Aus der Klinik für Herzchirurgie
der Heinrich-Heine-Universität Düsseldorf
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Fibrinolysis, D-dimers and Tranexamic Acid in Cardiac Surgery

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von
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2020

Als Inauguraldissertation gedruckt mit der Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachter: Prof. Dr. med. Alexander Albert

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“In the middle of difficulty lies opportunity.”

- Albert Einstein

Teile dieser Arbeit wurden veröffentlicht:

Besser, V., Albert, A., Sixt, S. U., Ackerstaff, S., Roussel, E., Ullrich, S., Lichtenberg, A. and Hoffmann, T., (2020), Fibrinolysis and the Influence of Tranexamic Acid Dosing in Cardiac Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, (34) 2664-2673 [1]

Summary (German)

Perioperative Blutungsereignisse spielen in der Herzchirurgie eine zentrale Rolle. Zu ihrer Vermeidung empfehlen Leitlinien eine interdisziplinäre Zusammenarbeit im Sinne eines *patient blood managements* mit *point-of-care* Diagnostik und Algorithmus-basierten Transfusionsstrategien. Blutungen können auf eine bereits bestehende Koagulopathie, die vorherige Anwendung von Antithrombotika, chirurgische Komplikationen, sowie die Aktivierung der Gerinnung und Fibrinolyse aufgrund eines Gewebetraumas, einer Gefäßverletzung oder der Herz-Lungen-Maschine (HLM) zurück zu führen sein. Als blutsparende Maßnahme wird in der Herzchirurgie das Fibrinolyse hemmende Medikament Tranexamsäure (TXA) eingesetzt. D-dimere als Fibrin Spaltprodukte können, zusammen mit anderen Parametern, zur Diagnose der Fibrinolyse verwendet werden. Sie wurden bereits untersucht als Prädiktor nicht nur für thrombotische Ereignisse wie der tiefen Beinvenenthrombose, sondern auch für gleichzeitiges Blutungs- und Thromboserisiko in bestimmten Patientenpopulationen. Es war unsere Hypothese, dass in der Herzchirurgie die perioperative fibrinolytische Aktivität abhängig ist von der kardiochirurgischen Grunderkrankung, des durchgeführten Eingriffs, sowie der Dosis der antifibrinolytischen Therapie. Darüber hinaus stellten wir die Hypothese, dass dieser Effekt mithilfe von D-dimer Messungen diagnostiziert werden kann. In der Klinik für Herzchirurgie des Universitätsklinikums Düsseldorf untersuchten wir retrospektiv die D-dimer Spiegel 3152 volljähriger Patienten, die sich zwischen Februar 2013 und Oktober 2016 einer standardmäßigen elektiven Herzoperation unterzogen. D-dimer Spiegel wurden intraoperativ an zwei Zeitpunkten ermittelt: zu Beginn der Operation ('S') und kurz vor der Gabe von Protamin ('bP'). Zusätzlich wurde die Dosierung von TXA während des analysierten Zeitrahmens erhöht, und die intraoperative D-dimer Entwicklung zwischen den Kohorten verglichen. Wir fanden eine hohe Variabilität der D-dimere zu Beginn der Operation zwischen den Krankheitsarten ($p<0,01$), und auch interindividuell. Prädisponierende Faktoren für erhöhte D-dimere waren Endokarditis, Aortendissektion und vorherige extrakorporale Zirkulation ($p\leq0,01$). Intraoperativ fanden wir fallende D-dimer Spiegel während koronarer Bypass Operationen mit und ohne HLM, Einzelklappenoperationen und *left ventricular assist device* (LVAD) Implantationen ($p\leq0,02$), sowie steigende Spiegel während aortenchirurgischer Eingriffe und Herztransplantationen ($p<0,01$). Die intraoperative D-dimer Dynamik wurde signifikant durch eine höhere oder niedrigere Tranexamsäuredosis ($p\leq0,01$) beeinflusst. Zusammenfassend konnten wir eine präoperative Variabilität der fibrinolytischen Aktivität bei herzchirurgischen Patienten nachweisen, die nicht vollständig durch zugrunde liegende Pathologien erklärt wurde. Zusätzlich war die intraoperative D-dimer Entwicklung abhängig vom durchgeführten Eingriff. Abgesehen von LVAD Implantationen korrelierten Eingriffe mit geringem Risiko mit fallenden, und Eingriffe mit hohem Risiko mit intraoperativ steigenden D-dimer Spiegeln. Im Vergleich zu vorhandener Literatur waren unsere beiden TXA Dosierungsprotokolle niedrig. Die klinischen Implikationen dieser Ergebnisse müssen weiter untersucht werden, aber eine perioperative Überwachung der Fibrinolyse, beispielsweise mit Hilfe des bereits etablierten Laborwerts D-dimere, könnte im Kontext der Herzchirurgie nützlich sein.

Summary (English)

Perioperative hemorrhagic complications are common in cardiac surgery. Current guidelines recommend patient blood management as an interdisciplinary approach for prevention and treatment of bleeding, involving point-of-care diagnostics and algorithm-based transfusion strategies. Bleeding may be a result of preexisting coagulopathy, prior use of antithrombotic drugs, surgical complications, as well as the activation of coagulation and fibrinolysis due to tissue trauma, vascular injury and cardiopulmonary bypass (CPB). The inhibition of fibrinolysis by routine perioperative application of antifibrinolytic drugs, such as tranexamic acid (TXA) is an effective strategy for prevention of blood loss. D-dimers as fibrin split products can be utilized, among other parameters, for diagnosis of fibrinolysis. They have been studied as a predictor not only for thrombotic events such as deep venous thrombosis, but also for bleeding and thrombosis simultaneously in several patient populations. We hypothesized that in cardiac surgery, perioperative fibrinolytic activity depends on underlying disease and performed surgery, as well as on the dose of antifibrinolytic therapy. Furthermore, we hypothesized that these effects can be diagnosed using D-dimer monitoring. At the Department of Cardiac Surgery at the Düsseldorf University Hospital, we retrospectively examined D-dimer levels from 3152 adult patients undergoing standard elective cardiac surgery between February 2013 and October 2016. D-dimer levels were obtained at two points during the surgery: at the start of surgery ('S'), and before the administration of protamine ('bP'). Dosing of TXA was increased during the analyzed timeframe, and D-dimer development was compared between the cohorts. We found a high variability of D-dimer levels at the start of surgery between types of disease ($p<0.01$), and also interindividually. Predisposing factors for increased D-dimers were endocarditis, aortic dissection and previous extracorporeal life support ($p\leq0.01$). Intraoperatively, under a fixed higher dose of tranexamic acid, we found decreasing D-dimer levels in on- and off-pump coronary bypass surgery, single valve surgery and left ventricular assist device (LVAD) implantation ($p\leq0.02$, respectively), and increasing levels in aortic surgery and heart transplants ($p<0.01$, respectively). Intraoperative D-dimer development was significantly influenced by a higher or lower dose of tranexamic acid ($p\leq0.01$). In conclusion, we were able to demonstrate preoperative variability of fibrinolytic activity in cardiac surgery patients, which could not entirely be explained by underlying pathologies. Intraoperative trends of D-dimer development were divergent between types of performed surgery. Apart from LVAD implantations, low-risk surgeries were correlated with decreasing, and high-risk surgeries with increasing intraoperative D-dimer levels. In comparison to existing literature, both our TXA dosing protocols were low. The clinical implications of these findings require further examination, but the use of the established laboratory value D-dimer for perioperative monitoring of fibrinolysis may be useful in the context of cardiac surgery.

Abbreviations

ATACAS	Aspirin and Tranexamic Acid for Coronary Artery Surgery
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
'bP'	before protamine administration
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CKD	chronic kidney disease
CPB	cardiopulmonary bypass
CRASH-2	Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2
DVT	deep venous thrombosis
EACA	epsilon aminocaproic acid
ECC	extracorporeal circulation
HD-TXA	higher dose of tranexamic acid
IE	infective endocarditis
LD-TXA	lower dose of tranexamic acid
LVAD	left ventricular assist device
OPCAB	off-pump coronary artery bypass
PAI-1	plasminogen activator inhibitor - 1
PBM	patient blood management
PE	pulmonary embolism
POC	point-of-care
ROTEM®	rotational thromboelastometry
RBC	red blood cells
'S'	start of surgery
t-PA	tissue-type plasminogen activator
TEG®	thromboelastography
TXA	tranexamic acid
u-PA	urinary-type plasminogen activator

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1 Introduction

More than 1 million patients undergo cardiac surgery per year worldwide [2]. Perioperative hemorrhage is a major complication in this specialty, causing morbidity and mortality [3]. Postoperative hemorrhage is more prevalent than in other specialties, and re-operation rates have been reported between 2.2 and 9.0 % [4]. For prevention of bleeding, there is a Class IA recommendation for the continuous intraoperative intravenous application of antifibrinolytic therapy, such as tranexamic acid (TXA) in cardiac surgery [5]. It has been extensively studied and is widely accepted that TXA has blood sparing effects compared with placebo during cardiac surgery and in other hemorrhagic conditions [6-9].

The use of extracorporeal circulation (ECC) such as cardiopulmonary bypass (CPB) presents additional challenges for hemostatic management in this field. CPB leads to activation of coagulation and fibrinolysis [10, 11] and is associated with an increased risk for bleeding [12, 13]. Furthermore, patients with coronary artery disease (CAD) commonly take antiplatelet therapy, and this further increases the risk for perioperative hemorrhage [14]. Nearly half of patients undergoing coronary artery bypass grafting (CABG) on CPB, which belongs to the lower risk category of cardiac surgeries, receive at least one unit of red blood cells (RBC) [15]. Therefore, optimization of perioperative hemostatic balance is necessary and has the potential of improving re-operation rates, morbidity and mortality. Thus, patient blood management (PBM) commissions have been implemented in most clinics. PBM is an interdisciplinary approach to the diagnostics and treatment of pre-, intra- and postoperative bleeding and coagulation in cardiac surgery patients and has been shown to reduce bleeding and transfusion [16]. The European Association for Cardio-Thoracic Surgery (EACTS) in collaboration with the European Association of Cardiothoracic Anesthesia (EACTA) has developed detailed guidelines for PBM in adult cardiac surgery [16].

In addition to the interdisciplinary approach and the thorough evaluation for prior antiplatelet or anticoagulant treatment and its correct intermission, one of the key

elements of PBM is intra- and postoperative bleeding management. This includes perioperative point-of-care (POC) monitoring of several hemostatic laboratory values and the establishment of transfusion algorithms based on these tests. Early efforts towards POC based treatment in cardiac surgery were already undertaken by Despotis *et al.* in 1994 [17], who implemented a transfusion algorithm based on perioperatively measured standard coagulation tests. Patients treated with the algorithm had lower mediastinal chest tube drainage perioperatively and received fewer transfusions. Since then, POC testing has expanded tremendously with the development of new laboratory technology. Viscoelastic testing in particular has been established in several clinical settings including cardiac surgery. It includes thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) [18], which continuously measure the viscoelasticity of coagulating whole blood. The utilization of TEG- or ROTEM- based transfusion algorithms has been shown to reduce transfusion rates of all blood products in cardiac surgery patients [19] as well as in patients with hemorrhage from other specialties [18]. Additionally, viscoelastic testing may distinguish surgical bleeding from coagulopathy in cardiac surgery [19].

In some cases the underlying cause for postoperative hemorrhage requiring re-exploration can be traced to a surgical site for bleeding [20], but hemostatic disturbances referred to as microvascular bleeding [21] or more broadly as coagulopathy [4] can be the source as well. The use of CPB specifically is associated with coagulation defects and bleeding with multifactorial origin [11, 22]. CPB has been shown to cause platelet lysis and loss of platelet function in particular [12, 23] and activation of coagulation and fibrinolysis [11, 24]. This is one of the reasons why antifibrinolytics are routinely applied for reduction of blood loss in this field.

Despite the unfavorable associations of CBP with disturbances of the hemostatic system, the use of CPB in particular also presents the opportunity for additional analyses. In cardiac surgery, due to the use of CPB, the onset of bleeding usually does not occur until reperfusion. RBC concentrates, platelets and fresh frozen plasma (FFP), as well as hemotherapeutic products such as fibrinogen or coagulation factors are often not transfused until after reversal of heparin. This gives us an intraoperative time span

which is relatively uninfluenced by transfusions and allows us to obtain valuable diagnostic information. Hemostatic changes during this time period will either be attributable to surgery, or to CPB, or to the preoperative hemostatic status. This will be discussed in the following chapters.

1.1 Activation of Coagulation

Coagulation and fibrinolysis are ongoing, self-regulating processes in healthy individuals [25]. Any disturbance can lead to thrombosis or hemorrhage. Diseases, such as coagulopathies or bleeding diathesis, widespread medications such as antiplatelet and anticoagulant treatment, as well as surgical trauma pose a major threat to hemostasis, which is why this topic has major clinical implications. Additionally, in cardiac surgery, ECC such as CPB is specifically associated with activation of coagulation as mentioned above [10]. Two pathways for this have been described. On the one hand, there is the contact activation via the intrinsic pathway, which starts with the activation of Factor XII. On the other hand, there is also activation through tissue trauma via the extrinsic pathway, which begins with tissue factor and activation of Factor VII. The coagulation cascade leading to thrombin activation and clot formation via both pathways has been described in detail by Mann *et al.* [26], and specific to cardiac surgery with CPB by Edmunds *et al.* [27]. There is, however, conflicting literature on this topic as following. It seems quite plausible that during the use of CPB, thrombin is generated via the intrinsic pathway through contact activation at the surface of the circuit [10]. On the other hand, Boisclair *et al.* [28] found no association of thrombin with Factor XIIa levels in patients under CPB, and thrombin generation preceded the increase in levels of Factor XIa in this study. Similarly, the same amount of thrombin formation was found in a pediatric patient with severe Factor XII deficiency as in healthy patients undergoing CPB [29]. Based on these findings, the role of the intrinsic pathway is unclear.

