, ectopic lipid accumulation, lipotoxicity but also hyperinsulinemia, may lead to accelerated IR,

DM and NAFLD progression. Furthermore, IR can lead to impairment of cardiovascular function [79, 81, 83]. Zaharia et al. [95] showed that individuals with T2D were not only identified by whole-body IR, but also by adipose tissue IR early after diabetes diagnosis [95]. Using comprehensive phenotyping, the current analyses similarly showed that whole-body and fasting insulin sensitivity were impaired in participants with T2D compared to those with NGT, regardless of whether they had STEMI or not. Interestingly, only in the STEMI cohort participants with T2D presented with impaired adipose tissue insulin sensitivity compared to NGT, whereas estimates of IR did not differ between different degrees of glucose tolerance within the event-free *GDS* subcohort. Of note, estimates of Adipo-IR were calculated as the product of fasting concentrations of insulin and FFA [193]. One possible explanation for the comparability of Adipo-IR estimates might be that all participants are under fasting condition and T2D participants of the *GDS* more frequently attempt to follow a healthier lifestyle (i.e. high physical activity, well-informed about nutrition), which may overall result in similar values of insulin and FFA, and therefore similar estimates between T2D and NGT.

A major finding of the *DISTEMI* study is that participants with T2D after STEMI exhibit greater whole-body IR under both, fasted and insulin-stimulated conditions, compared to event-free participants with T2D of similar age, BMI, gender, glycemic control and diabetes duration. At V1, participants with T2D after recent STEMI additionally showed greater IR of skeletal muscle, adipose tissue and liver, based on M-values, Adipo-IR and HOMA2-IR, compared to NGT. Currently, there is growing evidence that specific diabetes phenotypes are more insulin resistant and additionally at greater risk for related cardiovascular complications and associated diseases. Those studies [70, 71, 95] identically reported that among individuals with DM particularly the SIRD phenotype is at greatest risk for CVD and NAFLD. Consequently, the current results suggest that the SIRD phenotype is representative of the most common phenotype within the *DISTEMI* cohort, reflecting more than 14.1% of the participants, which corresponds to the proportion of SIRD among participants with T2D in the *GDS* [95]. The analyses further showed that participants with NGT after recent STEMI showed lower whole-body insulin sensitivity compared to event-free participants with NGT. In 2021, a refined classification of individuals without DM identified two phenotypes at greater risk for IR. In this study, cluster 5 and 6 were identified as obese and insulin resistant, whereas cluster 6 was even more insulin resistant than cluster 5 [139]. Interestingly, cluster 5 was additionally at greater risk for CVD [139]. Such findings could explain, why individuals with T2D and NGT after recent STEMI are more insulin resistant than event-free individuals of similar degree of glucose tolerance, since it might be that specific phenotypes might be more common within the population of the *DISTEMI* study than in the *GDS* subcohort. However, based on the results at V1, it is currently not possible to say whether the STEMI tiggers the development of IR or if this metabolic feature already preexisted and possibly triggered the new onset of STEMI.

Indeed, the overarching aim of the *DISTEMI* study within the following years is to develop a score comprising established and new multiomics-based markers, which will help to allocate individuals with STEMI to a specific cardiometabolic phenotype (cluster) by detecting subgroup-specific prevalence of IR, T2D, NAFLD and related complications as well as worse outcome after recent STEMI. The *DISTEMI* study was designed to allow clustering on both visits. Of note, the established clustering algorithms are based on simple clinical criteria including age at diabetes onset, HbA1c, BMI, estimates of HOMA2 and GAD antibodies [95]. As a final result, the *DISTEMI* study will show the differences in cluster allocation and migration patterns, which may be affected by changes in glucose, lipid and cardiac metabolism and treatment regimen over time. Consequently, current and future findings of the *DISTEMI* study will be of high clinical value, since they will pave the road to more precise preventive and subsequent therapeutic approaches in line with the concept of precision medicine.

5.3 Cardiac function and myocardial infarct size in individuals with recent STEMI

LV remodeling with cardiac dysfunction is common in individuals with MI and is associated with its poorer prognosis [20]. Stone et al. [21] found that particularly myocardial infarct size is a strong predictor for all-cause mortality and hospitalization for HF within the first 12 months after acute STEMI. After acute MI, LVEF is further a strong and independent predictor of MACE in individuals without DM [221]. However, individuals with DM are particularly at greater risk for those events than individuals without DM, but among individuals with T2D the prognostic value of LVEF for MACE is weakened [221]. Consequently, besides the assessment of LVEF, the assessment of myocardial infarct size represents a useful tool for risk assessment in clinical practice after STEMI.

