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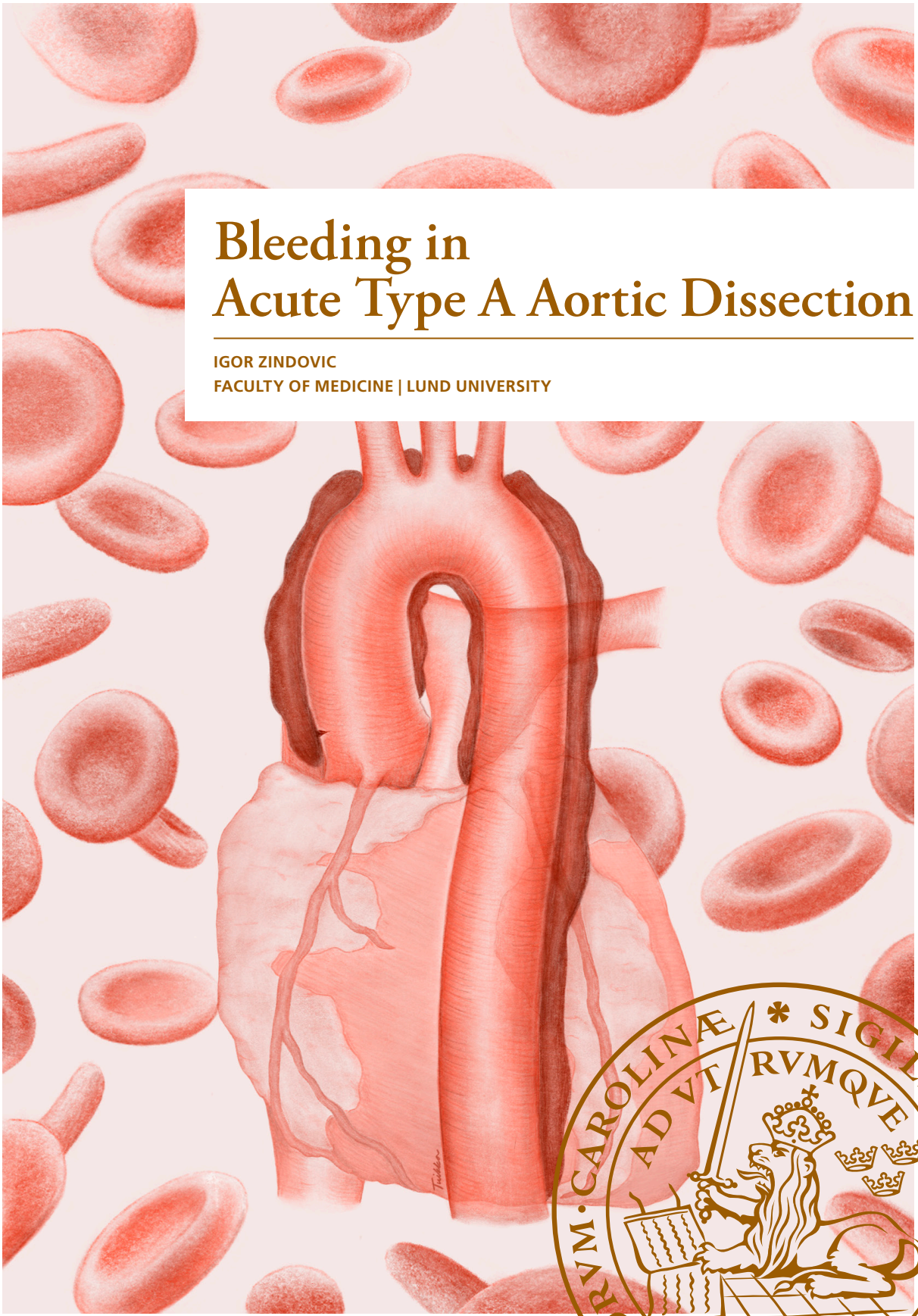

Dedicated to my precious and beloved sons, Oscar and August.
You will always be my greatest achievement.

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Bleeding in Acute Type A Aortic Dissection

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LUND
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DOCTORAL DISSERTATION

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Abstract

Background: Acute type A aortic dissection (ATAAD) is associated with high mortality. Surgery for ATAAD is often complicated by excessive bleeding, which has been reported to cause increased rates of postoperative complications and mortality in cardiac surgery.

Aims: I: to identify predictors of massive bleeding and evaluate the impact of bleeding complications on outcomes after ATAAD surgery; II: to assess the safety of using recombinant factor VIIa (rFVIIa) as a haemostatic agent in ATAAD surgery; III: to identify clinically relevant changes in blood analyses of the coagulation system caused by ATAAD and associated surgery and IV: to analyse the impact of ATAAD and aortic surgery on von Willebrand factor (VWF) activity, and evaluate the potential of using FVIII/VWF concentrate as a haemostatic agent in aortic surgery.

Methods: Study I had a retrospective design and included 256 patients who underwent ATAAD surgery at Skåne University Hospital between 2004 and 2016. Study II was based on 761 patients derived from the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) database. Patients treated with rFVIIa were compared to a propensity matched control group of patients who did not receive rFVIIa. Studies III and IV prospectively compared changes in coagulation analyses of 25 ATAAD patients to those of 20 control patents undergoing elective aortic surgery.

Results: Several predictors of massive bleeding were identified, including patient age, symptom duration, DeBakey Type 1 dissections, prolonged duration of cardiopulmonary bypass (CPB) and shorter duration of cross-clamping. Patients with massive bleeding had significantly higher in-hospital mortality rates than remaining patients (30% vs 8%, $p<0.001$). Re-exploration for bleeding was an independent predictor of both early and late mortality (OR, 3.109; 95% CI, 1.044–9.256, $p=0.042$ and HR, 3.039; 95% CI, 1.605–5.757, $p=0.001$, respectively). Patients who received rFVIIa in association with ATAAD surgery had a similar risk of in-hospital mortality (OR, 0.74; 95% CI, 0.34-1.55, $p=0.487$), postoperative stroke (OR, 1.75; 95% CI, 0.82-3.91, $p=0.163$) and renal replacement therapy (OR, 1.18; 95% CI, 0.48-2.92, $p=0.839$) as patients who did not receive rFVIIa. ATAAD caused reduced platelet counts, fibrinogen levels and antithrombin levels, and an increase of PT(INR) and D-dimer levels. Additionally, significant changes were caused by hypothermia and the use of CPB. Von Willebrand factor activity increased as a result of the aortic dissection but remained within the normal range during both acute and elective aortic surgery. Supernormal VWF activity was observed on the first and fifth postoperative day.

Conclusions: ATAAD caused significant changes in the haemostatic system, which were augmented by hypothermia and CPB. Numerous clinical factors predicted massive bleeding, and bleeding complications had adverse effects in terms of postoperative complications and mortality after ATAAD surgery. Recombinant FVIIa had an acceptable safety profile for treating refractory bleeding in ATAAD surgery but we could not find any indication that patients with profuse bleeding caused by aortic surgery would benefit from administration of FVIII/VWF concentrate

Key words: Aorta, Dissection, Haemorrhage, Blood coagulation, Factor VIIa, von Willebrand factor

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Bleeding in Acute Type A Aortic Dissection

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“Mänskligheten stora kroppspulsåder sträcker sig mellan krig och fred. Om den brister, så förblöder tron på en framtid. Glädje, lust, kärlek, sorg och hat kan inte lagas och botas med kirurgi”

“The aorta of mankind extends from war to peace. If it ruptures, faith in our future bleeds to death. Joy, desire, love, sorrow and hatred cannot be repaired or cured by surgery.

Björn Ranelid

2019

Contents

List of publications

This thesis is based on the following publications which are referred to in the text by their Roman numerals (I-IV).

I. **Zindovic I**, Sjögren J, Bjursten H, Björklund E, Herou E, Ingemansson R, Nozohoor S. Predictors and impact of massive bleeding in acute type A aortic dissection. Interact Cardiovasc Thorac Surg. 2017;1;24(4):498-505.

II. **Zindovic I**, Sjögren J, Ahlsson A, Bjursten H, Fuglsang S, Geirsson A, Gunn J, Ingemansson R, Jeppsson A, Mennander A, Olsson C, Ullén S, Nozohoor S. Recombinant factor VIIa use in acute type A aortic dissection repair: A multicenter propensity-score-matched report from the Nordic Consortium for Acute Type A Aortic Dissection. J Thorac Cardiovasc Surg. 2017;154:1852-9.

III. **Zindovic I**, Sjögren J, Bjursten H, Ingemansson R, Ingimarsson J, Larsson M, Svensson P J, Strandberg K, Wierup P, Nozohoor S. The Coagulopathy of Acute Type A Aortic Dissection. A Prospective, Observational Study. J Cardiothorac Vasc Anesth. 2019;33(10):2746-2754.

IV. **Zindovic I**, Sjögren J, Bjursten H, Ingemansson R, Larsson M, Svensson P J, Strandberg K, Wierup P, Nozohoor S. The role of von Willebrand factor in acute type A aortic dissection. Thromb Res. 2019;178:139-144.

Populärvetenskaplig sammanfattning

(Summary in Swedish)

Aortadissektion är en livsfarlig sjukdom och en konsekvens av att det uppstår ett hål i det innersta av kroppspulsåderns (aortans) tre lager. När detta sker, tränger sig blodet in mellan dessa kärllager på ett sätt som kan liknas vid att man stoppar in armen genom ett hål i fodret på en kavajärm. Detta orsakar en försvagning av aortan och att blodet riskerar hamna i en återvändsgränd och därmed inte når fram till sina målorgan, vilket kan leda till att kroppspulsådern brister eller att patienten får hjärtinfarkt, slaganfall (stroke) samt i somliga fall skador på ryggmärg eller bukens organ.

Den farligaste formen av aortadissektion, typ A, engagerar den del av kroppspulsådern som ligger närmast hjärtat och upp till hälften av de som drabbas dör redan innan de hinner till sjukhus. Orsakerna till detta är framför allt att den försvagade kroppspulsådern plötsligt brister eller att den läcker blod in i hjärtsäcken (en påse som omger hjärtat), som då sakta fylls med blod tills trycket i hjärtsäcken blir så högt att blodet från de stora hålvenerna inte kan tömma sig i hjärtat.

En aortadissektion typ A kräver omedelbar operation och generellt transporteras patienterna till en operationsavdelning så fort diagnosen är ställd. Trots akut kirurgi dör 15–20% av patienterna i samband med eller efter operationen och 20% av dessa dödsfall beror på blödningskomplikationer.

Tidigare forskning har visat att en aortadissektion medför en rubbning av blodets levringsförmåga. Däremot har man inte kunnat beskriva den blödningsrubbning som uppstår fullt ut eller på ett begripligt sätt förklarat hur dessa rubbningar kan hanteras i den kliniska vardagen. När det uppstår kraftiga blödningar under operationer använder man läkemedel som gör att blodet levrar sig bättre. Dock finns en risk att denna typ av läkemedel medför att blodet levrar sig för bra och istället orsakar proppar som kan resultera i organskador (exempelvis stroke och njursvikt). Ett väldigt potent sådant läkemedel är rekombinant faktor VIIa (rFVIIa). Läkemedlet har visat sig effektivt för att minska blödning vid hjärtkirurgi, men dess säkerhet har inte studerats tillräckligt vid kirurgi för aortadissektion.

Von Willebrand faktor (VWF) är en molekyl som gör att blodplättarna bättre fäster till skadad vävnad och VWF finns att ge i läkemedelsform. Förändringar i VWF-aktivitet har tidigare inte studerats vid aortadissektion och man har heller inte utvärderat om VWF i läkemedelsform skulle kunna vara en möjlig behandling mot blödning i samband med aortakirurgi.

Denna avhandling utgörs av fyra delarbeten vars syfte var att identifiera orsakerna till blödningskomplikationer vid kirurgi för aortadissektion typ A, analysera blödningskomplikationernas inverkan på kirurgiska resultat, utvärdera säkerheten av rFVIIa vid dissektionskirurgi samt studera huruvida VWF i läkemedelsform skulle kunna vara en alternativ behandlingsmetod vid blödningsproblem i samband med aortakirurgi.

Delarbete I var ett retrospektivt arbete baserat på 256 patienter som opererades 2004–2016 för akut aortadissektion typ A vid Skånes universitetssjukhus i Lund. Det andra delarbetet baserades på ett material från Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD)-databasen och inkluderade totalt 761 patienter från åtta nordiska sjukhus. Delarbete III och IV var båda prospektiva studier där vi jämförde koagulationssystemet hos 25 patienter som opererats för aortadissektion typ A med en kontrollgrupp bestående av 20 patienter som genomgått planerad aortakirurgi.

I delarbete I fann vi flertalet kliniska faktorer som ökar risken för massiv blödning i samband med kirurgi för aortadissektion typ A, däribland patientens ålder, symtomlängd samt dissektionens utbredning. Massiv blödning visade sig medföra signifikant ökad risk för andra postoperativa komplikationer och ökade risken för dödlig utgång efter kirurgi. Vidare visade studien att reoperation för blödning, oberoende av andra faktorer, ökade risken för att patienten avlider, såväl tidigt som sent i förloppet efter kirurgi för aortadissektion typ A.

Vi kunde med delarbete II påvisa att patienter som får rFVIIa har liknande överlevnad och inte löper någon förhöjd risk för njursvikt efter kirurgi för aortadissektion typ A, när de jämförs med en matchad patientgrupp som inte fått rFVIIa. Även om inga signifikanta skillnader mellan grupperna kunde påvisas, förmådde dock studien inte säkert utesluta en förhöjd risk för postoperativ stroke i gruppen som fick rFVIIa. Sammantaget bedömde vi dock att användandet av rFVIIa var behäftat med acceptabla risker och att rFVIIa fortsatt kan användas vid kraftiga blödningar i samband med kirurgi för aortadissektion.

I det tredje delarbetet demonstrerade vi att aortadissektion orsakar en förbrukning av blodplättar och koagulationsfaktorer och att dessa effekter förstärks av nedkylning och användning av hjärt-lungmaskin. Liknande mönster fann vi även hos patienter som genomgick planerad aortakirurgi.

Delarbete IV visade att aortadissektion orsakar en ökning av VWF-aktiviteten och att kirurgin inte påverkade VWF i någon större utsträckning.

Sammantaget har vi i denna avhandling visat att blödningskomplikationer är vanliga efter kirurgi för aortadissektion typ A och att de är behäftade med sämre kirurgiska resultat. Man kan med acceptabel säkerhet använda rFVIIa som blödningsstillande behandling vid akut aortadissektion typ A, men vi fann inget stöd för användning

av VWF i läkemedelsform som blödningsbehandling vid aortakirurgi. Ytterligare forskning krävs för att kartlägga ännu oklara orsaker till blödningsrubbningen vid aortadissektion samt identifiera läkemedel som skulle kunna reducera blödning i samband med aortakirurgi.

Abbreviations

AbSD	Absolute standardised difference
ACP	Antegrade cerebral perfusion
ACT	Activated clotting time
ADP	Adenosine diphosphate
AKI	Acute kidney injury
APTT	Activated partial thromboplastin time
ATAAD	Acute type A aortic dissection
AUC	Area under the curve
AVR	Aortic valve replacement
B	Blood
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BAV	Bicuspid aortic valve
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CT (imaging)	Computed tomography
CT (ROTEM®)	Coagulation time
DAPT	Dual antiplatelet therapy
DIC	Disseminated intravascular coagulation
DSWI	Deep sternal wound infection
EDS	Ehlers-Danlos syndrome
EPV	Events per variable
F	Factor
FET	Frozen elephant trunk
FFP	Fresh frozen plasma
FTAAD	Familial thoracic aneurysms and dissections
GERAADA	German Registry for Acute Aortic Dissection Type A
GP	Glycoprotein
HCA	Hypothermic circulatory arrest
HDR	Heparin dose response
HMWM	High molecular weight multimers
HR	Hazard ratio

ICU	Intensive care unit
IMH	Intramural haematoma
IQR	Interquartile range
IRAD	International Registry Of Acute Aortic Dissection
LMWM	Low molecular weight multimers
MCF	Maximum clot firmness
MFS	Marfan syndrome
MI	Myocardial infarction
ML	Maximum lysis
MRI	Magnetic resonance imaging
NORCAAD	Nordic Consortium for Acute Type A Aortic Dissection
OR	Odds ratio
PSGL1	P-selectin glycoprotein ligand 1
RCP	Retrograde cerebral perfusion
rFVIIa	Recombinant factor VIIa
P	Plasma
PCC	Prothrombin complex concentrate
PRBC	Packed red blood cells
PT(INR)	Prothrombin time/international normalised ratio
RRT	Renal replacement therapy
SCP	Selective cerebral perfusion
SD	Standard deviation
Sino-RAD	Registry of Aortic Dissection in China
TF	Tissue factor
TOE	Transoesophageal echocardiography
TP	T prostanoid receptor
TTE	Transthoracic echocardiography
TxA2	Thromboxane A2
U	Units
VWD	Von Willebrand disease
VWF	Von Willebrand factor
VWF:GPIbM	Spontaneous binding of VWF to a gain-of-function mutant GPIb
VWF:MS	Multimeric sizing of VWF

Introduction

Aortic dissection

Anatomy, pathophysiology and history

The aorta is the largest blood vessel of the human body, delivering blood from the heart to all end organs except for the lungs, which are supplied via the pulmonary artery (1). The aorta is an elastic vessel, and its elasticity aids the propulsion of blood while at the same time making it sensitive to diseases of the elastin and collagen rich tissue, potentially leading to dilatation and vessel wall injury (2, 3).

The aortic wall is a three-layer structure consisting of the intima, media and the adventitia. The intimal layer is composed of endothelial cells, a thin basal membrane and a subendothelial collagen layer; the media is constructed of smooth muscle cells and a network of collagen and elastic fibrils; and the adventitia consists of thick bundles of collagen fibrils (3).

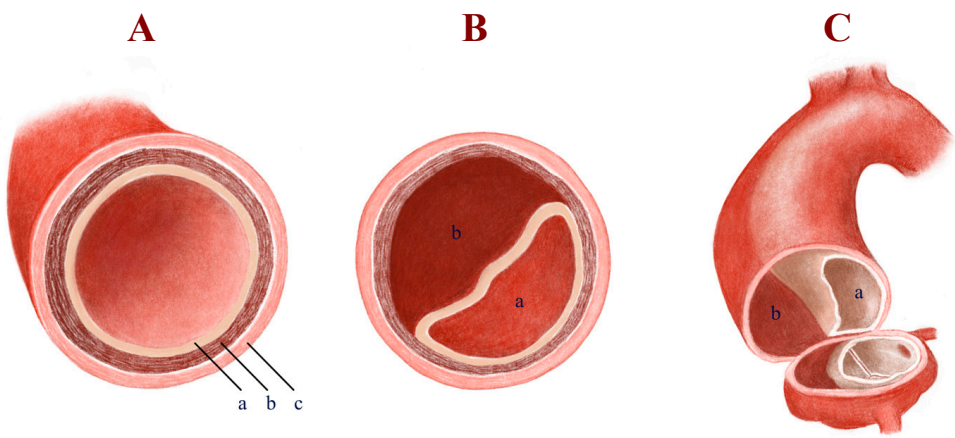

FIGURE 1 – A: cross-section of the aorta illustrating the intima (a), media (b) and the adventitia (c); B and C: aortic dissection with a true (a) and a false lumen (b). Copyright © 2019 Anni Tuikka and Tomas Gudbjartsson.

An aortic dissection is caused by an injury to the intimal layer of the aorta (intimal tear), causing blood to surge through the defect and separate the aortic layers in a longitudinal or circumferential direction (4). This creates a false lumen parallel to the true lumen. The false lumen can compress the true lumen and obstruct or occlude the branch vessels of the aorta causing end organ ischaemia or injury, dissection into

the aortic root, aortic valve insufficiency, pericardial tamponade or a weakening of the aortic wall, potentially resulting in aortic rupture (5).

The diagnosis was first recognised in an autopsy performed by Frank Nicholls on King George II of England who died while straining at stool. It was documented that "…the pericardium was found distended with a quantity of coagulated blood, nearly a pint […] the whole heart was so compressed as to prevent any blood contained in the veins from being forced into the auricles […] and in the trunk of the aorta we found a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed under its external coat and formed an elevated ecchymosis."(6).

Dr Michael DeBakey pioneered cardiovascular surgery, and in 1954, he performed the first successful surgical resection of an aortic dissection (7). At age 97, Dr DeBakey himself suffered an aortic dissection and became unresponsive. He had previously signed a directive that forbade surgery, but Dr DeBakey's wife Katherine sought up the hospital's ethics committee and "barged in to demand that the operation begin immediately". The ethics committee approved Mrs DeBakey's request, and the operation was successful. After several months of postoperative hospitalisation, Dr DeBakey was discharged, and he went on to practice medicine for a few hours each day until his death in 2008 at age 99 (8).

Classification

Aortic dissections are generally regarded as acute up to 14 days after symptom onset and chronic thereafter (9, 10). Intramural haematomas (IMH) are similar to dissections in the sense that blood is trapped between the aortic layers but without the presence of a false lumen. It has been speculated that IMHs are the result of injury to the vasa vasori of the aortic wall, but a recent study showed that 90% of IMHs are associated with atherosclerotic lesions of the aorta suggesting intimal injury as the primary pathophysiological mechanism (4, 11).

The Stanford classification system of aortic dissection was first described in 1970 and is based on the anatomical localisation of the dissection. All dissections involving the ascending aorta are considered type A aortic dissections, whereas dissections limited to the descending aorta are categorised as type B (12). Isolated dissections of the aortic arch are sometimes regarded as non-A non-B dissections. It has recently been suggested that if these dissections propagate into the ascending aorta, they are to be categorised as Arch A, whereas dissections with distal propagation are considered Arch B dissections (13).

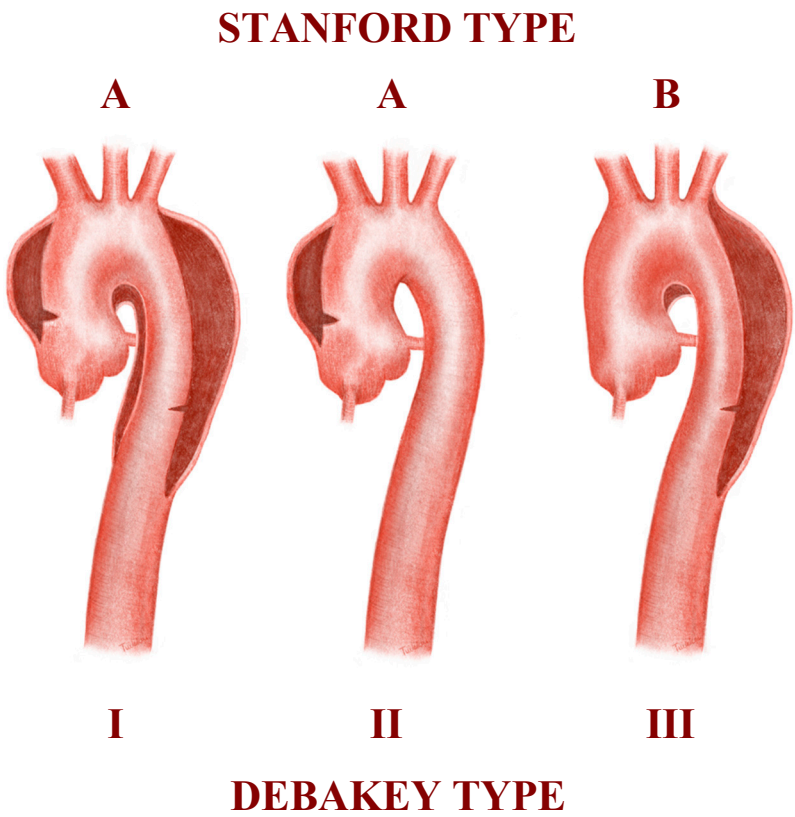

FIGURE 2 - The Stanford and DeBakey classification systems of aortic dissection.

In addition to the Stanford classification, the DeBakey classification is commonly used to make the distinction between different types of Stanford type A dissections. A DeBakey type I dissection involves both the ascending and the descending aorta, whereas DeBakey type II dissections are limited to the ascending aorta. In DeBakey type III dissections, only the descending aorta is affected (14).

Apart from the above-mentioned anatomical classifications, the Penn classification, first described by Augoustides et al., is used for categorising patients by severity of their clinical presentation: Penn class Aa, absence of organ ischaemia; Penn class Ab, localised ischaemia; Penn class Ac, generalised ischaemia; and Penn class Abc, both localised and generalised ischaemia (15).

Type B or DeBakey type III aortic dissections, primarily treated endovascularly or by medical therapy, are beyond the scope of this thesis and will not be discussed further (16).

Epidemiology and risk factors

Type A aortic dissections account for 58–62% of all aortic dissections (17, 18). The incidence of acute Type A aortic dissections (ATAAD) has been reported to be 2.5–6/100 000 patient years, reaching its peak during the seventh and eighth decades in life, and 35% of all aortic dissections occur in patients older than 75 years (18-24). Life expectancy is increasing, and therefore the incidence of ATAAD is expected to rise, potentially contributing to Landenhed et al. reporting an incidence of 8.7/100 000 patient years in 2015 (17, 20, 21).

Men constitute 62–68% of all patients with ATAAD, but females tend to dissect at a higher age and comprise the majority of patients older than 75 years (9, 23, 25). Smoking and atherosclerosis have been identified as independent predictors of ATAAD. However, hypertension is the most important risk factor, present in 67–86% of ATAAD patients, and estimated to account for 54% of the risk of developing ATAAD (17, 18, 25, 26).

Iatrogenic aortic dissections account for 1–5% of ATAADs and can be caused by coronary catheterisation and surgical trauma, e.g. arterial cannulation (9, 18, 23). Recently, Pasternak et al. reported that the use of fluoroquinolones was significantly associated with the development of aortic aneurysm, particularly during the first 10 days after start of treatment, but could not show that fluoroquinolone use increases the risk of aortic dissection (27).

Pregnancy is an uncommon cause of ATAAD and is often associated with connective tissue disease (28). The risk of dissection is highest from six months prior to delivery to three months after delivery, but the mechanisms of dissection are not fully understood (29).

It has been reported that 20% of patients with ATAAD have a first-degree relative with a dilated thoracic aorta, and aneurysms localised in the ascending aorta are more often associated with hereditary conditions whereas descending aortic aneurysms form as a result of atherosclerosis, advanced age and hypertension (2, 30, 31).

Marfan syndrome (MFS) has been reported in 3–7% of ATAAD patients and is a monogenic autosomal dominant disorder caused by a mutation of the FBN1 gene encoding the protein fibrillin-1 (9, 18, 23). The mutation leads to the loss of the protein's ability to form polymeric fibrillins, which leads to reduced strength of the elastin-rich tissue of the aortic wall. Patients with MFS demonstrate an overgrowth of long bones, chest wall deformities, arachnodactyly and dislocation of the lens. In typical cases, MFS patients present with a pear-shaped aneurysm of the aortic root, but the cardiovascular manifestations of the disease are the consequence of diffuse medial degeneration putting all medium-sized and large arteries at risk for dissection (2).

Ehlers-Danlos syndrome (EDS) is caused by a defect in the type III procollagen protein and was reported in 0.6% of patients with ATAAD in the German Registry for Acute Aortic Dissection Type A (GERAADA) (23). EDS causes thin and hyperextensible skin, articular hypermobility and is associated with spontaneous and non-spontaneous aortic ruptures and dissections (32). Loeys-Dietz syndrome is less common than EDS and is associated with a disseminated arteriopathy with central and peripheral dissections due to a mutation of the genes TGFBR1 or TGFBR2, encoding TGFβ (2).

Non-syndromic hereditary causes of ATAAD include familial thoracic aneurysms and dissections (FTAAD), which resemble the aortic manifestations of Marfan syndrome. FTAAD are caused by several different mutations of the gene encoding fibrillin-1, with consequent loss of elastic fibres and cystic medial degeneration (2). The prevalence of bicuspid aortic valve (BAV) is 0.5–1% in the normal population, and in 40–50% of patients with BAV, there is a dilatation of the ascending aorta or the aortic root. Therefore, BAV is likely the most common cause of aortic aneurysms, and patients with BAV are over-represented in ATAAD registries such as the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) database (6%) (2, 9).

In addition, inflammatory conditions of the aorta, including aortitis and vasculitis, may be associated with degeneration of the medial and adventitial layers of the aortic wall, potentially leading to aneurysm formation and aortic dissection (33).

Clinical presentation and diagnosis

In the majority of patients, aortic dissection occurs during some level of exertion (4). The cardinal symptom of ATAAD is a sudden onset of pain, which occurs in approximately 90% of patients, usually localised retrosternally or in the back, and in 12–20% of patients symptom onset results in syncope (18, 34). Dissection of the aortic root might cause aortic valve insufficiency and pericardial tamponade. Malperfusion syndromes have been reported in 27–48% of cases and may hinder the proper diagnosis of ATAAD (15, 35-38). It has been reported that up to one-third of ATAADs are misdiagnosed as acute coronary syndromes at initial presentation (39). Due to the dissection occluding or obstructing aortic branch vessels, ATAAD may mimic a variety of conditions and present with a wide plethora of symptoms, e.g. myocardial ischaemia or infarction, coma, hemiparesis, limb ischaemia, abdominal pain, paraplegia or anuria.

Approximately half of ATAAD patients are hemodynamically unstable at hospital admission, 17–20% present with cardiac tamponade and some 5–6% undergo preoperative cardiopulmonary resuscitation (34, 40, 41).

Computed tomography (CT) is available at most hospitals and in the majority of cases, it serves as the primary imaging modality for diagnosing aortic dissection. Transoesophageal echocardiography (TOE) and magnetic resonance imaging (MRI) are less frequently used for diagnosing aortic dissection (42).

In cases primarily misdiagnosed as acute coronary syndrome or in iatrogenic dissections, the first imaging modality might be a diagnostic coronary angiography. All three primary imaging modalities have sensitivities for discovering aortic dissections of approximately 95% whereas specificity is 87% for CT, 77% for TOE and 98% for MRI. The lower specificity of CT compared to MRI is compensated for by CT being less time-consuming and available at all hours of the day. Due to a poor imaging window, transthoracic echocardiography (TTE) has a sensitivity of only 59% and is not routinely employed for confirming suspected aortic dissection (43).

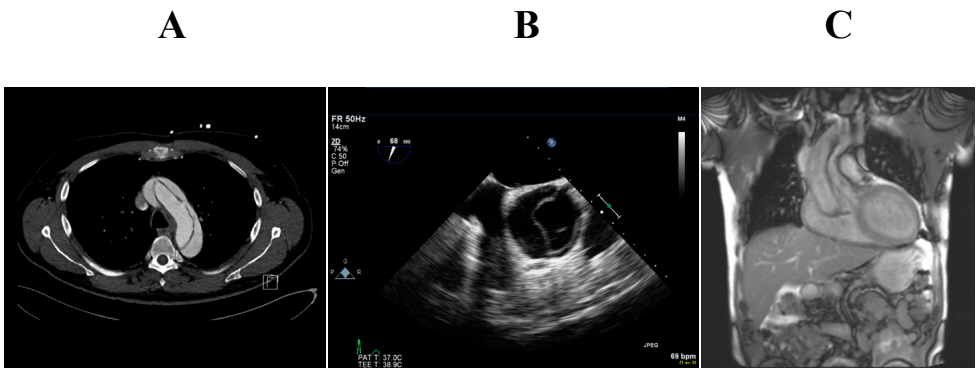

FIGURE 3 - ATAAD visualised on A: computed tomography; B: transoesophageal echocardiography; and C: magnetic resonance imaging. Courtesy of Dr Carl Meurling, Department of Heart and Lung Medicine and Dr Ellen Ostenfeld, Department of Medical Imaging and Clinical Physiology, Skåne University Hospital, Lund, Sweden.

Natural history and medical treatment

Prehospital death occurs in 18–49% of patients with ATAAD (19-22). For patients who decline surgery or are not offered surgical treatment, medical treatment aims to suppress systolic blood pressure to 110 mmHg, thus reducing stress on the aortic wall (5). However, mortality in medically treated patients increases by 1% to 2% for every hour after symptom onset reaching 30–68% within two days and 49–73% within the first two weeks (4, 18, 22, 44).