Tissue trauma will be prevalent during all surgery, and extrinsic activation of the coagulation cascade will occur during any surgery, this is not specific to the use of CPB. The establishment of off-pump cardiac surgery, which will be discussed in later chapters,

therefore offers the possibility for further insight on this matter. Biglioli *et al.* [30] compared inflammatory and coagulation markers between on- and off-pump cardiac surgery and found that tissue trauma plays an equal, possibly larger role in activation of coagulation in cardiac surgery than contact activation via the intrinsic pathway. Sniecinski *et al.* [31] presented in a literature review that there are several effects of CPB on coagulation which are described in detail in their work. While the intrinsic pathway via contact activation may or may not lead to thrombin formation under CPB, contact activation does cause production of kallikrein and bradykinin on the surface of the CPB circuit [31]. This is strongly relevant to our study, as bradykinin leads to increased t-PA-antigen (tissue-type plasminogen activator) levels [32]. t-PA enables fibrin degradation and therefore, fibrinolysis, which is a relevant cause of hemorrhage in cardiac surgery [31].

1.2 Fibrinolysis

While the examination of underlying pathophysiological mechanisms of fibrinolysis are not the focus of this work, they are relevant in the total context of CPB induced fibrinolysis and the discussion of antifibrinolytic therapy. The following text gives an overview.

A fibrin clot is formed at the end of the coagulation cascade [24], and can be dissolved in the process of fibrinolysis. Fibrin is degraded by plasmin, which is activated from plasminogen either by t-PA or urinary-type plasminogen activator (u-PA) [33]. The activation of plasminogen by u-PA is cell-bound and contributes to cell surface proteolytic activity unspecific to fibrinolysis [34]. It is therefore less of interest to this study. t-PA, however, plays a key element in fibrinolysis and is relevant to this study in the context of antifibrinolytic therapy. t-PA binds to plasminogen, which is activated to plasmin and degrades fibrin. As fibrin is a cofactor for t-PA, fibrinolysis a physiologic and self-regulatory process [35]. In a thrombotic or embolic state, fibrinolysis can be clinically induced by recombinant t-PA in patients with myocardial infarction [36].

Fibrinolysis is a coordinated physiological process [25] and the plasmin induced degradation of fibrin is counteracted by two main enzymes involved in inhibition of fibrinolysis. Firstly, the plasminogen activator inhibitor type 1 (PAI-1), which is released from endothelial cells, platelets and adipose tissue [37], forms a complex with t-PA, the t-PA/PAI-1 complex. This complex prevents t-PA from binding to plasminogen and activating it. Secondly, inhibition of fibrinolysis can also occur at the level of plasmin by the glycoprotein α2-antiplasmin [38], which, similarly to u-PA mentioned above, plays a subordinate role in this study.

In the process of fibrin degradation, D-dimers as fibrin split products are formed. Detailed descriptions of this process as well as the molecular structures of D-dimer [39], fibrin and fibrinogen [40] have been published elsewhere. In short, cross-linked fibrin polymer is degraded by plasmin in several steps. This produces the terminal D-dimer-E-complex, which contains D-dimer antigen epitopes. The clinical relevance lies in the ability of D-dimer antibody assays to recognize these antigen epitopes [39]. The measurement of D-dimers, as products of fibrin degradation are considered a useful laboratory value for clinical detection of fibrinolysis [41]. D-dimer measurements are now performed regularly in several clinical scenarios including cardiac surgery which will be described in the following paragraphs.

1.3 Clinical Applications of D-dimers

The clinical usefulness of D-dimers was originally determined in the context of exclusion of deep venous thrombosis (DVT) and pulmonary embolism (PE) [42], which are thrombotic events. D-dimers have a high negative predictive value in this setting, as assays can detect D-dimer antibody on only small amounts of crosslinked fibrin [39]. A negative D-dimer replaces expensive tests such as spiral CT scan and compression ultrasound [43], establishing D-dimers a standard laboratory value.

While DVT and PE and are thrombotic events, there are an increasing number of clinical investigations examining an association of elevated D-dimers not only with thrombosis

but also with bleeding events. Sub-studies of large trials evaluating anticoagulant treatment have published the association of D-dimer levels with concurrent thrombotic and hemorrhagic events in patients with atrial fibrillation [44, 45]. Christersson *et al.* [44] found that higher D-dimer levels predicted bleeding and thrombosis after a median follow-up time of 1.9 years in patients randomized to anticoagulant treatment (Warfarin or Apixaban) or no anticoagulant treatment. The addition of D-dimer levels to the $CHADS_2$-Score [46] improved the prediction of stroke, systemic embolism and death in both groups in this study, particularly in the group taking anticoagulants. Comparably, the addition of D-dimer levels to the HAS-BLED score [47] improved the prediction of major bleeding as well. Siegbahn *et al.* [45] found similar results in patients with atrial fibrillation under anticoagulative treatment with either dabigatran or warfarin. Patients with higher D-dimers had a higher risk of stroke, systemic embolism, cardiovascular death, and major bleeding.

D-dimer levels were analyzed in minute categories in these trials [44, 45]. The second lowest category of D-dimer levels in the trial by Siegbahn *et al.* [45] was between 298 and 473 µg/l, which is still considered a normal range, and the risk for thrombotic and bleeding events was significantly higher in this group compared to the lowest category of <298 µg/l. Both studies [44, 45] also showed lower baseline D-dimers in patients who received prior anticoagulant treatment, and Siegbahn *et al.* [45] found decreases in D-dimer levels over the course of three and six months on anticoagulant treatment. Similarly, the short-term effect of anticoagulative treatment in patients with acute PE can be monitored by decreasing levels of D-dimers as well [48].

In addition to the association of higher D-dimers with cardiovascular death found by Siegbahn *et al.* [45], is has been shown that elevated D-dimer levels may predict future myocardial infarctions in healthy men [49], although a causal association has not been proven [50]. Postoperative myocardial injury has also been associated with perioperative hypercoagulability, determined by elevated D-dimer levels among other parameters, in vascular patients [51, 52].

In addition to their implications in the prediction or diagnosis of venous thrombosis, myocardial injury and bleeding, D-dimers representing fibrinolysis have received increasing attention in the context of acute coagulopathy in severely injured trauma patients. The involved pathophysiological mechanisms of this coagulopathy have been described by Brohi *et al*. in several publications [53-55]. Trauma patients with hypoperfusion develop systemic hypocoagulation and hyperfibrinolysis, and hemorrhage is the major cause of death in this patient population. Brohi *et al.* [55] demonstrated an association of higher t-PA and D-dimers with hyperfibrinolysis. Higher D-dimer levels also correlated with increasing injury severity score (ISS), indicating worsening hyperfibrinolysis with more severe injury. Empiric application of antifibrinolytic therapy for treatment of hemorrhage in trauma patients has been added to the trauma guidelines in recent years, and this will be illustrated in a later paragraph.

1.4 D-dimers in Cardiac Surgery

In cardiac surgery, D-dimers as markers for fibrinolytic activity have been examined in several clinical outlines. They have been associated with CPB, as well as short- and long-term postoperative morbidity, such as bleeding and myocardial infarction.

In studies performed before the era of antifibrinolytic therapy, several authors have correlated increased intra- and postoperative D-dimer levels with CPB [56, 57]. One of the studies found D-dimer levels remained increased for the entire one-month follow-up period after coronary bypass surgery regardless of intraoperative antifibrinolytic treatment [56]. The authors conclude that the effect of CPB on the fibrinolytic system lasts up to thirty days after surgery. However, whether this effect was specific to CPB is not clear. Wang *et al.* [58] found a peak in D-dimer levels at the 1-month follow-up time point in patients who received cardiac surgery without CPB and without antifibrinolytic therapy. A normalization of D-dimer values did not occur until the 3-months follow-up time point. Also, postoperative morbidity was associated with higher D-dimers in this study, similarly to the findings in vascular surgery patients mentioned above [51, 52]. The authors [58] found that 10 % of patients suffered recurrent angina within the one-

year follow-up period after off-pump CABG and these patients had significantly higher D-dimer levels at the one-month follow-up point.

1.5 Antifibrinolytics

The most common antifibrinolytic agents are aprotinin, epsilon aminocaproic acid (EACA) and TXA [59]. Aprotinin is derived from bovine lung tissue [60], while EACA and TXA are synthetically produced lysine analogs [6]. This work focuses on TXA, as it was applied in our study. The mechanisms of action of TXA are as following: TXA inhibits the activation of plasminogen, and at higher doses the activity of plasmin directly [61]. The inhibition of fibrinolysis explains its antihemorrhagic effect. It is also useful diagnostically, as the antifibrinolytic effect of TXA can be monitored using D-dimer levels, as has been done in previous studies [62-64]. On a side note, TXA possesses a further antihemorrhagic effect by indirectly inhibiting the plasmin mediated activation of GP-Ib/IX receptors on the surface of platelets [65], which normally induces platelet activation, although this is less relevant to our work.

Due to its low cost and high clinical usefulness, TXA belongs to the list of essential medicines published by the World Health Organization [66]. It is used for prevention and treatment of surgical and non-surgical hemorrhage in several clinical settings, most commonly in trauma [67] and cardiac surgery [9]. However, certain predicaments in the uncritical application of TXA exist.

The CRASH-2 trial (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2) [67], a large multicenter, multinational randomized placebo-controlled trial on trauma patients, demonstrated a significant reduction of all-cause mortality and death due to bleeding in the group treated with TXA compared to placebo. The authors also found a decreased risk of death due to myocardial infarction, which had been a previous safety concern. The application of 1 g of TXA as a loading dose and an additional 1 g over an 8 hour infusion is now recommended by the European trauma guideline [68]. However, concerns with regards to safety persist in the context of trauma and surgery

[69, 70]. Hunt [71] points out that the CRASH-2 results should not be extrapolated uncritically to settings such as cardiac surgery, as TXA may have thromboembolic [70], and epileptogenic side effects [9] in this context. This may be due to coexisting coagulopathies in this specialty, as pointed out by Simmons *et al.* [72]. Concerns regarding safety of TXA remain in recent publications. The 2017 EACTS/EACTA guidelines [16] give the highest level of recommendation, Class IA, for the intraoperative administration of tranexamic acid or aprotinin, but additional research on safety is called for by the authors.

In terms of optimal dosing of TXA for reduction of bleeding, a relatively wide range has been examined. Earlier studies found conservative dosing strategies, such as a single bolus of 10 mg of TXA before sternotomy, effective [73]. Horrow *et al.* [62] found similar results. Intermediate doses were examined in subsequent studies, such as the "BART" dose (Blood Conservation Using Antifibrinolytics in a Randomized Trial) [74], and recently very high doses in a large trial by Myles *et al.* [9]. However, optimal doses have not been established. In contrast to the trauma guideline which gives a clear dosing protocol for TXA [68], the above-mentioned EACTS/EACTA guideline for TXA in cardiac surgery surprisingly does not give any recommendation for dosing [16]. It has recently been proposed [22, 75] to base dosing strategies on risk of performed surgery. A large meta-analysis for determination of safety and efficacy of TXA is under progress [76], and may give further insight.

1.6 Ethics Approval

Data collection for this work was approved by the local ethics committee (study number 4331) and the standards of good clinical practice were maintained with respect to all aspects of this work. A more detailed description referring to this can be found in our publication [1].

1.7 Objectives of this Work

Improving diagnostic and treatment options for cardiac surgery patients to decrease hemorrhage and transfusion rates is relevant to patient safety and is recommended by current guidelines [16]. D-dimers are an accessible laboratory value and have thoroughly been explored in non-cardiac scenarios. Their usefulness as a marker for fibrinolysis in the context of cardiac surgery, though, has not been fully understood. As the clinical setting of cardiac surgery presents several opportunities for disruption of hemostasis and fibrinolysis as described in the chapters above, it is our goal to examine whether differences in perioperative fibrinolytic activity exist, and whether they are reflected by D-dimer measurement. We hypothesize that preoperative fibrinolytic activity differs according to the underlying cardiac disease. Furthermore, tissue trauma, CPB and other factors may influence intraoperative fibrinolysis. Therefore, we hypothesize that intraoperative changes in fibrinolysis differ according to performed surgery, and that these changes may be monitored using D-dimers. In a secondary outline, we suggest that the effect of two doses of antifibrinolytic therapy may be reflected by differences in D-dimer dynamic during surgery.

2 Fibrinolysis and the Influence of Tranexamic Acid Dosing in Cardiac Surgery, Besser, V., Albert, A., Sixt, S. U., Ackerstaff, S., Roussel, E., Ullrich, S., Lichtenberg, A., Hoffmann, T., Journal of Cardiothoracic and Vascular Anesthesia, 34: 2664-2673, (2020)

Journal of Cardiothoracic and Vascular Anesthesia 34 (2020) 2664–2673

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Fibrinolysis and the Influence of Tranexamic Acid Dosing in Cardiac Surgery

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Objective: The present study aimed to determine whether underlying disease, performed surgery, and dose of tranexamic acid influence fibrinolysis measured with D-dimer levels.
Design: Retrospective analysis.
Setting: Single institution (Department of Cardiac Surgery and Section of Clinical Hemostaseology at the Düsseldorf University Hospital).
Participants: The study comprised 3,152 adult patients undergoing elective cardiac surgery between February 2013 and October 2016.
Interventions: Two doses of tranexamic acid during surgery were administered.
Measurements and Main Results: D-dimer levels were analyzed at the start of surgery and before protamine administration. D-dimer levels at the start of surgery were compared according to disease. Intraoperative D-dimer development was analyzed according to the type of surgery and within 2 cohorts with different tranexamic acid doses. Interindividual variability was pronounced for D-dimer levels at the start of surgery, with significant differences among patients with coronary artery disease, valve disease, and aortic disease and patients undergoing heart transplantation compared with patients receiving a left ventricular assist device ($p < 0.01$). Aortic dissection, endocarditis, and extracorporeal life support were associated with higher D-dimer levels ($p \leq 0.01$). With tranexamic acid at a fixed dose, intraoperative D-dimer levels decreased in on-pump and off-pump coronary bypass surgery, valve surgery, and left ventricular assist device surgery ($p \leq 0.02$), but levels increased in aortic surgery and heart transplantations ($p < 0.01$). A decrease or increase in D-dimer levels during surgery was influenced significantly by a higher or lower tranexamic acid dose ($p \leq 0.01$).
Conclusions: D-dimer testing allows for the assessment of individual fibrinolytic activity in cardiac surgery, which is influenced by disease type, surgery type, and dose of tranexamic acid. The assessment of the fibrinolytic status may have the potential to facilitate dose-adjusted antifibrinolytic therapy in the future.