Randomized trials [21] found that among STEMI cases, mean infarct size early after PCI is 17.9% of LV myocardial mass. In line with this finding, participants of the *DISTEMI* study showed a mean infarct size of 17±13% of LV myocardial mass. The results further showed that the infarct size did not differ between participants with NGT, IGM and T2D. Yet it should be emphasized, that the *DISTEMI* study enforces strict inclusion and exclusion criteria, which can moderately preselect the study population. Whereas Stone et al. [21] showed that larger myocardial infarct size is associated with the development of HF, but individuals with NYHA class ≥II were excluded from participation in the *DISTEMI* study, mean infarct size might be lower within the *DISTEMI* cohort than in the general population.

The results further showed that participants with NGT and T2D had lower LVEF after STEMI compared to event-free participants of similar BMI, gender, glycemia and diabetes duration. Interestingly, the analyses on both visits showed that after STEMI, LVEF is similar among participants with different degree of glucose tolerance. Literature [221] likewise showed that

LVEF is similar between individuals with and without DM after acute MI. However the study cohort of Backhaus et al. [221] consisted of participants with STEMI and NSTEMI, and/or recurrent MI. Thus, the *DISTEMI* study is more precise by focusing only on individuals with recent STEMI, whereas individuals with NSTEMI and history of previous MI were excluded from participation.

The results at V1 showed that among all STEMI cases, who underwent cardiac MRI, 53.3% had LVEF ≥50%. This finding is similar to the data of the SWEDEHEART registry [8], which showed that in 2013/14 the proportion of individuals with in-hospital LVEF ≥50% was 47.7%. The results at V1 additionally showed that in the *DISTEMI* cohort, 20.0% were diagnosed with HFmrEF and 26.7% were diagnosed with HFrEF. A previous study by van Veldhuisen [90] showed that prognosis in individuals with HFpEF and HFrEF is similar. This finding is of great importance, since the longitudinal analyses additionally showed that prevalence of HFrEF one year after STEMI was comparable to V1. The prevalence of HFrEF at V2 was further similar between females and males and also between participants with and without T2D. However, since impaired LVEF predicts the development of MACE in individuals without DM [221], and specifically glucose-lowering treatment in individuals with T2D are more effective in individuals belonging to a certain EF category [91], assessment of LVEF still has high prognostic value in the clinical setting.

MACE are established outcome parameters after MI, consisting of all-cause and CV death, recurrent MI, hospitalization for stroke or heart failure [8, 221]. One year after STEMI, no participant of the *DISTEMI* study had developed such an outcome-related event. Interestingly, analyses at follow-up show that, in addition to LVEF, ESV, EDV, stroke volume and cardiac output remained stable within the first year after STEMI. This finding might be attributed to the fact, that participants of the *DISTEMI* study are relatively healthy and under intensified care at the University Hospital in Düsseldorf and therefore are at lower risk for developing outcome-related complications, which might have an impact on cardiac function. Thus, the actual situation in the general population might be worse, than indicated by the results of the current study.

Finally, Jelenik et al. [81] showed that severe myocardial dysfunction after MI with impairment of LVEF is associated with IR and NAFLD. Interestingly, after STEMI, individuals with NGT and T2D likewise had impaired LVEF and reduced whole-body insulin sensitivity compared to event-free participants with NGT and T2D. These findings suggest that those participants might be at greater risk of severe myocardial dysfunction after STEMI, predisposing them as candidates for cardio-protective prevention and therapy.

5.4 Risk of NAFLD in individuals with recent STEMI

Macrovesical accumulation of lipids, specifically TG, in the cytoplasm of hepatocytes, defines NAFLD [156]. Increasing evidence from meta-analyses [73, 151] and previous clinical [181] and mechanistic studies [81] showed that lipotoxicity, cytokine release and impairment of mitochondrial function are driving the development of NAFLD, IR and T2D. In 2014, Szendroedi et al. [181] showed that impaired mitochondrial activity in muscle cells is associated with liver steatosis in human individuals. Four years later, Jelenik et al. [81] revealed that mitochondrial efficiency was lower in the heart of NAFLD-IR mices, which could lead to impaired cardiac function after acute myocardial function.