Surgical techniques

The high mortality rates in untreated or in medically treated patients clearly justify open surgery as the principal treatment option for ATAAD. The primary objectives of the operation are firstly, to protect the aortic root from dissection, which could cause severe aortic valve regurgitation, pericardial tamponade or aortic rupture, and secondly, to restore true lumen circulation and thus native blood flow of the aorta and its branch vessels. Resection of the intimal tear where the dissection started is desired but not mandatory as the tear might be localised in the descending aorta and may not be accessible by means of open repair.

The large international registries (International Registry Of Acute Aortic Dissection [IRAD], GERAADA and NORCAAD) all report 30-day and in-hospital mortality between 16% and 18%, but surgical mortality is decreasing (34, 35, 42). The NORCAAD registry reported a reduction in 30-day mortality from 24% to 13% between 2005 and 2014, and IRAD showed a drop in surgical mortality from 25% to 18% in the past two decades (34, 42).

Generally, the patients are cannulated through the femoral artery or the right subclavian artery. A recent meta-analysis has suggested that subclavian cannulation is associated with lower rates of early mortality and neurological complications (45). Results from the NORCAAD (unpublished data) and GERAADA registries show no significant differences between the two techniques in terms of early mortality (46). This was recently corroborated by a study by Kreibich et al. showing no differences in outcomes between direct aortic, femoral or axillary cannulation (47). Additional sites of arterial cannulation include the apex of the heart, left atrium, brachiocephalic trunk and direct cannulation in the ascending aorta or aortic arch, but these techniques are less frequently used (9, 48).

It has been demonstrated that repair using hypothermic circulatory arrest and an open distal anastomosis is superior to surgery performed with cross clamping of the aorta (49). Depending on the cannulation and cerebral protection strategy used, patients are cooled to a deep (18–20°C) or moderate (20–28°C) hypothermic state before the suturing of the distal anastomosis under circulatory arrest. Apart from cooling, cerebral protection might be accomplished using antegrade or retrograde cerebral perfusion (ACP and RCP). With ACP, oxygenated blood is delivered to the cerebral parenchyma under hypothermic circulatory arrest (HCA) whereas retrograde cerebral blood flow does not reach the brain tissue and provides no metabolic benefit (50). Therefore, it has been hypothesised that the primary effect of retrograde cerebral perfusion is topical cooling of the brain and the flushing of air from the supra-aortic vessels, thus prohibiting stroke caused by air embolisation. Tian et al. recently published a meta-analysis showing that RCP is associated with lower rates of stroke when compared to HCA only, and favourable results have been shown using ACP (51-53). However, large volume centres such as Cleveland Clinic

and Yale New Haven Hospital have shown excellent outcomes with straight HCA and therefore, the optimal strategy for cerebral protection is still debated (54, 55).

Once desired goal temperature is reached, circulatory arrest is instigated enabling inspection of the aortic arch and suturing of the distal anastomosis. Several aortic centres of excellence recently have advocated a more aggressive primary operation with extensive repair by aortic arch replacement with or without the frozen elephant trunk (FET) technique. False lumen patency is associated with increased risk of late mortality, aortic dilatation and reoperation of the distal aorta (56-58). Therefore, the aim of a more extensive approach is to resect or cover the intimal tear and thus prohibit circulation of blood in the false lumen, which would promote false lumen thrombosis.

Selected series on arch replacement in ATAAD surgery have shown excellent short-term results with early mortality rates as low as 0–12% (59-61). Currently, however, the less complex hemiarch replacement, with replacement of only the minor curvature of the aortic arch, is considered the standard approach for ATAAD repair (62, 63). Hemiarch repair was performed in 46% of patients in the GERAADA registry and 73% of IRAD patients. In both registries, approximately 25% of the procedures were extended to the aortic arch (46, 64). However, in the NORCAAD registry, only 6% were arch procedures, 22% were hemiarch replacements and the remaining procedures were isolated replacements of the ascending aorta, most likely reflective of NORCAAD being a collaboration between small- and medium-sized centres more inclined to simplify a low-volume procedure (34). In a large meta-analysis, Yan et al. demonstrated that extensive aortic repair including the aortic arch was associated with significantly higher early mortality (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.54-0.90), and the two strategies were similar with respect to long-term mortality despite patients with less extensive surgery being at higher risk of reoperation of the aorta (RR 3.14, 95% CI 1.74–5.67) (65). Zhang et al. showed that extensive aortic repair obliterated the false lumen in 100% of cases whereas the false lumen persisted in 75% of cases where limited approach was used. In the same study, patients with limited repair were at three times higher risk of re-intervention (16% vs 5%), but there was no significant difference in long-term mortality between the two cohorts (66). Other studies have shown that arch procedures in the setting of ATAAD are associated with early mortality rates of 17–29% (64, 67, 68).

Once the distal anastomosis is completed, the cardiopulmonary bypass (CPB) is instigated via a side-branch of the vascular graft. This enables antegrade circulation and re-warming of the patient while proximal repair is performed.

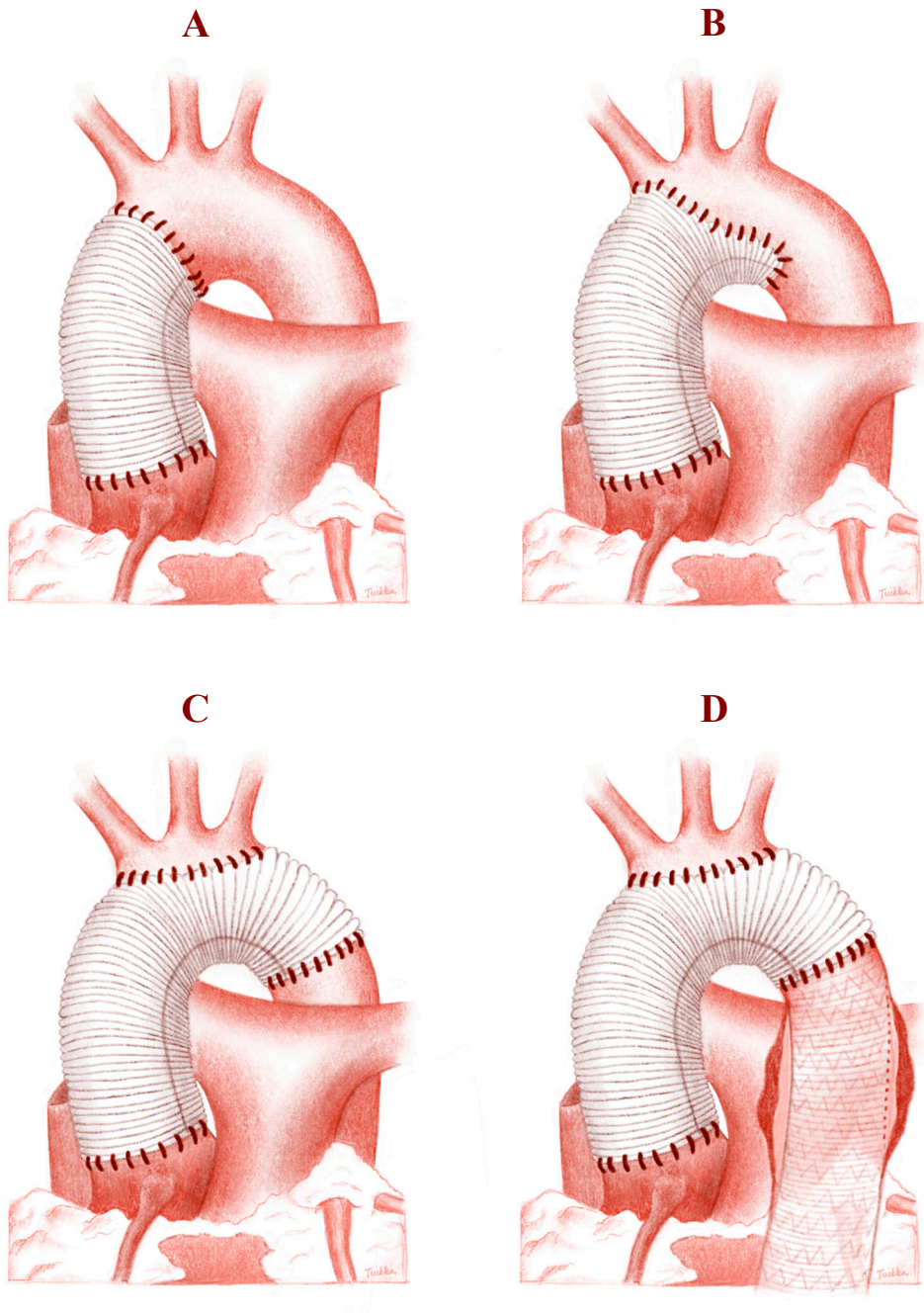

FIGURE 4 - Illustration of surgical techniques for distal ATAAD repair. A: replacement of the ascending aorta; B: hemiarch repair; C: arch replacement; and D: frozen elephant trunk technique. Copyright © 2019 Anni Tuikka.

In most instances, aortic valve competence is fully restored by resuspension of the aortic valve commissures with or without the application of glue between the dissected layers of the aorta (34, 69). A more aggressive primary approach is feasible in cases where the aortic root is destroyed by the dissection, the aortic valve is insufficient or stenotic, where there is a dissection into the coronary ostia, in the presence of an aortic root aneurysm exceeding 4.5cm and in cases with connective tissue disease (70). Published series show that, in most cases, the aortic root is managed with a limited surgical approach. Root replacement including an aortic valve prosthesis and re-implantation of the coronary ostia was performed in 19–26% of the cases, whereas 3–18% underwent valve sparing root replacements (34, 46, 64, 70, 71). Peterss and colleagues previously demonstrated that there was no difference in early or late mortality between patients undergoing root sparing surgery compared to those where a root replacement was performed. In the root replacement group, patients had significantly higher rates of postoperative bleeding and low cardiac output. Furthermore, it was demonstrated that when spared, the residual aortic root dilated with 0.40 mm/year with freedom from root events of 97% and 92% after 5 and 10 years, respectively (71). Additionally, Yang et al. demonstrated that preserving the native root is associated with similar early and late mortality rates when compared to the root replacement strategy. Therefore, available research seems to favour a limited approach when possible.

When the proximal repair is completed, and the patient is normothermic, the patient is weaned off CPB. Hereafter, tedious surgical and pharmacological efforts are necessary to achieve proper haemostasis until the operation can be finalised.

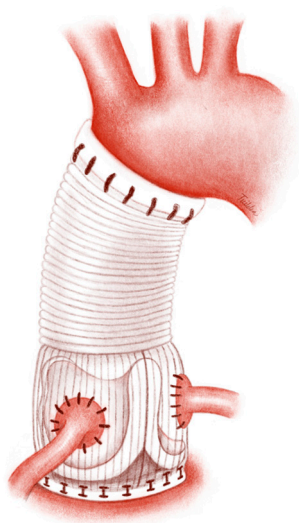

FIGURE 5 - Root replacement procedure with re-implantation of the coronary ostia and an aortic valve bioprosthesis. Copyright © 2019 Anni Tuikka.

Complications

Circulatory failure, rupture of the aorta, massive bleeding and stroke are reportedly the leading causes of in-hospital death in patients undergoing ATAAD surgery (21, 69).

The disturbances of the coagulation system in combination with the poor quality of the dissected aorta contribute to 25% of patients operated for ATAAD sustaining massive bleeding (39). When blood surges through the intimal tear, it is exposed to the subendothelial tissue of the false lumen. The contact between blood and tissue factor (TF) causes a coagulopathy resembling disseminated intravascular coagulation (DIC). Furthermore, there is an activation and consumption of platelets and coagulation factors and increased fibrinolysis. The use of CPB and hypothermia further negatively affect the coagulation system and platelet function (72-76). In several studies, bleeding has been identified as an independent predictor of early and late mortality after surgery for ATAAD and accounts for 20% of in-hospital deaths (39, 69, 77). The coagulopathic state caused by aortic dissection and associated surgery will be described in further detail in a separate chapter.

In a recent report from the NORCAAD registry, preoperative cardiac malperfusion was associated with considerable 30-day mortality (33%). This was primarily driven by intra-operative deaths, possibly due to cardiac infarction and the inability to wean the patients off CPB. However, of patients who survived surgery, only 7% suffered a perioperative myocardial infarction (78). Di Eusanio et al. reported that preoperative mesenteric malperfusion was associated with a mortality rate of 63%, but data from the NORCAAD registry demonstrated a mortality rate of 31% in patients with gastrointestinal malperfusion (79). Di Eusanio and colleagues also reported a 95% in-hospital mortality rate in medically treated patients with mesenteric malperfusion, and therefore, the data from NORCAAD suggest that patients with gastrointestinal malperfusion should not automatically be denied surgery.

In the large multi-centre registries postoperative stroke and coma occurred in 10–15% and 3–9% of the patients, respectively (34, 80, 81). Stroke is one of the leading causes of death after ATAAD surgery, but the mechanism of brain injury is not fully clear (21, 69). Data from the NORCAAD registry demonstrated that preoperative cerebral malperfusion was associated with a threefold increase in stroke rates when compared to patients with other sites of malperfusion. However, rates of coma did not follow a similar pattern, suggesting different injury mechanisms, at least in part (78). Several intra-operative risk factors for perioperative stroke have been identified, including duration of CPB and HCA (80, 82). It has also been hypothesised that femoral cannulation would cause retrograde embolisation, but to this date no definitive evidence has been presented that cannulation strategy has an impact on postoperative stroke rates (80, 82, 83). Tian et al. recently published a meta-analysis demonstrating that HCA with retrograde cerebral perfusion was associated with significantly lower

risk of both mortality and stroke when compared to HCA alone, warranting further studies of the optimal strategy for cerebral protection (51).

Acute kidney injury (AKI) is a common complication following ATAAD, and previous studies have reported AKI incidence ranges between 40% and 55% (84).

Reoperations of the aorta

Although associated with lower mortality, the inherent consequence of a limited surgical approach is potential dilatation of the aortic root and the distal aorta (67, 85-87). In a recent NORCAAD report, Pan et al. demonstrated freedom from reoperation rates of 98% and 95% at one and five years, respectively (88). Lansman et al. reviewed available literature and concluded that approximately 13% of patients require late reoperation of the aorta, and other studies have demonstrated 82–94% freedom from reoperation at five years (62, 89-91). While reoperation of the dissected aorta has been associated with in-hospital mortality rates of 26%, more recent studies have demonstrated in-hospital mortality in the 4–7% range (89, 92-94).

In any situation, the primary goal of surgery is to leave the operating room with an alive patient. The high mortality rates associated with extensive aortic repair and the low mortality rates associated with reoperation suggest that extensive aortic repair should be reserved for aortic centres of excellence whereas low- and medium-volume centres should adopt a more limited approach. However, Wang et al. demonstrated that patients with connective tissue disease were at a 45% risk of reoperation at a median follow up of 2.5 years, and Pan et al. showed that patients with connective tissue disease are at five times higher risk for proximal reoperation (88, 94). This indicates that a more aggressive primary approach might be feasible in patients with hereditary conditions.

NORCAAD

The Nordic Consortium for Acute Type A Aortic Dissection is a collaboration between eight low- and medium-volume tertiary referral centres in the Nordic countries, including Skejby University Hospital, Aarhus, Denmark; Tampere University Hospital, Tampere, Finland; Turku University Hospital, Turku, Finland; Landspitali University Hospital, Reykjavik, Iceland; Karolinska University Hospital, Stockholm, Sweden; Örebro University Hospital, Örebro, Sweden; Sahlgrenska University Hospital, Gothenburg, Sweden; Skåne University Hospital, Lund, Sweden.

The NORCAAD registry is a retrospective database with 1159 ATAAD patients who underwent surgery between 2005 and 2014. The database includes 194

variables on patient demographics, medical history, laboratory data, symptoms, surgical technique, postoperative complications, survival and reoperations (9).

To date, the collaboration has resulted in 13 publications and thus contributed significantly to knowledge on contemporary outcomes of ATAAD surgery.

The coagulation

Tissue factor pathway (extrinsic pathway)

Tissue injury initiates the tissue factor (TF) pathway (95). Tissue factor is a transmembrane protein expressed by vascular smooth muscle cells, pericytes and fibroblasts in the adventitial layer of blood vessels (96-98). It is also expressed in organ tissues including the heart, lungs and brain. In addition, circulating TF, presumably originating from monocytes, endothelial cells or platelets has been shown to play a role in thrombosis and DIC (96, 99). Upon tissue injury, TF is exposed to circulating factor (F) VII in the blood and activates FVII, creating a TF/FVIIa complex, which in turn converts FX to its active form (FXa) (100). Additionally, TF/FVIIa has been shown to be an activator of FIX (101), and a complex consisting of TF/FVIIa/FXa has been demonstrated to activate FVIII (102).

Contact activation pathway (intrinsic pathway)

The contact activation pathway plays less of an important role in thrombus formation than the TF pathway, and interference with the intrinsic pathway does not seem to have any major deleterious effects on coagulation in vivo (103). Nevertheless, exposure of circulating blood to negatively charged molecules and surfaces, circulating RNA, DNA or polyphosphate activates FXII (Hageman factor). FXIIa, in turn, converts FXI to FXIa, which activates FIX. FIXa forms a complex with FVIIIa (activated by thrombin and TF/FVIIa/FXa) which catalyses the generation of FXa (101).

Common pathway

The activated form of FX immediately binds to the phospholipid surface of platelets and forms a FXa/FVa complex (prothrombinase complex), which converts prothrombin (FII) to thrombin (FIIa) (100, 104, 105). Consequently, thrombin cleaves polymeric fibrinogen to monomeric fibrin and converts FXIII to FXIIIa. This creates a fibrin clot, which is cross-linked, and thus stabilised, by FXIIIa (100, 106).

Through a self-enhancing feedback loop, thrombin also activates FV, FVIII and FXI (107). .

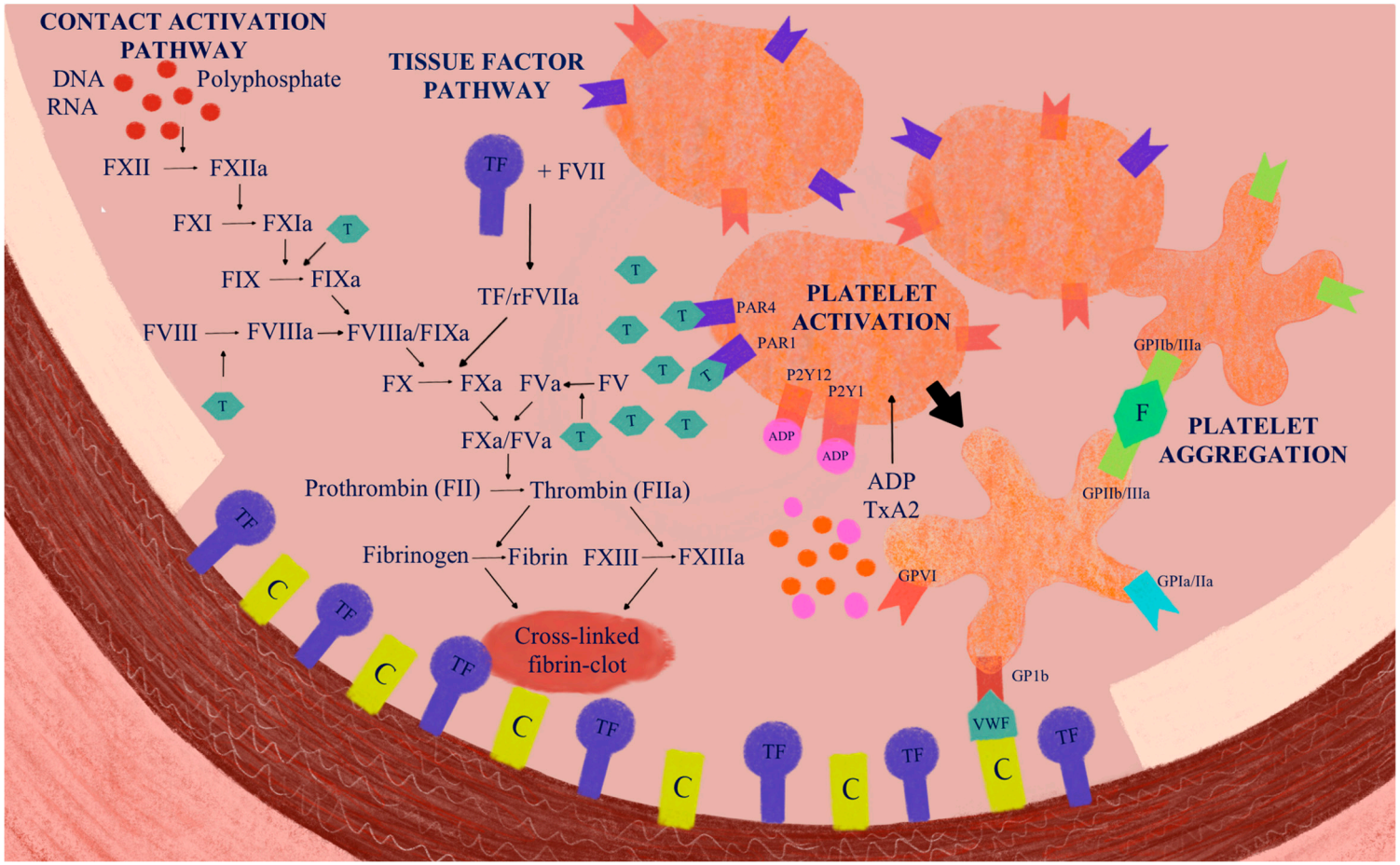

FIGURE 6 - Schematic overview of the coagulation system upon exposure of sub-intimal tissue. C: collagen; F: fibrinogen; T: thrombin; TF; tissue factor. Copyright © 2019 Anni Tuikka and Igor Zindovic.

Primary haemostasis

Parallel to the coagulation cascade, tissue injury also causes platelet activation, which is initiated by the binding of platelets to collagen exposed at the injury site. This is either accomplished via direct binding between collagen and platelets via the GPIa/IIa receptor or by circulating von Willebrand factor (VWF), which crosslinks collagen with platelets via the GP1b receptor of non-activated platelets and GPIIb/IIIa of activated platelets (108, 109). Alongside the effect caused by platelets binding to collagen, thrombin binds to protease-activated receptor 1 and 4 (PAR1 and PAR4), which causes intracellular calcium mobilisation and consequent platelet activation (104, 110). Activation causes the platelet to change its shape and initiates an aggregation of platelets by the cross linking of platelets with fibrinogen using the GPIIb/IIIa-receptor (111). Furthermore, the initial activation stimulates a generation of Thromboxane A2 (TxA2) followed by the secretion of α-granules containing VWF, dense granules containing adenosine diphosphate (ADP), and finally formation of microparticles and exposure of phosphatidylserine, which supports coagulation factor complex formation (104).

ADP is released from dense granules of platelets or from damaged cells at the site of injury and binds to platelet receptors P2Y1 and P2Y12, enhancing platelet activation and promoting thrombus stabilisation. In addition, TxA2 binds to T prostanoid receptors (TP) α and β on the surface of platelets, and its primary role includes platelet recruitment and retention in the outer shell of the thrombus (104).

The activated platelets expresses P-selectin on their surface. P-selectin binds to P-selectin glycoprotein ligand 1 (PSGL1), which is expressed by circulating TF-bearing leukocyte microparticles. This causes an accumulation of TF on the surface of the platelets, which initiates and augments thrombin generation (also known as the thrombin burst). This catalyses the conversion of fibrinogen to fibrin with subsequent clot formation (112).

Coagulation in aortic dissection and associated surgery

Aortic dissection causes an injury to the aortic wall and the contact of blood with a non-endothelialised false lumen. Here, the blood is exposed to collagen and subendothelial TF, which causes a consumption coagulopathy, much like that seen in DIC (72, 113). Cate et al. have demonstrated aortic dissection to cause a decrease of factors II, V, VII, X and XII, a decrease in factor VIII clotting activity, an elevation of fibrin and fibrinogen degradation products and thrombocytopenia due to depletion of platelets at sites of collagen exposure (72). Later studies have shown that the consumption of platelets caused by aortic dissection is associated with increased mortality and that dissection also causes a reduction in platelet aggregability (73, 114). Additionally, in similarity to DIC, aortic dissection causes a decrease in antithrombin activity and thus a reduction of the inhibition of factors IXa, Xa, XIa, plasmin, kallikrein and trypsin (115).

Apart from the coagulopathy induced by the aortic dissection itself, CPB causes haemodilution, platelet activation, a decrease in platelet counts, fibrinogen and factor V, VII, VIII, XI levels, increased activation of FXII, and an increase of fibrin/fibrinogen degradation products and plasmin-antiplasmin-complex levels (74, 75, 116). In addition to the above-mentioned factors, hypothermia, which is routinely induced during surgery for ATAAD, results in increased platelet activation and aggregation and reversible thrombocytopenia caused by hepatic and splenic sequestration. Hypothermia also impairs the recognition process between VWF and FVIII and disturbs VWF proteolysis causing malformed VWF deposits (76, 117). Additionally, hypothermia causes a prolongation of prothrombin time and thromboplastin time independent of coagulation factor levels (118).

Clinical implications of bleeding in cardiac surgery

Bleeding is a common and feared complication in cardiac surgery. It has been demonstrated that patients who require transfusions of blood products have poorer surgical outcomes, and in the general cardiac surgery population, re-exploration for bleeding has been associated with increased rates of postoperative complications including acute kidney injury and low cardiac output. However, most importantly, several studies have reported a fourfold increase of mortality rates in patients who required re-exploration for bleeding compared to patients who did not (39, 119-122).

Studies on the clinical effects of bleeding complications in ATAAD are scarce but re-exploration rates of 14–22% have been reported and it has been demonstrated that bleeding causes up to 20% of in-hospital deaths following ATAAD surgery (21, 34, 69, 123). Hansson et al. showed that in ATAAD patients who received dual antiplatelet therapy (DAPT), postoperative bleeding, red blood cell transfusions and DAPT were independent predictors of 30-day mortality. In the same study, 25% of ATAAD patients had massive bleeding, and massive bleeding was three times more frequent in patients who died within 30 days of surgery (59% vs 19%) (39). More recently, data from the NORCAAD registry showed that 39% of ATAAD patients had major bleeding and that major bleeding was an independent predictor of 30-day mortality, associated with a 30-day mortality rate of 27% compared to 11% in remaining patients (77).

Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa) (Novoseven®; NovoNordisk A/S, Bagsvaerd, Denmark) was introduced in 1996 for use in patients with haemophilia and stimulates clotting by two principally different mechanisms. The first mechanism forms a complex with TF, thereby activating FX which converts prothrombin to thrombin. The second mechanism is activated by pharmacological doses of rFVIIa and is mediated by the direct binding of rFVIIa to the phospholipid surface of platelets, forming a TF-independent complex that activates FX and prompts the

thrombin burst (124). It has been demonstrated that pharmacological doses of FVIIa increase initial thrombin generation and result in faster platelet activation (125).

Since first described in 2001, rFVIIa has been increasingly used as an off-label treatment for refractory bleeding in cardiac surgery (126). It has been reported that bleeding and transfusions of red blood cells were reduced by the use of rFVIIa in standard cardiac surgery but several studies have reported increased risk of thromboembolic events in non-haemophiliac patients who received rFVIIa (127-132).

In ATAAD surgery, Tritapepe et al. reported that administration of rFVIIa successfully reduced blood loss and Yan et al. have demonstrated reduced need for transfusions when a combination of platelets and rFVIIa was administered to ATAAD patients, but blood loss was similar between the groups (133, 134). No increase in adverse thromboembolic events in patients who received rFVIIa was reported, but these studies were limited by the small number of exposed patients (n=23 and n=25).

Von Willebrand factor

The von Willebrand factor is a multimeric glycoprotein and is produced in endothelial cells and megakaryocytes, the precursors of platelets (108). VWF acts as a bridging molecule between tissue collagen and platelets by binding to the GP1b or the GPIIb/IIIa receptor on the platelet surface. In addition, VWF acts as a carrier protein of FVIII, and it has been shown that the half-life of circulating FVIII is markedly reduced in the absence of VWF (135, 136).

In endothelial cells, VWF is stored in Weibel-Palade bodies and in platelets, VWF is contained within α-granules (108). The VWF molecules vary in size from dimers with a molecular weight of 500 kDa to ultra-large multimers >10 000 kDa (108, 137). The Weibel-Palade bodies and α-granules are rich in ultra-large multimers, but when secreted they are unfolded as an effect of shear stress, expose their A2 domain and are rapidly cleaved to smaller multimers by the metalloproteinase ADAMTS-13 (108). The larger the multimer, the more sensitive it is to shear stress. Under normal conditions, VWF circulates as a loosely coiled protein concealing its GP1b domain. In response to vascular injury or shear stress caused by turbulent flow near the site of injury, VWF unwinds and exposes its sites responsible for the binding of GP1b (138). Ultra large multimers and high molecular weight multimers (HMWM) with a molecule weight of 5 500–10 000 kDa have the greatest capacity to bind collagen and platelets, and VWF function has been shown to progressively decrease with decreasing multimer size (137).

In cardiac surgery, it has been reported that aortic stenosis, mechanical circulatory support and congenital heart disease can cause von Willebrand disease (VWD) type 2A, characterised by a relative loss of HMWM (108, 139-143). However, the use of CPB has been shown to cause an increase of VWF antigen levels and proportion of HMWM (144). Administration of FVIII/VWF concentrate has been proven as an

effective prophylactic treatment for bleeding in patients with VWD but it has only been used in anecdotal cases of major trauma and ATAAD surgery (145). The functional status of VWF in aortic dissection and aortic surgery has not previously been studied and thus, neither has the potential of FVIII/VWF concentrate as a haemostatic agent in bleeding associated with aortic surgery.

Aims

Study I

The aim of Study I was to identify clinical predictors of massive bleeding in ATAAD surgery and to investigate the impact of massive bleeding on postoperative complications and mortality.

Study II

Study II aimed to evaluate the impact of recombinant FVIIa use on in-hospital mortality and rates of postoperative stroke and renal replacement therapy after ATAAD surgery.

Study III

In Study III, we aimed to evaluate laboratory and clinical features of the haemostatic system in patients undergoing ATAAD surgery and to compare the cohort of ATAAD patients with patients undergoing elective aortic surgery.

Study IV

The aim of Study IV was to assess the activity of VWF in patients undergoing surgery for ATAAD and compare VWF activity of ATAAD patients to that of patients undergoing elective surgery for diseases of the ascending aorta or of the aortic root.

Material and methods

Patients and study design

Study I

This was a retrospective cohort study with prospectively and retrospectively collected data and included 256 patients surgically treated for ATAAD between January 2004 and January 2016 at the Department of Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden.

To define massive bleeding, we used the BART criteria as defined in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study (146). Patients with any of the following four criteria were assigned to Group I: postoperative chest tube output exceeding 1500 mL over any 8 h period; reoperation for bleeding or cardiac tamponade within 24 h of surgery; transfusion of >10 U of red blood cells within 24 h after surgery; or death from haemorrhage within 30 days of surgery. Group I patients were compared with remaining patients (Group II).

Primary endpoints were in-hospital mortality (defined as any mortality prior to hospital discharge), late mortality and incidence of postoperative complications related to massive bleeding. Pre-, peri- and postoperative variables were prospectively entered into the departmental computerised database and collected retrospectively. Medical records were reviewed as needed. Survival data was obtained from the Swedish National Board of Health and Welfare (Socialstyrelsen, Sweden).

Study II

Study II was a multi-centre, propensity score-matched study using retrospectively collected data from the NORCAAD database. The registry consisted of a total of 1,159 patients who underwent ATAAD surgery between the 1st of January 2005 and 31st of December 2014.

Information regarding the use of rFVIIa was available for 761 patients, 171 of whom received rFVIIa. The propensity score algorithm matched 120 patients who received rFVIIa with 120 control patients.

Primary endpoints were in-hospital mortality, perioperative stroke and renal replacement therapy (RRT). Secondary endpoints were re-exploration for bleeding and late mortality. In-hospital mortality was defined as any death during hospital stay; stroke was defined as a clinically significant loss of neurological function caused by an ischaemic event with or without confirmation using computed tomography (CT); and RRT was defined as any postoperative need for continuous venovenous haemofiltration or haemodialysis.