Key Words: fibrinolysis; tranexamic acid; D-dimers; cardiac surgery; antifibrinolytics; thromboelastometry

D-DIMERS are degradation products resulting from plasmin-induced clot lysis.[1] They can indicate a thrombotic or hemorrhagic status. In patients with increased fibrinolysis as a result of thrombus formation, elevated D-dimer levels give a prothrombotic signal, reflecting activation of coagulation and fibrinolysis.[2] In contrast, elevated D-dimer levels resulting from hyperfibrinolysis are indicative of a hemorrhagic risk.[3] Elevated D-dimer levels also can imply coexisting thrombotic and hemorrhagic propensity, such as in disseminated intravascular coagulation[4] or in atrial fibrillation with anticoagulative

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https://doi.org/10.1053/j.jvca.2020.03.040
1053-0770/

treatment.[5,6] In cardiac surgery, intraoperative fibrinolysis is relevant in the context of tissue trauma[7] and cardiopulmonary bypass (CPB),[8] which has been studied previously using D-dimer levels.[9,10] Higher D-dimer levels have been correlated with increased postoperative bleeding after coronary artery bypass grafting (CABG) and/or valve surgery[11,12] and with graft occlusion rates after CABG.[13]

The antifibrinolytic tranexamic acid (TXA) decreases bleeding in cardiac[14,15] and noncardiac surgery[16] and in postpartum hemorrhage.[17] Antifibrinolytics such as TXA inhibit the formation of plasmin from plasminogen,[18] which degrades fibrin. Their intraoperative administration is a class IA recommendation in cardiac surgery.[19] However, limited efficacy and safety data on TXA are available with respect to patient subgroups. Dosing schemes vary widely.[20] Usually, it is institutional routine to administer TXA at a fixed dose without taking the individual hemostatic and fibrinolytic statuses into account.[16] In a trauma setting, the administration of TXA to patients with physiological fibrinolysis is associated with increased mortality.[21] An individualized approach to dosing using standard and thromboelastometric coagulation tests for diagnostic evaluation of fibrinolytic activity is under discussion.[21-23]

For the present study, D-dimer levels were used as a marker for fibrinolysis in cardiac surgery patients and were assessed for their correlation with cardiac disease and surgery. As a secondary outline, the effect of 2 doses of TXA on fibrinolysis was analyzed.

Materials and Methods

Patients

Retrospective data analysis was approved by the local ethics committee (study number 4331). The study was registered at the German Clinical Trials Register (DRKS00005082) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Data from patients undergoing cardiac surgery between February 7, 2013, and October 31, 2016, were analyzed retrospectively. Eligible participants were older than 18 years and underwent elective cardiac surgery at the Department of Cardiac Surgery at the Düsseldorf University Hospital in Germany. Patients with one of the following types of diseases were included: coronary artery disease, valve disease, or a combination of both; aortic disease; heart failure requiring heart transplantation (HTX); or left ventricular assist device (LVAD) implantation. Types of surgery performed were off-pump CABG, on-pump CABG, single- valve surgery, multiple- valve surgery (including Ross procedures), combined CABG and valve surgery, aortic surgery, HTX, and LVAD implantation. Surgeries were performed using standard surgical technique.

The initial activated clotting time (ACT) was measured before induction of anesthesia with the ACT Plus System (Medtronic, Minneapolis, MN), and measurements were repeated every 30 minutes during CBP. Anticoagulation before CPB was standardized; patients received a bolus of 300 IU/kg of unfractionated heparin before initiation of CPB, and 5,000 U were added to the priming solution to maintain an ACT >400 seconds during CPB. In the off-pump group, 200 IU/kg were used with a target ACT >250 seconds. The temperature of patients on CPB was cooled to mild hypothermia with a target of 34°C. Protamine was administered to reverse the heparin effect at the end of CPB or off-pump surgery at a dose of 75% of the total amount of heparin administered during the procedure. Finally, the red blood cell transfusion policy was standardized and based on departmental practices with a transfusion trigger of 8 g/dL hemoglobin. Platelets were not transfused before blood withdrawal before protamine administration. If needed, 2 concentrates of fresh frozen plasma were transfused per concentrate of red blood cells.

Patients were given an intravenous bolus of TXA of 10 mg/kg of actual body weight at the time of incision, an additional 10 mg/kg of body weight if on CPB, and a continuous infusion during surgery. Between February 7 and August 8, 2013, patients received a continuous infusion of 2 mg/kg/h (lower dose of TXA [LD-TXA]). During a 2-week period in August 2013, no patients were enrolled in the study because of internal reorganization, and the dose of continuous TXA infusion was adjusted after this break as an institutional decision. Patients who underwent surgery between August 23, 2013, and October 31, 2016 received 8 mg/kg/h (higher dose of TXA [HD-TXA]) after the initial bolus. In cases of significant renal insufficiency, the dose of TXA was reduced by −1.3 mg/kg/h for every decrease in the glomerular filtration rate by −10 mL/min.

Methods

Anticoagulated blood samples (0.109 M buffered sodium citrate 3.2%) were taken from an arterial catheter at the start of surgery and before protamine administration. The before protamine administration sample was taken 15 to 20 minutes before protamine was administered while the patient was still on CPB. Protamine was given after declamping of the aorta and reperfusion. Laboratory samples taken after protamine administration were not included in the present analysis. Transport of the samples to the laboratory was conducted with use of a validated pneumatic tube system within n <5 minutes. Hemostatic assessment was performed as previously described.[24] Conventional laboratory methods were applied for the assessment of D-dimer levels (Innovance D-Dimer; Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) and factor XIII activity (Berichrom factor XIII; Siemens) using a BCS XP system (Siemens) at the start of surgery and before protamine administration. High sensitivity and precision have been shown for this D-dimer assay.[25] Viscoelastic testing was performed with thromboelastometry, and impedance aggregometry was conducted to assess the platelet function, also as previously described.[24] Conventional routine tests were used for the assessment of the platelet counts and creatinine.

For disease-specific analyses, patients were grouped according to the underlying disease, and baseline D-dimer levels (D-dimer level at the start of surgery) were compared between groups. Subgroup analyses were performed according to the

following disease-modifying conditions: endocarditis in valve disease, dissection in aortic disease, preexisting extracorporeal life support (ECLS) in recipients of an LVAD, or preexisting LVAD in patients undergoing HTX.

For surgery-specific analyses, in patients with HD-TXA only, the development of D-dimers at the start of surgery to D-dimers before protamine administration was ranked and analyzed for each of the 8 types of surgery (CABG here being divided into on-pump and off-pump). In addition, the absolute and relative intraoperative decrease in D-dimer levels for patients undergoing aortic surgery were analyzed, excluding patients with endocarditis. D-dimer levels of patients with aortic disease complicated by dissection were compared with those of the same number of consecutive patients without dissection from the same time period. Delta D-dimers (D-dimer levels before protamine administration minus D-dimer levels at the start of surgery) were calculated and correlated with the time interval between blood sampling at the start of surgery and before protamine administration. For the assessment of a TXA dose effect, propensity score matching (PSM) was used for matching HD-TXA with LD-TXA patients because it was clear before analysis that the number of HD-TXA patients would be greater because of the longer period during which HD-TXA had been given. Matching with a caliper width of 0.1 included the following parameters: D-dimer levels at the start of surgery, sex, weight, age, type of surgery, CPB, redo-surgery, endocarditis, and time interval between the start of surgery and before protamine administration. Furthermore, to reduce confounding, the following additional coagulation studies at the start of surgery were included in the PSM: platelet count, platelet function (adenosine diphosphate [ADP], arachidonic acid [ARA], thrombin receptor activating peptide [TRAP]); fibrinogen function (FIBTEM); FXIII activity (levels of FXIII); and coagulation times (INTEM, EXTEM). After matching, D-dimer values at the start of surgery and before protamine administration within and between both dose groups were compared, as was the transition of D-dimer levels from the start of surgery to before protamine administration after categorization into the following 4 groups: normal (≤0.50 mg/L), slightly elevated (0.51-2.00 mg/L), strongly elevated (2.01-5.00 mg/L), and greatly elevated (≥5.01 mg/L). The number of patients being moved into a lesser category (−1), staying the same (0), or moving to 1 or 2 higher categories (+1 or +2) were analyzed for both the LD-TXA and the HD-TXA groups. Categories for D-dimers at the start of surgery were defined a priori based on clinical relevance of D-dimer ranges.

Statistical Analysis

The authors' original hypothesis was that D-dimer levels in cardiac surgery patients vary according to underlying disease and to the type of surgery. Moreover, the authors hypothesized that interindividual variability of D-dimer levels goes beyond what can be explained by disease and surgery types. The effect of 2 doses of TXA on D-dimer development was defined retrospectively as a secondary outcome. D-dimer levels at the start of surgery and before protamine administration were defined as the primary outcome. With regard to intraoperative D-dimer development, relative changes seemed to present more interesting information than the absolute data, and the authors decided to use nonparametric statistical testing for this analysis. For comparisons of D-dimer levels at the start of surgery with levels before protamine administration according to dose of TXA, sample sizes were assessed to be sufficient for parametric testing. SPSS Statistics for macOS, Versions 24.0 and 25.0 (IBM Corp, Armonk NJ), was used for statistical testing. Data are presented as mean ± standard deviation. D-dimer comparisons were assessed as follows. An analysis of variance with Tamhane's T2 post hoc tests was used to calculate differences in D-dimers at the start of surgery among types of diseases. The Student 2-tailed *t* test was used for the subgroup comparisons of D-dimer levels at the start of surgery and for comparison of D-dimer levels at the start of surgery after PSM. Intraoperative D-dimer development according to surgery and the dose of TXA were calculated using the Wilcoxon signed rank test. A decrease in D-dimer levels in aortic surgery according to dissection and D-dimer changes between categories according to dose of TXA were analyzed using Pearson's chi-square test. Spearman's correlation was used to correlate the time of blood sampling between the start of surgery and before protamine administration with intraoperative D-dimer development. Results with a p value of < 0.050 were considered to be statistically significant.

Results

A total of 3,152 patients were enrolled. In the given time frame, the majority of patients undergoing elective cardiac surgery at the authors' institution provided consent. A negligible number of patients were not included for the sole reason of denial of consent, and there was no indication for a systematic error. Mean age was 68 years, mean weight was 82 kg, and 71% (2,239) of participants were male. LD-TXA was administered to 265 patients, and 2,887 patients received HD-TXA. Laboratory results were incomplete in 66 patients because of variable technical or logistic reasons, without evidence for a systematic error.

Within disease groups, a strong variability of disease-specific D-dimer levels before the start of surgery was found (Fig 1). There was a statistically significant difference in D-dimer levels at the start of surgery among the underlying types of diseases ($p < 0.001$); post hoc, this difference was between LVAD and all other types of surgery (p betwee$n$ <0.001 and 0.019, respectively). Patients with aortic disease in the absence of dissection ($n = 215$) had significantly lower mean D-dimer levels at the start of surgery than did patients with dissection ($n = 29$) (1.26 ± 2.61 mg/L *v* 12.28 ± 21.39 mg/L; $p = 0.010$). Patients who underwent valve surgery without endocarditis ($n = 1.106$) had mean D-dimer levels at the start of surgery of 1.04 ± 3.49 mg/L compared with 3.39 ± 3.67 mg/L in the presence of endocarditis ($n = 103$) ($p < 0.001$). The mean of D-dimer levels at the start of surgery in 22 patients who underwent HTX without preexisting LVAD ($n = 6$) was 0.49 ± 0.26 mg/L, compared with 3.04 ± 2.96 mg/L for patient with

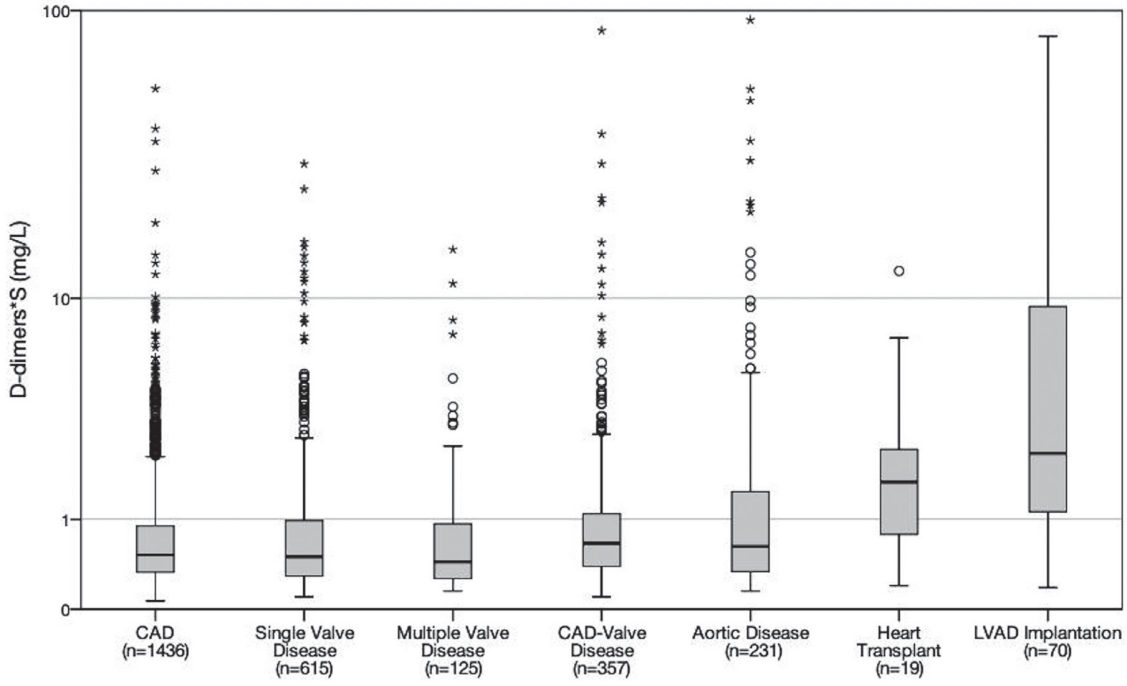

Fig. 1. Disease-specific D-dimer levels. *Boxes* show the 75th/25th percentiles and median. The *antennae* reach 1.5 interquartile range above/below the 75th/25th percentiles. The *circles* are 1.5 to 3 interquartile range away from the 75th/25th percentiles, and the *asterisks* interquartile range are >3 interquartile range away from the 75th/25th percentiles. The y-axis is logarithmic. CAD, coronary artery disease; LVAD, left ventricular assist device.

an LVAD ($n = 16$) ($p = 0.052$). Of the 82 patients who received an LVAD, 26 (32%) were on ECLS. Mean D-dimer levels at the start of surgery were 4.22 ± 11.27 mg/L without ECLS and 17.62 ± 16.58 mg/L with ECLS ($p = 0.001$) (Fig 2).