Various processes impairing mitochondrial function are linked to disturbed hepatic energy metabolism and increased hepatic IR [181, 222]. Adequate myocardial function contributes to fatty acid oxidation, whereas circulating FFAs are mainly released from lipolysis in adipose tissue. Visceral obesity promoted by lipid overload also leads to an increase of FFA, which can mediate IR in the liver [140]. Further evidence [142, 143] showed that high concentrations of FFA contribute to myocardial dysfunction, impairment of cardiac function and development of HF. However, the current study showed that FFA levels did not differ between participants with and without MI. After STEMI, FFA levels were also comparable between participants with NGT, IGM and T2D, and levels further remained stable within the first year after STEMI. However, these results are limited interpretable and have to be analyzed in more detail since increased FFA levels are associated with several cardiometabolic risk factors such as age, female gender, BMI, HOMA2-IR, hypertension and T2D [142].

Within the last years, several studies [73, 79-81] showed that NAFLD is strongly associated with the risk of CVD and CVD mortality. CVD represents the most common cause of death in individuals with NAFLD [82, 83]. Golabi et al. [171] found that specifically for individuals aged 60-74 years, NAFLD is associated with increased risk of all-cause and CVD mortality, whereas no association was seen for those older than 74 years. Since the results at V1 showed a mean age of 61.0±8.8 years among all STEMI cases, the *DISTEMI* cohort seems to represent individuals at highest risk of mortality by concomitant NAFLD. Yet it should be mentioned, that the study of Golabi et al. [171] used the FLI to diagnose NAFLD, whereby liver steatosis is ruled in by scores ≥30, included only individuals 60 years or older and followed participants for more than ten years. In contrast, in the *DISTEMI* study, liver steatosis is ruled in by FLI ≥60, according to Bedogni et al. [202], inclusion criterion is ≥18 to ≤80 years of age and follow-up time is only one year. Consequently, findings of the study of Golabi et al. are transferable only to a limited extent, since no conclusions can be drawn about risk of mortality in individuals aged <60 years. Furthermore, the follow-up time within the *DISTEMI* cohort might be too short to draw conclusions about morbidity and mortality following recent STEMI.

In 2019, the global prevalence of NAFLD was estimated to be 29.8% [152]. In particular individuals with T2D are at greatest risk of NAFLD with an estimated prevalence of >70% [79, 151]. Previous studies [95, 159] showed that HCL content correlated positively with the FLI, a well-established estimate of liver steatosis. Consequently, FLI is useful in clinical practice, specifically in the absence of the gold standard liver biopsy and the quantifying hepatic MRS, and therefore is recommended by international guidelines for NAFLD screening [158]. Interestingly, the current analyses showed that FLI was comparable between participants with and without MI, independent of the degree of glucose tolerance. There is currently conflicting evidence on CVD risk in individuals with NAFLD. Previous studies demonstrated that NAFLD associates with CVD [79, 80] and affects the outcome [81-83]. However, it was recently shown that NAFLD is associated with a higher risk of nonfatal CVD but did not affect the risk of CVD mortality [223]. The analyses further showed, that after one year after STEMI, FLI was even lower within total cohort comparison and also among participants with initial NGT and IGM compared to V1. Even that the prevalence of liver steatosis based on FLI among all STEMI cases was lower at V2 compared to V1. These findings suggest that individuals without T2D early after recent STEMI could be at lower risk for the development and progression of liver steatosis one year after STEMI. Of note, calculation of FLI is based on fasting TG, BMI, GGT and WC. Whereas BMI remained stable in NGT and IGM between both visits, fasting TG, GGT and WC were lower in NGT, and GGT was additionally lower in IGM at V2 compared to V1. These significant differences in anthropometric data and laboratory variables, which might be influenced by lifestyle changes or changes in medical treatment, have strong impact on the calculation of FLI and the risk assessment of liver steatosis, and might be responsible for the lower values of FLI at V2.