Studies III and IV

These were single-centre, prospective, observational studies comparing patients with ATAAD to control patients undergoing elective surgery of the ascending aorta or the aortic root in mild to moderate hypothermia. Inclusion criteria for the ATAAD group were adult patients undergoing surgery for ATAAD using deep hypothermic circulatory arrest and ATAAD confirmed by computed tomography with symptom duration <48h. Patients were excluded if they received anticoagulants or antiplatelet drugs other than aspirin, if imaging showed an intramural haematoma or if surgical approach deviated from routine. Included in the elective group were adult patients with aortic aneurysm requiring surgery by replacement of the ascending aorta and/or the aortic root. Patients on anticoagulants or antiplatelet therapy other than aspirin were excluded.

Between September 2015 and October 2017, 27 patients undergoing ATAAD surgery were enrolled in the study. Two patients were later excluded: one patient had not been cooled to a deep hypothermic state and the other required a second run on CPB because of damage to the pulmonary artery. An additional patient was excluded from Study IV due to missing blood samples. The control group consisted of 20 patients who underwent elective procedures of the ascending aorta or the aortic root between December 2016 and April 2018. All patients with acute aortic syndromes (i.e. ATAAD and intramural haematomas) referred to our clinic during the inclusion period were registered and are presented in Figure 7.

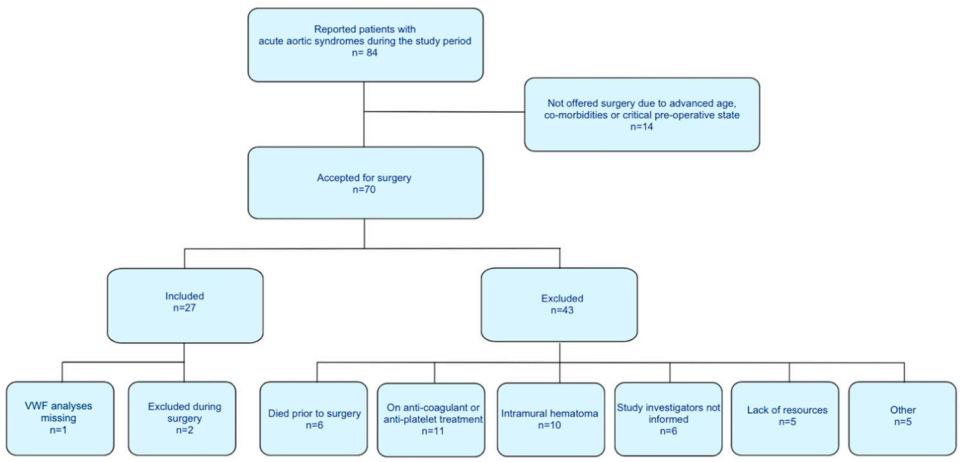

FIGURE 7 - Flowchart of all patients with acute aortic syndromes reported to our institution during the inclusion period.

Blood samples were collected at six time points: T0- anaesthesia induction; T1- at core temperature nadir before rewarming was initiated (only collected in elective patients with core temperature ≤32 °C, n=14); T2- prior to protamine reversal; T3- end of surgery; T4- 24 h after surgery; and T5- five days after surgery (four days if

an elective patient was transferred to local hospital prior to the fifth postoperative day). Samples at T0, T4 and T5 were collected from a central venous line, whereas the arterial line of the CPB circuit was used at T1 and T2. The T3 sample was collected from a radial artery line.

In Study III, blood samples were analysed by the Department of Clinical Chemistry, Division of Laboratory Medicine, Skåne University Hospital, Lund, Sweden, on a CS-5100 automated analyser (Siemens, Marburg, Germany). Prothrombin time/international normalised ratio (PT(INR)) was measured using the reagent Owren PT (Medirox, Sweden), reference (ref) interval: <1.2 and activated partial thromboplastin time (APTT) with the Actin FSL reagent (Siemens), reference interval: 26–33 s. For measurement of antithrombin, a factor Xa-based chromogenic reagent INNOVANCE™ antithrombin (Siemens) was used, ref. interval: 0.8–1.2 kIU/L. Fibrinogen was measured with the Dade Thrombin reagent (Siemens), ref. interval: 2–4 g/L. D-dimer was measured with Medirox D-dimer reagent (Medirox; cut off <0.25 mg/L). Platelet counts were analysed on the Sysmex XN instrument (Sysmex corp., Japan), ref. interval: 165–387 $x10^9$/L for female patients and 145–348 $x10^9$/L for male patients.

In Study IV, von Willebrand factor activity was analysed with an immunoassay relying on the spontaneous binding of VWF to a gain-of-function mutant glycoprotein Ib (GPIb) fragment (VWF:GPIbM) (Innovance VWF:Ac; Siemens, Marburg, Germany) on a BCS instrument (Siemens). This method is used as the routine screening method for VWD in clinical practice at our institution. Our locally established ref. interval was 0.5–2.0 kIU/L. Multimeric sizing of VWF (VWF:MS) was performed with SDS agarose gel and Western-blotting technique. Optical densitometry representing the concentrations of VWF antigen and multimers of different molecular weights were analysed using the open-source software ImageJ (v.1.52k, National Institute of Health, Bethesda, MD, USA).

In Studies III and IV, we defined in-hospital death as death prior to hospital discharge. Intraoperative bleeding was defined as blood loss collected and quantified between the termination of CPB and end of operation using intraoperative cell salvage and surgical gauze swabs. The definition of postoperative stroke was an ischaemic neurologic deficit with or without confirmation using computed tomography (CT). Renal replacement therapy (RRT) was defined as postoperative need for continuous veno-venous haemofiltration or haemodialysis and cardiac tamponade as pericardial effusion that required pericardial drainage or re-exploration. We reported transfusions as units (U) of packed red blood cells (PRBC), platelets or plasma per patient, administered perioperatively.

The primary endpoints of Study III were levels of blood (B)–platelet count, plasma (P)–PT(INR), P-APTT, P-fibrinogen, P-D-dimer and P-antithrombin at the predefined time points. Secondary endpoints included intraoperative bleeding, 24 h chest-tube output, re-exploration for bleeding, transfusions of PRBC, platelets or plasma and in-hospital mortality.

In Study IV, primary endpoints were measured VWF:GPIbM at the predefined time points, intraoperative bleeding and 24 h chest-tube output. Re-exploration for bleeding and transfusion of red blood cells, platelets and plasma in relation to VWF:GPIbM were regarded as secondary endpoints.

Ethical aspects

All studies were performed according to the principles of the Helsinki Declaration of Human Rights and were approved by the regional Ethics Review Board at Lund University, Sweden (ref. 2015/197). A written informed consent was obtained from all patients included in Studies III and IV. In ATAAD cases where patients were determined unfit to give their preoperative consent to participate in the study, informed consent was collected postoperatively or from next of kin.

Surgical technique

General anaesthesia was induced and sustained with propofol. If necessary, a volatile anaesthetic agent (isoflurane or sevoflurane) was used throughout the procedure, supplemented with fentanyl and a neuromuscular blocking agent as required.

Median sternotomy, CPB and intermittent cold blood cardioplegic arrest were routinely used. For arterial cannulation, the femoral artery was used in most cases. Venous access was achieved through bicaval cannulation or a two-stage cannula. In general, resection of the ascending aorta, inspection of the aortic arch and completion of the distal anastomosis was performed under deep (<20 °C) or moderate (20–32 °C) hypothermic circulatory arrest. The extent of aortic repair was determined by the location of the intimal tear and the anatomical properties of the dissection. Hemiarch procedures included resection of the minor curvature of the aortic arch whereas arch procedures were defined as those where any of the supra-aortic branches were re-implanted. Perfusion was subsequently instituted through a side branch of the vascular graft, enabling distal circulatory flow and rewarming during suturing of the proximal anastomosis. Root replacement was performed on involvement of the coronary ostia or aortic valve or in the presence of an aortic root aneurysm. When required, valvular competence was restored via subcommissural plication, commissural resuspension and valvuloplasty. In some cases, isolated aortic valve replacement with sparing of the aortic root was performed. Concomitant procedures, e.g. coronary artery bypass, were performed when necessary.

Cooling strategies in patients undergoing elective aortic surgery included: hemiarch procedure, 25 °C; valve sparing aortic root replacement (ad modum David), 30 °C; root replacement (ad modum Bentall), root remodeling or combined aortic valve replacement with or without supracoronary replacement of the ascending aorta, 32 °C; and isolated replacement of the ascending aorta, 32–36 °C.

Hepcon HMS Plus system (Medtronic, Minneapolis, MN, USA) was used for calculation of the heparin dose required to achieve an activated clotting time (ACT) of >480 s. If the heparin dose response (HDR) slope was <70 s/U/mL, 1000 U of antithrombin were given and 10 minutes later, a new measurement of HDR was performed.

At our institution we used a ROTEM® and blood analysis guided bleeding management protocol as routine practice. Transfusions of PRBC were administered at B-Haemoglobin <90 g/L and platelets were given at maximum clot firmness (MCF) EXTEM <50 mm and MCF FibTEM >10 mm or platelet count <100 x10^9. Fibrinogen and/or plasma were used at MCF FIBTEM <15 mm or P-fibrinogen <2 g/l. Prothrombin complex concentrate (PCC) or plasma were used at coagulation time (CT) EXTEM >100 s, CT INTEM >240 s, P-PT(INR) >1.5 or P-APTT >1.5 x normal value. Per routine, all patients received a total of 4g of tranexamic acid, distributed as 2–3 g at the start of the procedure and 1–2 g after cessation of CPB. Additional tranexamic acid was administered when maximum lysis (ML) exceeded 15%.

However, final decision-making regarding transfusions and pharmacological bleeding management was at the discretion of the surgeon in charge. Recombinant FVIIa was used mainly during surgery or at the intensive care unit (ICU) upon failure of primary pharmacological treatment to reduce bleeding.

Statistical analysis

Categorical data was reported as proportions, and continuous variables were expressed as the mean ± standard deviation (SD) in normally distributed data or as medians and interquartile ranges (IQRs) in skewed distributions. Proportions were compared using the chi-square test. When the expected frequency was <5, Fisher's exact test was employed. For continuous variables, Student's t-test and Mann-Whitney U test were used in normally distributed and skewed distributions, respectively. Wilcoxon sign ranked test was used for analysing related samples.

Event rates ±1 standard error during follow-up were estimated and survival was plotted using the Kaplan-Meier method. Groups were compared using the log-rank test. Uni- and multivariable logistic regression analyses were performed to determine independent predictors of massive bleeding and in-hospital mortality. The effects of the preoperative and operative variables on survival were assessed with the Cox proportional hazard model in a stepwise manner. The inclusion criterion for the full regression models was $p<0.200$, and the limit for stepwise backward elimination was $p<0.100$. The results of logistic regression analyses were expressed as odds ratios (OR) and those of the Cox regression analysis as hazard ratios (HR) with 95% confidence intervals (CI).

In Study II, a propensity matched analysis was performed to adjust for differences between the two groups (147). First, univariate logistic regression analyses with

group as outcome were performed for all variables in Table 1. All variables with a p-value <0.200 were subsequently included in a multivariable logistic regression model, which computed the propensity scores. The variables included in the model were bicuspid aortic valve, previous cardiac surgery, history of stroke, cerebral malperfusion, Penn class, proximal surgical technique, CPB time, cross-clamp time and the lowest core temperature. A nearest-neighbour matching with caliper 0.2 was performed using the propensity scores. This resulted in the match of 120 out of a maximum of 127 possible pairs. The remaining patients did not have the necessary data for inclusion in the model. The matching was evaluated using standardised mean differences.

The paired samples were compared using conditional logistic regression for binary variables. The comparisons of the primary endpoints were presented as ORs with 95% CIs and were illustrated using Forest plots. The ORs were generated by the conditional logistic regression and were based on the discordant pairs. The McNemar-Bowker test was used for categorical variables with more than two categories. All continuous variables in the matched sample met the conditions for a paired t-test, which was subsequently used for analysis.

In Study IV, optical density values indicating the concentrations of VWF antigen and multimers of different molecular weights were analysed and area under the curve (AUC) representing the protein-loading was quantified for the five top bands and five bottom bands of the western blot. The results were presented as a ratio between the protein-loading of study samples compared to the protein-loading of a control sample with pooled plasma analysed on the same gel.

Unless otherwise stated, a *p*-value <0.05 was considered statistically significant. Statistical analyses relied on SPSS versions 21.0 and 25.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Mac, Version 21.0. Armonk, NY and IBM Corp, IBM Corp. Released 2017. IBM SPSS Statistics for Mac, Version 25.0 Armonk, NY: IBM Corp) and R version 3.2.5. (The R Project for Statistical Computing; https://www.r-project.org/). The MatchIt package in R (https://cran.r-project.org/web/packages/MatchIt/index.html) was used for propensity matching.

Results

Study I

Study population and patient follow-up

Study I included 256 patients surgically treated for ATAAD between January 2004 and January 2016 at the Department of Cardiothoracic Surgery of Skåne University Hospital (Lund, Sweden). Follow-up was performed in March 2016, was 98% complete and included 975 patient-years with a mean follow-up time of 3.9 ±3.2 years (median 3.3 years, IQR 0.8–6.4). Six patients were lost to follow-up due to emigration and one patient due to an unknown date of death. Massive bleeding as per the BART criteria was identified in 66 patients who constituted Group I. Group II consisted of the remaining 190 patients.

Preoperative characteristics

Preoperative characteristics of the study population are presented in Table I.1. Patients in Group I (n=66) were older (65.2 years vs 62.2 years, p=0.042), had shorter symptom duration (3.8 h vs 6.9 h, p=0.003), and were more likely to have a history of hypertension (64% vs 46%, p=0.015), diabetes mellitus (44% vs 30%, p=0.039) and coronary artery disease (14% vs 4%, p=0.007). Group I patients had also lower systolic blood pressure at admission (113 mmHg vs 125 mmHg, p=0.042), higher P-creatinine (92 μmol/l vs 80μmol/l, p<0.001) and presented more often with organ malperfusion (47% vs 31%, p=0.016) and cardiac tamponade (18% vs 9%, p=0.041). Clopidogrel and dual antiplatelet treatment was significantly more prevalent in Group I (17% vs 5%, p=0.008 and 20% vs 8%, p<0.001, respectively) than in Group II (n=190).

Intraoperative characteristics

There were no between-group differences in terms of surgical techniques used (Table I.2). The median duration of CPB was longer in Group I (221 min [157–258 min] vs 180 min [151–223 min], p=0.002) as was circulatory arrest time (22 [17–30] min vs 18 [12–23] min, p=0.014). Core temperature nadir was similar between the two groups (19.2±5.4 °C and 19.3±4.6 °C in Group I and Group II, respectively, [p=0.812]).

Postoperative bleeding and complications

Median chest tube output 12 h after surgery was 1180 mL (150–2763 mL) in Group I and 430 (280–560) mL in Group II (p<0.001) (Table I.3). Re-exploration for bleeding was significantly higher in Group I patients (55.9% vs 1.1%, p<0.001). Patients in Group I received significantly more transfusions of PRBC (8.5 [5.3–12.5] U vs 3 [1–6] U, p<0.001), platelets (9 [4.5–12.8] U vs 4 [2–6] U, p<0.001) and plasma (5.5 [4.3–7.5] vs 1 [0–4] U, p<0.001), and were treated with more fibrinogen concentrate (9.8 ±4.2 g vs 4.4 ±3.0 g, p<0.001) and rFVIIa (4.1 ±3.0 mg

vs 1.6 ±2.3 mg, $p<0.001$) than patients in Group II. Group I patients required renal replacement therapy significantly more often (22.0% vs 3.8%, $p<0.001$) than patients in Group II as well as prolonged ventilatory support (88.1% vs 31.1%, $p<0.001$) and longer ICU stay (12 [5.5–17] days vs 3 [3–5] days, $p<0.001$). They were also more likely to suffer from postoperative stroke (39.0% vs 23.0%, $p=0.016$) and deep sternal wound infection (6.8% vs 1.1%, $p=0.033$).

Predictors of massive bleeding

Age (OR, 1.060 [per year increment]; 95% CI, 1.019–1.103, $p=0.004$), symptom duration (OR, 0.974 [per hour increment]; 95% CI, 0.950–0.999, $p=0.041$), hypertension (OR, 3.007; 95% CI, 1.361–6.645, $p=0.006$), coronary artery disease (OR, 5.852; 95% CI, 1.477–23.182, $p=0.012$), organ malperfusion (OR, 2.241; 95% CI, 1.024–4.904, $p=0.044$), DeBakey Type 1 dissection (OR, 2.652; 95% CI, 1.004–7.008, $p=0.049$), dual antiplatelet therapy (OR, 6.110; 95% CI, 1.748–21.355, $p=0.005$), preoperative P-creatinine (OR, 1.008 [per 1 µmol/L increment]; 95% CI, 1.000–1.016, $p=0.037$), CPB time (OR, 1.018 [per min increment]; 95% CI, 1.009–1.028, $p<0.001$) and cross-clamp duration (OR, 0.986 [per min increment]; 95% CI, 0.975–0.997, $p=0.014$) were all identified as independent predictors of massive bleeding (Table I.4).

TABLE I.1 - Preoperative characteristics of the study population

Characteristic	Group I (n=66)	Group II (n=190)	*p*
Age (years)	65.2 (±9.4)	62.2 (±12.0)	0.042
Female gender	22 (33.3)	70 (36.8)	0.602
BMI (kg/m2)	25.9 (±3.5)	26.6 (±5.2)	0.323
Symtom duration (h)	3.80 (2.86–7.59)	6.91 (4.58–13.49)	0.003
Smoking history	27 (40.9)	65 (34.2)	0.329
Marfan syndrome	4 (6.1)	21 (11.1)	0.239
Previous aortic surgery[a]	1 (1.5)	5 (2.6)	1.000
Hypertension	42 (63.6)	88 (46.3)	0.015
Hyperlipidaemia	6 (9.1)	11 (5.8)	0.391
Diabetes mellitus	29 (43.9)	57 (30.0)	0.039
Coronary artery disease	9 (13.6)	7 (3.7)	0.007
Peripheral vascular disease	2 (3.0)	5 (2.6)	1.000
Stroke	4 (6.1)	12 (6.3)	1.000
COPD	7 (10.6)	7 (3.7)	0.054
Dialysis	1 (1.5)	1 (0.5)	0.450
Preoperative blood pressure (mmHg)			
Systolic blood pressure	113.2 (±39.6)	124.5 (±35.3)	0.042
Diastolic blood pressure	69.4 (±19.0)	72.7 (±21.2)	0.370
Organ malperfusion	31 (47.0)	58 (30.5)	0.016
Cardiac tamponade	12 (18.2)	17 (8.9)	0.041
Penn class			
Aa	23 (34.3)	111 (58.1)	<0.001
Ab	19 (28.4)	44 (23.0)	0.383
Ac	17 (25.4)	23 (12.0)	0.009
Abc	8 (11.9)	13 (6.8)	0.186
DeBakey type 1	52 (78.8)	135 (71.1)	0.222
Intramural haematoma	1 (1.5)	10 (5.3)	0.298
Aspirin	21 (31.8)	56 (29.5)	0.720
Clopidogrel	11 (16.7)	10 (5.3)	0.004
Ticagrelor	4 (6.1)	5 (2.6)	0.242
DAPT	13 (19.7)	15 (7.9)	0.008
Warfarin	3 (4.5)	9 (4.7)	1.000
P-creatinine (µmol/l)	92.0 (75.5–107.5)	80 (58.5–103.5)	<0.001
P-lactate (mmol/l)	1.2 (1.1–2.6)	1.4 (1.0–2.5)	0.079

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR). [a]Surgery of the descending aorta. BMI: body mass index; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy.

TABLE I.2 - Intraoperative characteristics of the study population

Characteristic	Group I (n=66)	Group II (n=190)	*p*
Distal surgical technique[a]			
Supracoronary graft	51 (77.3)	152 (80.0)	0.638
Hemiarch procedure	10 (15.2)	25 (13.2)	0.685
Aortic arch procedure	4 (6.1)	13 (6.8)	1.000
Proximal surgical technique[a]			
Supracoronary graft[b]	41 (62.1)	124 (65.3)	0.646
Bentall procedure	18 (27.3)	53 (27.9)	0.923
David or Yacoub procedure	1 (1.5)	5 (2.6)	1.000
Aortic valve replacement	5 (7.6)	8 (4.2)	0.338
Arterial cannulation site[a]			
Femoral artery	49 (74.2)	136 (71.6)	0.677
Ascending aorta/aortic arch	13 (19.7)	46 (24.2)	0.453
Subclavian/brachiocephalic artery	2 (3.0)	5 (2.6)	1.000
Left ventricle	1 (1.5)	3 (1.6)	1.000
CPB time (min)	221 (157–258)	180 (151–223)	0.002
Aortic cross-clamp time (min)	118 (±61.6)	107 (±56.0)	0.182
Circulatory arrest (n)[c]	33 (50.8)	106 (55.8)	0.483
Circulatory arrest duration (min)	22 (17–30)	18 (12–23)	0.014
Lowest core temperature (°C)	19.2 (±5.4)	19.3 (±4.6)	0.812
Antegrade cerebral perfusion (n)	8 (12.3)	16 (8.4)	0.354
Antegrade cerebral perfusion (min)	35.8 (±17.4)	31.1 (±14.7)	0.460
Retrograde cerebral perfusion (n)	24 (36.9)	68 (35.8)	0.870
Retrograde cerebral perfusion (min)	27.8 (±10.0)	24.6 (±7.9)	0.114
Primary tear exclusion	41 (63.1)	125 (65.8)	0.692

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR). [a] One patient in Group I died prior to attempt to repair the aorta; [b] With or without commissural resuspension; [c] Without the use of selective cerebral perfusion. CPB: cardiopulmonary bypass.

TABLE I.3 - Postoperative characteristics of the study population

Characteristic	Group I	Group II	*p*
Postoperative bleeding (mL)[a]			
12 h	1180 (1150–2763)	430 (280–560)	<0.001
24 h	1705 (1460–3315)	660 (500–780)	<0.001
Total	3990 (3458–4612)	990 (760–1600)	<0.001
PRBC (U)[a]	8.5 (5.3–12.5)	3 (1–6)	<0.001
Platelets (U)[a]	9 (4.5–12.8)	4 (2–6)	<0.001
Plasma (U)[a]	5.5 (4.3–7.5)	1 (0–4)	<0.001
Fibrinogen concentrate (g)[a]	9.8 (±4.2)	4.4 (±3.0)	<0.001
Tranexamic acid (g)[a]	3.4 (±2.1)	3.6 (±1.5)	0.545
rFVIIa (mg)[a]	4.1 (±3.0)	1.6 (±2.3)	<0.001
Re-exploration for bleeding[a]	33 (55.9)	2 (1.1)	<0.001
RRT[a]	13 (22.0)	7 (3.8)	<0.001
Stroke[a]	23 (39.0)	42 (23.0)	0.016
DSWI[a]	4 (6.8)	2 (1.1)	0.033
Ventilatory support >48h[a]	52 (88.1)	57 (31.1)	<0.001
ICU-days[a]	12 (5.5–17)	3 (3–5)	0.001
Postop atrial fibrillation[a]	32 (54.2)	73 (39.9)	0.053
P-creatinine at discharge[a]	234 (134–326)	101 (72–124)	<0.001
Postoperative P-lactate[a]	4.8 (2.6–7.3)	2.2 (1.6–2.9)	0.007
Postoperative P-CKMB[a]	91.6 (34.7–147.0)	34.8 (17.2–58.9)	0.176
Intra-operative mortality[b]	7 (10.6)	7 (3.7)	0.054
In-hospital mortality[b]	20 (30.3)	15 (8.0)	<0.001
Late reoperation of the aorta[c]	7 (15.9)	10 (5.6)	0.053

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR). [a] Group I, n=59, Group II, n=183. Patients who died intra-operatively were excluded from analysis; [b] Group I, n=66, Group II, n=190. All patients were included in analysis; [c] Group I, n= 44, Group II, n=170. Patients who died during hospital stay or were lost to follow-up were excluded from analysis. PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; RRT: renal replacement therapy; DSWI: deep sternal wound infection

Early mortality

Intraoperative mortality was 10.6% in Group I and 3.7% in Group II (p=0.054) (Table I.3), and in-hospital mortality was significantly higher in Group I (30.3% vs 8.0%; p<0.001). Multivariable logistic regression analysis identified preoperative cardiac tamponade (OR, 4.281; 95% CI, 1.425–12.866, p=0.010) and re-exploration for bleeding within 24 h after surgery (OR, 3.109; 95% CI, 1.044–9.256, p=0.042) as independent predictors of in-hospital mortality (Table I.5).

TABLE I.4 - Uni- and multivariable logistic regression analysis of variables associated with massive bleeding according to the BART criteria[a]

	Univariable analysis (n=242)			Multivariable analysis (n=242)		
Characteristic	OR	95% CI	*p*	OR	95% CI	*p*
Age (per 1 year increment)	1.024	0.998–1.051	0.072	1.060	1.019–1.103	0.004
Female gender	0.857	0.475–1.547	0.609			
BMI	0.970	0.899–1.046	0.427			
Symtom duration (per h increment)	0.977	0.955–1.001	0.055	0.974	0.950–0.999	0.041
Smoking history	1.331	0.749–2.366	0.329			
Marfan syndrome	0.519	0.171–1.573	0.24			
Previous aortic surgery[b]	0.569	0.065–4.963	0.610			
Hypertension	2.028	1.139–3.612	0.016	3.007	1.361–6.645	0.006
Hyperlipidaemia	1.627	0.577–4.589	0.357			
Diabetes mellitus	1.829	1.027–3.256	0.040			
Coronary artery disease	4.128	1.471–11.587	0.007	5.852	1.477–23.182	0.012
Peripheral vascular disease	1.156	0.219–6.107	0.864			
Stroke	0.957	0.298–3.077	0.941			
COPD	3.102	1.045–9.207	0.041			
Dialysis	2.908	0.179–47.156	0.453			
Organ malperfusion	2.016	1.136–3.577	0.017	2.241	1.024–4.904	0.044
Cardiac tamponade	2.261	1.016–5.031	0.045			
DeBakey type 1 (ref. type 2)	1.513	0.776–2.952	0.224	2.652	1.004–7.008	0.049
Intramural haematoma	0.277	0.035–2.206	0.225			
Aspirin	1.117	0.610–2.044	0.721			
Clopidogrel	3.600	1.452–8.926	0.006			
Ticagrelor	2.387	0.621–9.170	0.205			
DAPT	2.567	1.106–5.955	0.028	6.110	1.748–21.355	0.005
Warfarin	0.958	0.251–3.649	0.949			
P-creatinine (per 1 µmol/l increment)	1.010	1.002–1.017	0.014	1.008	1.000–1.016	0.037
P-lactate (per 1 mmol/l increment)	1.072	0.928–1.240	0.344			
CPB time (per min increment)	1.006	1.002–1.009	0.001	1.018	1.009–1.028	<0.001
Aortic cross-clamp time (per min increment)	1.003	0.998–1.008	0.183	0.986	0.975–0.997	0.014
Lowest core temperature (per 1°C increment)	0.993	0.936–1.053	0.811			
Primary tear exclusion	0.888	0.494–1.596	0.692			

Values expressed as odds ratio (OR) with 95% confidence interval (CI). [a] Patients who died intra-operatively were excluded from this analysis; [b]Surgery of the descending aorta. BMI: body mass index; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy; CPB: cardiopulmonary bypass.

TABLE I.5 - Independent predictors of in-hospital mortality after multivariable logistic regression[a]

	Multivariable logistic regression (n=242)		
Characteristic	OR	95% CI	*p*
Cardiac tamponade	4.281	1.425–12.866	0.010
Re-exploration for bleeding within 24 h	3.109	1.044–9.256	0.042

Values expressed as odds ratio (OR) with 95% confidence interval (CI). [a] Patients who died intra-operatively were not analysed

Late survival and aortic reoperation

Kaplan-Meier estimates of survival (Figure I.1) indicated poorer survival at 1, 3 and 5 years in Group I (68.8 ±5.9% vs 92.8 ±1.9%, 65.2 ±6.2% vs 85.3 ±2.7% and 53.9 ±6.9% vs 82.1 ±3.3%, respectively, [log rank $p<0.001$]). Survival in Group I also was significantly poorer when only patients who survived to hospital discharge were analysed (survival at 1, 3 and 5 year: 93.1 ±3.9% vs 98.8 ±0.8%, 88.1 ±5.0% vs 90.9 ±2.5% and 71.8 ±7.8% vs 87.4 ±33.1% in Group I and II, respectively [log rank $p=0.001$]). Group I demonstrated a trend towards a higher rate of late aortic reintervention (15.9% vs 5.6%, p=0.053) (Table I.3). Cox regression analysis identified age (HR, 1.048 [per year increment]; 95% CI, 1.017–1.080, $p=0.002$), preoperative cardiac tamponade (HR, 2.211; 95% CI, 1.128–4.335, $p=0.021$) and re-exploration for bleeding (HR, 3.039; 95% CI, 1.605–5.757, $p=0.001$) as independent predictors of late mortality (Table I.6).

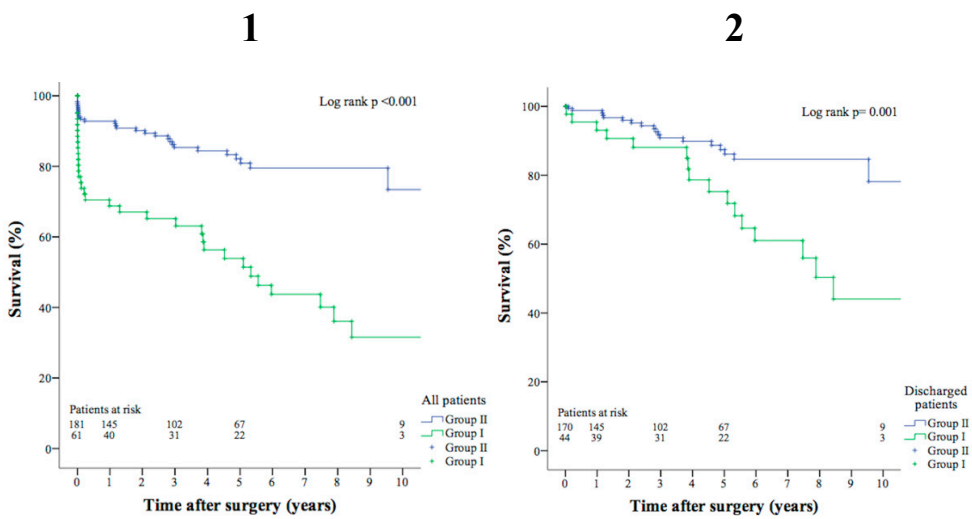

FIGURE I.1 - Kaplan-Meier survival curves of all patients, plotted by group.
FIGURE I.2 - Kaplan-Meier survival curves of patients who survived to hospital discharge, plotted by group.

TABLE I.6 - Cox regression analysis of independent predictors of late mortality[a]

	Cox regression analysis (n=236)		
Characteristic	HR	95% CI	*p*
Age (per year increment)	1.048	1.017–1.080	0.002
Cardiac tamponade	2.211	1.128–4.335	0.021
Re-exploration for bleeding within 24 h	3.039	1.605–5.757	0.001

Values expressed as hazard ratio (HR) with 95% confidence interval (CI). [a] Patients who died intra-operatively were excluded from this analysis.

Study II

Study population and patient follow-up

A total of 1,159 patients were included in the NORCAAD database up to March 2017. Follow-up was performed in January 2015 and was 99.5% complete with a median follow-up time of 2.3 years (range, 0.25–5.23 years). Data regarding the use of rFVIIa was available for 761 patients (99.5% complete, median follow-up time of 2.2 years [range, 0.59–4.63 years]). Of these 761 patients, 171 received treatment with rFVIIa (rFVIIa group).

Unmatched population

The baseline characteristics and intraoperative data for the unmatched groups are presented in Table II.1. The rFVIIa group showed a trend towards more often having a history of stroke (5.8% vs 2.9%, p=0.07) and presenting with cerebral malperfusion (12.9% vs 8.1%, p=0.08) than did the control group. Patients treated with rFVIIa underwent more complex aortic root surgery (p=0.01), had longer duration of CPB (212 [173–268] min vs 189 [153–228] min, p<0.01) and cross-clamping (100 [70–146] min vs 87 [65–124] min, p<0.01), and had a lower core temperature nadir (18 [18–21] °C vs 20 [18–24] °C, p<0.01). Postoperative results of the unmatched population are presented in Supplementary Tables II.1–II.3).