Raw data for surgery-type–specific D-dimer development (Delta D-dimers) are shown in Fig 3; respective rank of the development of D-dimers from the start of surgery to before protamine administration are given in Table 1. Antifibrinolytic therapy with the TXA dose chosen (HD-TXA) was associated with the following: (1) a predominant decrease of D-dimer levels in patients undergoing off-pump CABG or, to a lesser degree, on-pump CABG, single- valve surgery; and LVAD implantation; (2) a predominant increase of D-dimer levels in aortic surgery and HTX; and (3) variable development of D-dimers in patients with multiple- valve surgery or a combination of CABG and valve surgery. Intraoperative D-dimer development in aortic surgery (HD-TXA) with or without dissection is shown in Supplemental Fig 1. Eleven patients with

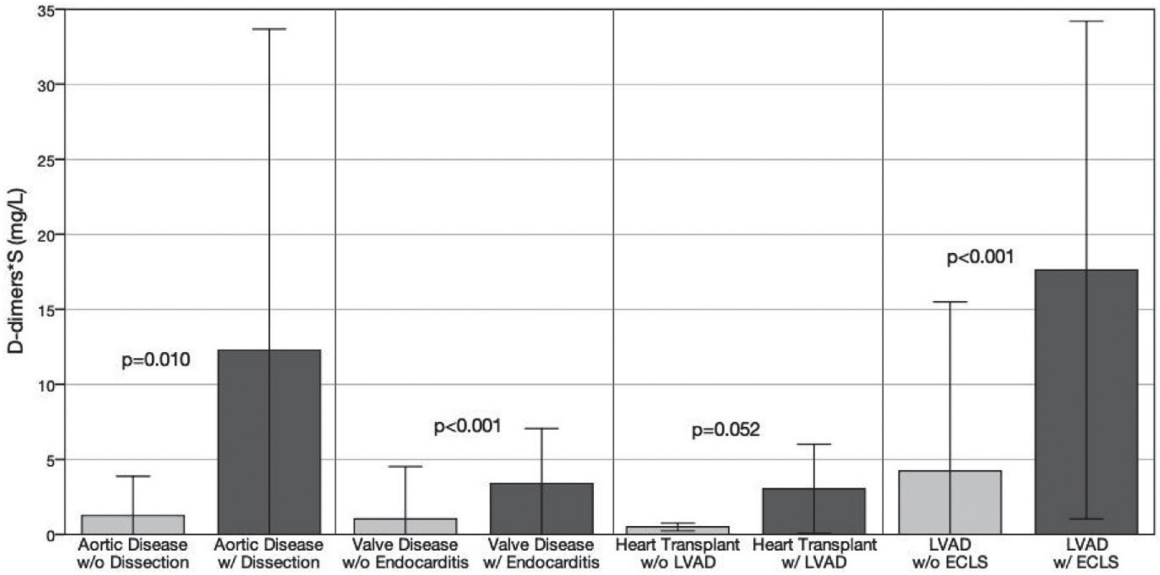

Fig. 2. Fibrinolysis-modifying conditions. Values are presented as mean ± 1 standard deviation. ECLS, extracorporeal life support; LVAD, left ventricular assist device.

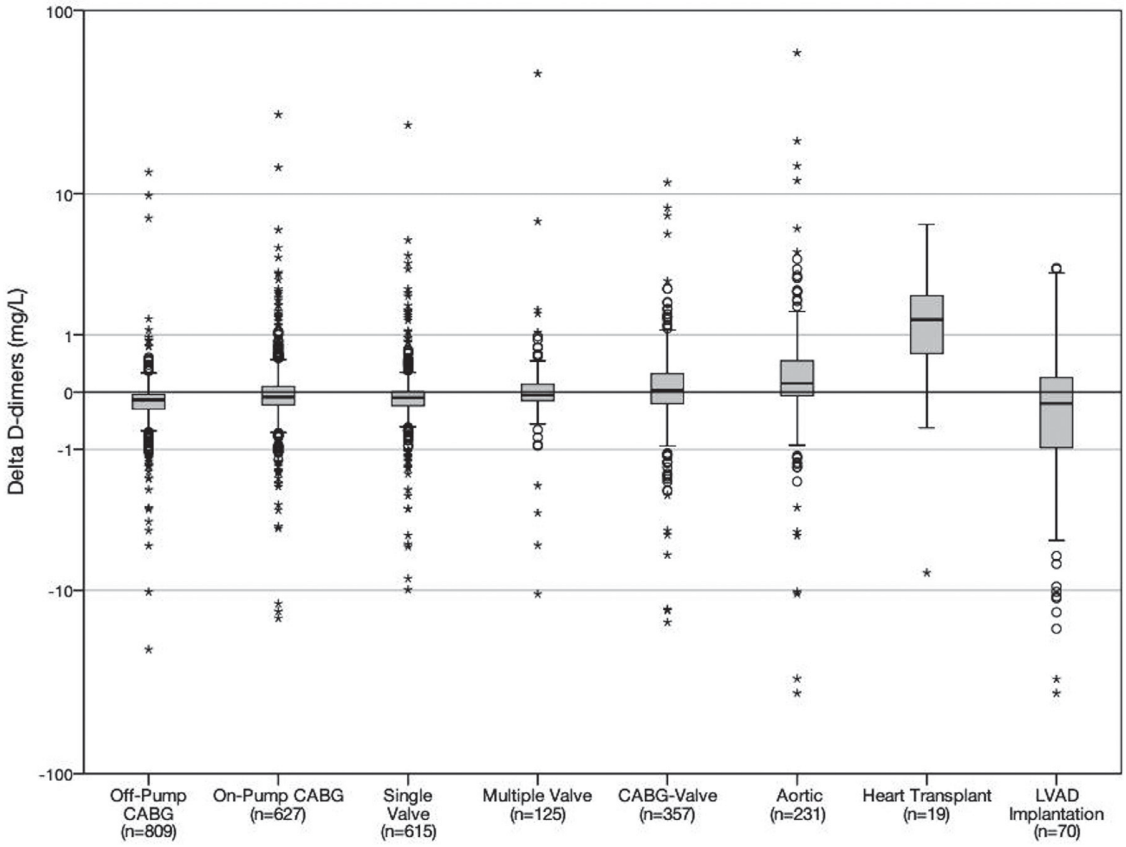

Fig. 3. Intraoperative course of D-dimer levels according to the type of surgery in the higher-dose tranexamic acid group (8 mg/kg/h). The *boxes* show the 75th/25th percentiles and median. The *antennae* reach 1.5 interquartile range above/below the 75th/25th percentiles. The *circles* are 1.5 to 3 interquartile range away from the 75th/25th percentiles, and the *asterisks* are >3 interquartile range away from the 75th/25th percentiles. The y-axis is logarithmic. Delta D-dimers = D-dimers before the administration of protamine minus D-dimers at the start of surgery. CABG, coronary artery bypass grafting; LVAD, left ventricular assist device.

aortic disease were excluded from the subanalysis because of coexisting endocarditis. D-dimer levels decreased from the start of surgery to before protamine administration in 42% of patients with aortic dissection compared with 31% of patients without dissection (n = 26; p = 0.388), with a decrease in D-dimer levels >10% in 38% *v* 15%, respectively (p = 0.061). A significant positive correlation of length of timebetween 'S' and 'bP' with increasing D-dimer levels was found; however, the correlation coefficient was low (r = 0.117; p < 0.001) (Supplemental Fig 2).

For the assessment of a TXA dose effect, 201 patients from the LD-TXA group were matched with 201 patients from the HD-TXA group (Table 2 and Supplemental Fig 3 for matching results). Mean D-dimer levels at the start of surgery did not differ significantly between groups (1.06 *v* 1.12 mg/L; p = 0.801). Intraoperative D-dimer levels from the start of surgery to before protamine administration increased significantly in the LD-TXA group and, in contrast, decreased significantly in the HD-TXA group (p < 0.001 and p = 0.004, respectively). The box plots in Fig 4 show the distribution of respective values. Based on the pragmatic categorization of D-dimer levels described in the Methods section, the transition between categories during surgery (Fig 5) was found to be significantly different between the LD-TXA and HD-TXA groups (p = 0.012). The major effects of HD-TXA compared with LD-TXA were prevention of normal D-dimer levels to pass into the slightly elevated category and increased transition from the slightly elevated category to normal values (Table 3).

Discussion

D-dimers have been used for the clinical assessment of fibrinolysis in cardiac surgery. Sample sizes, however, were small and only CABG and/or valve surgeries were examined.[9,10] In the present study, preoperative and intraoperative D-dimer levels of a large number of patients across all major cardiac surgeries were presented.

Although significant differences were found among disease types, the major finding was a strong interindividual variability within disease types (see Fig 1). However, the study demonstrated that preexisting conditions modified coagulability and fibrinolytic activity in a subgroup analysis (see Fig 2). In addition, aortic dissection, endocarditis, and extracorporeal circulation devices were associated with increased baseline D-dimer levels, which supported previous research.[26-29] Again, in this subgroup analysis, standard deviations of D-dimer levels were high. According to the detailed subgroup comparison, the assessment of fibrinolytic activity for diagnostic or therapeutic

Table 1
Ranks for D-Dimer Levels Before Protamine Administration Versus Levels at the Start of Surgery With HD-TXA

Type of Surgery	D-Dimer Levels at the Start of Surgery to Before Protamine Administration	*n*	*p* Value
Off-pump CABG	Negative*	665	< 0.001
n = 809	Positive†	101	
	Tie‡	43	
On-pump CABG	Negative	398	
n = 627	Positive	209	< 0.001
	Tie	20	
Single valve surgery	Negative	410	
n = 615	Positive	154	< 0.001
	Tie	51	
Multiple valve surgery	Negative	74	
n = 125	Positive	43	0.301
	Tie	8	
CABG + valve surgery	Negative	166	
n = 357	Positive	184	0.064
	Tie	7	
Aortic surgery	Negative	71	
n = 231	Positive	150	< 0.001
	Tie	10	
Heart transplantation	Negative	3	
n = 19	Positive	16	0.004
	Tie	0	
LVAD implantation	Negative	45	
n = 70	Positive	23	0.019
	Tie	2	

Abbreviations: CABG, coronary artery bypass grafting; HD-TXA, higher dose of tranexamic acid (8 mg/kg/h); LVAD, left ventricular assist device.
* Negative: D-dimer level before the administration of protamine (mg/L) < D-dimer level before the start of surgery (mg/L).
† Positive: D-dimer level before the administration of protamine (mg/L) > D-dimer level before the start of surgery (mg/L).
‡ Tie: D-dimer level before the administration of protamine (mg/L) = D-dimer level before the start of surgery (mg/L).

purposes must be performed individually because it can neither be deduced from disease type nor disease-modifying factors.

In addition to these disease-related D-dimer findings, surgery-related D-dimer development between the start of surgery and before protamine administration varied among and within types of surgery in terms of trend (decrease or increase) and absolute values. These observations were made with a standard dose of TXA (HD-TXA). D-dimer levels decreased significantly in off-pump and on-pump CABG, valve surgery, and LVAD implantation (see Table 1). This may be considered as the cumulative result of D-dimer elimination and D-dimer replenishment, the latter being influenced by TXA. Previous studies examining the intraoperative development of D-dimers without antifibrinolytic therapy found no change or an increase in D-dimer levels during CABG or valve surgery with CPB.[10,12] Additional studies are needed to compare hemorrhagic and thrombotic outcomes in patients with or without an intraoperative increase of fibrinolysis. The fibrin turnover differs markedly between CABG/valve surgery and LVAD implantation according to the absolute D-dimer levels at the start of surgery. A substantial proportion of LVAD patients had preceding ECLS support. Because LVAD implantation preceding ECLS acts as a hot spot for fibrin generation and degradation,[30] the pronounced surgery-specific decrease of D-dimer levels as observed in LVAD patients (see Fig 3) may at least be explained partially by the removal of the ECLS.

Even though the dose of TXA for CABG and valve surgeries was the same for aortic and HTX surgeries, the D-dimer levels significantly increased in the latter procedures. An increase in fibrinolysis can be a result of tissue trauma and the activation of coagulation in the CPB circuit.[7,8,31] If CPB effects were dominating, all types of on-pump surgery should have shown an increase in fibrinolysis, which was not observed in the present study. Tissue trauma inherently is more pronounced in aortic and transplantation surgery, and activation of coagulation and fibrinolysis may be especially high in surgery involving the aorta.[32] Aortic and transplantation surgeries take longer, and a positive correlation of length of surgery with an increase of D-dimer levels was found in the present study. However, the intensity of this effect seemed to be too weak to explain the observed increase in D-dimer levels. Notably, in aortic surgery, there seems to be a dependence of fibrinolysis on the presence of an aortic dissection. Even though in the present study, overall there was a statistically significant increase in D-dimer levels during aortic surgery (see Fig 3 and Table 1), the level decreased in almost half the patients with an aortic dissection (see Supplemental Fig 1). This observation went together with a higher baseline fibrinolytic activity in patients with dissection (see Fig 2). This high fibrin turnover may be assumed to originate from the false lumen. Intraoperative cessation of the false lumen to be perfused may be responsible for the reversal of fibrinolytic activity. The authors acknowledge that intraoperative development of D-dimers likely was influenced by the absolute baseline D-dimer values in all patients, and this was only evaluated in the aforementioned aortic dissection subanalysis.