A major finding of the last years was that some individuals are at greater risk for NAFLD development and progression. Among the novel diabetes phenotypes, the SIRD phenotype has the highest risk for liver steatosis at disease onset, and for liver fibrosis progression after five years [95]. In this study, liver steatosis was assessed non-invasively using FLI, NAFLD was assessed based on NFS and liver fibrosis was assessed based on the aspartat aminotransferase (AST) to platelet ratio index [95]. In contrast, in the *DISTEMI* study, liver steatosis was also assessed by FLI, whereas risk of liver fibrosis was assessed based on NFS and FIB-4, estimates which had been shown to offer the best non-invasive diagnostic performance for detecting advanced fibrosis [162]. It was recently shown, that among individuals without T2D, the cluster 5 was identified as a phenotype at increased risk of CVD, where individuals additionally had obesity, insulin resistance and high levels of fatty liver [139]. However, cluster 6 was also identified as insulin-resistant, obese phenotype, but presented with less liver fat and did not show significantly increased cardiovascular risk [139]. Thus, it might be, that these two phenotypes reflect the majority of the DISTEMI cohort without

presence of T2D, supporting the findings of similar FLI between participants with and without STEMI.

Liver fibrosis is defined as non-physiological scarring of liver tissue caused by injury or inflammation. Whereas liver fibrosis represents a reversible metabolic feature, ongoing liver damage results in more severe complications such as liver cirrhosis, liver failure and carcinoma. Liver biopsy still remains the gold standard method for diagnosing liver fibrosis [158]. However, in the absence of liver biopsy, ^{1}H-MRE [167] and estimates of liver fibrosis such as the NFS [160] and FIB-4 score [161], serve as well-established surrogate parameter for liver fibrosis [162]. Ekstedt et al. [84] found that particularly increasing liver fibrosis strongly predicts mortality in individuals with NAFLD. It this study, participants were followed up for 26.4 years on average and NAFLD diagnosis was assessed by the gold standard liver biopsy. However, despite this and other complex studies, the relationship between STEMI and liver fibrosis is not yet fully understood. To deepen the knowledge in this field, the *DISTEMI* study was designed and performed as the first study assessing the risk of development and progression of liver fibrosis twice within the first year after STEMI. Interestingly, early after the acute event, participants with IGM had lower NFS and FIB-4 scores compared to event-free participants with IGM. As described in 3.3.9., calculation of NFS is based on age, BMI, AST/ALT ratio, platelet count, serum albumin and diagnosis of IFG or diabetes, whereas calculation of FIB-4 is based on age, AST, ALT and platelet count. Since in IGM, participants with STEMI are younger than event-free participants, age differences might have contributed to the lower values of FLI at V1.

Interestingly, the analyses within the DISTEMI population showed that participants with NGT and IGM had higher values of NFS, and participants with IGM additionally had higher values of FIB-4. These findings are of great interest, since they support the hypothesis that individuals are at risk for liver fibrosis development and progression after recent STEMI. However, the analyses also showed that the prevalence of advanced liver fibrosis, based on NFS and FIB-4, among all STEMI cases was stable between both visits. The significant increase in values of NFS and FIB-4 within the first year post-STEMI might be explainable by the fact, that presence of IFG and T2D impact on NFS calculation (IFG or T2D: yes = +1, no = 0) and new onset of IGM and T2D was further common within study participation. In addition, the increasing age during study participation may affect the calculation of NFS and FIB-4. Taken together, it would be of interest to clarify, if the increase in values of NFS and FIB-4, which might lead to increased risk of liver fibrosis progression, is specific for individual STEMI phenotypes. Consequently, it remains to be investigated if cluster analyses may provide additional value with further implications for targeted lifestyle interventions to improve the outcome after MI by preventing liver fibrosis.

5.5 Strengths and limitations

The main strength of this current study is the comprehensive spectrum of deep cardiometabolic phenotyping in individuals with recent STEMI, compared to event-free individuals of similar gender, BMI and glycemia. The examinations combine high-specialized gold standard methods, such as the HEC tests for the assessment of insulin sensitivity, with well-established non-invasive diagnostic methods for the assessment of STEMI-related complications and comorbidities (e.g. estimates of NAFLD).

The *DISTEMI* study represents a very complex longitudinal cohort study with several variables, observed and calculated twice within the first year after STEMI. Therefore, the study includes a one-year follow-up, which makes it unique by providing deep insights into the interaction between metabolic and cardiologic alterations within an early period following MI. Data have been prospectively collected and most of the variables are mandatory of the study, resulting in a high degree of data completeness.

The large group of STEMI cases at the University Hospital at the HHU in Düsseldorf (*SYSTEMI* cohort), which serve as source for the recruitment of an adequate number of participants for the *DISTEMI* study in a reasonable period, is further a major strength of the current study. The compliance for participating in the *DISTEMI* study was quite high among those, who were eligible for participating (inclusion rate at V1: 14.3%, drop-out rate at V2: 14.3%). Even the drop-rate at V1 was quite low, since only one participant, who had elevated creatinine levels, was excluded from study participation and another participant with T1D was excluded in the current analyses.