Matched population

The propensity score algorithm matched 120 patients who received rFVIIa with 120 control patients. The baseline characteristics and intraoperative data for the matched groups are presented in Table II.2. After propensity score matching, there were no significant differences between the groups, except for rFVIIa patients more frequently being on preoperative warfarin treatment (11.7% vs 4.2%, p=0.049).

A sensitivity analysis of the primary outcomes was performed adjusting for all variables with a standardised absolute difference exceeding 10%. These variables were adjusted for in the conditional logistic regression of the matched dataset. Minor effects on the odds ratios were identified but did not impact the conclusions of the main analyses. Additionally, a multivariable logistic regression was performed adjusting for the same variables as those included in the propensity score matching. Still, we could not show any significant effects on the primary outcomes.

TABLE II.1 - Baseline and surgical characteristics in the unmatched populations

Characteristic	rFVIIa (n=171)	Control (n=590)	AbSD (%)	*p*	Missing (n)
Age	62.0 (54.0– 68.0)	64.0 (53.6–70.8)	3.9	0.65	0
Male gender	122 (71.3)	394 (66.8)	9.8	0.26	0
Hypertension	89 (52.0)	311 (52.7)	1.3	0.88	0
History of aortic aneurysm	20 (11.7)	51 (8.7)	10.3	0.24	4
Connective tissue disease	3 (1.8)	20 (3.4)	9.6	0.28	3
Bicuspid aortic valve	6 (3.5)	39 (6.7)	13.6	0.13	10
Previous aortic surgery	7 (4.1)	14 (2.4)	10.3	0.24	6
Previous cardiac surgery	7 (4.1)	12 (2.0)	13.2	0.14	0
Diabetes mellitus	4 (2.3)	12 (2.0)	2.0	0.82	4
Hyperlipidaemia	16 (9.4)	74 (12.6)	9.9	0.26	4
History of stroke	10 (5.8)	17 (2.9)	16.0	0.07	3
Chronic kidney disease	5 (2.9)	9 (1.5)	10.3	0.24	3
COPD	8 (4.7)	33 (5.6)	4.2	0.63	4
History of smoking	62 (45.9)	181 (41.7)	8.5	0.39	192
BMI (kg/m^2)	25.4 (23.5–28.2)	26.0 (23.5–29.0)	9.3	0.32	96
Aspirin	52 (30.4)	155 (26.5)	8.9	0.31	4
Other antiplatelet treatment	23 (13.5)	61 (10.4)	9.7	0.27	4
Warfarin treatment	16 (9.4)	38 (6.5)	11.2	0.20	4
Blood pressure medicine	70 (41.7)	255 (44.2)	5.1	0.56	16
Organ malperfusion (any)	51 (30.0)	152 (26.0)	9.0	0.31	7
Cerebral malperfusion	20 (12.9)	39 (8.1)	16.4	0.08	127
DeBakey type 1	130 (76.5)	435 (74.2)	5.2	0.55	5
Intramural haematoma	15 (9.0)	55 (9.5)	1.7	0.85	18
Penn class			24.3	0.07	9
Aa	97 (57.1)	385 (66.2)			
Ab	40 (23.5)	122 (21.0)			
Ac	20 (11.8)	54 (9.3)			
Abc	13 (7.6)	21 (3.6)			
Proximal surgical technique			30.4	0.01	1
Supracoronary graft	108 (63.2)	447 (75.9)			
Bentall procedure	46 (26.9)	104 (17.7)			
David/Yacoub procedure	4 (2.4)	14 (2.4)			
Other	13 (7.6)	24 (4.1)			
Distal surgical technique			13.3	0.48	8
Ascending aorta	130 (76.5)	418 (71.7)			
Hemiarch procedure	33 (19.4)	126 (21.6)			
Arch procedure	5 (2.9)	31 (5.3)			
Other	2 (1.2)	8 (1.4)			
CPB time (min)	212 (173–268)	189 (153–228)	38.7	<0.01	60
Cross-clamp time (min)	100 (70–146)	87 (65–124)	25.9	<0.01	84
HCA time (min)	24 (16–32)	25 (18–34)	12.0	0.24	75
Lowest core temperature (°C)	18.0 (18.0–21.0)	20.0 (18.0–24.0)	40.5	<0.01	56

Values were expressed as number and percentage (%) or as median and interquartile range (IQR). COPD: chronic obstructive pulmonary disease; BMI: body-mass index; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest.

TABLE II.2 - Baseline and surgical characteristics in the propensity score-matched populations

Characteristic	rFVIIa (n=120)	Control (n=120)	AbSD (%)	*p*	Missing (n)
Age	62 (54.8–69.0)	62 (49.0–68.8)	16.2	0.22	0
Male gender	83 (69.2)	74 (61.7)	16.1	0.25	0
Hypertension	60 (50.0)	68 (56.7)	13.4	0.34	0
History of aortic aneurysm	14 (11.7)	11 (9.2)	8.6	0.66	0
Connective tissue disease	2 (1.7)	5 (4.2)	14.6	0.45	0
Bicuspid aortic valve	5 (4.2)	5 (4.2)	<0.1	1.00	0
Previous aortic surgery	6 (5.0)	5 (4.2)	5.1	1.00	0
Previous cardiac surgery	4 (3.3)	2 (1.7)	10.7	0.69	0
Diabetes mellitus	3 (2.5)	4 (3.3)	5.8	1.00	0
Hyperlipidaemia	10 (8.3)	9 (7.5)	2.6	1.00	0
History of stroke	5 (4.2)	7 (5.8)	9.0	0.75	0
Chronic kidney disease	5 (4.2)	3 (2.5)	12.4	0.73	0
COPD	5 (4.2)	6 (5.0)	3.7	1.00	0
History of smoking	35 (47.9)	41 (56.2)	13.3	0.36	94
BMI (kg/m^2)	25.1 (23.4–28.1)	24.8 (23.4–28.1)	1.0	0.64	50
Aspirin	34 (28.3)	31 (25.8)	5.6	0.75	0
Antiplatelet treatment	17 (14.2)	12 (10.0)	13.3	0.44	0
Warfarin treatment	14 (11.7)	5 (4.2)	29.2	0.05	0
Blood pressure medicine	48 (41.0)	55 (47.0)	14.7	0.41	6
Organ malperfusion (any)	42 (35.0)	44 (36.7)	3.8	0.89	0
Cerebral malperfusion	14 (11.7)	15 (12.5)	2.9	1.00	0
DeBakey type 1	34 (28.6)	33 (27.7)	2.5	1.00	2
Intramural haematoma	7 (6.3)	6 (5.4)	3.3	1.00	0
Penn class			6.2	0.12	0
Aa	68 (56.7)	71 (59.2)			
Ab	34 (28.3)	31 (25.8)			
Ac	10 (8.3)	10 (8.3)			
Abc	8 (6.7)	8 (6.7)			
Proximal surgical technique			13.9	0.76	0
Supracoronary graft	77 (64.2)	79 (65.8)			
Bentall procedure	30 (25.0)	28 (23.3)			
David/Yacoub procedure	3 (2.5)	5 (4.2)			
Other	10 (8.3)	8 (6.7)			
Distal surgical technique			20.9	0.57	2
Ascending aorta	86 (72.3)	81 (68.1)			
Hemiarch procedure	28 (23.5)	27 (22.7)			
Arch procedure	1 (0.8)	2 (1.7)			
Other	4 (3.4)	9 (7.6)			
CPB time (min)	210 (129–257)	198 (164–234)	2.6	0.82	0
Cross-clamp time (min)	95 (67–146)	88 (61–128)	4.5	0.75	0
HCA time (min)	25 (17 –32)	27 (20–36)	14.0	0.23	18
Lowest core temperature (°C)	18.0 (17.2–21.4)	18.2 (18.0–21.4)	1.6	0.88	0

Values were expressed as number and percentage (%) or median and interquartile range (IQR). COPD: chronic obstructive pulmonary disease; BMI: body mass index; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest.

Bleeding, transfusions and re-exploration for bleeding

Patients in the rFVIIa group had greater chest tube output during the first 24 h (1500 [835–2500] mL vs 990 [520–1720] mL] than controls; however, numerous missing values deemed a comparative analysis between the matched groups impossible (Table II.3). In the unmatched samples, data was available for 444 of 761 patients and showed that patients who received rFVIIa bled significantly more during the first 24 h (1160 [670–2215] mL vs 780 [520–1230] mL, $p<0.01$) (Supplementary Table II.2). Patients treated with rFVIIa received a median of 5 mg (range, 2–10 mg) of rFVIIa and more transfusions of PRBC (9.0 [4.0–17.0] U vs 5.0 [2.0–11.0] U, $p<0.01$), platelets (4.0 [2.0–8.0] U vs 2.0 [1.0–4.4] U $p<0.01$), and plasma (8.0 [4.0–18.0] U vs 5.5 [2.0–10.3] U, $p=0.01$). Furthermore, patients in the rFVIIa group were treated with more fibrinogen concentrate (2.0 [2.0–6.0] g vs 0.0 [0.0–2.0] g, $p<0.01$) and had higher rates of postoperative tamponade (23.9% vs 9.7%, $p=0.01$) and re-exploration for bleeding (31.0% vs 16.8%, $p=0.01$).

TABLE II.3 - Intra- and postoperative bleeding data in the propensity score-matched populations

Characteristic	rFVIIa (n=120)	Control (n=120)	*p*	Missing (n)
Bleeding during first 24 h (mL)	1500 (835–2500)	990 (520–1720)	[1]	194
PRBC (U)	9.0 (4.0–17.0)	5.0 (2.0–11.0)	<0.01	14
Platelets (U)	4.0 (2.0–8.0)	2.0 (1.0–4.4)	<0.01	4
FFP (U)	8.0 (4.0–18.0)	5.5 (2.0–10.3)	0.01	8
rFVIIa (mg)	5.0 (2.0–10)	0 (0–0)	<0.01	0
Fibrinogen concentrate (g)	2.0 (2.0–6.0)	0.0 (0.0–2.0)	<0.01	12
Tranexamic acid (U)	3000 (0–4000)	2000 (0–4000)	0.14	46
Cardiac tamponade	27 (23.9)	11 (9.7)	0.01	14
Reoperation for bleeding	35 (31.0)	19 (16.8)	0.01	14

Values were expressed as number and percentage (%) or median and interquartile range (IQR). [1] Statistical analysis not possible due to missing data. rFVIIa: recombinant factor VIIa; PRBC: packed red blood cells; FFP: fresh frozen plasma.

Early mortality and postoperative complications

There were no significant differences between patients who received rFVIIa compared to control patients in terms of in-hospital mortality (OR, 0.74; 95% CI, 0.34–1.55, $p=0.49$), postoperative stroke (OR, 1.75; 95% CI, 0.82–3.91, $p=0.16$) or renal replacement therapy (OR, 1.18; 95% CI, 0.48–2.92, $p=0.84$) (Figure II.1, Table II.4). In-hospital mortality in the rFVIIa and control group was 12.5% vs 16.7%, respectively, and postoperative stroke was identified in 25.6% of rFVIIa group patients compared to 17.9% in the control group. Renal replacement therapy rate was 12.4% and 10.6% in the rFVIIa and control group, respectively. Remaining postoperative complications were similar between the two groups except that rFVIIa

group, patients more frequently required prolonged time on mechanical ventilation (44.1% vs 27.0%, $p<0.01$).

TABLE II.4 - Postoperative complications and early mortality in the propensity score-matched populations

Characteristic	rFVIIa (n=120)	Control (n=120)	*p*	Missing (n)
Postoperative stroke	30 (25.6)	21 (17.9)	0.16	6
RRT	14 (12.4)	12 (10.6)	0.84	14
DSWI	3 (2.6)	5 (4.3)	0.73	6
Septicaemia	10 (8.9)	8 (7.1)	0.82	16
Ventilatory support >48h	49 (44.1)	30 (27.0)	<0.01	18
Cardiac arrest	6 (5.4)	7 (6.3)	1.00	16
Perioperative MI	6 (5.3)	5 (4.4)	1.00	16
Intraoperative mortality	2 (1.7)	9 (7.5)	0.07	0
30-day mortality	19 (15.8)	22 (18.3)	0.74	0
In-hospital mortality	15 (12.5)	20 (16.7)	0.49	0
Late reoperation of the aorta	4 (9.5)	1 (2.4)	0.45	156

Values were expressed as number and percentage (%). RRT: renal replacement therapy; DSWI: deep sternal wound infection; MI: myocardial infarction.

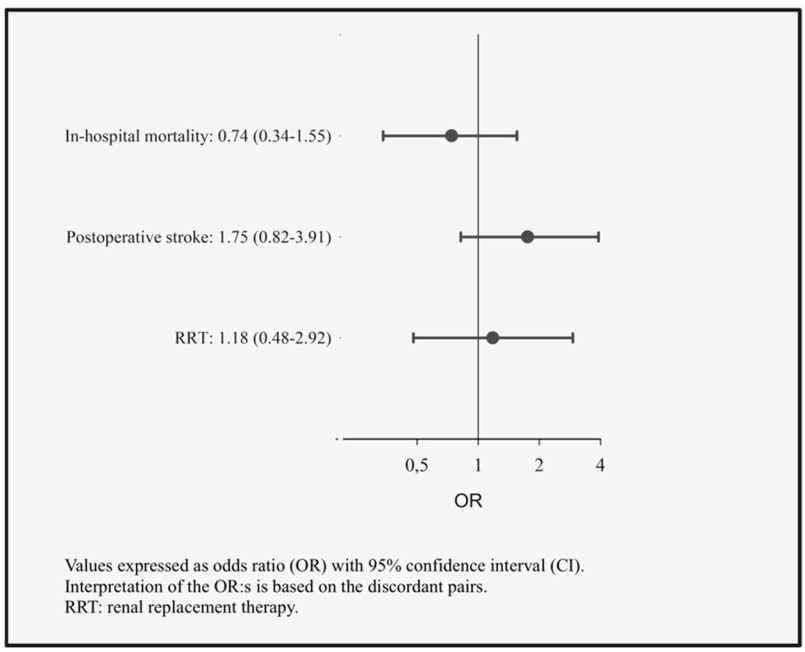

FIGURE II.1 - Forest plot illustrating the associations between rFVIIa treatment and primary endpoints.

Late mortality

Kaplan-Meier estimates of survival in the matched cohorts are shown in Figure II.2. There was no significant difference in survival at 1, 3 and 5 years after surgery between the rFVIIa and control group (76.7% vs 76.8%, 74.1% vs 72.9% and 70.9% vs 70.6%, respectively, [log rank test p=0.25]).

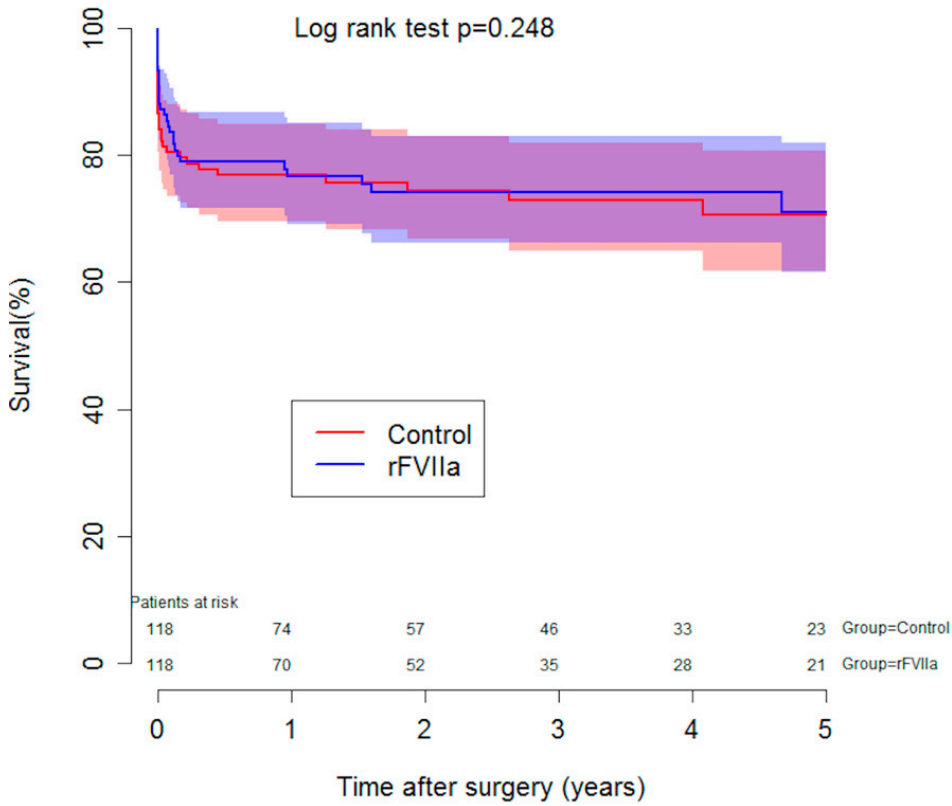

FIGURE II.2 - Kaplan-Meier survival curves in ATAAD patients from the matched populations, plotted by group. Data on late survival was missing for two patients in the rFVIIa group.

Study III

Study population and patient follow-up

Between September 2015 and October 2017, a total of 27 patients with ATAAD were enrolled in the study. Two patients were later excluded: one patient had not been cooled to a deep hypothermic state and one patient required a second run on CPB due to damage to the pulmonary artery (Figure 7). The control group was comprised of 20 patients undergoing elective surgery of the ascending aorta or the aortic root between December 2016 and April 2018.

Pre- and intraoperative characteristics

Patient age did not differ significantly between the groups (62 [56–75] years vs 59 [52–71] years, p=0.248), whereas patients in the ATAAD group had lower prevalence of bicuspid aortic valves (0% vs 32%, p=0.004) and underwent less extensive proximal surgery (p<0.001) (Table III.1). ATAAD patients had shorter duration of CPB (159 [130–185] min vs 203 [173–250] min, p=0.001) and cross-clamping (65 [51–92] min vs 136 [110–178] min, p<0.001). The ATAAD patients were cooled to a mean core temperature of 19.4 (18–20.8) °C and the control patients to 32 (30–32) °C, (p=0.001).

Biomarker measurements

At induction of anaesthesia (T0), platelet counts were significantly lower in ATAAD patients (188 [156–217] x10^9/L vs 221 [196–240] x10^9/L, p=0.018) and decreased significantly to 63 (53–118) x10^9/L and 129 (97–154) x10^9/L in the ATAAD group and the elective group, respectively, at lowest core temperature (p<0.001 and p=0.003) (Figure III.1A). At the end of surgery (T3), there was no significant difference between the groups (p=0.770), although platelet counts were significantly lower than preoperative levels for both groups (157 [127–168] x10^9/L and 151 [129–185] x10^9/L, p=0.001 and p<0.001).

At T0, patients with ATAAD presented with significantly lower fibrinogen levels compared with the elective group (1.9 [1.6–2.4] g/L vs 2.8 [2.2–3.0] g/L, p=0.003) (Figure III.1B). The fibrinogen levels decreased significantly for both groups during CPB (p<0.001 and p=0.002 in the ATAAD and elective group, respectively). After surgery, fibrinogen levels were similar to the preoperative level in the ATAAD group (2.1 [1.9–2.3] g/L, p=0.456), whereas fibrinogen levels in the elective group decreased significantly (2.2 [1.9–2.2] g/L, p<0.001). On the fifth postoperative day, both groups demonstrated supernormal values, but the fibrinogen levels were significantly higher in the elective group (5.0 [4.6–7.0] g/L vs 7.6 [6.6–8.0] g/L, p=0.001).

Prior to surgery, D-dimer was significantly higher in the ATAAD group (2.9 (1.7–9.7) mg/L vs 0.1 (0.1–0.2) mg/L, p<0.001) and remained significantly higher until the fifth postoperative day when no difference between the groups was observed (1.0 [0.7–2.8] mg/L vs (0.9 [0.6–1.2] mg/L, p=0.517) (Figure III.2C).

Before surgery, PT(INR) was significantly higher in ATAAD patients (1.15 [1.1–1.2] vs 1.0 [0.93–1.0], p=0.001) compared to control patients (Figure III.1D). In both groups, there was a significant increase of PT(INR) during CPB. After surgery, PT(INR) was similar to that at T0 in the ATAAD group (1.1 [0.8–1.2], p=0.136) while there was a significant increase of PT(INR) compared to the preoperative value in elective patients (1.2 [1.1–1.4], p<0.001).

Preoperative APTT did not differ significantly between the groups (27 [26–30] s vs 27 (26–28) s, p=0.139) (Figure III.1E). After surgery, median APTT in the ATAAD group exceeded the reference value and was significantly higher than in control patients (34 [32–41] s vs 27 [25.3–28.8]) s, p<0.001). The ACT and heparin concentrations measured at T3 showed that the heparin concentration was 0 (0–0) U/mL in both groups (p=0.941) whereas ACT was significantly longer in the ATAAD group (120 [114–127] s vs 108 [102–115] s, p=0.018). At T4 (24 h after surgery), there was no significant difference between the two groups and both groups demonstrated a median APTT below the lower reference boundary (25.5 [24.8–28.0] s vs 25.5 [23.5–28.8] s, p=1.000).

Antithrombin levels at anaesthesia induction were significantly lower in ATAAD patients (0.81 [0.73–0.94] kIU/L vs 0.96 [0.92–1.00] kIU/L, p=0.003) (Figure III.1F). The levels of antithrombin decreased significantly in the ATAAD group until T1and a trend towards lower antithrombin levels in the elective group was observed (0.65 [0.61–0.70] kIU/L vs 0.89 [0.76–1.05] kIU/L, p=0.010 and p=0.099 for T0 vs T1, in ATAAD and elective patients, respectively). Antithrombin levels did not recover during surgery and at T3, the levels of antithrombin were lower for both groups when compared to the preoperative values (p=0.002 and p<0.001 in the ATAAD group and elective group, respectively).

TABLE III.1 - Baseline and surgical characteristics of the study populations

Characteristic	ATAAD (n=25)	Elective (n=20)	*p*
Age	62 (56–75)	59 (52–71)	0.248
Female gender	8 (32)	3 (15)	0.297
Hypertension	14 (56)	11 (55)	0.947
History of aortic aneurysm	7 (25)	20 (100)	<0.001
Marfan	0 (0)	2 (10)	0.192
Bicuspid aortic valve	0 (0)	6 (32)	0.004
Diabetes mellitus type II	0 (0)	1 (5)	0.444
Hyperlipidaemia	1 (4)	6 (30)	0.034
History of stroke	1 (4)	0 (0)	1.000
Chronic kidney disease	1 (4)	0 (0)	1.000
COPD	0 (0)	1 (5)	0.444
History of smoking	8 (32)	4 (27)	1.000
Aspirin	3 (12)	2 (10)	1.000
Any organ malperfusion	16 (64)	NA	NA
DeBakey type 1	22 (88)	NA	NA
Proximal surgical technique			<0.001
Supracoronary graft only	22 (88)	3 (15)	
Supracoronary graft + AVR	1 (4)	1 (5)	
Root replacement	1 (4)	8 (40)	
Valve repair	0 (0)	8 (40)	
Not completed	1 (4)	0 (0)	
Distal surgical technique			0.124
Ascending aorta	22 (88)	16 (80)	
Hemiarch procedure	1 (4)	4 (20)	
Arch procedure	2 (8)	0 (0)	
Operating time (min)	293 (263–332)	312 (286–381)	0.075
CPB time (min)	159 (130–185)	203 (173–250)	0.001
Cross-clamp time (min)	65 (51–92)	136 (110–178)	<0.001
HCA time (min)	19 (14–25.8)	0 (0–0)	<0.001
Antegrade SCP	5 (20)	4 (20)	1.000
Retrograde SCP	4 (16)	0 (0)	0.117
Antegrade SCP time (min)	30.5 (22.3–44)	0 (0–4.5)	0.001
Retrograde SCP time (min)	18 (13.5–27.8)	0 (0–0)	<0.001
Lowest core temperature (°C)	19.4 (18–20.8)	32 (30–32)[a]	<0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). COPD: chronic obstructive pulmonary disease; AVR: aortic valve replacement; SCP: selective cerebral perfusion; HCA: hypothermic circulatory arrest. [a]Median lowest core temperature of the 14 elective patients analysed at T1 was 31 (25–32) °C (*p* vs ATAAD group <0.001).

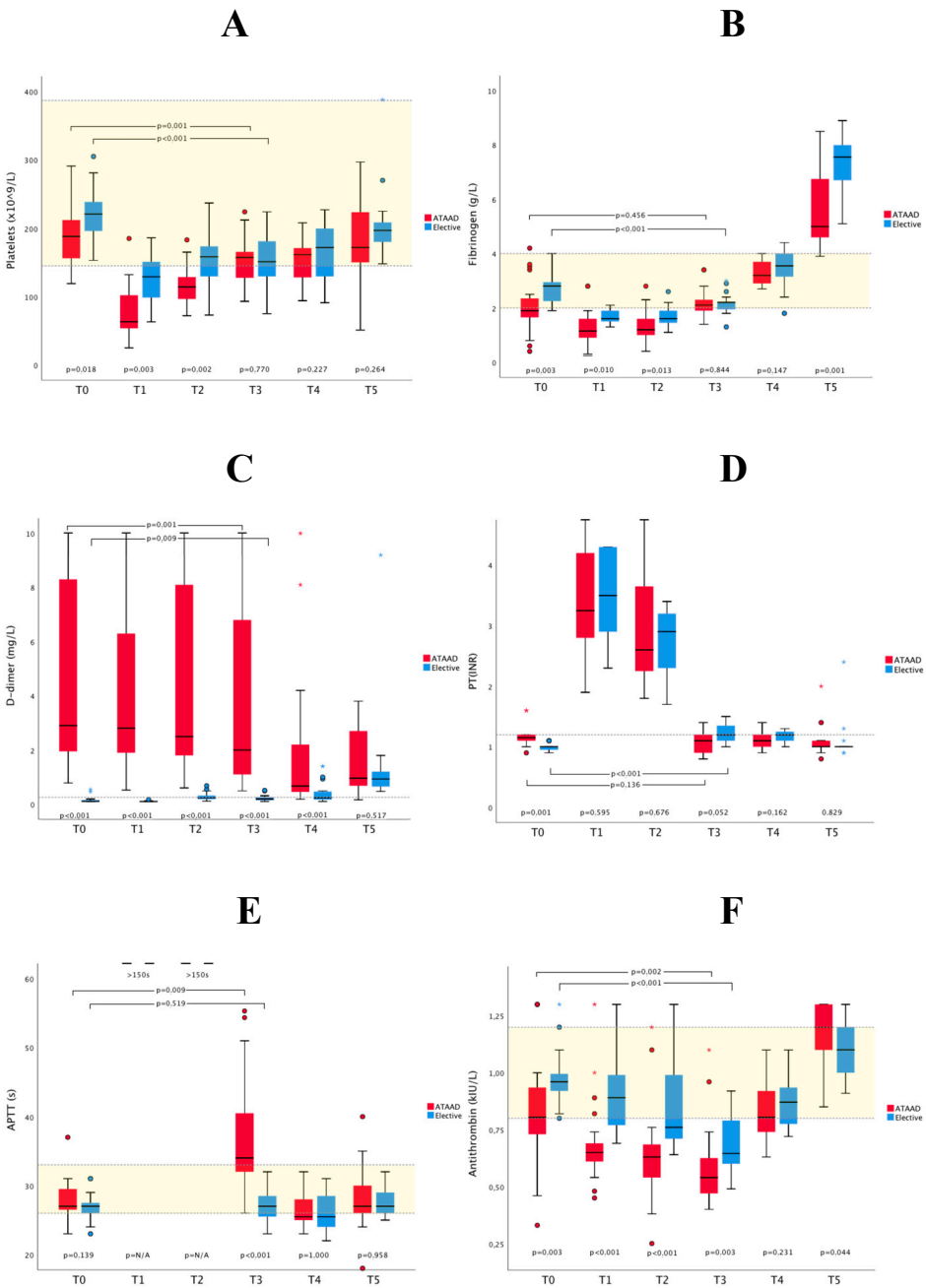

FIGURE III.1 – Box-plots illustrating levels of platelets (A), fibrinogen (B), D-dimer (C), PT(INR) (D), APTT (E) and antithrombin (F) at T0- induction of anaesthesia; T1- core temperature nadir; T2- prior to protamine reversal; T3- end of operation; T4- 24 h after surgery; T5- five days after surgery, plotted by group.

Bleeding data and postoperative outcomes.

Patients in the ATAAD group demonstrated larger intraoperative bleeding volumes (2407 [1804–3209] mL vs 1212 [917–1920] mL, $p<0.001$), while 24 h chest tube output did not differ significantly from that of the control patients (720 [585–963] mL vs 695 [555–848] mL, $p=0.645$) (Table III.2). Patients undergoing ATAAD received significantly more transfusions of PRBC (2.5 [0.25–4.75] U vs 0 [0–2.75] U, $p=0.022$), platelets (4 [3.25–6] U vs 2 [2–4] U, $p=0.002$) and plasma (2 [0–4] U vs 0 [0–0] U, $p=0.004$). Patients undergoing ATAAD surgery also received significantly more rFVIIa (0 [0–1.5] mg vs (0 [0–0] mg, $p=0.018$) fibrinogen concentrate (5.5 [4–8] g vs 2.5 [1.25–5.50] g, $p=0.002$) and PCC (2000 [1000–2250] IU vs 750 [0–1000] IU, $p=0.004$).

One patient in the ATAAD group (4%) and none of the elective patients required re-exploration for bleeding. In the ATAAD group, there was one intraoperative death due to aortic rupture (4%) and one patient died during hospital stay due to cerebral infarctions. No patients in the elective group died during hospital admission.

TABLE III.2 - Early mortality and postoperative data of the study populations

Characteristic	ATAAD (n=25)	Elective (n=20)	*p*
Intraoperative mortality	1 (4)	0 (0)	1.000
In-hospital mortality	2 (8)	0 (0)	0.495
Intraoperative bleeding (mL)	2407 (1804–3209)	1212 (917–1920)	<0.001
Chest tube output (mL)			
12 h	480 (280–628)	480 (340–613)	0.786
24 h	720 (585–963)	695 (555–848)	0.645
PRBC (U)	2.5 (0.25–4.75)	0 (0–2.75)	0.022
Platelets (U)	4 (3.25–6)	2 (2–4)	0.002
Plasma (U)	2 (0–4)	0 (0–0)	0.004
rFVIIa (mg)	0 (0–1.5)	0 (0–0)	0.018
Fibrinogen concentrate (g)	5.5 (4–8)	2.5 (1.25–5.50)	0.002
Tranexamic acid (g)	4 (3–4)	4 (4–4)	0.040
PCC (IU)	2000 (1000–2250)	750 (0–1000)	0.004
Desmopressin (µg)	0 (0–30)	11.3 (0–30)	0.441
Antithrombin (IU)	0 (0–0)	0 (0–0)	0.371
Reoperation for bleeding	1 (4)	0 (0)	1.000
Cardiac tamponade	1 (4)	0 (0)	1.000
Postoperative stroke	5 (21)	1 (5.9)	0.198
RRT	3 (13)	0 (0)	0.239
Ventilatory support >48h	8 (32)	0 (0)	0.005
Length of ICU stay	4.5 (3–7.75)	1 (1–2)	<0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; PCC: prothrombin complex concentrate; RRT: renal replacement therapy; MI: myocardial infarction; ICU: intensive care unit.

Study IV

Study population and patient follow-up

Between September 2015 and October 2017, 24 ATAAD patients were enrolled in this study. A total of 20 control patients undergoing elective aortic surgery were included between December 2016 and April 2018 (Figure 7). Data was 100% complete up to hospital discharge.

Pre- and intraoperative characteristics

Preoperative characteristics were similar between the groups, with the exception of ATAAD patients less often presenting with a history of aortic aneurysm (29% vs 100%, $p<0.001$), bicuspid aortic valve (0% vs 32%, $p=0.004$) and hyperlipidaemia (4% vs 30%, $p=0.035$) (Table IV.1). Less extensive proximal and distal aortic surgery was performed in ATAAD patients ($p<0.001$ and $p=0.039$, respectively) with significantly shorter duration of CPB (161 [133–187] min vs 203 [173–250] min, $p=0.002$), aortic cross-clamping (65 [50–95] min vs 136 [110–178] min, $p<0.001$) and hypothermic circulatory arrest (19 [15–26] min vs 0 [0–0] min, $p<0.001$). ATAAD patients had significantly lower body temperature nadir when compared to elective patients analysed at T1 (19 (18–21) °C vs 31 (25–32) °C, $p<0.001$).