The present study also demonstrated that intraoperative fibrinolytic activity depended on the dose of TXA. The effects of 2 doses of TXA on D-dimer development during surgery were examined. The study distinguished between HD-TXA and LD-TXA, and both were less than the standard "Blood Conservation Using Antifibrinolytics in a Randomized Trial

Table 2
Number of Cases After PSM in LD-TXA Versus HD-TXA Groups

Type of Surgery	LD-TXA (*n*)	HD-TXA (*n*)
Off-pump CABG	38	47
On-pump CABG	43	45
Single valve surgery	53	42
Multiple valve surgery	12	11
CABG + valve surgery	30	29
Aortic surgery	18	14
Heart transplantation	1	1
LVAD implantation	6	12
Total	201	201

Abbreviations: CABG, coronary artery bypass grafting; HD-TXA, higher dose of tranexamic acid (8 mg/kg/h); LD-TXA, lower dose of tranexamic acid (2 mg/kg/h); LVAD, left ventricular assist device; PSM, propensity score matching.

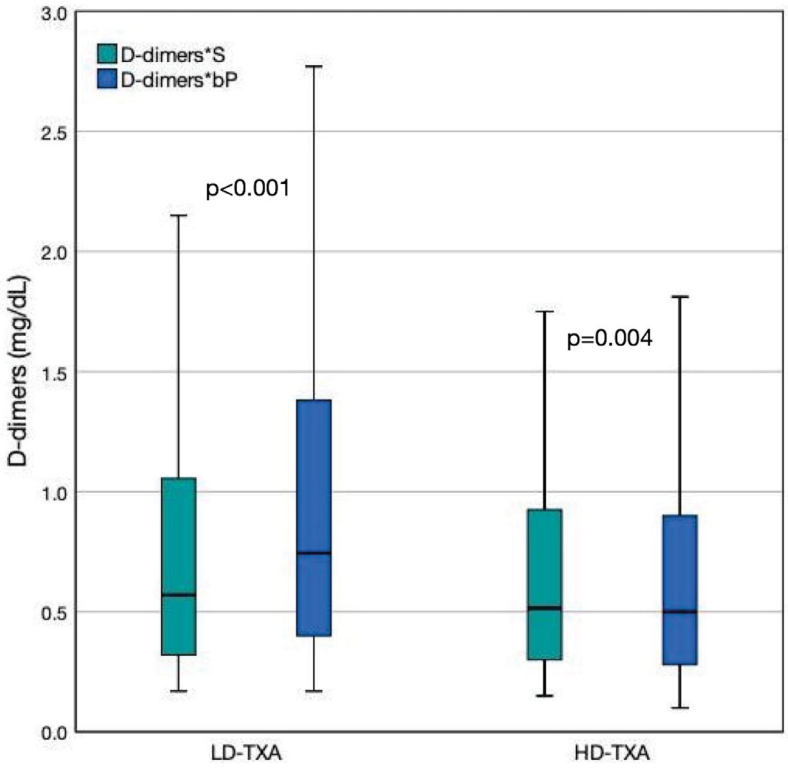

Fig. 4. Course of intraoperative D-dimer levels according to the dose of tranexamic acid. The *boxes* show the 75th/25th percentiles and median, and the *antennae* reach 1.5 interquartile range above/below the 75th/25th percentiles. Values exceeding the *antennae* are not displayed. HD-TXA, higher dose of tranexamic acid (8 mg/kg/h); LD-TXA, lower dose of tranexamic acid (2 mg/kg/h).

(BART)" dose.[33] PSM was performed to provide equal baseline D-dimer levels between groups. Other confounding variables also were matched successfully (see Supplemental Fig 3). From the start of the surgery until before the administration of protamine, there was a statistically significant increase in D-dimer levels in the LD-TXA group compared with a decrease in the HD-TXA group. Of note, the study matched according to type of surgery, and the majority of procedures were bypass, valve, and LVAD surgeries (see Table 2), which explained why D-dimer levels decreased overall in the HD-TXA group. It has been published that the short-term effect of TXA can be detected by changes in D-dimer levels in women with postpartum hemorrhage[17] and in cardiac surgery.[34-36] However, Faraoni et al.,[36] by comparing different TXA doses, were not able to demonstrate a dose-dependent antifibrinolytic effect on the basis of D-dimer measurement. One explanation for the discrepancy in the present study's findings was that patients with a disease-related increase of fibrinolytic activity were excluded from the study by Faraoni et al. Furthermore, continuous infusion doses were greater than in the present study's groups. The clinical significance of minute differences of D-dimer levels in cardiac surgery is unclear. Thus, the authors of the present study extended their analyses to a fibrinolysis assessment based on D-dimer categories. As shown in

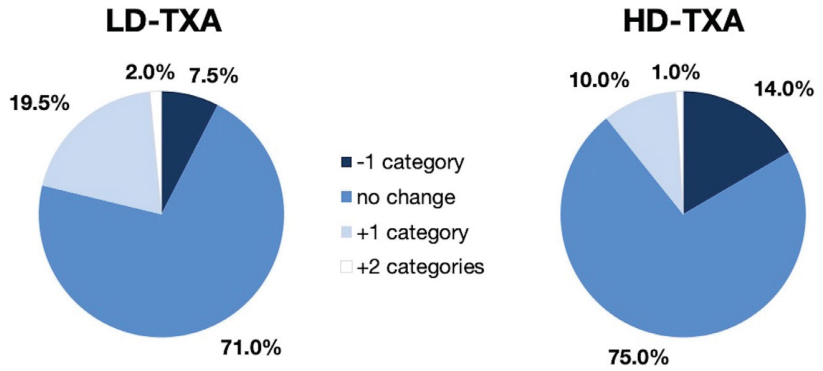

Fig. 5. Change of D-dimer level category according to the dose of tranexamic acid. Time span is from start of surgery to before administration of protamine. Categories for D-dimers are as follows: normal (≤0.50 mg/L), slightly elevated (0.51-2.00 mg/L), strongly elevated (2.01-5.00 mg/L), greatly elevated (≥5.01 mg/L). HD-TXA, higher dose of TXA (8 mg/kg/h); LD-TXA, lower dose of TXA (2 mg/kg/h).

Table 3
Transition Between D-Dimer Categories From the Start of Surgery to Before Protamine Administration Depending on TXA Dose

			D-Dimer Levels Before Protamine Administration (mg/dL)				
			Normal (≤0.50)	Slightly Elevated (0.51-2.00)	Strongly Elevated (2.01-5.00)	Greatly Elevated (≥5.01)	Total
D-dimer levels at the start of surgery (mg/dL)	Normal (≤0.50)	LD-TXA	62 (67.4%)	28 (30.4%)	2 (2.2%)	0	92 (100%)
		HD-TXA	80 (81.4%)	17 (17.3%)	1 (1.0%)	0	98 (100%)
	Slightly elevated (0.51-2.00)	LD-TXA	9 (10.1%)	69 (77.5%)	9 (10.1%)	2 (2.2%)	89 (100%)
		HD-TXA	22 (26.2%)	58 (69.0%)	3 (3.6%)	1 (1.2%)	84 (100%)
	Strongly elevated (2.01-5.00)	LD-TXA	0	6 (37.5%)	8 (50.0%)	2 (12.5%)	16 (100%)
		HD-TXA	0	5 (50.0%)	5 (50.0%)	0	10 (100%)
	Greatly elevated (≥5.01)	LD-TXA	0	0	0	3 (100%)	3 (100%)
		HD-TXA	0	0	1 (12.5%)	7 (87.5%)	8 (100%)
	Total	LD-TXA	71 (35.5%)	103 (51.5%)	19 (9.5%)	7 (3.5%)	200 (100%)
		HD-TXA	102 (51.0%)	80 (40.0%)	10 (5.0%)	8 (4.0%)	200 (100%)

Abbreviations: HD-TXA, higher dose of tranexamic acid (8 mg/kg/h); LD-TXA, lower dose of tranexamic acid (2 mg/kg/h); TXA, tranexamic acid.

Fig 5, D-dimer transition to a lower category was induced by HD-TXA, which also prevented D-dimer transition to a higher category. The present study's results suggested that D-dimer assessment may be used for pharmacodynamic monitoring of TXA.

Although a recent meta-analysis found no increased risk for thromboembolic events with TXA in cardiac surgery,[37] the risk for arterial and venous thromboembolic events has been studied incompletely because studies have been insufficiently powered.[38-40] TXA also has epileptogenic potential, which is considered a relevant adverse effect of the drug in cardiac surgery,[41,42] and lowering the dose for patients with other risk factors could be reasonable.[43] It was suggested in a recent review[44] that TXA dosing needs to be tailored to at least subgroups, or even individually. The authors of the present study point out that antifibrinolytics commonly are used to decrease bleeding in cardiac surgery, but there is a lack of clinical and laboratory predictors of bleeding.[44] TXA in a trauma setting has been linked to an increased risk for in-hospital thromboembolic events[45] and mortality in patients with physiological fibrinolysis assessed using thromboelastography.[21] Thus, the use of TXA has gained affirmative[46,47] and critical[21,45,48] attention. Altogether, based on existing evidence, it could be hypothesized that fixed-dose TXA in the individual patient may result in undertreatment with persisting bleeding risk or overtreatment leading to thrombotic risk. Dose adjustments may be based on D-dimer levels, among other factors. In a study on probands undergoing CABG,[35] D-dimer levels were reduced even by miniscule doses of TXA, which meant TXA had a clinically measurable effect on fibrinolysis in these patients. The accompanying reduction of blood loss in these patients[35] was moderate in this study. Patients with a low risk for bleeding (eg, CABG or single valve surgeries) with low fibrinolytic activity as indicated by low D-dimer levels may not benefit from intensive TXA dosing. On the other hand, patients with a high risk for bleeding who simultaneously have high D-dimer levels, such as aortic surgery patients in the present study, may require higher doses of antifibrinolytic therapy than what was used, as has been recommended previously.[49] The authors acknowledge that the present study's data could not support this theory because they did not evaluate for a dose dependency of perioperative bleeding or thrombosis. Additional research is needed to address the potential of fibrinolysis monitoring with goal-directed dosing for improvement of the risk-to-benefit ratio of antifibrinolytic therapies.

The present study had the following limitations. External validity was limited because of the observational single-center design. For the TXA dose analysis, the LD-TXA sample size was very small compared with that of the HD group. PSM results (see Supplemental Fig 3) demonstrated successful matching with a narrow caliper of 0.1. Still, the 2 doses of TXA were applied consecutively and not concurrently, and confounding was possible. Furthermore, an effect of hemodilution on D-dimer levels at the measurement before protamine administration was not excluded. In addition, coagulation and fibrinolysis are complex processes involving many hemostatic parameters in addition to D-dimer analysis.[50,51] Viscoelastic testing would provide more specific information on ongoing fibrinolysis; however, D-dimers are a well-known standard laboratory value and may be more accessible. Another limitation was inadequate heparin dosing, which could have over- or under- affected coagulation and influenced D-dimer levels, although the ACT was closely monitored during all surgeries. Lastly, preexisting coagulopathy was not evaluated and prior antiplatelet or anticoagulation therapy was not considered.

In conclusion, cardiac surgery patients present with substantial variability in fibrinolytic activity according to D-dimer assessment. Fibrinolysis is influenced dose dependently by TXA. The clinical relevance of the dose-response effect of TXA on fibrinolysis must be addressed in future studies.

Conflict of Interest

The authors declare no competing interests.

Acknowledgments

The authors gratefully acknowledge the contribution of all coworkers in the Department of Transfusion Medicine and Clinical Hemostaseology, particularly Kantharupan

Balasubramaniam, and in the Departments of Cardiac Surgery and Anesthesiology, for maintaining the standard for intraoperative diagnostics and hemotherapeutic care.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.03.040.

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3 Discussion

3.1 Preoperative Variability in Fibrinolysis

Our findings confirm our hypothesis that preoperative fibrinolytic activity in cardiac surgery patients is distinct according to underlying disease. An additional, only partially anticipated finding was a very wide standard deviation of D-dimers*S (Fig. 1 in [1]), even within types of disease. Some of this variation is examined in Fig. 2 of our publication [1], in which certain previous conditions correlated significantly with increased preoperative fibrinolytic activity. These conditions were endocarditis, aortic dissection and previous ECC and these findings are in line with previous research.

Weber *et al.* [77] demonstrated an association of elevated D-dimers with the presence and extent of aortic dissection. Differences in extent of dissection may explain why in aortic disease in Fig. 2 in [1], the standard deviation was much higher in the dissection group. There may have been a greater exposure of tissue in the aortic wall, activating the coagulation cascade and fibrinolysis. Tissue exposure along with infection might also play a role in the elevation of D-dimers in infective endocarditis (IE), as shown in Fig. 2 of [1]. D-dimers are elevated in IE and higher levels predict mortality [78]. In diseased heart valves, platelets and fibrin clots form around the valve endothelium and are colonized by bacteria [79]. Additionally, as in any infective process, the inflammation leads to activation of coagulation, as we have learned from the pathology of disseminated intravascular coagulation (DIC) in sepsis [80]. Notably, standard deviations were lower in this sub-analysis than in aortic dissections – the extent of endocarditis may be less relevant to fibrinolytic activity than the extent of dissection.

In addition to internal processes like vessel dissection or endocarditis, we found that fibrinolysis measured by D-dimers was activated preoperatively due to iatrogenic manipulation such as ECC, and this is in line with previous findings. Rising D-dimers are used clinically as an indicator of the need for a change of membrane oxygenator in patients on ECC [81]. It has also been shown that baseline D-dimer levels are elevated in patients supported with a left ventricular assist device (LVAD) due to the

prothrombotic properties of the surface of the device [82]. The underlying pathological mechanisms may be similar to those of CPB.