As far as the limitations are concerned, results of metabolic phenotyping, in particular at V1, might be affected by the short period between the acute event and the examination day. Consequently, inflammation, impaired physical and cardiac fitness, as well as changes in dietary habits, may affect the assessment of cardiac function, HbA1c and insulin sensitivity as well as the development and progression of T2D and NAFLD within study participation. As an observational study, changes of metabolic features after MI can be influenced by lifestyle changes, but also by changes in treatment strategies. The latter may also have impact on laboratory parameters and thereby, calculation of NAFLD estimates. Consequently, residual confounding can never be excluded.

Furthermore, potential bias includes selection bias since study participation is limited by several inclusion and exclusion criteria, as presented in Table 5. Assessment of cardiac functional parameters was further limited by specific exclusion criteria for MRI (e.g. claustrophobia, pacemaker). However, those limitations will continue to play a major role and cannot be influenced.

Furthermore, recruitment of event-free participants with IGM was quite difficult. Whereas IGM represents an absolute exclusion criterion for participation in the *GDS* at baseline, IGM can only be diagnosed during the 5-, 10- or 15-years follow-up examinations. While the *DISTEMI* study is ongoing and participants with IGM currently represent 38.8% of the study cohort, this limitation will become a big hurdle in the future. In addition, inclusion in the *GDS* is based on a lower maximal age limit than in the *DISTEMI* study. Those limitations result in a delay in the identification of suitable participants without STEMI, in particular those with IGM.

Finally, the Covid-19-pandemic was also a major limitation of the study. The first case of a SARS-CoV-2 infection in Germany was confirmed on January 27th, 2020. As a result of sharp increases in absolute numbers of infected individuals, two nationwide lockdowns made study participation impossible for weeks.

6. Conclusion

First, as a major finding, the study demonstrated that recent STEMI associates with impaired LVEF and impaired insulin sensitivity of skeletal muscle, assessed by ^{1}H-MRI and the HEC test, in participants with NGT and T2D, but not in participants with IGM. Participants with T2D after recent STEMI additionally showed impaired fasting insulin sensitivity, by presenting with higher HOMA estimates, compared to event-free participants of similar age, gender, BMI, glycemic control and diabetes duration. The results further showed that prognostic cardiac variables, including myocardial infarct size and levels of LVEF, did not differ between participants with different glucose tolerance within the first year after STEMI. These findings underline the importance of rapid intervention in primary care after STEMI (e.g. cardiac catheterization) in individuals with and without T2D, in order to stop the progression of death of myocardial tissue, which may predict a prolonged period of hospitalization, new onset of MACE and impairment of insulin sensitivity of distinct tissues.

Second, case-control-analyses showed that early after recent STEMI participants were not necessarily at greater risk for NAFLD compared to event-free participants. However, one year after STEMI, participants without T2D had higher estimates of NAFLD (NFS and FIB-4 scores) compared to V1, and therefore, were at greater risk for the development of liver fibrosis. Thus, this finding qualifies those participants as candidates for preventive and subsequent therapeutic strategies in order to impede liver fibrosis with further worsening of the outcome.

Third, longitudinal analyses revealed that participants without T2D early after STEMI were at risk for new onset of IGM and T2D, diagnosed by OGTT and HbA1c criteria, within the first year post-STEMI. Findings showed that every tenth participant without T2D at V1 newly developed T2D and every forth participant with NGT at V1 newly developed IGM one year after STEMI. While participants with NGT and IGM were not treated with antihyperglycemic drugs, screening strategies, discovering constellations that favor migration into a deteriorated glucometabolic status with the risk of developing further related complications and comorbidities, are highly important in the follow-up period of individuals with recent STEMI.

In conclusion, the *DISTEMI* study highlights the importance of deep cardiometabolic phenotyping after recent STEMI, since evidence showed that HF, IR and NAFLD impact on the outcomes. Thus, the knowledge gained from the current study is not only of high clinical value but also in charge of future detection of specific cardiometabolic phenotypes of STEMI with specific prevalence of STEMI-related outcomes (e.g. HF), metabolic outcomes (e.g. IR, T2D) and related extra-cardiac comorbidities (e.g. NAFLD). Finally, this approach will help to establish personalized preventive strategies in line with the concept of precision medicine to impede a worse outcome after the first cardiovascular event.

7. References

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