Von Willebrand factor activity (VWF:GPIbM)

The VWF:GPIbM at each time point is plotted in Figure IV.1. A significantly higher preoperative VWF:GPIbM was demonstrated in ATAAD patients compared to the control group (1.58 [1.40–2.05] kIU/L vs 1.25 [1.02–1.42] kIU/L, $p=0.003$). The VWF:GPIbM decreased significantly in the ATAAD group at core temperature nadir (1.24 [0.98–1.44] kIU/L, T0 vs T1 $p<0.001$) but remained stable in the elective group (1.25 [1.04–1.43] kIU/L, T0 vs T1 $p<0.625$). Compared to preoperative levels, the postoperative VWF:GPIbM was unchanged in the ATAAD group (1.55 [1.22–1.72] kIU/L, T0 vs T3 $p=0.438$), but a significant increase in VWF:GPIbM was observed in the control group (1.83 [1.43–2.13] kIU/L, T0 vs T3 $p=0.001$). At T4, VWF:GPIbM was supernormal in both groups, but ATAAD patients demonstrated lower activity compared to control patients (2.32 [1.71–2.74] kIU/L vs 3.11 [2.57–3.56] kIU/L, respectively, $p<0.001$). Five days after surgery, there was no significant difference in VWF:GPIbM between the groups (3.72 [2.76–4.51] kIU/L vs 3.66 [3.01–4.45] kIU/L, $p=0.729$).

The VWF multimeric sizing (VWF:MS) was performed in four randomly selected ATAAD patients at all intraoperative time points. No changes in multimer distribution throughout the operation were observed (Supplementary Figure IV.1). Consequently, we limited VWF:MS to T0 and T1 in a total of 10 patients (the five patients with the largest drop in VWF:GPIbM from T0 to T1 and additional five patients randomly selected) (Figure IV.2). Semi-quantification of VWF antigen showed that the ratio of protein-loading of ATAAD patients compared to pooled normal plasma was similar between high molecular weight multimers (HMWM)

and low molecular weight multimers (LMWM) at T0 (1.49 [1.23–2.70] vs 1.53 [0.76–2.03], p=0.721) and T1 (1.67 [1.24–3.06] vs 1.55 [0.76–2.10], p=0.953) (Supplementary Table IV.1). Thus, we found no indication of a VWD type 2A multimer pattern.

Bleeding, transfusions and medical management

Patients in the ATAAD group bled significantly more intraoperatively (2415 [1780–3219] mL vs 1212 [917–1920], p<0.001) but there was no significant difference in 24 h chest tube output (700 [580–940] mL vs 695 [555–848] mL, p=0.779) between the groups (Table IV.2). Patients in the ATAAD group received significantly more transfusions of PRBC (2 [0–5] U vs 0 [0–2.75] U, p=0.028), platelets (4 [4–6] U vs 2 [2–4] U, p=0.006) and plasma (2 [2–4] U vs 0 [0–0] U, p=0.001), rFVIIa (0 [0–0] mg vs (0 [0–0] mg, p=0.029), fibrinogen (5 [4–8] g vs 2.5 [1.25–5.50] g, p= 0.003), tranexamic acid (4 [3–4] g vs 4 [4–4] g, p=0.034) and PCC (2000 [1000–2375] IU vs 750 [0–1000] IU, p=0.004).

ATAAD patients and control patients also were split into two groups depending on preoperative VWF:GPIbM (Table IV.3). The 12 ATAAD patients who presented with the lowest preoperative VWF activity showed a trend towards larger intraoperative bleeding volumes (2742 [2084–4183] mL vs 1900 [1741–3000] mL, p=0.079) and bleeding through chest tubes, primarily driven by output during the first 12 h (540 [398–720] mL vs 280 [250–520] mL, p=0.051). There were no trends towards an impact of VWF activity on postoperative bleeding in elective patients.

Mortality and complications

In the ATAAD group, two patients (8%) died during hospital admission, one due to intraoperative aortic rupture and one on the seventh postoperative day as a consequence of cerebral watershed infarctions (Table IV.2). Patients in the ATAAD group more frequently required prolonged mechanical ventilatory support (35% vs 0%, p<0.001) and also remained longer in the ICU (5 (3–7.5) days vs 1 (1–1.5) days, p=0.004). There were no re-explorations for bleeding in any of the groups.

TABLE IV.1 - Baseline and surgical characteristics of the study populations

Characteristic	ATAAD (n=24)	Elective (n=20)	*p*
Age	63 (58–75)	59 (52–71)	0.179
Female gender	8 (33)	3 (15)	0.162
Hypertension	14 (58)	11 (55)	0.824
History of aortic aneurysm	7 (29)	20 (100)	<0.001
Marfan	0 (0)	2 (10)	0.201
Bicuspid aortic valve	0 (0)	6 (32)	0.004
Diabetes mellitus type II	0 (0)	1 (5)	0.455
Hyperlipidaemia	1 (4)	6 (30)	0.035
History of stroke	1 (4)	0 (0)	1.000
Chronic kidney disease	1 (4)	0 (0)	1.000
COPD	0 (0)	1 (5)	0.455
History of smoking	8 (33)	4 (27)	0.734
Aspirin	3 (13)	2 (10)	1.000
Any organ malperfusion	15 (63)	0 (0)	<0.001
DeBakey type 1	21 (88)	NA	NA
Proximal surgical technique			
Supracoronary graft only	21 (88)	3 (15)	<0.001
Supracoronary graft + AVR	1 (4)	1 (5)	
Root replacement	1 (4)	8 (40)	
Valve repair	0 (0)	8 (40)	
Not completed	1 (4)	0 (0)	
Distal surgical technique			
Ascending aorta	21 (88)	16 (80)	0.039
Hemiarch procedure	1 (4)	4 (20)	
Arch procedure	2 (8)	0 (0)	
Operating time (min)	291 (260–327)	312 (286–381)	0.100
CPB time (min)	161 (133–187)	203 (173–250)	0.002
Cross–clamp time (min)	65 (50–95)	136 (110–178)	<0.001
HCA time (min)	19 (15–26)	0 (0–0)	<0.001
Lowest core temperature (°C)	19 (18–21)	32 (30–32)	<0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). COPD: chronic obstructive pulmonary disease; AVR: aortic valve replacement; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest. [a] Median lowest core temperature of the 14 elective patients analysed at T1 was 31 (25–32) °C (*p* vs ATAAD group <0.001)

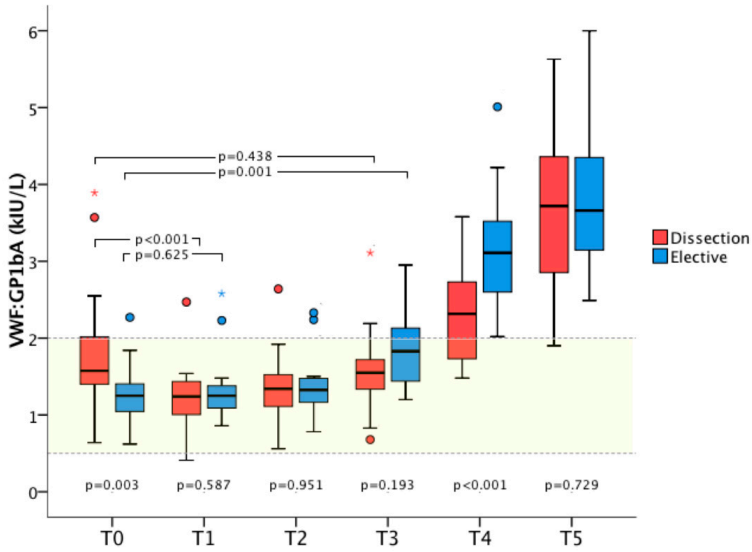

FIGURE IV.1 - Box-plot illustrating VWF:GPIbM at T0- anaesthesia induction; T1- core temperature nadir; T2- prior to protamine reversal; T3- end of operation; T4- 24 h after surgery; T5- five days after surgery, plotted by group. VWF:GPIbM: GPIb binding activity of von Willebrand factor.

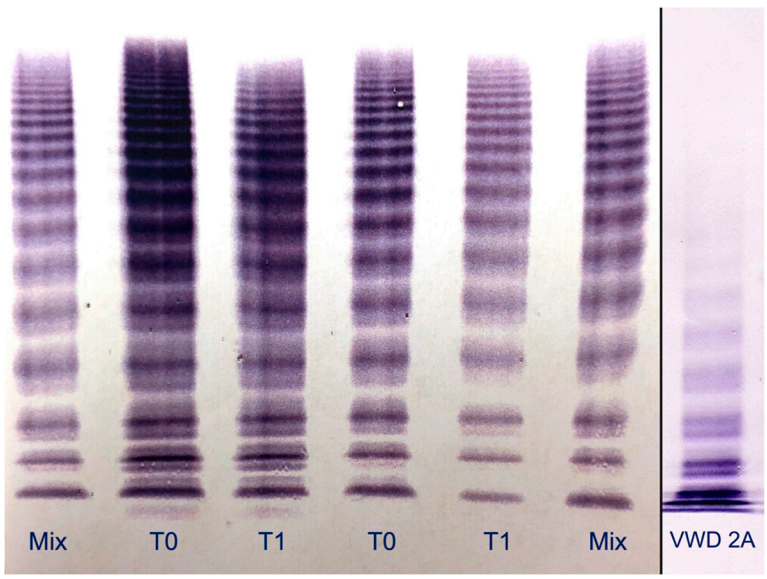

FIGURE IV.2 - Multimeric composition in two ATAAD patients showing typically normal proportion of high molecular weight multimers at T0 and T1. Pooled control samples from the normal population constitute mixed-samples and typical multimeric composition in von Willebrand disease 2A, showing the lack of several top bands presented as additional reference.

TABLE IV.2 - Early mortality and postoperative data of the study populations

Characteristic	ATAAD (n=24)	Elective (n=20)	*p*
Intraoperative mortality	1 (4)	0 (0)	1.000
In-hospital mortality	2 (8)	0 (0)	0.493
Intraoperative bleeding (mL)	2415 (1780–3219)	1212 (917–1920)	<0.001
Chest tube output (mL)			
12 h	450 (280–620)	480 (340–613)	0.635
24 h	700 (580–940)	695 (555–848)	0.779
PRBC (U)	2 (0–5)	0 (0–2.75)	0.028
Platelets (U)	4 (4–6)	2 (2–4)	0.006
Plasma (U)	2 (2–4)	0 (0–0)	0.001
rFVIIa (mg)	0 (0–0)	0 (0–0)	0.029
Fibrinogen concentrate (g)	5 (4–8)	2.5 (1.25–5.5)	0.003
Tranexamic acid (g)	4 (3–4)	4 (4–4)	0.034
PCC (IU)	2000 (1000–2375)	750 (0–1000)	0.004
Desmopressin (μg)	0 (0–30)	11 (0–30)	0.509
Antithrombin (IU)	0 (0–0)	0 (0–0)	1.000
Reoperation for bleeding	0 (0)	0 (0)	NA
Cardiac tamponade	0 (0)	0 (0)	NA
Postoperative stroke	5 (22)	1 (5)	0.192
RRT	3 (13)	0 (0)	0.236
Ventilatory support >48h	8 (35)	0 (0)	0.004
Length of ICU stay	5 (3–7.5)	1 (1–1.5)	<0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; PCC: prothrombin complex concentrate; RRT: renal replacement therapy; MI: myocardial infarction; ICU: intensive care unit.

TABLE IV.3 - Early mortality and postoperative data of the study populations, stratified per preoperative VWF:GPIbM and group

Characteristic	ATAAD lowest VWF:GPIbM (n=12)[a]	ATAAD highest VWF:GPIbM (n=11)[b]	*p*	Elective lowest VWF:GPIbM (n=10)[c]	Elective highest VWF:GPIbM (n=10)	*p*
Preoperative VWF:GPIbM (kIU/L)	1.40 (1.02–1.50)	2.02 (1.68–2.49)	<0.001	1.05 (0.88–1.21)	1.41 (1.32–1.62)	<0.001
Intraoperative bleeding (mL)	2742 (2084–4183)	1900 (1741–3000)	0.079	984 (826–2027)	1293 (947–1791)	0.353
Chest tube output (mL)						
12 h	540 (398–720)	280 (250–510)	0.051	480 (318–570)	510 (375–723)	0.579
24 h	905 (625–1030)	620 (440–770)	0.059	725 (530–780)	685 (605–995)	0.631
PRBC (U)	2.5 (1.25–4.75)	2 (0–5.0)	0.608	0 (0–1.5)	2 (0–3.25)	0.218
Platelets (U)	4 (3.25–6)	4 (4–6)	1.000	2 (1.5–4)	4 (1.5–4)	0.393
Plasma (U)	2.5 (0–3.75)	1 (0–4)	0.695	0 (0–0.75)	0 (0–0.5)	0.912
rFVIIa (mg)	0 (0–0)	0 (0–4)	0.235	0 (0–0)	0 (0–0)	1.000
Fibrinogen concentrate (g)	4.5 (4–9.5)	6 (4–8)	0.880	2.5 (0–6.3)	2.5 (1.8–4.5)	1.000
Tranexamic acid (g)	4 (3–4)	4 (2–4)	0.786	4 (4–4)	4 (4–4)	0.481
PCC (IU)	1750 (1125–2375)	2000 (1000–3000)	0.799	500 (0–2000)	750 (0–1000)	0.853
Desmopressin (μg)	0 (0–28)	23 (0–30)	0.551	11 (0–30)	15 (0–30)	0.739
Antithrombin (IU)	0 (0–0)	0 (0–0)	1.000	0 (0–0)	0 (0–0)	1.000
Reoperation for bleeding	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000

Values were expressed as number and percentage (%) or median and interquartile range (IQR). VWF:GPIbM: GPIb binding activity of von Willebrand factor; PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; PCC: prothrombin complex concentrate. [a] VWF:GPIbM ≤1.55 kIU/L; [b] Patient who died intraoperatively is not reported in this table; [c] VWF:GPIbM ≤1.25 kIU/L.

Discussion

Acute type A aortic dissection is a lethal condition with up to half of patients succumbing to the disease before they receive medical attention (19-22). Despite improvements in surgical outcomes of ATAAD in recent years, early mortality is still considerable (26, 34, 42). Early fatalities caused by aortic dissection might be the result of unmanageable complications inflicted by the inherent nature of the disease, including aortic rupture, cardiac ischaemia, pericardial tamponade, severe heart failure due to aortic valve insufficiency or malperfusion-related organ injuries such as stroke or mesenteric infarction (4, 21, 69, 78). Therefore, the best way of reducing mortality from ATAAD is to get the patient to proper surgical care as soon as possible.

The next step is to reduce mortality and morbidity after ATAAD surgery by addressing modifiable factors: patient selection, preoperative malperfusion, extent of aortic repair, cannulation strategy, cerebral protection strategy and also, perioperative bleeding.

Considerable changes in the haemostatic system are associated with ATAAD, and it has been reported that up to 20% of all hospital deaths following ATAAD surgery are related to bleeding (21, 69, 72). In routine cardiac surgery, re-exploration for bleeding has been reported to carry a fourfold increase of surgical mortality rates (119-121). In ATAAD surgery, re-exploration rates of 14–22% have been reported, and major bleeding has been identified as an independent predictor of 30-day mortality (34, 77, 123).

Therefore, with the overarching purpose of reducing bleeding in the setting of ATAAD surgery, this thesis aimed to identify clinically relevant causes of excessive bleeding in ATAAD surgery, to assess the impact of bleeding on postoperative complications and survival, to analyse the safety of the established but debated procoagulant treatment using rFVIIa and to investigate whether FVIII/VWF concentrate could be used as an additional haemostatic agent in ATAAD surgery.

Clinical predictors of massive bleeding

In Study I, we identified several independent predictors of massive bleeding as defined by the BART criteria including patient age, symptom duration, hypertension, coronary artery disease, malperfusion, DeBakey type I dissection, DAPT, preoperative P-creatinine level, and duration of CPB and cross-clamping (146).

The use of CPB has significant adverse effects on the coagulation system and therefore, it was not surprising that CPB run time was an independent predictor of massive bleeding (74, 75). Neither was it surprising that increasing patient age was an independent predictor of massive bleeding as older patients tend to have more fragile tissues and therefore, more profuse bleeding might be expected from the suture lines.

Nakajima et al. previously reported that the length of the dissection had no impact on perioperative coagulopathy but found a correlation between the width of the dissected aorta and platelet function and coagulation/fibrinolysis system activation (148). This led the authors to speculate that coagulopathy associated with aortic dissection may be caused by a turbulent flow in the false lumen rather than by the extent of the dissection. However, since the coagulation system is activated by TF, one might still hypothesise that a more extensive dissection, with exposure of larger areas of sub-endothelial tissue and thereby more TF, would induce a stronger activation of the coagulation system and increase the risk of bleeding complications. Therefore, we forced DeBakey type 1 dissections into the multivariable regression model, and our analysis showed that DeBakey type 1 dissection was an independent predictor of massive bleeding (OR, 2.652; 95% CI; 1.004–7.008, p=0.049). This indicated that, at least in part, bleeding associated with ATAAD surgery is related to the extent of the dissected aorta.

Furthermore, Study I demonstrated an inverse correlation between symptom duration and risk for massive bleeding. This could be explained by a major immediate activation and consumption of platelets and coagulation factors as an attempt to occlude the false lumen. This might lead to thrombus formation in the false lumen and subsequent exposure of less subendothelial tissue, which would cause less extensive consumption of coagulation factors and a decrease in fibrinolysis over time. It has previously been described that mortality from ATAAD increases by 1–2% per hour after symptom onset, and the effects of symptom duration that we identified in this study were relatively small (OR, 0.974 [per hour increment]; 95% CI, 0.950–0.999, p=0.041) (4, 18, 22). Therefore, although interesting from a theoretical standpoint and potentially warranting further research, this finding does not support the idea of delaying surgery until the coagulopathic state wears off.

Impact of massive bleeding on surgical outcomes

Major bleeding was associated with significantly higher rates of postoperative renal replacement therapy and stroke, higher postoperative P-lactate and higher P-creatinine levels at hospital discharge.

Sodeck et al. have previously reported that the levels of antithrombin are decreased in patients undergoing ATAAD surgery (115). Antithrombin

circulates in the blood and under normal circumstances it inhibits coagulation activity where no tissue injury is present. Therefore, in theory, decreased levels of antithrombin could lead to a paradoxical procoagulant state in the healthy peripheral vascular bed and manifest itself as ischaemic organ injury, e.g. renal failure, stroke or increased lactate levels. This could be augmented by patients with major bleeding receiving significantly more procoagulant drugs, including rFVIIa and fibrinogen concentrate (4.1 g vs 1.6 g, $p<0.001$ and 9.8 g vs 4.4 g, $p<0.001$, respectively).

Patients with massive bleeding had significantly higher in-hospital mortality rates than other patients (30% vs. 8%, $p< 0.001$). When patients who died intraoperatively were excluded, the comparative proportion of patients with major bleeding who died during hospital stay was even higher (22% vs. 4%, $p<0.001$). Major bleeding according to the BART criteria was a composite variable, and therefore, introducing major bleeding in a multivariable model would lead to considerable risk of interaction. Thus, to analyse the impact of bleeding on in-hospital mortality, we used re-exploration for bleeding and excluded remaining variables from the BART criteria in our multivariable model. The analysis identified re-exploration for bleeding within 24 h after surgery as an independent predictor of in-hospital mortality in patients who survived surgery (OR, 3.109; 95% CI, 1.044–9.256, $p=0.042$), which is concurrent with previous reports from the general cardiac surgery population (119-121).

In patients who were discharged from the hospital, late mortality was significantly higher in the group that experienced major bleeding (93.1 ±3.9% vs 98.8 ±0.8%, 88.1 ±5.0% vs 90.9 ±2.5% and 71.8 ±7.8% vs 87.4 ±33.1% at 1, 3 and 5 years in in Group I and II, respectively [log rank $p=0.001$]). A Cox regression analysis identified re-exploration for bleeding as an independent predictor of late mortality (HR, 3.204; 95% CI, 1.772–5.792, $p=0.001$).

Safety of recombinant factor VIIa

The first line of treatment for bleeding at our institution consists of transfusion of blood products, prothrombin complex concentrate, fibrinogen concentrate and tranexamic acid, but since its introduction in 1996, rFVIIa has emerged as a last resort alternative for treating refractory bleeding in the setting of cardiac surgery. Previous studies have analysed the use of rFVIIa in a variety of cardiac procedures (130, 149). However, only studies with small study cohorts have focused on patients undergoing ATAAD surgery (133, 134).

In Study II, we could not demonstrate any significant difference in in–hospital mortality between patients who received rFVIIa and control patients (12.5% vs. 16.7%, $p=0.486$; OR, 0.74; 95% CI, 0.34–1.55; p=0.487), which is consistent with the findings of a randomised study by Gill et al. in patients undergoing routine

cardiac surgery (130). Our findings also are supported by the findings of Tritapepe et al. and Yan et al. who analysed ATAAD populations and found no differences in survival or adverse events between patients treated with rFVIIa and controls (133, 134). However, these studies consisted of small study cohorts with only 23 and 25 treated patients. In contrast to our findings, Alfirevic et al. did report impaired survival in patients treated with rFVIIa in association with complex cardiac surgery (149). The authors suggested that renal morbidity, possibly caused by prothrombotic effects of rFVIIa in the renal vascular bed, could contribute to increased mortality. However, Alfirevic and colleagues did not report any data on bleeding volumes or re-exploration for bleeding, and therefore, it is not certain that their findings are the effect of rFVIIa treatment per se, but might rather be a consequence of the primary reason for the rFVIIa treatment- bleeding. Study II also explored the issue of renal failure but we did not detect any differences in the postoperative RRT incidence between the two groups.

Tissue factor is normally present in the circulating blood and tissue injury following aortic dissection and the use of CPB further increases the expression of circulating TF. In theory, this provides a substrate for thromboembolism and may contribute to rFVIIa having the potential to cause thromboembolic complications (96, 150). In a meta-analysis of six clinical trials in the setting of cardiac surgery, Ponschab et al. reported that patients treated with rFVIIa had a higher incidence of postoperative stroke, and Gill et al. demonstrated a trend towards higher incidence of stroke in patients undergoing standard cardiac surgery (127, 130). In Study II, stroke was identified in 26% of patients who received rFVIIa compared to 18% in control patients (OR, 1.75; 95% CI, 0.82–3.91, p=0.163). In Study I, we showed that 39% of patients with massive bleeding had postoperative stroke compared to 23% in the remaining study population (p=0.016). The disparity in incidence of postoperative stroke between the studies is mainly explained by postoperative coma being regarded as stroke in Study I but not Study II. Nonetheless, despite the fact that patients treated with rFVIIa had significantly larger bleeding volumes and required more transfusions of blood products and re-exploration for bleeding, Study II could not detect any significant differences in postoperative incidence of stroke between the groups.

As previously described, ATAAD and its associated surgery causes a significant coagulopathy affecting both the intrinsic and extrinsic pathway as well as platelet function and activation (72, 75, 117). Therefore, the effects of rFVIIa in routine cardiac procedures should not be extrapolated to those in ATAAD surgery. It has been shown that bleeding complications in ATAAD surgery are associated with increased incidence of postoperative complications and increased rates of in-hospital and long-term mortality (39, 151). In Study II, patients treated with rFVIIa had significantly larger blood loss volumes, underwent re-exploration for bleeding more frequently, had greater incidence of postoperative cardiac tamponade and

received more transfusions of blood products. Most likely, this is attributed to the fact that patients were only treated with rFVIIa in the event of a significant intraoperative or postoperative bleeding. Consequently, patients in the rFVIIa group were inherently at a greater risk of mortality and adverse events (including stroke and RRT) before administration of rFVIIa. Therefore, rather than increasing the risk of mortality, treatment with rFVIIa appeared to reduce the risks of complications caused by excessive bleeding.

Changes in coagulation analyses

Previous studies describing serial analyses of haemostatic changes caused by ATAAD and associated surgery have reported elevated levels of thrombin-antithrombin complex, prothrombin fragment 1+2, D-dimer, plasmin-antiplasmin complex and platelet factor 4, suggesting activation of the coagulation system and platelets. Furthermore, the reports demonstrated a consumption of platelets, fibrinogen, plasminogen and antithrombin (152-154). Guan et al. based their results on 87 patients undergoing ATAAD surgery with replacement of the aortic arch, but they did not compare their findings to a control group. Paparella et al. also did not compare their findings to a control group, and demonstrated changes were based on analyses for research purposes, not available as routine tests. Nomura et al., on the other hand, did compare ATAAD patients to a control group but the controls were healthy individuals and not patients undergoing complex surgery (155).

In order to analyse the specific effects of the aortic dissection, ATAAD patients in studies III and IV were compared to a control group consisting of patients undergoing surgery of the ascending aorta or the aortic root. In Study III, we demonstrated that ATAAD causes a significant activation of the coagulation system, which is further intensified by the surgical procedure for ATAAD and elective aortic surgery.

Aortic dissection has previously been shown to cause a consumption of platelets associated with impaired survival after ATAAD surgery (72, 73, 153). The use of CPB causes platelet activation and consumption, which results in reduced platelet reactivity (74, 75). Hypothermia causes platelet activation and a reversible depletion of platelets caused by splenic and hepatic sequestration (117). Study III confirmed these findings and showed significantly lower preoperative platelet counts in patients with ATAAD. During hypothermia, platelet counts were reduced in both groups, but significantly lower in ATAAD patients. At the end of the operation, platelet counts were similar between the groups. This indicated that, on one hand, platelets counts seem to correspond to the level of hypothermia, but on the other hand, by receiving significantly more transfusions of platelets, ATAAD patients reach similar postoperative platelet counts as those undergoing elective aortic surgery.

Previously, decreased fibrinogen levels have been demonstrated to predict in-hospital mortality after surgery for ATAAD (156). Our results showed that in contrast to the elective controls, ATAAD patients demonstrated preoperative consumption of fibrinogen and increased fibrinolysis with elevated D-dimer levels, but neither fibrinogen nor D-dimer levels were affected by hypothermia. Nevertheless, compared to the preoperative levels, the control patients had significantly lower levels of fibrinogen after surgery, indicating a substantial consumption of fibrinogen caused by the surgical procedure itself. In addition to its haemostatic properties, fibrinogen is an acute phase reactant. On the first operative day, there is a trend towards fibrinogen levels rising in both groups, and by postoperative day five, fibrinogen concentrations reach supernormal levels. Interestingly, the elective group had significantly higher fibrinogen levels at this point, most likely reflective of persisting fibrinogen consumption in the patent false lumen in those cases where primary surgical treatment does not lead to false lumen thrombosis.

Patients with ATAAD presented with significantly higher PT(INR) than the elective controls, which arguably is explained by the previously described consumption of coagulation factors caused by aortic dissection (72). The postoperative PT(INR) level of the ATAAD patients did not differ significantly from preoperative values due to adequate substitution of relevant factors using PCC and plasma, but the operation had contributed to a significant elevation of PT(INR) in the elective group, which was not fully compensated for by pro-coagulants.

Despite a total protamine reversal of heparin effect, postoperative median APTT exceeded the upper reference limit in ATAAD patients. This indicates that the specific properties of ATAAD surgery, e.g. profound hypothermia, seemingly have a non-heparin dependent deleterious effect on the contact activation pathway.

Although intraoperative bleeding volumes were significantly larger in ATAAD patients compared to elective controls, postoperative bleeding volumes were similar between the groups. Most likely, this is the result of ATAAD patients receiving significantly more rFVIIa, PCC and transfusions of plasma and platelets. Previously, re-exploration for bleeding after ATAAD surgery has been reported to be in the 14–22% range (34, 123, 151). In Study III, only one patient (4%) underwent re-exploration for bleeding. Anticoagulant treatment and DAPT are associated with a higher risk of bleeding complications and the low frequency of re-exploration might partly be explained by the exclusion of this category of patients in Study III (39). However, it could also be argued that the serial analyses performed in the studied patients lead to better monitoring of the coagulation system, and thereby improved haemostatic management using pro-coagulants and transfusions.

Von Willebrand factor

Study IV investigated the dynamics of VWF activity in ATAAD and aortic surgery and demonstrated that aortic dissection caused a significant increase of VWF:GPIbM. Most likely this was caused by an immediate release of VWF from α-granules of activated platelets and from Weibel-Palade-bodies of endothelial cells, induced by the contact between blood and sub-endothelial tissue. Previous reports have demonstrated shear stress, triggered by aortic stenosis and the use of mechanical circulatory support to cause a reduction of VWF activity despite normal VWF antigen levels, due to depletion of high molecular weight multimers (HMWM) (139-142). These HMWMs are essential for effective GP1b and collagen binding, whereas all multimers act as carrier proteins for FVIII (157). Study IV did not detect any changes in VWF multimer patterns and thus, platelet adhesion and aggregation in ATAAD patients and patients undergoing elective aortic surgery are not affected by a reduction of HMWMs.

Hypothermia has been shown to cause VWF to lose its ability to unfold into long cell surface strings and instead form globular structures that hide their binding sites for platelets and collagen, resulting in poorer haemostatic function (117). Low temperature also has been shown to slow down the release of VWF from Weibel-Palade bodies in endothelial cells (158). In Study IV, the deep hypothermic state induced in ATAAD patients caused a significant decrease in VWF:GPIbM, whereas VWF activity remained unchanged in elective patients cooled to a median of 31°C. Therefore, it seems that only major changes in body temperature have an effect on VWF:GPIbM, but despite this, VWF activity never dropped below the reference interval for the normal population.

It has previously been demonstrated that increased VWF levels are associated with increased rates of venous thromboembolism and arterial occlusive disease (159, 160). Study IV demonstrated that VWF:GPIbM reached supernormal levels in both groups after surgery, and it could be speculated that this could enhance the pro-coagulant effects of reduced antithrombin activity and supernormal fibrinogen levels as described previously. However, the study sample was too small to allow any analysis of thrombo-embolic complications.

Factor VIII/VWF concentrate has been used successfully as a prophylactic treatment for bleeding in patients with von Willebrand disease (145). It also has been used anecdotally as an off-label treatment for massive bleeding in trauma and ATAAD but without scientific evaluation or documentation. However, Icheva et al. did report successful use of FVIII/VWF concentrate when used in patients with acquired VWD in the setting of congenital cardiac surgery (143). Therefore, one aim of study IV was to evaluate the potential of FVIII/VWF concentrate as a haemostatic agent in aortic surgery. Study IV, however, showed that patients undergoing surgery for ATAAD or stable aortic disease had normal or supernormal

VWF:GPIbM. Although we cannot speculate upon the potential effects of supernormal VWF activity as opposed to activity within the normal range, Study IV did not provide any clear indication that patients undergoing aortic surgery would benefit from administration of FVIII/VWF concentrate or desmopressin acetate (161)

Limitations

Studies I and II were limited by the inherent shortcomings of their retrospective design and given the size of the study populations, the risk of type II errors cannot be ruled out. In Study I, causes of death were not known and, therefore, we cannot with certainty state that there is a true causality between major bleeding and late mortality. Furthermore, in Study I, we performed regression analyses with less than the recommended 10 events per variable (EPV) (162). However, the study was regarded as a hypothesis generating study and allowed us to accept a lower EPV, well aware that the large number of analyses introduced the risk of type I errors.

Study II was further limited by a non-standardised protocol for rFVIIa administration and a variety of surgical approaches and protocols for bleeding management and re-exploration. The exact timing of rFVIIa administration was not specified, but rFVIIa was administered intraoperatively or in the intensive care unit. Additionally, in contrast to randomised studies, propensity score matching does not compensate for differences in unmeasured confounders. Patients in Study II were treated with rFVIIa due to severe bleeding. Thus, the results of the rFVIIa group might have been influenced by the negative effects of bleeding and therefore, any positive or negative effects observed in Study II cannot be entirely attributed to the use of rFVIIa.

The two groups compared in Studies III and IV were not identical in terms of baseline and surgical data, and bleeding management was not strictly standardised. Firstly, patients in the ATAAD group had an aortic dissection as compared to elective controls, most often presenting with a stable aortic aneurysm. Secondly, ATAAD patients were cooled to a significantly lower body temperature and patients undergoing elective aortic procedures had significantly longer CPB run times- two factors that have a known negative effect on the haemostatic system. However, despite these differences, patients undergoing elective surgery of the ascending aorta or the aortic root represent the patient category closest resembling surgical ATAAD patients, and since previous research on the coagulopathy of ATAAD has lacked surgical control groups, we consider this to be the major strength of studies III and IV.