Fig. 1 of [1] also shows that in CAD or single or multiple valve disease, half of patients had D-dimers around 0.5 mg/dL, which is the cut-off value for normal in the Innovance® assay [83]. Furthermore, three quarters of D-dimer levels lay within ≤1 mg/dL in these patients. The 50. and 75. percentile was only slightly higher for CAD-valve disease patients. One could argue that a majority of these patients do not present with high preoperative fibrinolytic activity and routine D-dimer testing would be obsolete. On the other hand, with the exception of endocarditis as discussed above, it is not clear why a quarter of these patients with lower risk diseases (CABG and valve) had highly outlying D-dimers (Fig. 1 in [1]). For patients with aortic disease or heart failure requiring heart transplant or LVAD implantation, variability was partially explained in Fig. 2 of [1], but high standard deviations remained here as well. These results may be due to interindividual differences or other factors that we did not examine in this work.

3.2 Cardiopulmonary Bypass and Fibrinolysis

The analysis of the effect of CPB on fibrinolysis was not the focus of our work. However, we did divide CABG surgeries into on- and off-pump CABG for the analysis of intraoperative D-dimer development. The reason for this was, as mentioned in the introduction, the association of CPB with activation of coagulation, fibrinolysis and hemorrhage [12]. As illustrated, the contact system is activated by CPB, and this probably leads to bradykinin and t-PA induced fibrinolysis [31]. The literature on the association of CPB with fibrinolysis is limited. Any trauma or surgery causes vascular injury, which can be the cause for systemic plasmin activation and fibrinolysis [84]. This is unrelated to the use of CPB. On a side note, this systemic plasmin activation may explain why systemic infusion of antifibrinolytic therapy is superior to local application [85], and also why TXA has blood sparing benefits during off-pump surgery as well [86]. Vascular injury is highly prevalent in cardiac surgery, and it may therefore difficult to distinguish the surgical effect on fibrinolysis from the effect of CPB.

The discovery of CPB was a major milestone in cardiac surgery and many procedures require cardioplegia and subsequently, the use of ECC in the form of CPB. Still, the development of off-pump coronary artery bypass (OPCAB) grafting [87] offers to opportunity to relate intraoperative fibrinolytic changes to CPB using an OPCAB patient population as a control group. The purpose of our study was not the comparison of on-pump vs. off-pump CABG surgery, but we would like to discuss our findings, as well as the existing literature in the following section.

As shown in Table 1 of our publication [1], in the OPCAB group (n = 809), there were 101 patients (12.5 %) with increasing intraoperative D-dimer levels. The number of increasing intraoperative D-dimer levels in the on-pump group (n=627) was 209 (33.3 %) in comparison. We did not undertake further calculations of this, and therefore cannot comment on statistical significance, but there was a higher proportion of intraoperative D-dimer increases in the on-pump group compared to the off-pump group. Furthermore, as shown in Fig. 3 of our publication [1], the overall median of the absolute Delta D-dimer values was negative in both groups, although the third quartile was slightly negative in the off-pump group, and slightly positive in the on-pump group. The decrease from 'S' to 'bP' was statistically significant in both groups. Importantly, these data were obtained under the same dose of continuous infusion of TXA (HD-TXA). From these data, one can conclude that fibrinolytic activity is influenced by the use of CPB, and also that D-dimer levels often decrease during both on- and off-pump CABG under antifibrinolytic therapy.

In contrast to our findings, Casati *et al.* [88] found an intraoperative increase in D-dimer levels during CPB as well as during OPCAB. The main increase in D-dimer levels was seen from time point 2 (5 min after heparin) to time point 3 (arrival at the ICU). However, we took the second measurement which we compared to baseline earlier than Casati *et al.* [88]. The second blood sample was taken before reversal at heparin, not at the arrival in the ICU. It is possible that, D-dimers would have been higher than at baseline upon arrival in the ICU if we had obtained additional later samples in our study population. Also, the discrepancy to our findings may be explained by the fact that in the study

population of Casati *et al.* [88], no antifibrinolytic therapy was applied. The association of D-dimer and antifibrinolytic therapy will be discussed in the TXA chapters.

In addition, fibrinolytic changes in response to CPB may be individual with respect to absolute as well as time-dependent changes. A study using intraoperative measurements of t-PA, PAI-1 and t-PA antigen as markers for fibrinolysis (instead of D-dimers as we did) found varying responses to CPB in cardiac surgery [89]. The most common response occurred in 40 % of patients, which showed a rapid intraoperative increase in active and total t-PA. Others responded with no change in t-PA intraoperatively with postoperative increases in PAI-1 or vice versa. Interestingly, in 10% of patients there was no change in any of the measured parameters regardless of the use of CPB in all patients.

Summing up these results and existing literature, the associations of fibrinolysis, D-dimer and CPB are heterogenous, and dosing of antifibrinolytic therapy should be considered during interpretation of literature. Further research is required, and the measurement of additional fibrinolytic laboratory values may be reasonable.

3.3 D-dimer Development Based on Preoperative Values

In our publication [1], Table 1 and Fig. 3 present D-dimer development according to type of performed surgery and findings are examined in the discussion section. In the aortic dissection sub-analysis [1], it was indicated that intraoperative development was influenced by baseline D-dimer values. It seems likely that this was the case in other types of surgery as well, which is why further analysis of intraoperative D-dimer dynamic in relation to baseline D-dimer values was undertaken. In this work, Figures 1-8 present these data per type of surgery graphically. Data, as in Fig. 3 and Table 1 of our publication [1] are only shown from the HD-TXA group. For facilitated comparisons, only data sets with D-dimer*S levels ≤5.0 mg/dL, and Delta D-dimers between -3.0 and +5.0 mg/dL are displayed. Most low risk patients had baseline D-dimer levels lower than 1.0 mg/dL (Fig. 1 in [1]). However, this does exclude several data sets of aortic and LVAD patients, who

had D-dimers*S higher than 5.0 mg/dL (Fig. 2 in [1]). Therefore, the complete data set for aortic surgery and LVAD implantation patients are presented in Suppl. Fig. 1 and 2 in the appendix of this work.

Suppl. Fig. 1 confirms the suggestion in our publication [1] that in LVAD patients, intraoperative D-dimer decreases occurred with higher baseline D-dimers, which correlated with the previous use of ECC (Fig. 2 in [1]). Fig. 8 of this work shows unspectacular D-dimer development in LVAD patients with low D-dimer*S levels in contrast.

Results of Fig. 6 and 7 give mostly increasing intraoperative D-dimer levels regardless of baseline values during heart transplant and aortic surgery. This is coherent with the high amount of vascular injury during these surgeries, stimulating fibrinolysis.

Findings in the lower risk surgeries (Fig. 1 – 5) are less easily explained. The highest positive Delta D-dimer values were related with relatively low D-dimer*S level in CABG, valve and combination surgeries. Per trend, the higher preoperative D-dimer levels were, the more often there was a negative Delta D-dimer. Parts of these findings can be explained mathematically, as there is more latitude for absolute decrease with higher baseline value. What is interesting, though, is that high baseline fibrinolytic activity more often correlated with decreasing than with increasing intraoperative development. Possible reasons for D-dimer decreases were reviewed in our publication [1]. What it did not account for, however, is the lack of data sets showing increasing fibrinolysis in patients with high baseline fibrinolytic activity. This may be due to high effectiveness of antifibrinolytic therapy under very active fibrinolysis, or the intraoperative removal of a stimulus that we are not aware of. It may be worthwhile to examine these values in the postoperative time period. It should be noted that only baseline values up to D-dimer*S of 5.0 mg/dL are displayed, because these constitute the vast majority of data sets for the lower risk surgeries. Patients with higher baseline activity may have different intraoperative courses, though, and it would be interesting to examine these as well.

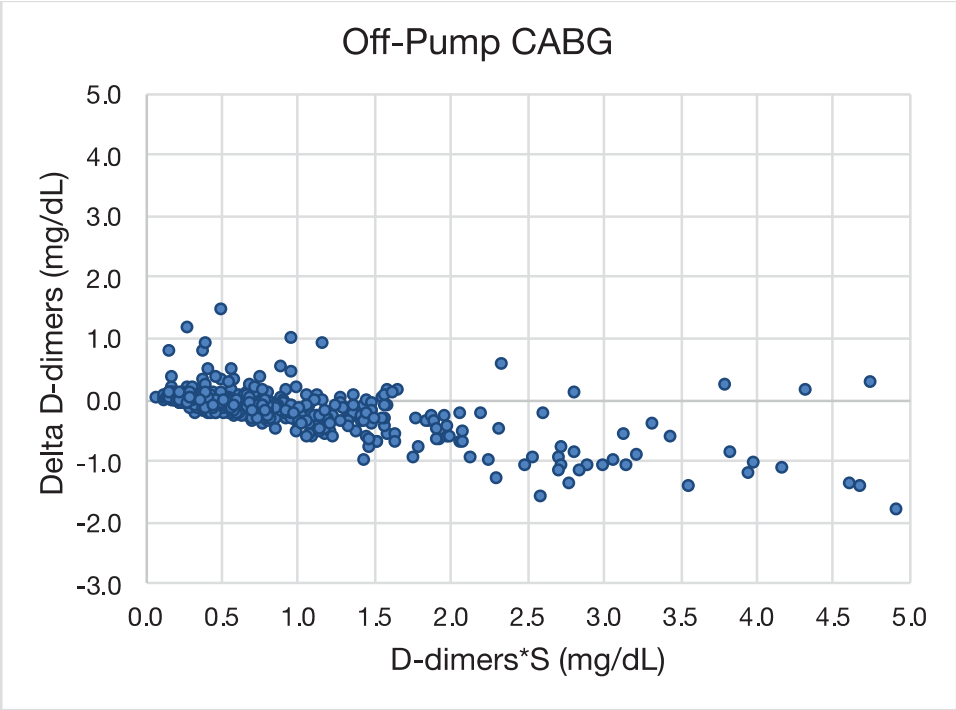

Fig. 1: **D-dimer development in Relation to Baseline in Off-Pump CABG under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
CABG: coronary artery bypass grafting; HD-TXA: higher dose of tranexamic acid

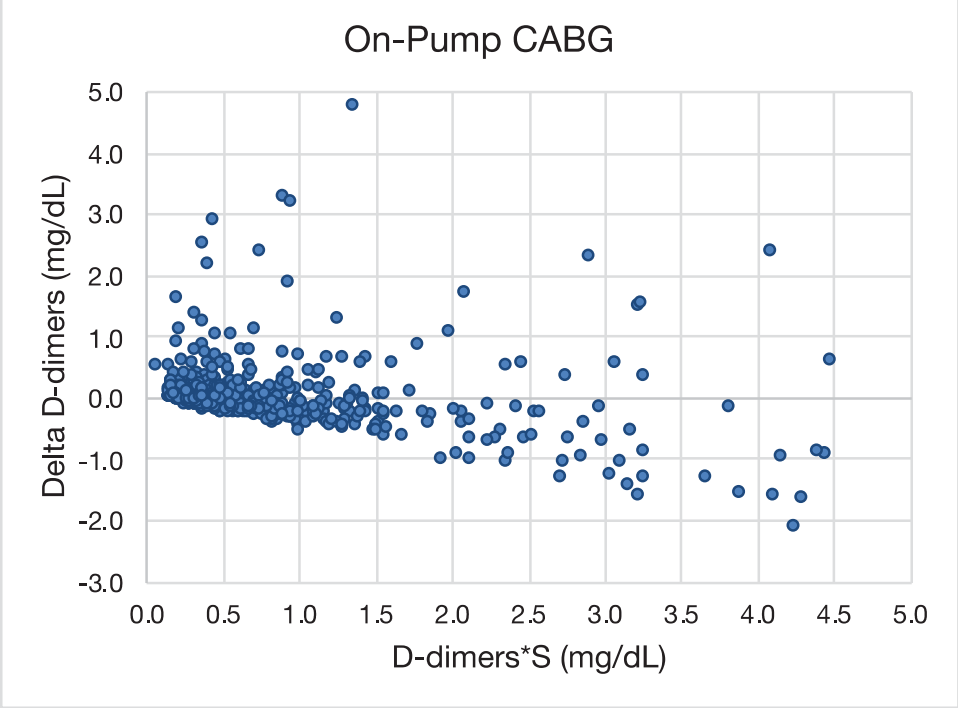

Fig. 2: **D-dimer development in Relation to Baseline in On-Pump CABG under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
CABG: coronary artery bypass grafting; HD-TXA: higher dose of tranexamic acid

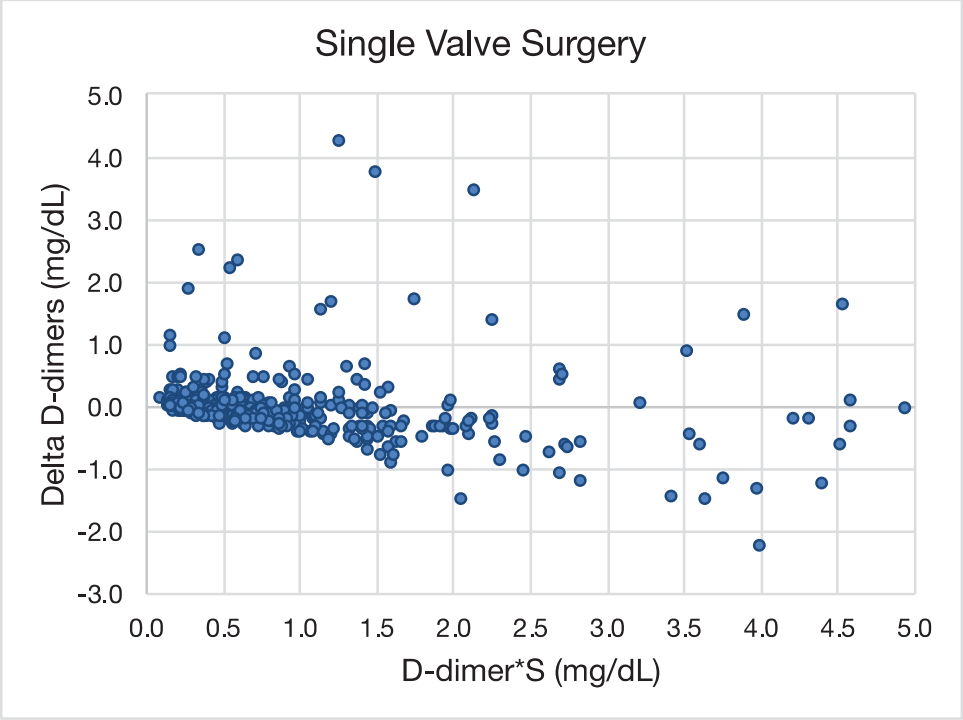

Fig. 3: **D-dimer development in Relation to Baseline in Single Valve Surgery under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
HD-TXA: higher dose of tranexamic acid

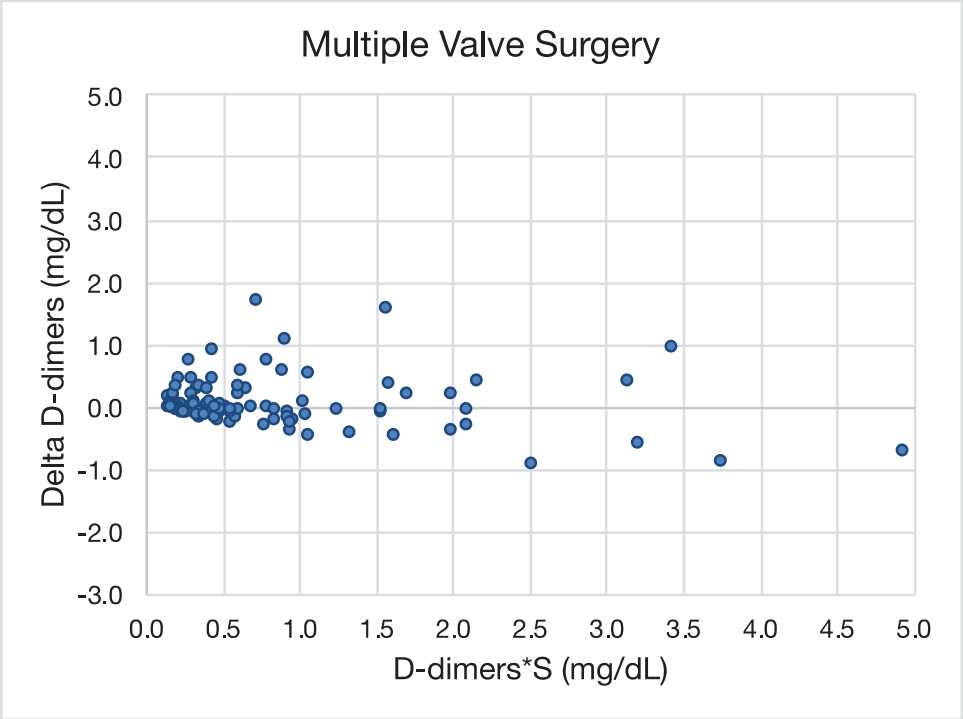

Fig. 4: **D-dimer development in Relation to Baseline in Multiple Valve Surgery under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
HD-TXA: higher dose of tranexamic acid

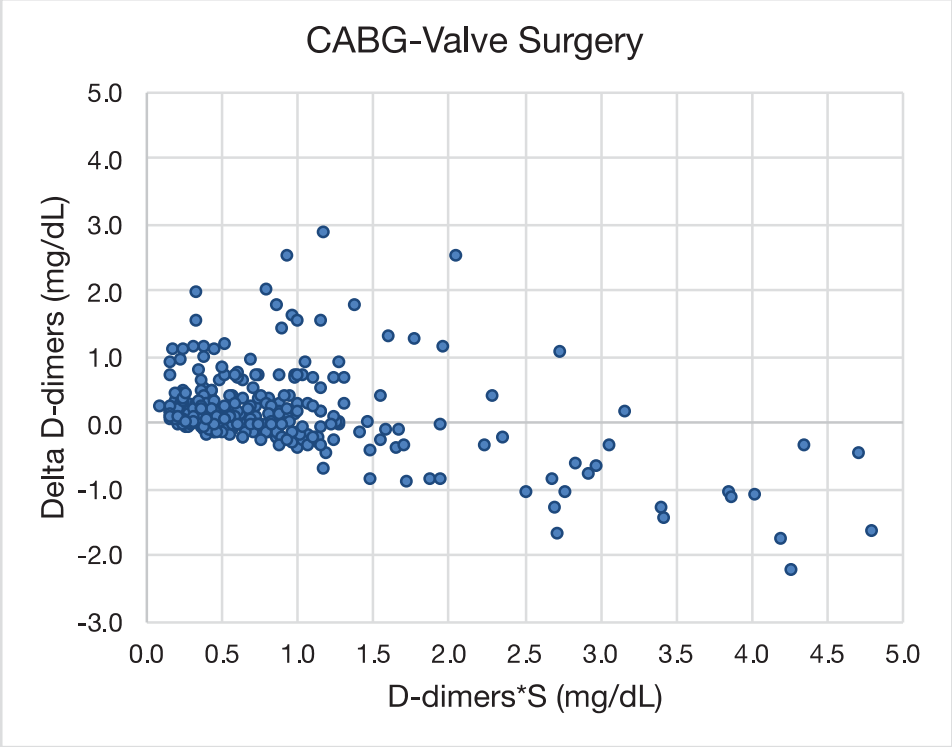

Fig. 5: **D-dimer development in Relation to Baseline in CABG-Valve Surgery under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
CABG: coronary artery bypass grafting; HD-TXA: higher dose of tranexamic acid

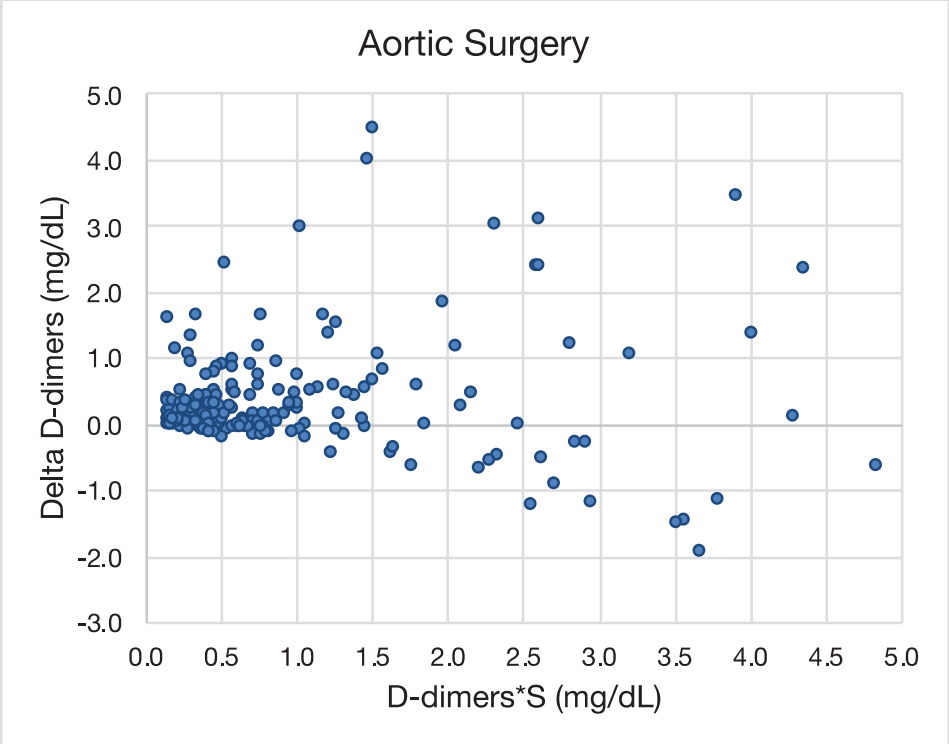

Fig. 6: **D-dimer development in Relation to Baseline in Aortic Surgery under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
HD-TXA: higher dose of tranexamic acid

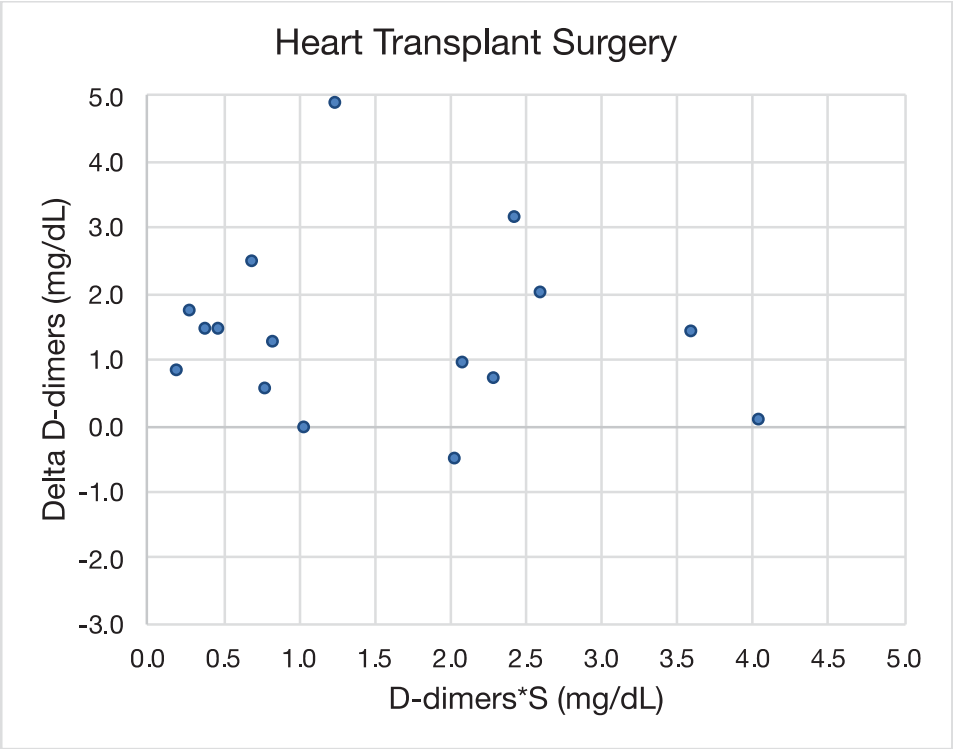

Fig. 7: **D-dimer development in Relation to Baseline in Heart Transplant Surgery under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
HD-TXA: higher dose of tranexamic acid

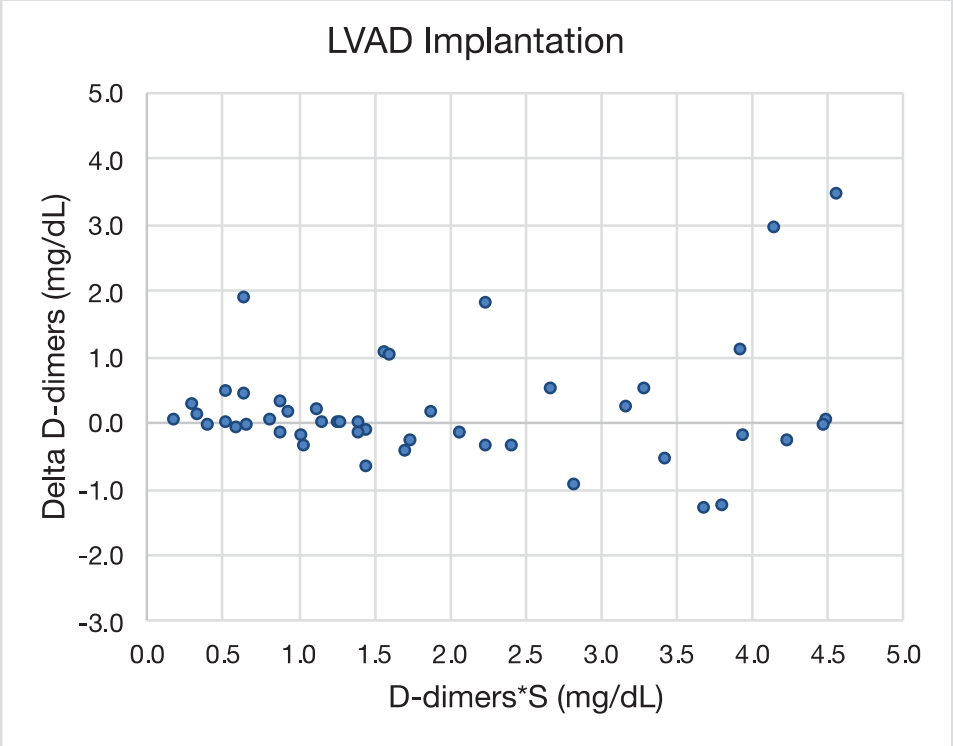

Fig. 8: **D-dimer development in Relation to Baseline in LVAD Implantation under HD-TXA**
Only data sets of D-dimers*S ≤5.0 and Delta D-dimers between -3.0 and +5.0 are shown
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
LVAD: left ventricular assist device; HD-TXA: higher dose of tranexamic acid

3.4 D-dimers and Tranexamic Acid

TXA has previously been shown to influence D-dimer development in cardiac surgery, with inconsistent results regarding dosing. We used D-dimer level monitoring to determine the effect of two doses of TXA on fibrinolysis.