The study samples in Studies III and IV were limited and most likely, the studies were under-powered to detect all existing differences between the groups. On the other hand, the small sample sizes increase the chance of significant findings

showing clinically relevant differences between the groups. Furthermore, the studies represented real-world data. Consecutivity was desired but not completely achieved. Due to the urgency of ATAAD, we operated at all hours of the day but resources for research purposes were limited during night hours.

Conclusions

Study I

In Study I, we identified several clinical predictors of massive bleeding associated with ATAAD surgery, including patient age, symptom duration and extent of the dissection. Furthermore, massive bleeding was associated with increased rates of postoperative complications and re-exploration for bleeding predicted both in-hospital and late mortality.

Study II

Study II demonstrated that despite having larger bleeding volumes and receiving more transfusions of blood products, patients who received rFVIIa in association with ATAAD surgery had similar rates of in-hospital mortality, late mortality and renal replacement therapy when compared to a propensity-matched control group of patients who did not receive rFVIIa. The study could not definitively exclude an association between rFVIIa use and increased risk of postoperative stroke, but despite this, rFVIIa was regarded as having an acceptable safety profile for treatment of refractory bleeding in the setting of ATAAD surgery.

Study III

Study III showed that aortic dissection causes a consumption of coagulation factors and increased fibrinolysis, further prompted by hypothermia and the use of CPB. Similar consumptive coagulopathy, caused by the surgical procedure itself, was identified in patients undergoing elective aortic surgery.

Study IV

In Study IV, we demonstrated that aortic dissection caused an increase in VWF activity (VWF:GPIbM), which was counteracted by hypothermia. After surgery, VWF:GPIbM reached supernormal levels in both ATAAD and elective patients. The multimer pattern of VWF was not affected by aortic dissection nor by aortic surgery. In summary, the results of Study IV did not indicate that patients would benefit from administration of FVIII/VWF concentrate as a treatment for excessive bleeding in aortic surgery.

Future perspectives

As described in this thesis, bleeding complications are associated with increased rates of postoperative complications and mortality after ATAAD surgery. Therefore, further efforts are necessary to identify reversible changes of the coagulation system caused by aortic dissection. Point-of-care coagulation testing, e.g. ROTEM®, has been increasingly used at our institution. Although it is a compelling option due to its accessibility and simplicity, ROTEM® has not been properly evaluated in the setting of the complex haemostatic disturbance caused by aortic dissection. Additionally, in Study III we demonstrated that ATAAD causes a consumption of platelets, but the function of the remaining platelets has not been fully described. A future study should investigate the content of platelet microparticles and assess their potential impact on bleeding associated with ATAAD surgery.

Furthermore, Study III showed that surgery for ATAAD can be performed with low rates of re-exploration for bleeding and postoperative blood loss volumes comparable to those of elective aortic surgery. However, in Study III, patients with preoperative DAPT and anticoagulant treatment were excluded. It has previously been shown that up to one-third of patients with ATAAD are initially misdiagnosed as having ACS and therefore run the risk of receiving DAPT prior to surgery (39). Future research should aim to identify factors or combinations of symptoms, specifically setting aortic dissection patients apart from other diagnoses with symptoms resembling those of organ malperfusion, thus reducing the risk of misdiagnosis and delay of definitive surgical treatment.

Although there is a vast amount of research available, there is no consensus on the optimal strategy for arterial cannulation, cerebral protection or extent of surgical repair of ATAAD. Since ATAAD is a fairly uncommon disease, the prospect of providing solid evidence-based surgical recommendations lies with large multi-centre databases. IRAD, GERAADA and NORCAAD have thus far made significant contributions to this field of research, and during 2020, the NORCAAD collaboration plans to expand with additional Nordic centres, including Copenhagen and Helsinki, and initiate prospective data collection in the NORCAAD 2.0 database. It will also be interesting to follow the research derived from the Sino-RAD database that uses data from 15 Chinese cardiothoracic centres. During a period of two years (2012–2013), the Sino-RAD database collected 1033 patients with ATAAD, but have since then not published any results from their registry (163).

Endovascular approaches of tackling end-organ malperfusion prior to open ATAAD surgery and the use of the elephant trunk technique might reduce the impact of malperfusion-related complications in ATAAD surgery. Malperfusion is still one of the most crucial issues in aortic dissection, but recent research has shown that ATAAD surgery in patients with cardiac, mesenteric or cerebral malperfusion is associated with better survival than medical treatment alone (78). Mortality rates after ATAAD surgery have decreased in recent years but future efforts perhaps should not focus blindly on surgical mortality rates but aim to optimize the selection of patients suitable for surgery (34, 42). A more generous inclination towards offering surgery for patients with cardiac, mesenteric or cerebral malperfusion would potentially lead to increased surgical mortality rates but it would also most likely lead to reduced overall mortality from ATAAD.

“All bleeding stops sometime”

Norman E. Shumway

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Supplementary material

Study II

SUPPLEMENTARY TABLE II.1 - Primary outcomes in the unmatched populations

	rFVIIa (n=171)	Control (n=590)	OR (95% CI)
In-hospital mortality	23 (13.5)	78 (13.2)	1.02 (0.58–1.72)
Postoperative stroke	44 (26.0)	100 (17.2)	1.69 (1.09–2.58)
Renal replacement therapy	36 (21.3)	59 (10.2)	2.37 (1.45–3.82)

Values are expressed numbers (%) and as odds ratio (OR) with 95% confidence interval (CI).

SUPPLEMENTARY TABLE II.2 - Intra- and postoperative bleeding data in the unmatched populations

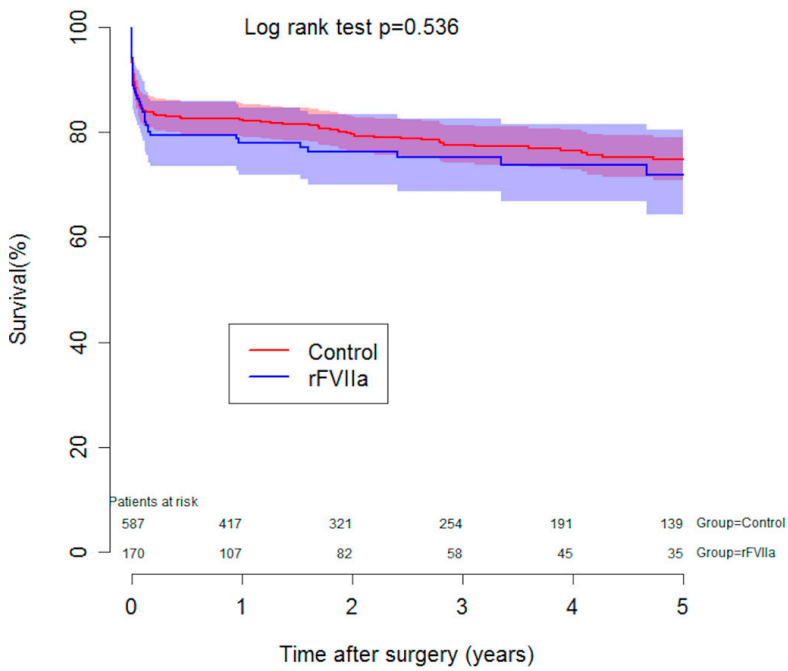
	rFVIIa (n=171)	Control (n=590)	*p*	Missing (n)
Bleeding during first 24 h (mL)	1160 (670–2215)	780 (520–1230)	<0.01	317
PRBC (U)	10.0 (5–22)	5.0 (2.0–10.0)	<0.01	22
Platelets (U)	4.0 (2.0–9.0)	2.0 (1.0–4.0)	<0.01	13
FFP (U)	9.0 (4.0–22.0)	4.4 (2.0–9.0)	<0.01	24
rFVIIa	5.0 (2.0–10)	0 (0–0)	<0.01	0
Fibrinogen concentrate (g)	2.0 (1.0–6.0)	0.0 (0.0–2.0)	<0.01	9
Tranexamic acid (U)	3260 (0–4000)	4000 (0–4000)	0.87	44
Cardiac tamponade (N)	43 (25.4)	63 (10.9)	<0.01	15
Reoperation for bleeding (N)	57 (33.7)	92 (16.0)	<0.01	17

Values expressed as number (%) or median and interquartile range (IQR). rFVIIa: recombinant factor VIIa; PRBC: packed red blood cells; FFP: fresh frozen plasma.

SUPPLEMENTARY TABLE II.3 - Postoperative complications and early mortality in the unmatched populations

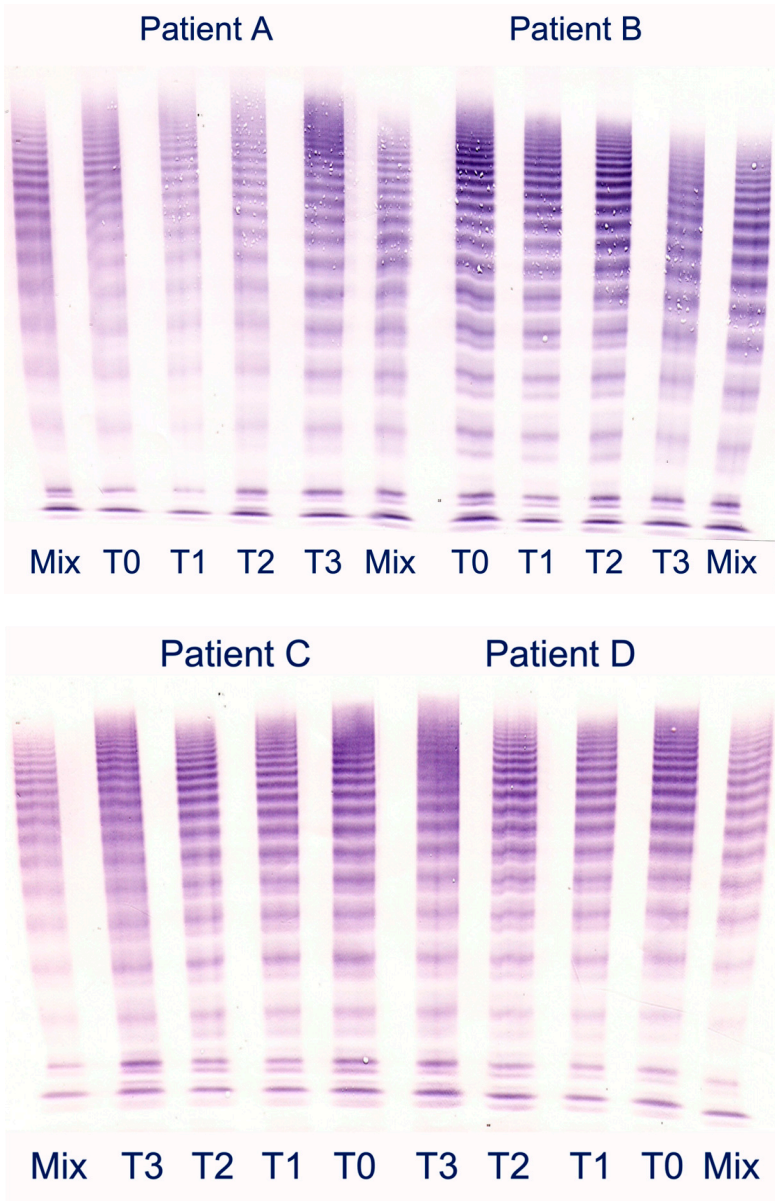
	rFVIIa (n=171)	Control (n=590)	*p*	Missing (n)
Postoperative stroke	44 (26.0)	100 (17.2)	0.01	12
RRT	36 (21.3)	59 (10.2)	<0.01	16
DSWI	4 (2.4)	11 (1.9)	0.76	13
Septicaemia	25 (14.9)	68 (11.8)	0.29	16
Ventilatory support >48h	83 (49.4)	133 (23.5)	<0.01	27
Cardiac arrest	14 (8.3)	22 (3.9)	0.03	24
Perioperative MI	10 (5.9)	31 (5.4)	0.85	13
Intraoperative mortality	2 (1.2)	33 (5.6)	0.01	0
30-day mortality	26 (15.2)	91 (15.4)	1.00	0
In-hospital mortality	23 (13.5)	78 (13.2)	0.90	0
Late reoperation of the aorta	9 (9.3)	20 (5.7)	0.24	313

Values expressed as number (%). RRT: renal replacement therapy; DSWI: deep sternal wound infection; MI: myocardial infarction.



SUPPLEMENTARY FIGURE II.1 - Survival curves (Kaplan-Meier method) in ATAAD patients from the unmatched populations, plotted by group.

Study IV



SUPPLEMENTARY FIGURE IV.1 - Multimeric composition of four randomly selected ATAAD patients showing no difference in multimer patterns between any of the intraoperative time points (T0–T3). Pooled control samples from the normal population constitute mixed-samples.

Study I

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Predictors and impact of massive bleeding in acute type A aortic dissection

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Abstract

OBJECTIVES: Bleeding complications associated with acute type A aortic dissection (aTAAD) are a well-known clinical problem. Here, we evaluated predictors of massive bleeding related to aTAAD and associated surgery and assessed the impact of massive bleeding on complications and survival.

METHODS: This retrospective study of 256 patients used Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) criteria to define massive bleeding, which was met by 66 individuals (Group I) who were compared to the remaining patients (Group II). Multivariable logistic regression was used to identify independent predictors of massive bleeding and in-hospital mortality, Kaplan–Meier estimates for analysis of late survival, and Cox regression analysis to evaluate independent predictors of late mortality.

RESULTS: Independent predictors of massive bleeding included symptom duration (odds ratio [OR], 0.974 per hour increment; 95% confidence interval [CI], 0.950–0.999; $P = 0.041$) and DeBakey type 1 dissection (OR, 2.652; 95% CI, 1.004–7.008; $P = 0.049$). In-hospital mortality was higher in Group I (30.3% vs 8.0%, $P < 0.001$). Kaplan–Meier estimates of survival indicated poorer survival for Group I at 1, 3 and 5 years (68.8 ± 5.9% vs 92.8 ± 1.9%; 65.2 ± 6.2% vs 85.3 ± 2.7%; 53.9 ± 6.9% vs 82.1 ± 3.3 %, respectively; log rank $P < 0.001$). Re-exploration for bleeding was an independent predictor of in-hospital (OR, 3.109; 95% CI, 1.044–9.256; $P = 0.042$) and late mortalities (hazard ratio, 3.039; 95% CI, 1.605–5.757; $P = 0.001$).

CONCLUSIONS: Massive bleeding in patients with aTAAD is prompted by shorter symptom duration and longer extent of dissection and has deleterious effects on outcomes of postoperative complications as well as in-hospital and late mortalities.

Keywords: Aorta • Aneurysm • Dissecting • Haemorrhage • Reoperation

INTRODUCTION

Acute type A aortic dissection (aTAAD) is a serious disease with high mortality [1, 2]. Surgery has proven successful in reducing mortality, but despite timely surgical intervention, mortality and morbidity remain high [3, 4]. In clinical practice, excessive bleeding related to surgery for aTAAD is a well-recognized problem. Bleeding complications during cardiac surgery in general have been shown to increase mortality [5–7], but have not been fully assessed in the setting of aTAAD surgery.

Previous studies have shown that aTAAD causes dysregulation of the coagulation system [8, 9], but the clinical predictors of massive bleeding associated with aTAAD are poorly described. In a previous study by Hansson *et al.* [5], dual antiplatelet therapy was associated with postoperative massive bleeding concurring with increased mortality. However, few reports describe the clinical predictors of massive bleeding or the influence of bleeding on complications and mortality after aTAAD surgery. Therefore, the aim of the present study was to evaluate predictors of massive bleeding related to aTAAD and its associated surgery and to assess the impact of massive bleeding on complications and survival.

METHODS

Study design

This was a retrospective cohort study with prospectively collected data. The study was approved by the Ethics Committee for Clinical Research at Lund University, Sweden (ref. 2015/197).

Definition of massive bleeding

The BART criteria for massive bleeding as defined in the Blood Conservation using Antifibrinolytics in a Randomized Trial study

[10] were used in the present study. Patients with any of the following four criteria were assigned to Group I and were compared with patients not fulfilling any of the criteria (Group II): postoperative bleeding through chest tubes exceeding 1500 ml over any 8-h period; reoperation for bleeding or cardiac tamponade within 24 h of surgery; transfusion of more than 10 U of red blood cells within 24 h after surgery; death from haemorrhage within 30 days.

Endpoints

Primary outcome measures were in-hospital mortality (defined as any mortality prior to hospital discharge), late mortality and incidence of postoperative complications related to massive bleeding. Pre-, peri- and postoperative variables were prospectively collected and entered into the departmental computerized database for retrospective analysis, and medical records were reviewed as needed. Symptom duration was defined as time from symptom onset to skin incision. Survival data was obtained from the Swedish National Board of Health and Welfare (Socialstyrelsen, Sweden).

Surgical techniques

As previously described [11], standard median sternotomy, cardiopulmonary bypass and intermittent cold blood cardioplegic arrest were routinely used. For arterial cannulation, femoral artery was used in most cases. Venous access was achieved through bicaval cannulation or a two-stage cannula. Resection of the ascending aorta and inspection of the aortic arch was performed under deep (<20 °C) or moderate (21–32 °C) hypothermic circulatory arrest in all but 29 patients where aortic cross-clamp was used. Depending on the location of the intimal tear and extent of dissection, the ascending aorta or aortic arch was replaced, with a root replacement performed on involvement of the coronary ostia or aortic valve or in the presence of an aortic root aneurysm. Arch procedures entailed reimplantation of any supra-aortic branch. When required, valvular competence was restored via sub-commissural plication, commissural resuspension and valvuloplasty. If possible, distal anastomosis was completed under circulatory arrest. Perfusion was subsequently instituted through a side branch of the vascular graft, enabling distal circulatory flow and rewarming during suturing of the proximal anastomosis.

Statistical analysis

Categorical data were given as proportions and continuous variables were expressed as the mean ± standard deviation. In skewed distributions, medians and interquartile ranges were reported. Proportions were compared using the chi-square test. If the expected frequency was <5, Fisher's exact test was applied. For continuous variables, Student's *t*-test was used. Event rates ±1 standard error during follow-up were estimated and survival was plotted using the Kaplan–Meier method, with the differences between Groups I and II compared using the log-rank test. Uni- and multivariable logistic regression analyses were performed to determine independent predictors of massive bleeding and in-hospital mortality. The effect of the preoperative and operative variables on survival and event-free survival was assessed with the Cox proportional hazard model in a stepwise manner. The proportional hazards assumptions were verified by adequate diagnostic tools [12] and no adjustments to meet the assumptions were needed for any variable. To avoid interactions in the regression model using a composite variable for massive bleeding reoperation for bleeding within 24 h after surgery was selected as the bleeding variable of choice. Thus, patients who died intraoperatively ($n = 14$) were excluded from regression analyses of major bleeding, in-hospital and late mortalities. The inclusion criterion for the full regression model was $P \leq 0.200$, and the limit for stepwise backward elimination was $P < 0.100$. The results of logistic regression analyses are expressed as odds ratios (ORs) and those of the Cox regression analysis as hazard ratios (HRs) with 95% confidence intervals (CIs). A P-value <0.05 was considered statistically significant unless otherwise stated. Statistical analysis relied on standard software (IBM Corp. Released 2012. IBM SPSS Statistics for Mac, Version 21.0. Armonk, NY, USA: IBM Corp).

RESULTS

Study population and patient follow-up

A total of 256 patients surgically treated for aTAAD between January 2004 and January 2016 at the Department of Cardiothoracic Surgery of Skane University Hospital (Lund, Sweden) were studied.

Follow-up, performed in March 2016, was 98% complete and included 975 patient-years with a mean follow-up time of 3.9 ± 3.2 years (median, 3.3 years; interquartile range, 0.8–6.4). Six patients were lost to follow-up, having emigrated, and 1 patient due to an unknown date of death (after hospital discharge).

Preoperative characteristics

Preoperative clinical characteristics of the study population are shown in Table 1. Patients in Group I ($n = 66$) were older ($P = 0.042$), with shorter symptom duration ($P = 0.003$), and were significantly more likely to suffer from hypertension ($P = 0.015$), diabetes mellitus ($P = 0.039$), and coronary artery disease ($P = 0.007$). Patients in Group I also had lower systolic blood pressure at admission ($P = 0.042$), higher p-creatinine levels ($P < 0.001$), and presented more often with organ malperfusion ($P = 0.016$) and cardiac tamponade ($P = 0.041$). Clopidogrel and dual antiplatelet treatments were significantly more common among patients in Group I ($P = 0.008$ and $P < 0.001$, respectively) than those in Group II ($n = 190$).

Perioperative characteristics

Perioperative characteristics are presented in Table 2. There were no between-group differences in surgical technique. The median cardiopulmonary bypass time was longer in Group I than in Group II (221 min [157–258 min] vs 180 min [151–223 min], $P = 0.002$) as was the circulatory arrest time (22 [17–30] min vs 18 [12–23] min, $P = 0.014$). Circulatory arrest was instigated in 54% of patients, with a lowest core temperature of 19.2 ± 5.4 °C and 19.3 ± 4.6 °C, ($P = 0.812$) in Groups I and Group II, respectively.

Postoperative bleeding and complications

Postoperative variables are presented in Table 3. Mean bleeding volume in chest tubes 12 h after surgery was 1180 ml (150–2763 ml) in Group I and 430 (280–560) ml in Group II, ($P < 0.001$).

Table 1: Preoperative characteristics of study population

	Group I (*n* = 66)	Group II (*n* = 190)	*P*-value
Age (years)	65.2 (±9.4)	62.2 (±12.0)	0.042
Female gender	22 (33.3)	70 (36.8)	0.602
BMI (kg/m^2)	25.9 (3.5)	26.6 (±5.2)	0.323
Symptom duration (h)	3.80 (2.86–7.59)	6.91 (4.58–13.49)	0.003
Smoking history	27 (40.9)	65 (34.2)	0.329
Marfan syndrome	4 (6.1)	21 (11.1)	0.239
Previous aortic surgery[a]	1 (1.5)	5 (2.6)	1.000
Hypertension	42 (63.6)	88 (46.3)	0.015
Hyperlipidaemia	6 (9.1)	11 (5.8)	0.391
Diabetes mellitus	29 (43.9)	57 (30.0)	0.039
Coronary artery disease	9 (13.6)	7 (3.7)	0.007
Peripheral vascular disease	2 (3.0)	5 (2.6)	1.000
Stroke	4 (6.1)	12 (6.3)	1.000
COPD	7 (10.6)	7 (3.7)	0.054
Dialysis	1 (1.5)	1 (0.5)	0.450
Preoperative blood pressure (mmHg)			
Systolic blood pressure	113.2 (±39.6)	124.5 (±35.3)	0.042
Diastolic blood pressure	69.4 (±19.0)	72.7 (±21.2)	0.370
Organ malperfusion	31 (47.0)	58 (30.5)	0.016
Cardiac tamponade	12 (18.2)	17 (8.9)	0.041
DeBakey type 1	52 (78.8)	135 (71.1)	0.222
Penn Class			
Aa	23 (34.3	111 (58.1)	<0.001
Ab	19 (28.4)	44 (23.0)	0.383
Ac	17 (25.4)	23 (12.0)	0.009
Abc	8 (11.9)	13 (6.8)	0.186
Intramural haematoma	1 (1.5%)	10 (5.3)	0.298
Aspirin	21 (31.8)	56 (29.5)	0.720
Clopidogrel	11 (16.7)	10 (5.3)	0.004
Ticagrelor	4 (6.1)	5 (2.6)	0.242
DAPT	13 (19.7)	15 (7.9)	0.008
Warfarin	3 (4.5)	9 (4.7)	1.000
P-creatinine (μmol/l)	92.0 (75.5–107.5)	80 (58.5–103.5)	<0.001
P-lactate (mmol/l)	1.2 (1.1–2.6)	1.4 (1.0–2.5)	0.079

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR).
BMI: body mass index; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy.
[a]Surgery of the descending aorta.

The rate of re-exploration for bleeding at any time after surgery was significantly higher in Group I (55.9% vs 1.1%, $P < 0.001$). Compared with those in Group II, patients in Group I received significantly more red blood cell units (8.5 [5.3–12.5] U vs 3 [1–6] U, $P < 0.001$), platelets (9 [4.5–12.8] U vs 4 [2–6] U, $P < 0.001$), fresh frozen plasma (5.5 [4.3–7.5] vs 1 [0–4] U, $P < 0.001$), fibrinogen concentrate (9.8 ± 4.2 g vs 4.4 ± 3.0 g, $P < 0.001$) and recombinant factor VIIa (4.1 ± 3.0 mg vs 1.6 ± 2.3 mg, $P < 0.001$) peri- and postoperatively. Patients in Group I more often required renal replacement therapy (22.0% vs 3.8%, $P < 0.001$), prolonged ventilatory support (88.1% vs 31.1%, $P < 0.001$), longer ICU stay (12 [5.5–17] days vs 3 [3–5] days, $P < 0.001$) and were more likely to suffer from postoperative stroke (39.0% vs 23.0%, $P = 0.016$) and deep sternal wound infection (6.8% vs 1.1%, $P = 0.033$) than those in Group II.

Predictors of massive bleeding

Predictors of massive bleeding as defined by the Blood Conservation using Antifibrinolytics in a Randomized Trial criteria are presented in Table 4. Age (OR, 1.060 per year increment; 95% CI, 1.019–1.103; $P = 0.004$), symptom duration (OR, 0.974 per hour increment; 95% CI, 0.950–0.999; $P = 0.041$), hypertension (OR, 3.007; 95% CI, 1.361–6.645; $P = 0.006$), coronary artery disease (OR, 5.852; 95% CI, 1.477–23.182; $P = 0.012$), organ malperfusion (OR, 2.241; 95% CI, 1.024–4.904; $P = 0.044$) DeBakey type 1 dissections (OR, 2.652; 95% CI, 1.004–7.008; $P = 0.049$), preoperative dual antiplatelet therapy (OR, 6.110; 95% CI, 1.748–21.355; $P = 0.005$), preoperative p-creatinine (OR, 1.008 per 1 μmol/l increment; 95% CI, 1.000–1.016; $P = 0.037$), duration of cardiopulmonary bypass (OR, 1.018 per min increment; 95% CI, 1.009–1.028; $P < 0.001$), and duration of aortic cross-clamp (OR, 0.986 per min increment; 95% CI, 0.975–0.997; $P = 0.014$) were all identified as predictors of massive bleeding.

Early mortality

Intraoperative mortality was 10.6% in Group I and 3.7% in Group II ($P = 0.054$). In-hospital mortality was significantly higher in Group I (30.3% vs 8.0%; $P < 0.001$). The difference in in-hospital mortality remained significant after patients who died intraoperatively were excluded from the analysis (22.0% vs 4.4%, $P < 0.001$). Multivariate regression analysis results revealed preoperative cardiac tamponade (OR, 4.281; 95% CI, 1.425–12.866; $P = 0.010$) and re-exploration for bleeding within 24 h after

Table 2: Perioperative characteristics of study population

	Group I (n = 66)	Group II (n = 190)	P-value
Distal surgical technique[a]			
Supracoronary graft	51 (77.3)	152 (80.0)	0.638
Hemiarch procedure	10 (15.2)	25 (13.2)	0.685
Aortic arch procedure	4 (6.1)	13 (6.8)	1.000
Proximal surgical technique[a]			
Supracoronary graft[b]	41 (62.1)	124 (65.3)	0.646
Bentall procedure	18 (27.3)	53 (27.9)	0.923
David or Yacoub procedure	1 (1.5)	5 (2.6)	1.000
Aortic valve replacement	5 (7.6)	8 (4.2)	0.338
Arterial cannulation site[a]			
Femoral artery	49 (74.2)	136 (71.6)	0.677
Ascending aorta/aortic arch	13 (19.7)	46 (24.2)	0.453
Subclavian/brachiocephalic artery	2 (3.0)	5 (2.6)	1.000
Left ventricle	1 (1.5)	3 (1.6)	1.000
CPB time (min)	221 (157–258)	180 (151–223)	0.002
Aortic cross-clamp time (min)	118 (±61.6)	107 (±56.0)	0.182
Circulatory arrest (n)[c]	33 (50.8)	106 (55.8)	0.483
Circulatory arrest duration (min)	22 (17–30)	18 (12–23)	0.014
Lowest core temperature (°C)	19.2 (±5.4)	19.3 (±4.6)	0.812
Antegrade cerebral perfusion (n)	8 (12.3)	16 (8.4)	0.354
Antegrade cerebral perfusion (min)	35.8 (±17.4)	31.1 (±14.7)	0.460
Retrograde cerebral perfusion (n)	24 (36.9)	68 (35.8)	0.870
Retrograde cerebral perfusion (min)	27.8 (±10.0)	24.6 (±7.9)	0.114
Primary tear exclusion	41 (63.1)	125 (65.8)	0.692

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR).
CPB: cardiopulmonary bypass.
[a]One patient in Group I died prior to attempt to repair the aorta.
[b]With or without commissural resuspension.
[c]Without the use of selective cerebral perfusion.

surgery (OR, 3.109, 95% CI, 1.044–9.256; $P = 0.042$) as independent predictors of in-hospital mortality (Table 5).

Late survival and aortic reoperation

Kaplan–Meier estimates of survival in Groups I and II (Fig. 1) indicated poorer survival at 1, 3, and 5 years in Group I (68.8 ± 5.9% vs 92.8 ± 1.9%; 65.2 ± 6.2% vs 85.3 ± 2.7%; 53.9 ± 6.9% vs 82.1 ± 3.3%, respectively; log rank $P < 0.001$). Group I had a trend towards higher rate of reoperation for late complications (e.g. aortic root aneurysm, dilatation of the descending aorta) of aortic dissection and aTAAD surgery (15.9% vs 5.6%, $P = 0.053$) (Table 3). Fig. 2 shows the Kaplan–Meier estimate of survival for patients who survived to discharge. A significant difference between the groups remained, with poorer survival in Group I (1, 3 and 5 years, respectively: 93.1 ± 3.9% vs 98.8.8 ± 0.8%; 88.1 ± 5.0% vs 90.9 ± 2.5%; 71.8 ± 7.8% vs 87.4 ± 33.1%; log rank $P = 0.001$). Multivariate Cox regression analysis showed that age (HR, 1.048 per year increment; 95% CI, 1.017–1.080; $P = 0.002$), preoperative cardiac tamponade (HR, 2.211; 95% CI, 1.128–4.335; $P = 0.021$) and re-exploration for bleeding within 24 h after surgery (HR, 3.039; 95% CI, 1.605–5.757; $P = 0.001$) were independent predictors of late mortality (Table 6).

DISCUSSION

Despite increasing knowledge of the alterations in haemostasis following aTAAD and associated surgery, management of peri- and postoperative bleeding still poses a crucial clinical challenge.

Aortic dissection causes the flow of blood through a non-endothelialized false lumen. The contact between the blood and subendothelial tissue factor, collagen and the adventitial layer of the aortic wall causes a consumption coagulopathy resembling disseminated intravascular coagulation [8, 9]. Cate *et al.* [8] showed that aortic dissection causes a decrease in factors II, V, VII X and XII with a significant elevation in fibrin/fibrinogen degradation products. Data from that same study also indicated a decrease in factor VIII clotting activity by either consumption during the clotting process or digestion by plasmin, and thrombocytopaenia due to depletion of platelets at sites of collagen exposure. Later studies have shown that aortic dissection causes not only a consumption of platelets associated with increased mortality [13] but also a reduction in the ability of platelets to aggregate [14]. In addition, cardiopulmonary bypass causes haemodilution and decreases in platelet counts, factor V, VII, VIII and XI levels, and fibrinogen as well as increases in fibrin/fibrinogen degradation products, plasmin-antiplasmin complex, and factor XIIa. Moreover, it causes an activation of platelets, resulting in reduced reactivity [15, 16]. In addition, hypothermia, routinely induced during surgery for aTAAD, results in increased platelet activation and aggregation and a reversible thrombocytopaenia caused by hepatic and splenic sequestration as well as disturbances in both the intrinsic and extrinsic coagulation pathway [17–19].

Predictors of massive bleeding

Previous studies have not shown any association between coagulopathy and the longitudinal extent of dissection and thus the

Table 3: Postoperative data of study population

	Group I	Group II	*P*-value
Postoperative bleeding (ml)[a]			
12 h	1180 (1150–2763)	430 (280–560)	<0.001
24 h	1705 (1460–3315)	660 (500–780)	<0.001
Total	3990 (3458–4612)	990 (760–1600)	<0.001
Red blood cells (U)[a]	8.5 (5.3–12.5)	3 (1–6)	<0.001
Platelets (U)[a]	9 (4.5–12.8)	4 (2–6)	<0.001
Plasma (U)[a]	5.5 (4.3–7.5)	1 (0–4)	<0.001
Fibrinogen concentrate (g)[a]	9.8 (±4.2)	4.4 (±3.0)	<0.001
Tranexamic acid (g)[a]	3.4 (±2.1)	3.6 (±1.5)	0.545
rFVIIa (mg)[a]	4.1 (±3.0)	1.6 (±2.3)	<0.001
Re-exploration for bleeding[a]	33 (55.9)	2 (1.1)	<0.001
RRT[a]	13 (22.0)	7 (3.8)	<0.001
Stroke[a]	23 (39.0)	42 (23.0)	0.016
DSWI[a]	4 (6.8)	2 (1.1)	0.033
Ventilatory support >48 h[a]	52 (88.1)	57 (31.1)	<0.001
ICU (days)[a]	12 (5.5–17)	3 (3–5)	0.001
Postoperative atrial fibrillation[a]	32 (54.2)	73 (39.9)	0.053
Creatinine at discharge[a]	234 (134–326)	101 (72–124)	<0.001
Postoperative lactate[a]	4.8 (2.6–7.3)	2.2 (1.6–2.9)	0.007
Postoperative CKMB[a]	91.6 (34.7–147.0)	34.8 (17.2–58.9)	0.176
Intraoperative mortality[b]	7 (10.6)	7 (3.7)	0.054
In-hospital mortality[b]	20 (30.3)	15 (8.0)	<0.001
Late reoperation of the aorta[c]	7 (15.9)	10 (5.6)	0.053

Values expressed as number (%), mean (±SD), or median and interquartile range (IQR).
rFVIIa: recombinant factor VIIa; RRT: renal replacement therapy; DSWI: deep sternal wound infection.
[a]Group I, $n = 59$, Group II, $n = 183$. Patients who died intraoperatively were excluded from analysis.
[b]Group I, $n = 66$, Group II, $n = 190$. All patients were included in analysis.
[c]Group I, $n = 44$, Group II, $n = 170$. Patients who died during hospital stay or were lost to follow-up were excluded from analysis.

quantity of exposed subendothelial tissue, suggesting alternative triggers of the coagulation system. Nakajima *et al.* [20] showed that platelet function and coagulation/fibrinolysis system activation correlated with the width of the dissected aorta, leading to the assumption that coagulopathy associated with aortic dissection may be caused by a turbulent flow in the false lumen. Nomura *et al.* [21] have shown the coagulopathic state to remain for several months after surgery. Although the specific reason for reoperation was not specified in the present study, these previous findings may be supported by our results that showed reoperations of the aorta were more frequent among patients in Group I than those in Group II (14% vs 5.6%, $P = 0.047$). To evaluate a hypothesis primarily suggested by Cate *et al.* [8], DeBakey type 1 dissections were included in the regression model, despite not reaching the defined inclusion limit of $P < 0.200$ in the univariable analysis. Nevertheless, our data showed that DeBakey type 1 dissection was an independent predictor of massive bleeding (OR, 2.652; 95% CI; 1.004–7.008; $P = 0.049$), supporting the notion that coagulopathy, at least in part, is associated with the extent of the false lumen. Interestingly, our analysis showed an inverse correlation between symptom duration and risk for massive bleeding (OR, 0.974 per hour increment; 95% CI, 0.950–0.999; $P = 0.041$). A possible explanation for this finding might be an immediate major activation and consumption of platelets and coagulation factors in an attempt to occlude the false lumen. Consequently, thrombus formation in the false lumen ought to lead to exposure of less subendothelial tissue, and thus a lesser consumption of haemostatic agents and a decrease in fibrinolysis as time after dissection passes. Although this time frame needs to be analysed more thoroughly, the idea of opting to wait for the coagulopathy to wear off before proceeding to surgery is intuitively difficult to support, considering that mortality from aTAAD increases by 1–2% per hour in the acute state [22, 23].

Complications and early mortality

Compared with those in Group II, patients in Group I had significantly higher rates of postoperative renal replacement therapy and stroke, higher postoperative p-lactate, and higher p-creatinine levels at discharge. Aortic dissection, similar to disseminated intravascular coagulation, causes a decrease in antithrombin III, which has been associated with an increase in 30-day mortality and multiple organ failure, possibly due to micro- and macrovascular thromboses [24]. This may be a contributing factor to hypoperfusion, causing elevated p-lactate levels and higher rates of stroke and renal failure.

It has previously been reported that re-exploration for bleeding has an adverse impact on complications and survival [6, 7, 25]. Our study showed a significantly higher mortality rate in Group I than in Group II (30.3% vs 8.0%, $P < 0.001$). Because intraoperative death from bleeding was one of the inclusion criteria of Group I, and might be the result of aortic rupture, we excluded from the multivariable analyses those patients who died intraoperatively. However, patients in Group I still had a significantly higher mortality rate than those in Group II (22.0% vs 4.4%, $P < 0.001$). More red blood cells were transfused into Group I patients, and red blood cells transfusions have previously been

Table 4: Uni- and multivariable logistic regression analysis of variables associated with massive bleeding according to the BART criteria[a]

	Univariable analysis (n = 242)			Multivariable analysis (n = 242)		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (per 1 year increment)	1.024	0.998–1.051	0.072	1.060	1.019–1.103	0.004
Female gender	0.857	0.475–1.547	0.609			
BMI	0.970	0.899–1.046	0.427			
Symptom duration (per hour increment)	0.977	0.955–1.001	0.055	0.974	0.950–0.999	0.041
Smoking history	1.331	0.749–2.366	0.329			
Marfan syndrome	0.519	0.171–1.573	0.24			
Previous aortic surgery[b]	0.569	0.065–4.963	0.610			
Hypertension	2.028	1.139–3.612	0.016	3.007	1.361–6.645	0.006
Hyperlipidaemia	1.627	0.577–4.589	0.357			
Diabetes mellitus	1.829	1.027–3.256	0.040			
Coronary artery disease	4.128	1.471–11.587	0.007	5.852	1.477–23.182	0.012
Peripheral vascular disease	1.156	0.219–6.107	0.864			
Stroke	0.957	0.298–3.077	0.941			
COPD	3.102	1.045–9.207	0.041			
Dialysis	2.908	0.179–47.156	0.453			
Organ malperfusion	2.016	1.136–3.577	0.017	2.241	1.024–4.904	0.044
Cardiac tamponade	2.261	1.016–5.031	0.045			
DeBakey type 1 (ref. type 2)	1.513	0.776–2.952	0.224	2.652	1.004–7.008	0.049
Intramural haematoma	0.277	0.035–2.206	0.225			
Aspirin	1.117	0.610–2.044	0.721			
Clopidogrel	3.600	1.452–8.926	0.006			
Ticagrelor	2.387	0.621–9.170	0.205			
DAPT	2.567	1.106–5.955	0.028	6.110	1.748–21.355	0.005
Warfarin	0.958	0.251–3.649	0.949			
Creatinine (per 1 μmol/l increment)	1.010	1.002–1.017	0.014	1.008	1.000–1.016	0.037
Lactate (per 1 mmol/l increment)	1.072	0.928–1.240	0.344			
CPB time (per min increment)	1.006	1.002–1.009	0.001	1.018	1.009–1.028	<0.001
Aortic cross-clamp time (per min increment)	1.003	0.998–1.008	0.183	0.986	0.975–0.997	0.014
Lowest core temperature (per 1 °C increment)	0.993	0.936–1.053	0.811			
Primary tear exclusion	0.888	0.494–1.596	0.692			

BMI: body mass index; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy; CPB: cardiopulmonary bypass; BART: Blood Conservation using Antifibrinolytics in a Randomized Trial; OR: odds ratio; CI: confidence interval.
[a]Patients who died intraoperatively were excluded from this analysis.
[b]Surgery of the descending aorta.

Table 5: Independent predictors of in-hospital mortality after multivariable logistic regression[a]

	Multivariable logistic regression (n = 242)		
	OR	95% CI	P-value
Cardiac tamponade	4.281	1.425–12.866	0.010
Re-exploration for bleeding within 24 h	3.109	1.044–9.256	0.042

OR: odds ratio; CI: confidence interval.
[a]Patients who died intraoperatively were excluded from this analysis.

shown to be an independent predictor of increased morbidity and mortality [5, 7, 26]. To assess whether in-hospital mortality was increased due to bleeding, rather than to the significantly higher occurrence of stroke, deep sternal wound infections, and decreased renal function, we performed a multivariable regression analysis for independent predictors of in-hospital mortality. Because using a composite variable for massive bleeding would lead to an interaction risk in the analysis, we selected re-exploration as our indicator of profuse bleeding. The analysis revealed preoperative cardiac tamponade (OR, 4.281; 95% CI, 1.425–12.866; P = 0.010) and re-exploration for bleeding within 24 h after surgery (OR, 3.109; 95% CI, 1.044–9.256; P = 0.042) as independent predictors of in-hospital mortality in patients who survived surgery.

Late survival

Patients in Group I had a significantly poorer late survival than patients in Group II, as shown in Fig. 1. However, this might be influenced by the significantly higher in-hospital mortality of Group I. Therefore, Fig. 2 shows survival of patients that were alive at hospital discharge and reveals that significantly poorer survival was maintained in Group I. To adjust for differences in baseline characteristics, a Cox regression analysis was performed, and the results showed that re-exploration for bleeding was a strong independent predictor of late mortality (HR, 3.204; 95% CI, 1.772–5.792; P = 0.001).

The present study was limited by its retrospective design and the challenge of evaluating independent predictors in multifactorial conditions, which include bleeding disorders associated

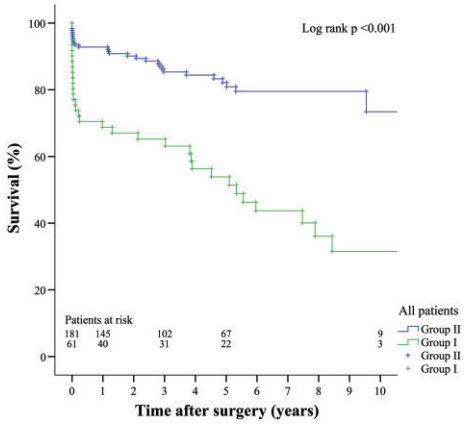

Figure 1: Kaplan–Meier survival curves of all patients plotted by group.

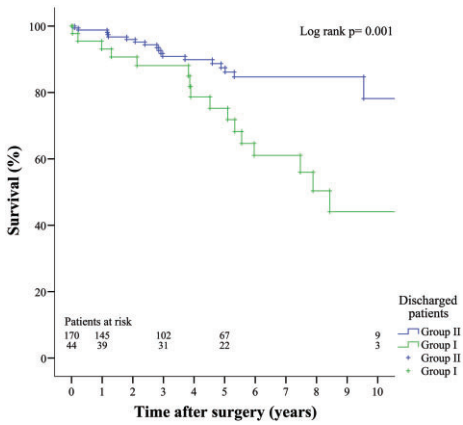

Figure 2: Kaplan–Meier survival curves of patients who survived to hospital discharge, plotted by group.

Table 6: Cox regression analysis of independent predictors of late mortality[a]

	Cox regression (n = 236)		
	HR	95% CI	P-value
Age (per year increment)	1.048	1.017.1.080	0.002
Cardiac tamponade	2.211	1.128–4.335	0.021
Re-exploration for bleeding within 24 h	3.039	1.605–5.757	0.001

OR: odds ratio; CI: confidence interval; HR: hazard ratio.
[a]Patients who died intraoperatively were excluded from this analysis.

with aTAAD. Despite the use of multivariable analyses to limit the effect of confounding variables, the effect of baseline differences as confounders could not be ruled out. Bleeding complications might be a surrogate measure for critical preoperative state or complex surgery. Nevertheless, regardless of cause, major bleeding remains an indicator of poorer outcome in patients undergoing surgery for type A aortic dissection. Furthermore, causes of death were unknown and a Cox regression analysis is insufficient in fully explaining the causality between bleeding complications and late mortality. In addition, massive bleeding may be caused by surgical haemorrhage due to insufficient anastomoses, suture lines or even sternal bleeding. Still, our study revealed several interesting findings, which will require confirmation in studies with larger sample sizes.

CONCLUSION

Despite the above-mentioned limitations, the present study showed that massive bleeding in patients with aTAAD is promoted by numerous clinical factors and has deleterious effects on the outcomes of postoperative complications as well as in-hospital and late mortalities.

Conflict of interest: none declared.

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Study II

Recombinant factor VIIa use in acute type A aortic dissection repair: A multicenter propensity-score-matched report from the Nordic Consortium for Acute Type A Aortic Dissection

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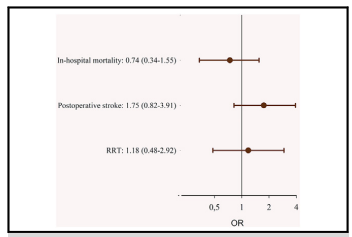
ABSTRACT

Background: Surgery for acute type A aortic dissection (ATAAD) is often complicated by excessive bleeding. Recombinant factor VIIa (rFVIIa) effectively treats refractory bleeding associated with ATAAD surgery; however, adverse effects of rFVIIa in these patients have not been fully assessed. Here we evaluated rFVIIa treatment in ATAAD surgery using the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) database.

Methods: This was a multicenter, propensity score–matched, retrospective study. Information about rFVIIa use was available for 761 patients, of whom 171 were treated with rFVIIa. We successfully matched 120 patients treated with rFVIIa with 120 controls. Primary endpoints were in-hospital mortality, postoperative stroke, and renal replacement therapy (RRT). Survival data were presented using Kaplan-Meier estimates.

Results: Compared with controls, patients treated with rFVIIa received more transfusions of packed red blood cells (median, 9.0 U [4.0-17.0 U] vs 5.0 U [2.0-11.0 U]; $P = .008$), platelets (4.0 U [2.0-8.0 U] vs 2.0 U [1.0-4.4 U]; $P < .001$), and fresh frozen plasma (8.0 U [4.0-18.0 U] vs 5.5 U [2.0-10.3 U]; $P = .01$) underwent reexploration for bleeding more often (31.0% vs 16.8%; $P = .014$); and had greater 24-hour chest tube output (1500 L [835-2500 mL] vs 990 mL [520-1720 mL]). Treatment with rFVIIa was not associated with significantly increased rates of in-hospital mortality (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.34-1.55; $P = .487$), postoperative stroke (OR, 1.75; 95% CI, 0.82-3.91; $P = .163$), or RRT (OR, 1.18; 95% CI, 0.48-2.92; $P = .839$).

Conclusions: In this propensity-matched cohort study of patients undergoing ATAAD surgery, treatment with rFVIIa for major bleeding was not associated with a significantly increased risk of stroke, RRT, or mortality. (J Thorac Cardiovasc Surg 2017;154:1852-9)



Forest plot illustrating the associations between rFVIIa treatment and primary endpoints.

Central Message

The results of this study showed that patients undergoing rFVIIa treatment in association to ATAAD surgery did not display significantly greater rates of mortality, renal replacement therapy or stroke.

Perspective

In previous studies on standard and complex cardiac surgery, use of recombinant factor VIIa (rFVIIa) has been associated with increased rates of mortality and stroke. In this study of a large sample of patients undergoing acute type A aortic dissection surgery, treatment with rFVIIa for major bleeding was not associated with a significantly increased risk of stroke, the need for renal replacement therapy (RRT), or mortality.

See Editorial Commentary page 1860.

Despite significant surgical advances in recent years, acute type A aortic dissection (ATAAD) still poses a great clinical challenge, with high mortality and morbidity.[1,2] Bleeding complications related to cardiac surgery adversely affect surgical outcomes.[3,4] The pathology of aortic dissection is known to cause dysregulation of the

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Abbreviations and Acronyms

ATAAD	= acute type A aortic dissection
BMI	= body mass index
CI	= confidence interval
COPD	= chronic obstructive pulmonary disease
CPB	= cardiopulmonary bypass
FFP	= fresh frozen plasma
HCA	= hypothermic circulatory arrest
IQR	= interquartile range
MI	= myocardial infarction
NORCAAD	= Nordic Consortium for Acute Type A Aortic Dissection
OR	= odds ratio
PRBC	= packed red blood cells
rFVIIa	= recombinant factor VIIa
RRT	= renal replacement therapy

Scanning this QR code will take you to supplemental figure, tables, and video for this article.

coagulation system, augmented by cardiopulmonary bypass (CPB) and deep hypothermia.[5-7] Consequently, massive intraoperative and postoperative bleeding is a feared complication associated with considerably elevated morbidity and mortality.[8,9]

Since first described in 2001,[10] recombinant factor VIIa (rFVIIa) (Novoseven; Novo Nordisk A/S, Bagsvaerd, Denmark) has gained increasing use for treating refractory bleeding in the off-label setting of cardiothoracic surgery. Previous studies have reported that rFVIIa effectively reduces blood loss and the need for allogeneic blood transfusions in standard cardiac surgery[11,12]; however, questions have been raised as to whether the prothrombotic properties of rFVIIa lead to an increased risk of thromboembolic complications when used in patients without hemophilia.[13,14] Data on the use of rFVIIa in ATAAD surgery are scarce, and previous studies are limited by small sample sizes.[11,15]

The Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) is a joint database consisting of 1159 patients who underwent surgery for ATAAD at 8 tertiary centers in Denmark, Finland, Iceland, and Sweden between 2005 and 2014.[16] In the present study, we used the NORCAAD database to evaluate the effect of rFVIIa on mortality and rates of postoperative stroke and renal replacement therapy (RRT) after ATAAD surgery.

METHODS

This study was approved by the Institutional Review Board of each participating center.

Study Design

This was a multicenter, propensity score–matched study using data collected retrospectively from the NORCAAD database for patients who underwent ATAAD surgery between January 1, 2005, and December 31, 2014, at 8 Nordic centers. A total of 194 clinical variables were collected from 1159 patients, including demographic data, previous medical history, preoperative medications, clinical symptoms on presentation, diagnostic methods, operative variables, complications, bleeding and blood transfusions, laboratory values, and outcome data.[16]

Primary endpoints were in-hospital mortality, perioperative stroke, and RRT. Secondary endpoints were reexploration for bleeding and long-term mortality. In-hospital mortality was defined as death occurring during the hospital stay. Stroke was defined as a clinically significant loss of neurologic function caused by an ischemic event with or without confirmation by computed tomography scan. RRT was defined as the postoperative need for continuous venovenous hemofiltration or hemodialysis.

Postoperative bleeding was defined as total chest tube output volume during the first 24 hours after surgery. Postoperative cardiac tamponade was defined as pericardial effusion necessitating pericardial drainage or reexploration. Transfusions were reported as units of packed red blood cells (PRBCs), platelets, or fresh frozen plasma (FFP), administered at any time during the hospital stay.

Surgical Procedures

The decision to operate for ATAAD and the specific techniques used were at the discretion of the responsible surgeons at each center. Standard median sternotomy, CPB, and intermittent cardioplegic arrest were routinely used as described previously.[16] Cannulation sites varied by center, patient, and surgeon. In cases where a cross-clamp was not used, resection and inspection of the aortic arch were performed with the patient under deep (<20°C) or moderate (21°C-32°C) hypothermic circulatory arrest, with or without the use of antegrade cerebral perfusion.

The method of ascending aorta or aortic arch replacement depended on the location of the intimal tear and the extent of dissection. Root replacement was performed when the tear involved the coronary ostia or aortic valve, or in the presence of an aortic root aneurysm. Operations that involved the aortic arch entailed reimplantation of any supra-aortic branch. When required, the competence of the aortic valve was restored as feasible via subcommissural plication, commissural resuspension, or valvuloplasty. Concomitant procedures (eg, coronary artery bypass) were performed when required.

Management of intraoperative and postoperative bleeding varied depending on the center and time. However, rFVIIa was used mainly during surgery or in the intensive care unit when primary pharmacologic treatment to reduce bleeding had failed.

Statistical Analysis

Categorical variables were expressed as number and percentage, and continuous variables are presented as median and interquartile range (IQR). A propensity analysis was performed to adjust for differences between the 2 groups.[17] As a first step, univariate logistic regression analyses with group as outcome were performed for all variables listed in Table 1. All variables with a P value < .20 were subsequently included in the multivariable logistic regression model, which computed the propensity scores. These variables were bicuspid aortic valve, previous cardiac surgery, history of stroke, cerebral malperfusion, Penn class, proximal surgical technique, CPB and cross-clamp times, and lowest core temperature. A nearest-neighbor matching with caliper 0.2 was

TABLE 1. Baseline and surgical characteristics in the unmatched populations

Characteristic	rFVIIa (n = 171)	Control (n = 590)	AbSD, %	*P* value	Missing, n
Age, y, median (IQR)	62.0 (54.0-68.0)	64.0 (53.6-70.8)	3.9	.65	0
Male sex, n (%)	122 (71.3)	394 (66.8)	9.8	.26	0
Hypertension, n (%)	89 (52.0)	311 (52.7)	1.3	.88	0
History of aortic aneurysm, n (%)	20 (11.7)	51 (8.7)	10.3	.24	4
Connective tissue disease, n (%)	3 (1.8)	20 (3.4)	9.6	.28	3
Bicuspid aortic valve, n (%)	6 (3.5)	39 (6.7)	13.6	.13	10
Previous aortic surgery, n (%)	7 (4.1)	14 (2.4)	10.3	.24	6
Previous cardiac surgery, n (%)	7 (4.1)	12 (2.0)	13.2	.14	0
Diabetes mellitus, n (%)	4 (2.3)	12 (2.0)	2.0	.82	4
Hyperlipidemia, n (%)	16 (9.4)	74 (12.6)	9.9	.26	4
History of stroke, n (%)	10 (5.8)	17 (2.9)	16.0	.07	3
Chronic kidney disease, n (%)	5 (2.9)	9 (1.5)	10.3	.24	3
COPD, n (%)	8 (4.7)	33 (5.6)	4.2	.63	4
History of smoking, n (%)	62 (45.9)	181 (41.7)	8.5	.39	192
BMI, kg/m^2, median (IQR)	25.4 (23.5-28.2)	26.0 (23.5-29.0)	9.3	.32	96
Aspirin, n (%)	52 (30.4)	155 (26.5)	8.9	.31	4
Other antiplatelet treatment, n (%)	23 (13.5)	61 (10.4)	9.7	.27	4
Warfarin treatment, n (%)	16 (9.4)	38 (6.5)	11.2	.20	4
Blood pressure medicine, n (%)	70 (41.7)	255 (44.2)	5.1	.56	16
Organ malperfusion (any), n (%)	51 (30.0)	152 (26.0)	9.0	.31	7
Cerebral malperfusion, n (%)	20 (12.9)	39 (8.1)	16.4	.08	127
DeBakey type 1, n (%)	130 (76.5)	435 (74.2)	5.2	.55	5
Intramural hematoma, n (%)	15 (9.0)	55 (9.5)	1.7	.85	18
Penn class, n (%)			24.3	.07	9
Aa	97 (57.1)	385 (66.2)			
Ab	40 (23.5)	122 (21.0)			
Ac	20 (11.8)	54 (9.3)			
Abc	13 (7.6)	21 (3.6)			
Proximal surgical technique, n (%)			30.4	.01	1
Supracoronary graft	108 (63.2)	447 (75.9)			
Bentall procedure	46 (26.9)	104 (17.7)			
David/Yacoub procedures	4 (2.4)	14 (2.4)			
Other	13 (7.6)	24 (4.1)			
Distal surgical technique, (%)			13.3	.48	8
Ascending aorta	130 (76.5)	418 (71.7)			
Hemiarch procedure	33 (19.4)	126 (21.6)			
Arch procedure	5 (2.9)	31 (5.3)			
Other	2 (1.2)	8 (1.4)			
CPB time, min, median (IQR)	211.5 (173.2-267.8)	189.0 (153.0-228.0)	38.7	<.001	60
Cross-clamp time, min, median (IQR)	99.5 (69.5-145.8)	87.0 (65.0-123.5)	25.9	.005	84
HCA time, min, median (IQR)	24.0 (16.0-32.0)	25.0 (18.0-34.0)	12.0	.24	75
Lowest core temperature, °C, median (IQR)	18.0 (18.0-21.0)	20.0 (18.0-24.0)	40.5	<.001	56

rFVIIa, Recombinant factor VIIa; *AbSD*, absolute standardized difference; *IQR*, interquartile range; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *CPB*, cardiopulmonary bypass; *HCA*, hypothermic circulatory arrest.

performed using the propensity scores. This resulted in the matching of 120 out of a maximum of 127 possible pairs. The remaining patients did not have the data required for inclusion in the model. The matching was evaluated using standardized mean differences.

The paired samples were compared using conditional logistic regression for binary variables. Comparisons of the primary endpoints were presented as odds ratios (ORs) with 95% confidence intervals (CIs), and were illustrated using forest plots. Note that these ORs were given by the conditional logistic regression and were based on the discordant pairs. The McNemar–Bowker test was used for categorical variables with more than two categories. All continuous variables in the matched sample met the conditions for a paired *t* test, which was subsequently used for analysis. The original unpaired sample was compared using the Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables.

Late survival was calculated using Kaplan-Meier estimates, and the groups were compared using the log-rank test. A stratified version was applied for the paired samples. Statistical analyses were performed using R version 3.2.5. (R Project for Statistical Computing; https://www.r-project.org/), and the MatchIt package in R (https://cran.r-project.org/web/packages/MatchIt/index.html) was used for propensity matching.

RESULTS

Study Population and Follow-up

A total of 1159 patients were included in the NORCAAD database up to March 2017. Follow-up was performed in January 2015 and was 99.5% complete, with a median follow-up time of 2.3 years (range, 0.25-5.23 years). Data on the use of rFVIIa was available for 761 patients (99.5% complete; median follow-up time of 2.2 years; IQR, 0.59-4.63 years). Of these 761 patients, 171 received treatment with rFVIIa (rFVIIa group).

Unmatched Population

The baseline characteristics and intraoperative data for the unmatched groups are presented in Table 1. Compared with the control group, the rFVIIa group had a more frequent history of stroke (5.8% vs 2.9%; $P = .07$) and cerebral malperfusion (12.9% vs 8.1%; $P = .08$). Patients in the rFVIIa group more frequently underwent complex aortic root surgery ($P = .01$), had longer median durations of CPB (212 minutes [IQR, 173-268 minutes] vs 189 [IQR, 153-228 minutes]; $P < .001$) and cross-clamp time (100 minutes [IQR, 70-146 minutes] vs 87 minutes [IQR, 65-124 minutes]; $P = .005$), and had a lower median core temperature nadir (18°C [IQR, 18°C-21°C] vs 20 °C [IQR, 18°C-24°C]; $P < .001$). The outcome results for the unmatched population are presented in the Supplementary Materials.

Matched Population

The propensity score algorithm successfully matched 120 patients who received rFVIIa with 120 control patients. The baseline characteristics and intraoperative data for the matched groups are presented in Table 2. After propensity score matching, there were no significant differences between the groups, except in preoperative warfarin treatment (11.7% vs 4.2%; $P = .049$).

A sensitivity analysis of the primary outcomes was performed adjusting for all variables with a standardized absolute difference exceeding 10%. The variables were adjusted for in the conditional logistic regression of the matched dataset, which resulted in minor effects on the ORs, but with no impact on the conclusions of our main analyses.

To further evaluate the propensity score matching, we performed a multivariable logistic regression adjusting for the same variables as those included in the propensity score matching. Even after this adjustment, we found no significant effect on between-group differences in the primary outcomes.

Transfusions and Reexploration for Bleeding

Patients in the rFVIIa group had greater chest tube output during the first 24 hours than controls (mean, 1500 mL [IQR, 835-2500 mL] vs 990 mL [IQR, 520-1720 mL]); however, a comparative analysis of chest tube output between the matched groups was not possible owing to numerous missing values (Table 3). In the unmatched samples, data were available for 444 of 761 patients, demonstrating that patients who received rFVIIa bled significantly more during the first 24 hours (median, 1160 mL [IQR, 670-2215 mL] vs 780 mL [IQR, 520-1230 mL]; $P < .001$) (Table E2). Compared with control patients, patients treated with rFVIIa received a median of 5 mg (IQR, 2-10 mg) of rFVIIa; received more transfusions of PRBCs (median, 9.0 U [IQR, 4.0-17.0 U] vs 5.0 U [IQR, 2.0-11.0 U]; $P = .008$), platelets (median, 4.0 U [IQR, 2.0-8.0 U] vs 2.0 U [IQR, 1.0-4.4 U]; $P < .001$), and FFP (median, 8.0 U [IQR, 4.0-18.0 U] vs 5.5 U [IQR, 2.0-10.3 U]; $P = .010$); and were treated with more fibrinogen concentrate (median, 2.0 g [IQR, 2.0-6.0 g] vs 0.0 g [IQR, 0.0-2.0 g; $P < .001$). Patients in the rFVIIa group had more frequent postoperative tamponade (23.9% vs 9.7%: $P = .011$) and reexploration for bleeding (31.0% vs 16.8%; $P = .014$).

Early Mortality and Postoperative Complications

Comparisons between the rFVIIa and control groups for the primary outcomes showed no significant differences in in-hospital mortality (OR, 0.74; 95% CI, 0.34-1.55; $P = .487$), postoperative stroke (OR, 1.75; 95% CI, 0.82-3.91; $P = .163$), or RRT (OR, 1.18; 95% CI, 0.48-2.92; $P = .839$) (Figure 1). The binary results for early mortality and postoperative complications are shown in Table 4. In-hospital mortality was 12.5% in the rFVIIa group and 16.7% in the control group ($P = .486$), whereas 30-day mortality in the two groups was 15.8% and 18.3%, respectively ($P = .743$). The postoperative stroke rate was 25.6% in the rFVIIa group and 17.9% in the control group

TABLE 2. Baseline and surgical characteristics in the propensity-score-matched populations

Characteristic	rFVIIa (n = 120)	Control (n = 120)	AbSD, %	*P* value	Missing, n
Age, y, median (IQR)	62 (54.8-69.0)	62 (49.0-68.8)	16.2	.22	0
Male sex, n (%)	83 (69.2)	74 (61.7)	16.1	.25	0
Hypertension, n (%)	60 (50.0)	68 (56.7)	13.4	.34	0
History of aortic aneurysm, n (%)	14 (11.7)	11 (9.2)	8.6	.66	0
Connective tissue disease, n (%)	2 (1.7)	5 (4.2)	14.6	.45	0
Bicuspid aortic valve, n (%)	5 (4.2)	5 (4.2)	<0.1	1.00	0
Previous aortic surgery, n (%)	6 (5.0)	5 (4.2)	5.1	1.00	0
Previous cardiac surgery, n (%)	4 (3.3)	2 (1.7)	10.7	.69	0
Diabetes mellitus, n (%)	3 (2.5)	4 (3.3)	5.8	1.00	0
Hyperlipidemia, n (%)	10 (8.3)	9 (7.5)	2.6	1.00	0
History of stroke, n (%)	5 (4.2)	7 (5.8)	9.0	.75	0
Chronic kidney disease, n (%)	5 (4.2)	3 (2.5)	12.4	.73	0
COPD, n (%)	5 (4.2)	6 (5.0)	3.7	1.00	0
History of smoking, n (%)	35 (47.9)	41 (56.2)	13.3	.36	94
BMI, kg/m^2, median (IQR)	25.1 (23.4-28.1)	24.8 (23.4-28.1)	1.0	.64	50
Aspirin, n (%)	34 (28.3)	31 (25.8)	5.6	.75	0
Anti-platelet treatment, n (%)	17 (14.2)	12 (10.0)	13.3	.44	0
Warfarin treatment, n (%)	14 (11.7)	5 (4.2)	29.2	.05	0
Blood pressure medicine, n (%)	48 (41.0)	55 (47.0)	14.7	.41	6
Organ malperfusion (any), n (%)	42 (35.0)	44 (36.7)	3.8	.89	0
Cerebral malperfusion, n (%)	14 (11.7)	15 (12.5)	2.9	1.00	0
DeBakey type 1, n (%)	34 (28.6)	33 (27.7)	2.5	1.00	2
Intramural hematoma, n (%)	7 (6.3)	6 (5.4)	3.3	1.00	0
Penn class, n (%)			6.2	.12	0
Aa	68 (56.7)	71 (59.2)			
Ab	34 (28.3)	31 (25.8)			
Ac	10 (8.3)	10 (8.3)			
Abc	8 (6.7)	8 (6.7)			
Proximal surgical technique, n (%)			13.9	.76	0
Supracoronary graft	77 (64.2)	79 (65.8)			
Bentall procedure	30 (25.0)	28 (23.3)			
David/Yacoub procedure	3 (2.5)	5 (4.2)			
Other	10 (8.3)	8 (6.7)			
Distal surgical technique, n (%)			20.9	.57	2
Ascending aorta	86 (72.3)	81 (68.1)			
Hemiarch procedure	28 (23.5)	27 (22.7)			
Arch procedure	1 (0.8)	2 (1.7)			
Other	4 (3.4)	9 (7.6)			
CPB time, min, median (IQR)	209.5 (129.0-256.5)	198.0 (163.5-233.5)	2.6	.82	0
Cross-clamp time, min, median (IQR)	95.0 (67.0-146.2)	87.5 (60.8-128.2)	4.5	.75	0
HCA time, min, median (IQR)	25.0 (17.0 -32.0)	27.0 (20.0-36.0)	14.0	.23	18
Lowest core temperature, °C, median (IQR)	18.0 (17.2-21.4)	18.2 (18.0-21.4)	1.6	.88	0

rFVIIa, Recombinant factor VIIa; *AbSD*, absolute standardized difference; *IQR*, interquartile range; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *CPB*, cardiopulmonary bypass; *HCA*, hypothermic circulatory arrest.