While in our study, D-dimers increased from 'S' to 'bP' in the lower dose of TXA (LD-TXA) group, this stands in contrast to previous literature. Horrow *et al.* [62] found no intraoperative D-dimer increase in cardiac surgery patients under several dosing schemes of TXA, of which the lowest was 0.25 mg * kg^{-1} * h^{-1}. This dose is miniscule in comparison even to our lower dose. Another study conducted by Faraoni *et al.* [64] examined D-dimer development under two doses of TXA and placebo in CAGB and valve surgery. 30 mg * kg^{-1} and 16 mg * kg^{-1} * h^{-1} in the high dose group and 5 mg * kg^{-1} and 5 mg * kg^{-1} * h^{-1} in the low dose group were used. The authors found that D-dimer levels did not differ significantly between two dosing schemes of TXA intraoperatively and postoperatively. Several reasons might explain the lack of difference in D-dimer development compared to our findings, as briefly discussed in our publication [1]. The study [64] analyzed a total number of 33 data sets, compared to 400 in our analysis, and only patients receiving CABG or aortic valve replacement, or a combination were included. Our study included high-risk surgeries such as heart transplants and aortic surgery and patients were matched via propensity score accordingly. Also, the continuous lower dose was higher than our lower dose of 2 mg * kg^{-1} * h^{-1}. It is possible that continuous doses above 5 mg * kg^{-1} * h^{-1} do not provide additional benefit, as concluded by the authors. We might have found similar results if our higher dose had only been 5 mg * kg^{-1} * h^{-1}. Still, LD-TXA, which was higher than the continuous dose of only 0.25 mg * kg^{-1} * h^{-1} used by Horrow *et al.* [62], was not sufficient to inhibit an intraoperative D-dimer increase in our patients.

It seems that the dose-dependent effect of TXA on D-dimer levels remains unclear, as findings of the discussed literature [62, 64] as well as our own are discrepant. Therefore, we altogether provide limited additional insight on optimal dosing strategy for TXA. However, our results suggest that fibrinolysis, represented by D-dimer levels, is

influenced by relatively low doses of TXA and it should be examined whether higher doses provide clinical benefit.

3.5 Safety of Tranexamic Acid

No data on possible adverse effects of TXA, nor on a dose-response-dependency was gathered in this study. The next chapter will put the doses we applied in the context of the existing literature on dosing and adverse effects of TXA.

A pertinent adverse effect of TXA is its epileptogenic potential. The occurrence of seizures has been reported after administration of relatively low doses of TXA, for example a 2 g bolus at the start of surgery, another 2 g bolus for the CPB priming solution and 0.5 g * h^{-1} intraoperatively [90]. The rate of seizures was 4.6% in 1188 patients after a one-year follow-up in this study. This dose of TXA is lower than both of ours. Other studies using higher doses of TXA have also reported an increase in postoperative seizure rates with TXA and this seems to be the case especially in open chamber surgery [91] and aortic surgery [92]. Also, a cumulative dose of more than 100 mg * kg^{-1} has been found to be an independent risk factor for the occurrence of postoperative seizures after CPB [93]. It should be noted that the definition of seizure may vary across these studies and that the baseline seizure rate in cardiac surgery patients not treated with antifibrinolytic therapy has been reported at 2.7 %, not 0 % [94]. Also, multivariate analyses have found additional risk factors associated with postoperative seizures in cardiac surgery patients. This needs to be considered when comparing results on seizure rates and TXA doses between trials [95, 96].

A very high dose of TXA was used in the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial published my Myles *et al.* in 2017 [9]. Patients received 100 mg * kg^{-1} initially. The dose was halved to 50 mg * kg^{-1} after the incidence of seizures was reported. Seizures occurred in 0.7% of patients in the TXA groups and 0.1% in the placebo group. These absolute rates are low in contrast to other findings, but due to the

limitations pointed out above, relative comparisons may be of higher value, and the difference of seizure rates was statistically significant (p=0.002) in this trial [9].

We did not analyze seizure rates, but even in the lower dose regimen we used, which was not effective in preventing an intraoperative D-dimer increase, seizures could have occurred. It might be necessary to tolerate a higher seizure rate for the benefit of blood sparing effects of higher doses of TXA. Still, one could argue that we should increase our efforts to keep doses as low as justifiable.

3.6 Limitations

There are several limitations to our work, some of which are discussed in the limitations chapter of our publication [1]. Additional aspects are presented as following.

There are many factors that have been shown to be associated with increased D-dimer levels, such as age, female gender [44, 45], as well as malignancy and pregnancy [97]. Malignancy and pregnancy are uncommon in cardiac surgery patients, and three quarters of our population were male. However, our age groups were heterogenous, and we did not correct for any of these possible confounders, age in particular, in our analyses.

It is under ongoing discussion that different commercially available D-dimer assays have limitations regarding sensitivity and specificity. The utilized monoclonal antibodies detect D-dimer fragments of varying molecular weight and varying epitopes. Cut-off values should be determined taking this into account [39]. Although it has been used in several other contexts, the Innovance® D-dimer assay used in this study was approved for the thrombotic clinical setting of DVT [83] and not for detection of fibrinolysis.

The following point is more a clarification than a limitation, but it is highly relevant to the overall topic of this work and therefore discussed as well. In a trauma setting, it has been suggested that D-dimer testing alone without viscoelastic testing cannot reliably

predict hyperfibrinolysis, as tissue injury will cause their elevation as well [98]. ROTEM® has been implemented for detection of coagulopathy in trauma patients [35] and has been described as the only reliable test [99]. This requires clarification. Fibrinolysis and hyperfibrinolysis have been used somewhat interchangeably in the context of cardiac surgery, but hyperfibrinolysis in trauma patients and fibrinolysis in cardiac surgery patients are separate pathophysiological entities. Acute coagulopathy of trauma, as described in the introduction section, is characterized by hyperfibrinolysis and hypocoagulation [55]. Its main trigger is tissue hypoperfusion, hypothermia, acidosis, as well as dilution by fluids and packed RBC which activate protein C and cause systemic anticoagulation [54]. It has been found that only severely injured patients in shock are in a hyperfibrinolytic state on arrival in the emergency room [54]. Hypoperfusion and shock do also occur in a regulated operation room setting during cardiac surgery, and this might cause similar hyperfibrinolysis to trauma patients. The increase of antifibrinolytic therapy may be warranted in these patients. However, the hyperfibrinolysis described in a trauma setting is distinct from the fibrinolytic changes associated with the use of cardiopulmonary bypass and local tissue trauma in cardiac surgery patients. These changes are multifactorial, and some of them are specific to the use of CPB, such as platelet dysfunction [12]. Kuiper *et al.* [100] briefly discuss this as well. Viscoelastic testing has been described as poor in prediction postoperative bleeding in cardiac surgery patients [101, 102], and preoperative ROTEM® or TEG® is not recommended in the 2017 EACTS/EACTA guidelines [16]. Still, viscoelastic testing in addition to D-dimer levels is helpful for the analysis of fibrinolysis in cardiac surgery patients, as well as in trauma patients.

Furthermore, on a pathophysiologic level, t-PA has been shown to be released from vascular endothelial cells in response to several stimuli, including β-adrenergic agents [103], which are routinely applied during cardiac surgery at our clinic, and which are obviously also secreted physiologically during stress such as surgery. Interestingly, there was no strong correlation between duration of surgery (‘S’ to ‘bP’), which is probably associated with more infusion of norepinephrine and more surgical stress, with D-dimer level increase in our study. Further research may be valuable.

Lastly, there are limitations to clinical applicability of our study. D-dimer levels were determined at the start of surgery and before protamine. The development of D-dimers from 'S' to 'bP' is only available after 'bP'. At this point, dosing of tranexamic will already have been calculated and applied. There may be a need for another in between blood sample, or TXA dosing could be adjusted after measurement of the 'bP' sample.

3.7 Conclusion

Hemostatic balance is potentially disrupted by several factors in cardiac surgery. This entails challenges for prevention and management of bleeding. Cardiac surgery patients present with a high variability of preoperative fibrinolytic activity, measured by D-dimer levels. Increased baseline fibrinolytic activity is present also in lower risk patients, and persists in patients with high risk cardiac diseases after examining certain predisposing conditions. Furthermore, other conditions may modify preoperative fibrinolytic activity in cardiac surgery, such as prior antiplatelet therapy, preexisting coagulopathies, prior myocardial injury, and non-conclusively, interindividual variability.

Intraoperative fibrinolytic development is influenced by type of performed surgery and by preoperative fibrinolytic status and development is heterogenous in some patients as well. Two dosing protocols of TXA, which are low in relation to previously published dosing schemes, can lead to divergent intraoperative D-dimer level development. The clinical relevance of this is unclear, and optimal dosing should be established in upcoming trials with perioperative hemorrhage as the primary outcome.

Until then, after consideration of the discussed limitations, our findings may have clinical implications as follows: Individual perioperative fibrinolytic assessment may be useful in cardiac surgery and may be achieved using D-dimer measurements and other tests. Dosing strategies of TXA could be established specific to type of surgery, as implied in recent research. Then individual dose adjustments could be made after determination of baseline fibrinolytic activity. These proposed strategies should be evaluated for clinical usefulness and effectiveness in future investigations.

4 References

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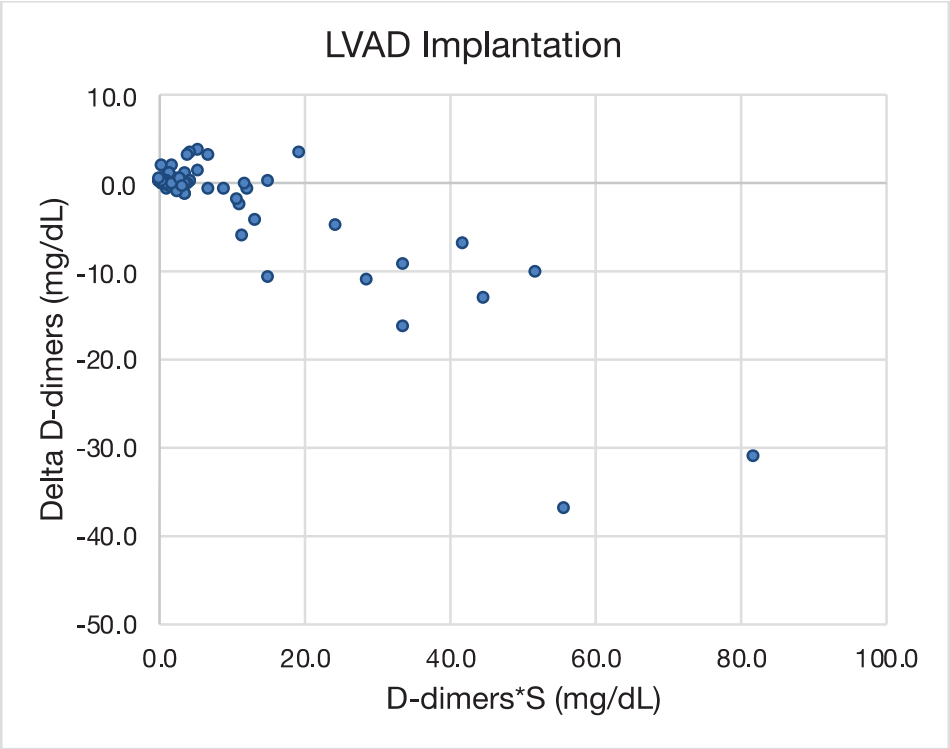
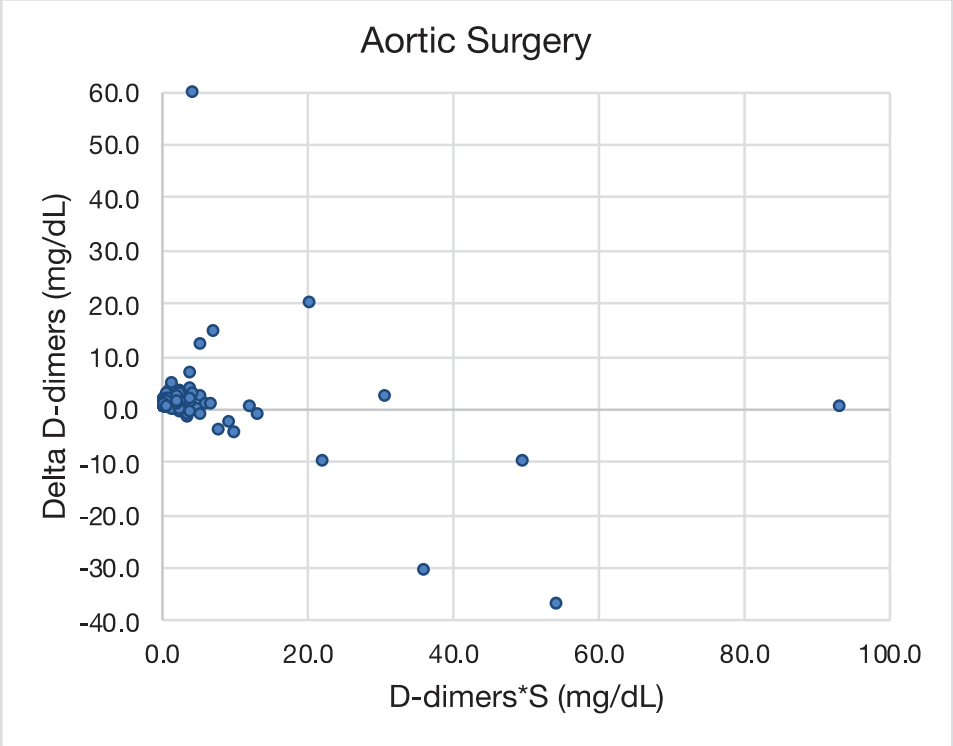
5 Appendix



Suppl. Fig. 1: **D-dimer development in Relation to Baseline in LVAD Implantation under HD-TXA**
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
LVAD: left ventricular assist device; HD-TXA: higher dose of tranexamic acid



Suppl. Fig. 2: **D-dimer development in Relation to Baseline in Aortic Surgery under HD-TXA**
D-dimers*S and Delta D-dimers (D-dimers*bP – D-dimers*S) are in mg/dL, respectively
HD-TXA: higher dose of tranexamic acid

Acknowledgements

It is my honor to thank Prof. Dr. Alexander Albert for offering the opportunity to work on this topic with him, and for sharing his remarkable clinical and research experience. Furthermore, the exceptional thinking patterns and clinical expertise of Dr. Till Hoffmann were the cornerstone of this work and I am grateful for our many intriguing discussions. Ms. Elisabeth Roussel provided outstandingly positive and continuous encouragement throughout the project. Lastly, I would like to thank the entire SUBITO team for letting me take part in this project and for continuously providing excellent patient care.