TABLE 3. Intraoperative and postoperative bleeding data in the propensity score–matched populations

Characteristic	rFVIIa (n = 120)	Control (n = 120)	*P* value	Missing, n
Bleeding in first 24 h, mL, median (IQR)	1500 (835-2500)	990 (520-1720)	*	194
PRBCs, U, median (IQR)	9.0 (4.0-17.0)	5.0 (2.0-11.0)	.008	14
Platelets, U, median (IQR)	4.0 (2.0-8.0)	2.0 (1.0-4.4)	<.001	4
FFP, U, median (IQR)	8.0 (4.0-18.0)	5.5 (2.0-10.3)	.010	8
rFVIIa, mg, median (IQR)	5.0 (2.0-10)	0 (0-0)	<.001	0
Fibrinogen concentrate, g, median (IQR)	2.0 (2.0-6.0)	0.0 (0.0-2.0)	<.001	12
Tranexamic acid, U, median (IQR)	3000 (0-4000)	2000 (0-4000)	.138	46
Cardiac tamponade, n (%)	27 (23.9)	11 (9.7)	.011	14
Reoperation for bleeding, n (%)	35 (31.0)	19 (16.8)	.014	14

rFVIIa, Recombinant factor VIIa; *IQR*, interquartile range; *PRBC*, packed red blood cell; *FFP*, fresh frozen plasma. *Statistical analysis not possible due to missing data.

($P = .163$), and The respective RRT rates were 12.4% and 10.6% ($P = .839$). A prolonged duration of mechanical ventilation was more common in the rFVIIa group than in the control group (44.1% vs 27.0%; $P = .008$).

Late Mortality

Kaplan–Meier estimates of survival are shown in Figure 2. There were no significant between-group differences in survival at 1, 3, and 5 years after surgery: 76.7% versus 76.8%, 74.1% versus 72.9%, and 70.9% versus 70.6%, respectively ($P = .248$, log-rank test).

DISCUSSION

The results of this multicenter, propensity score–matched, retrospective study demonstrated that rFVIIa treatment did not significantly increase the risk of in-hospital mortality, stroke, or RRT after ATAAD surgery. Excessive bleeding poses a significant threat to patients undergoing ATAAD surgery. Transfusion of platelets and FFP together with prothrombin-complex concentrate, fibrinogen concentrate, and tranexamic acid have been used to prevent bleeding complications with varying degrees of success. rFVIIa was first approved in 1996 for use in patients with hemophilia,[18] but over the last 15 years it has emerged as an off-label treatment of last resort for refractory bleeding after open heart surgery. Previous studies on the use of rFVIIa have described outcomes for a variety of cardiac procedures,[12,19] whereas reports specifically describing the use of rFVIIa in ATAAD surgery have been limited by small sample sizes and risk of type II errors.[11,15]

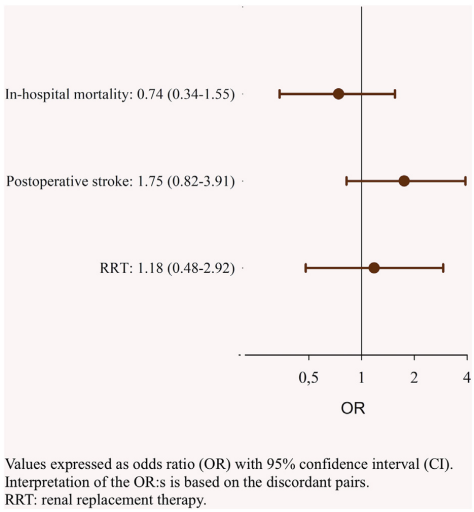

FIGURE 1. Forest plot illustrating the associations between rFVIIa treatment and primary endpoints.

In the present study, we did not detect any significant differences in in-hospital mortality between patients who received rFVIIa and control patients (12.5% vs 16.7%; $P = .486$). Our results are consistent with a randomized study conducted by Gill and colleagues[12] in patients undergoing coronary artery bypass grafting and mitral valve or aortic valve surgery. Two previous studies on isolated ATAAD populations did not report any differences in survival or adverse events between patients treated with rFVIIa and controls, although those studies were limited by the small number of cases (23 and 25 patients, respectively).[11,15]

In contrast, our results are not consistent with those of a previous propensity-matched analysis of patients receiving rFVIIa in association to complex cardiac surgery, where Alfirevic and colleagues[19] reported impaired survival in patients treated with rFVIIa. The authors suggested that renal morbidity, possibly caused by prothrombotic effects in the renal vascular bed associated with the use of rFVIIa, could have contributed to the increased mortality. In the present study, we did not find any difference in the incidence of postoperative RRT between the two groups.

Tissue injury following aortic dissection and CPB increases the expression of tissue factor in circulating blood, which provides a substrate for thromboembolism.[20]

TABLE 4. Postoperative complications and early mortality in the propensity score–matched populations

Characteristic	rFVIIa (n = 120)	Control (n = 120)	*P* value	Missing, n
Postoperative stroke, n (%)	30 (25.6)	21 (17.9)	.163	6
RRT, n (%)	14 (12.4)	12 (10.6)	.839	14
DSWI, n (%)	3 (2.6)	5 (4.3)	.727	6
Septicemia, n (%)	10 (8.9)	8 (7.1)	.815	16
Ventilatory support >48 h, n (%)	49 (44.1)	30 (27.0)	.008	18
Cardiac arrest, n (%)	6 (5.4)	7 (6.3)	1.000	16
Perioperative MI, n (%)	6 (5.3)	5 (4.4)	1.000	16
Intraoperative mortality, n (%)	2 (1.7)	9 (7.5)	.065	0
30-d mortality, n (%)	19 (15.8)	22 (18.3)	.743	0
In-hospital mortality, n (%)	15 (12.5)	20 (16.7)	.487	0
Late reoperation of the aorta, n (%)	4 (9.5)	1 (2.4)	.453	156

rFVIIa, Recombinant factor VIIa; *RRT*, renal replacement therapy; *DSWI*, deep sternal wound infection; *MI*, myocardial infarction.

This may explain why rFVIIa can cause thromboembolic complications, primarily when used in patients without hemophilia. In a meta-analysis of 6 clinical studies, Ponschab and colleagues[14] reported an increased incidence of stroke in patients receiving rFVIIa, and Gill and colleagues[12] found a trend toward a higher incidence of stroke in patients undergoing standard cardiac surgery. Despite the unfavorable effects of increased bleeding volumes, transfusions, and reexploration for bleeding, in the present study we found no significant differences in the incidence of postoperative stroke between patients receiving rFVIIa and controls.

The pathology of aortic dissection causes consumptive coagulopathy,[5] and surgery is often performed under deep hypothermia. Therefore, the effects of rFVIIa in routine cardiac procedures should not be extrapolated to those in ATAAD surgery, and vice versa. It has previously been shown that bleeding complications in ATAAD surgery increase the incidence of adverse events and in-hospital and long-term mortality.[8,9] In the present study, the patients treated with rFVIIa had significantly larger volumes of blood loss, underwent reexploration for bleeding more frequently, had greater incidence of postoperative cardiac tamponade, and received more transfusions of PRBCs, platelets, and FFP. These effects could be attributed to the fact that patients were not treated with rFVIIa unless there was significant intraoperative or postoperative bleeding. Thus, patients in the rFVIIa group were inherently at a greater risk of mortality and adverse events (including stroke and RRT) before administration of rFVIIa. Therefore, rather than increasing the risk of mortality, treatment with rFVIIa appeared to reduce the risk of adverse effects caused by excessive bleeding.

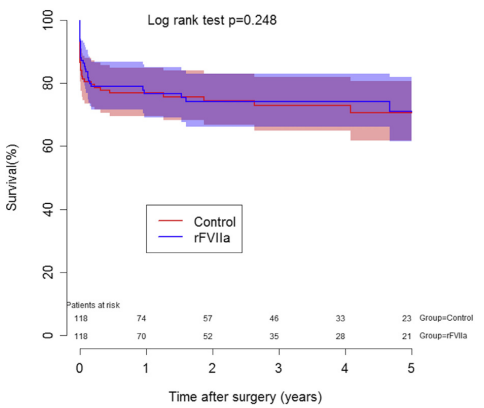

FIGURE 2. Survival curves (Kaplan-Meier method) in ATAAD patients from the matched populations, plotted by group. Late survival data were available for only 118 patients in the rFVIIa group. *rFVIIa*, Recombinant factor VIIa.

The present study has several limitations, including its retrospective design. Although to the best of our knowledge, this study is the largest analysis of rFVIIa treatment in an isolated ATAAD population reported to date. Its multicenter nature inherently introduced various surgical techniques, triggers for rFVIIa administration, and protocols for bleeding management and reexploration. The multicenter design also introduced difficulties in terms of collecting missing data. For example, rFVIIa was administered intraoperatively or in the intensive care unit, but the exact timing of rFVIIa administration was not specified in the database. The NORCAAD database enabled us to analyze a comparatively large patient population; however, the risk of type II errors cannot be overlooked. Propensity score matching is associated with a lower grade of evidence than that achieved with a randomized clinical trial. The use of propensity score matching does not control for unmeasured confounders, and missing data among the confounders might decrease the power of the study. In addition, the patients in our study received rFVIIa due to

VIDEO 1. Associate Professor Arnar Geirsson, Yale University, on NORCAAD and the current study. Video available at: http://www.jtcvsonline.org/article/S0022-5223(17)31773-7/fulltext.

excessive bleeding, which led to selection bias that could have potentially skewed our findings. Administration of rFVIIa is often a treatment of last resort for refractory bleeding in ATAAD surgery; as such, it might be a surrogate for diligent efforts in achieving hemostasis. Thus, despite the efforts to eliminate confounders, the positive or negative effects of rFVIIa observed in this study cannot be attributed exclusively to the use rFVIIa.

CONCLUSIONS

This multicenter, propensity score–matched, retrospective study used data from the NORCAAD database. Our results show that despite the known adverse effects of bleeding and transfusions, patients receiving rFVIIa treatment in ATAAD surgery did not have greater early or late mortality or a significantly greater incidence of postoperative renal failure. However, this study cannot with certainty exclude an association between rFVIIa use and increased risk of postoperative stroke. Prospective, randomized, and placebo-controlled trials are needed to further define the safety and efficacy of rFVIIa in ATAAD surgery (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: aorta, aneurysm, dissecting, hemorrhage

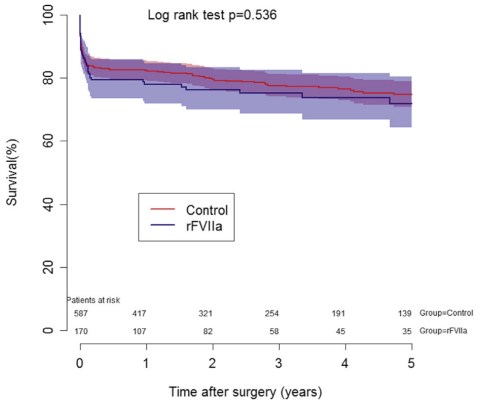

FIGURE E1. Survival curves (Kaplan-Meier method) in ATAAD patients from the unmatched populations, plotted by group. *rFVIIa*, Recombinant factor VIIa.

TABLE E1. Primary outcomes in the unmatched populations

Outcome	rFVIIa (n = 171), n (%)	Control (n = 590), n (%)	OR (95% CI)
In-hospital mortality	23 (13.5)	78 (13.2)	1.02 (0.58-1.72)
Postoperative stroke	44 (26.0)	100 (17.2)	1.69 (1.09-2.58)
Renal replacement therapy	36 (21.3)	59 (10.2)	2.37 (1.45-3.82)

rFVIIa, Recombinant factor VIIa; *OR*, odds ratio; *CI*, confidence interval.

TABLE E2. Intraoperative and postoperative bleeding data in the unmatched populations

Variable	rFVIIa (n = 171)	Control (n = 590)	*P* value	Missing, n
Bleeding in first 24 h, mL, mean (IQR)	1160 (670-2215)	780 (520-1230)	<.001	317
PRBCs, U, mean (IQR)	10.0 (5-22)	5.0 (2.0-10.0)	<.001	22
Platelets, U, mean (IQR)	4.0 (2.0-9.0)	2.0 (1.0-4.0)	<.001	13
FFP, U, mean (IQR)	9.0 (4.0-22.0)	4.4 (2.0-9.0)	<.001	24
rFVIIa, mean (IQR)	5.0 (2.0-10)	0 (0-0)	<.001	0
Fibrinogen concentrate, g, mean (IQR)	2.0 (1.0-6.0)	0.0 (0.0-2.0)	<.001	9
Tranexamic acid, U, mean (IQR)	3260 (0-4000)	4000 (0-4000)	.874	44
Cardiac tamponade, n (%)	43 (25.4)	63 (10.9)	<.001	15
Reoperation for bleeding, n (%)	57 (33.7)	92 (16.0)	<.001	17

rFVIIa, Recombinant factor VIIa; *IQR*, interquartile range; *PRBC*, packed red blood cell; *FFP*, fresh frozen plasma.

TABLE E3. Postoperative complications and early mortality in the unmatched populations

Outcome	rFVIIa (n = 171), n (%)	Control (n = 590), n (%)	*P* value	Missing, n
Postoperative stroke	44 (26.0)	100 (17.2)	.014	12
RRT	36 (21.3)	59 (10.2)	<.001	16
DSWI	4 (2.4)	11 (1.9)	.756	13
Septicemia	25 (14.9)	68 (11.8)	.290	16
Ventilatory support >48 h	83 (49.4)	133 (23.5)	<.001	27
Cardiac arrest	14 (8.3)	22 (3.9)	.025	24
Perioperative MI	10 (5.9)	31 (5.4)	.848	13
Intraoperative mortality	2 (1.2)	33 (5.6)	.012	0
30-d mortality	26 (15.2)	91 (15.4)	1.000	0
In-hospital mortality	23 (13.5)	78 (13.2)	.899	0
Late reoperation of the aorta	9 (9.3)	20 (5.7)	.242	313

rFVIIa, Recombinant factor VIIa; *RRT*, renal replacement therapy; *DSWI*, deep sternal wound infection; *MI*, myocardial infarction.

Study III

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Original Article

The Coagulopathy of Acute Type A Aortic Dissection: A Prospective, Observational Study

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Objective: To evaluate the hemostatic system in patients undergoing surgery for acute type A aortic dissection (ATAAD) compared with those undergoing elective aortic procedures.
Design: This was a prospective, observational study.
Setting: The study was performed at a single university hospital.
Participants: Twenty-five patients with ATAAD were compared with 20 control patients undergoing elective surgery of the ascending aorta or the aortic root.
Interventions: No interventions were performed.
Measurements and Main Results: Platelet count and levels of fibrinogen, D-dimer, prothrombin time/international normalized ratio, activated partial thromboplastin time, and antithrombin were analyzed perioperatively and compared between the 2 groups. Patients with ATAAD had lower preoperative levels of platelets (188 [156-217] $\times$ 10^9/L *v* 221 [196-240] $\times$ 10^9/L; p = 0.018), fibrinogen (1.9 [1.6-2.4] g/L *v* 2.8 [2.2-3.0] g/L; p = 0.003), and antithrombin (0.81 [0.73-0.94] kIU/L *v* 0.96 [0.92-1.00] kIU/L; p = 0.003) and significantly higher levels of D-dimer (2.9 [1.7-9.7] mg/L *v* 0.1 [0.1-0.2] mg/L; p < 0.001) and prothrombin time/international normalized ratio (1.15 [1.1-1.2] *v* 1.0 [0.93-1.0]; p = 0.001). Surgery caused significant changes of the coagulation system in both groups. Intraoperative bleeding volumes were larger in the ATAAD group (2,407 [1,804-3,209] mL v 1,212 [917-1,920] mL; p < 0.001), and patients undergoing ATAAD surgery received significantly more transfusions of red blood cells (2.5 [0.25-4.75] U *v* 0 [0-2.75] U; p = 0.022), platelets (4 [3.25-6] U *v* 2 [2-4] U; p = 0.002), and plasma (2 [0-4] U *v* 0 [0-0] U; p = 0.004) compared with the elective group.
Conclusions: This study demonstrates that ATAAD is associated with a coagulopathic state. Surgery causes additional damage to the hemostatic system in ATAAD patients, but also in patients undergoing elective surgery of the ascending aorta or the aortic root.

Key Words: aorta; aneurysm; dissection; bleeding

ACUTE TYPE A aortic dissection (ATAAD) is a critical condition with considerable early surgical mortality rates, partly owing to bleeding complications. The contact between blood and the false lumen of the dissected aorta causes a

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consumption coagulopathy, augmented by the use of cardiopulmonary bypass, including deep hypothermia.[1–9] Bleeding complications associated with ATAAD surgery have been reported to significantly affect survival[10,11] and account for 20% of in-hospital deaths.[12] Previous studies on surgery for ATAAD have shown an activation of the coagulation system and a consumption coagulopathy, but have relied on advanced analyses, which are not accessible in standard patient care and have limited clinical applicability.[13–15] Furthermore, none of the previous studies has presented results in relation to a relevant control group, enabling the distinction between effects intrinsic to aortic dissection and those caused by the surgical procedure.

The aim of the present study was to evaluate the hemostatic system in patients undergoing ATAAD surgery. Because randomized controlled trials are not feasible in this particular setting the results of ATAAD patients were compared with those of patients undergoing elective surgery of the ascending aorta or the aortic root.

Methods

This study was approved by the Ethics Committee for Clinical Research at Lund University, Lund, Sweden (ref. 2015/197).

Study Design

This was a single-center, prospective, observational study comparing patients with ATAAD with control patients undergoing elective surgery of the ascending aorta or the aortic root in mild-to- moderate hypothermia. Inclusion criteria for the ATAAD group were adult patients undergoing surgery for ATAAD using deep hypothermic circulatory arrest and ATAAD confirmed by computed tomography with symptom duration <48 hours. Patients were excluded if they received anticoagulants or antiplatelet drugs other than aspirin, if imaging showed an intramural hematoma, and if the surgical approach deviated from routine (as described in the following). Inclusion criteria for the elective group were adult patients with aortic aneurysm requiring surgery by replacement of the ascending aorta and/or the aortic root. Patients on anticoagulants or antiplatelet therapy other than aspirin were excluded. All patients with acute aortic syndromes (eg, ATAAD and intramural hematomas) referred to the authors' clinic during the study period were registered and are presented in Fig 1.

End Points

The authors hypothesized that both aortic dissection per se and the surgical treatment for aortic disease cause deleterious effects of the coagulation system and that these effects are more pronounced in patients with ATAAD. Consequently, the primary end points were measured levels of blood (B)-platelet count, plasma (P)-prothrombin time/international normalized ratio (PT/INR), P-activated partial thromboplastin time (APTT), P-fibrinogen, P-D-dimer, and P-antithrombin at predefined time points. Secondary end points were intraoperative bleeding; 24-hour chest-tube output; reexploration for bleeding; transfusions of red blood cells, platelets, or plasma; and in-hospital mortality.

Definitions

Acute aortic dissection was defined as an intimal tear with resulting separation of the aortic layers, with the presence of a true and a false lumen, presenting within 14 days of symptom onset. In-hospital mortality was defined as death before hospital discharge. Intraoperative bleeding was defined as blood loss, collected and quantified between the termination of cardiopulmonary bypass and the end of surgery using intraoperative cell salvage and surgical gauze swabs. Postoperative stroke was defined as loss of neurologic function caused by an ischemic event with or without confirmation using computed tomography. Renal replacement therapy was defined as any need for postoperative continuous venovenous hemofiltration or hemodialysis. Cardiac tamponade was defined as pericardial effusion that required pericardial drainage or reexploration. Transfusions were reported as units of packed red blood cells, platelets, or plasma (fresh frozen from single donor or pooled from multiple donors) per patient, administered perioperatively.

Biomarker Measurements

Blood samples were obtained at the following 6 time points: T0: anesthesia induction; T1: core temperature nadir before rewarming was initiated (only collected in elective patients with core temperature $\leq$32°C [n = 14]); T2: before protamine reversal; T3: end of surgery; T4: 24 hours after surgery; and T5: 5 days after surgery (4 d if an elective patient was transferred to a local hospital). Samples at T0, T4, and T5 were collected using a central venous line. The arterial line of the cardiopulmonary bypass circuit was used at T1 and T2. The T3 sample was collected from a radial artery line.

Blood samples were analyzed at the Department of Clinical Chemistry, Division of Laboratory Medicine, Skåne University Hospital, Lund, Sweden, on a Sysmex CS-5100 automated analyzer (Siemens, Marburg, Germany). PT/INR was measured with the reagent Owren PT (Medirox, Studsvik, Sweden), reference interval: <1.2; and APTT with Actin FSL reagent (Siemens), reference interval: 26 to 33 seconds. For antithrombin, a factor Xa–based chromogenic reagent, Innovance Antithrombin test (Siemens), was used, reference interval: 0.8 to 1.2 kIU/L. Fibrinogen was measured with the Dade Thrombin reagent (Siemens), reference interval: 2 to 4 g/L. D-dimer was measured with Medirox D-dimer reagent (Medirox; cutoff <0.25 mg/L). Platelet count was analyzed on the Sysmex XN instrument (Sysmex Corp, Kobe, Japan), reference intervals: 165 to 387 $\times$ 10^9/L in female patients and 145 to 348 $\times$ 10^9/L for male patients.

Surgical Procedures

General anesthesia was induced and maintained with propofol. If necessary, a volatile anesthetic agent (isoflurane or sevoflurane) was used throughout the procedure, supplemented

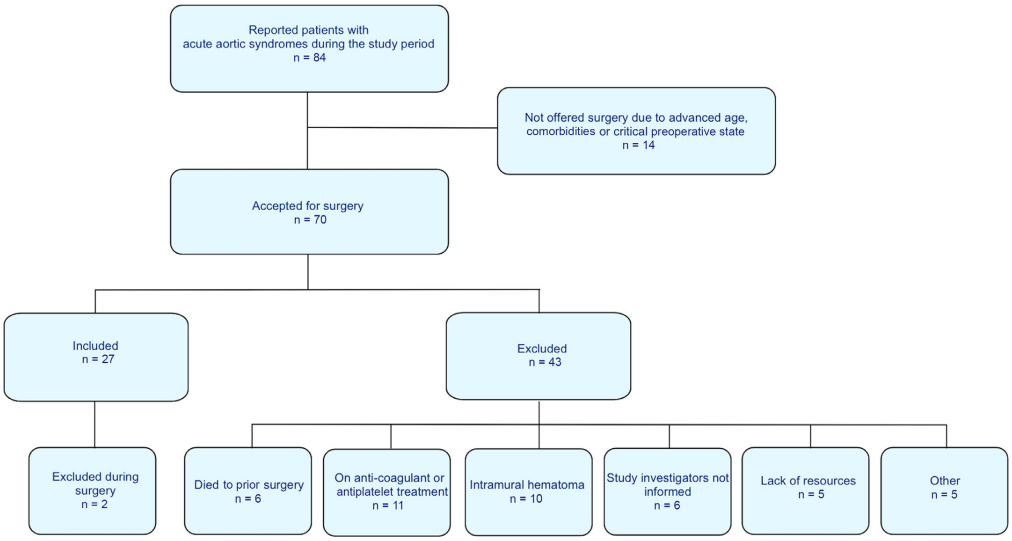

Fig 1. Flow chart of patients with acute aortic syndromes referred to the Department of Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden, during the inclusion period. ATAAD, acute type A aortic dissection.

with fentanyl and a neuromuscular blocking agent as needed. The surgical technique used in the setting of ATAAD at the authors' clinic has been described previously.[12] Patients underwent surgery using standard median sternotomy, cardiopulmonary bypass, and intermittent cold blood cardioplegic arrest. In most cases, the femoral artery was used for arterial cannulation. Bicaval cannulation or a 2-stage cannula was used for venous drainage. Resection of the ascending aorta and inspection of the aortic arch were performed with the patient under deep (<20°C) hypothermic circulatory arrest. In selected patients, antegrade or retrograde selective cerebral perfusion was used. Distal repair was performed with the patient under circulatory arrest. Perfusion was instituted subsequently through a side branch of the vascular prosthesis, enabling distal circulatory flow and rewarming during suturing of the proximal anastomosis. Valvular competence was accomplished via commissural resuspension. In one case, a root replacement procedure (ad modum Bentall) was performed owing to extensive damage to the aortic root, and in another case, an isolated aortic valve replacement was performed. Cooling strategies in the elective group included hemiarch procedure (25°C); aortic valve repair (ad modum David) (30°C); root replacement (ad modum Bentall), root remodeling, or combined aortic valve replacement with or without supracoronary replacement of the ascending aorta (32°C); and isolated replacement of the ascending aorta (32°C-36°C). The-Hepcon HMS (Hemostasis Management System) Plus system (Medtronic, Minneapolis, MN) was used for calculation of the heparin dose necessary to achieve a target activated clotting time (ACT) of >480 seconds. If the heparin dose response slope was <70 s/U/mL, 1,000 U of antithrombin was administered, and 10 minutes later, a new heparin dose response measurement was conducted. Two patients in the elective group and 2 patients in the ATAAD group received 2,000 U of antithrombin before cardiopulmonary bypass was initiated.

Routinely, a rotational thromboelastometry- and blood analysis–guided bleeding management protocol was used at the authors' clinic. Red blood cell transfusions were given at B-hemoglobin <90 g/L. Platelets were administered at maximum clot firmness (MCF) Extem <50 mm and MCF Fibtem >10 mm or platelet count $<100 \times 10^9$. Fibrinogen and/or plasma were used at MCF Fibtem <15 mm or P-fibrinogen <2 g/L. Plasma or prothrombin complex concentrate (PCC) was used at coagulation time Extem >100 seconds, coagulation time Intem >240 seconds, P-PT/INR >1.5, or P-APTT >1.5 × normal value. Patients routinely received a total of 4 g of tranexamic acid, distributed as 2 to 3 g at the start of the procedure and 1 to 2 g after cessation of cardiopulmonary bypass. Additional tranexamic acid was administered when maximum lysis exceeded 15%. However, final decision-making regarding transfusions and pharmacologic bleeding management was up to the discretion of each surgeon.

Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as medians and quartiles and visualized using box plots. Reference values are illustrated as dashed lines or shaded areas and are based on 95% confidence intervals of the Swedish population. Proportions were compared using the chi-square test. The Fisher

exact test was used when the number of cases was <5, and continuous variables were evaluated using the Mann-Whitney test. The Wilcoxon sign ranked test was used for analyzing related samples. A p value < 0.05 was considered to be statistically significant, and analyses were performed using standard software (IBM SPSS Statistics for Mac, Version 25; IBM Corp, Armonk, NJ).

Results

Study Population and Follow-Up

Between September 2015 and October 2017, 27 patients with ATAAD were enrolled in the study. Two patients were later excluded, 1 because the patient was not cooled to a deep hypothermic state and 1 because a second run on cardiopulmonary bypass was necessary owing to damage of the pulmonary artery. The control group consisted of 20 patients undergoing elective surgery of the ascending aorta or the aortic root between December 2016 and April 2018.

Baseline and Intraoperative Data

Baseline and intraoperative data of the study population are presented in Table 1. Patient age was similar between the groups (62 [56-75] y *v* 59 [52-71] y; p = 0.248), whereas patients in the ATAAD group had lower incidence of bicuspid aortic valves (0% *v* 32%; p = 0.004) and underwent less extensive proximal surgery ($p < 0.001$). ATAAD patients demonstrated shorter duration of cardiopulmonary bypass (159 [130-185] min *v* 203 [173-250] min; p = 0.001) and aortic cross-clamping (65 [51-92] min *v* 136 [110-178] min; $p < 0.001$). Patients in the ATAAD group were cooled to a mean core temperature of 19.4°C (18°C-20.8°C) and control patients to 32°C (30°C-32°C) (p = 0.001).

Biomarker Measurements

At anesthesia induction (T0), platelet counts were lower in ATAAD patients (188 [156-217] $\times 10^9$/L *v* 221 [196-240] $\times 10^9$/L; p = 0.018). Platelet counts decreased significantly to 63 (53-118) $\times 10^9$/L and 129 (97-154) $\times 10^9$/L in the ATAAD group and the elective group, respectively, at lowest core temperature ($p < 0.001$ and p = 0.003) (Fig 2, A). At the end of surgery (T3), there was no group difference (p = 0.770), but platelet counts were significantly lower than preoperative levels for both groups (157 [127-168] $\times 10^9$/L and 151 (129-185) $\times 10^9$, in the ATAAD and elective group, respectively; p = 0.001 and $p < 0.001$).

Preoperatively, ATAAD patients presented with significantly lower fibrinogen levels than did the elective group (1.9 [1.6-2.4] g/L *v* 2.8 [2.2-3.0] g/L; p = 0.003) (Fig 2, B). The fibrinogen levels for both groups decreased significantly during cardiopulmonary bypass ($p < 0.001$ and p = 0.002, in the ATAAD and elective groups, respectively). After surgery, there was no significant difference in fibrinogen levels compared with the preoperative value in the ATAAD group (2.1 [1.9-2.3] g/L; p = 0.456), whereas fibrinogen levels in the elective group decreased significantly during surgery (2.2 [1.9-2.2] g/L; $p < 0.001$). Five days after surgery, both groups demonstrated supernormal fibrinogen, but the levels were significantly higher in the elective group (5.0 [4.6-7.0] g/L *v* 7.6 [6.6-8.0] g/L; p = 0.001).

Before surgery, D-dimer was significantly higher in the ATAAD group (2.9 [1.7-9.7] mg/L *v* 0.1 [0.1-0.2] mg/L; $p < 0.001$) and remained significantly higher until 5 days after surgery (T5) when no differences were found (1.0 [0.7-2.8] mg/L *v* (0.9 (0.6-1.2) mg/L; p = 0.517) (Fig 2, C).

At T0, PT/INR was significantly higher in ATAAD patients (1.15 [1.1-1.2] *v* 1.0 [0.93-1.0]; p = 0.001) compared with elective control patients (Fig 2, D). In both groups, PT/INR was elevated markedly during cardiopulmonary bypass and after surgery, PT/INR was similar to that at T0 in the ATAAD group (1.1 [0.8-1.2]; p = 0.136), whereas there was a significant increase in PT/INR in the elective group (1.2 [1.1-1.4]; $p < 0.001$).

Preoperative APTT was similar between the groups (27 [26.3-29.8] s *v* 27 [26-27.8] s; p = 0.139) (Fig 2, E). After surgery, median APTT in the ATAAD group exceeded the reference value and was significantly higher than that of the elective group (34 [32-41] s *v* 27 [25.3-28.8] s; $p < 0.001$). The ACT and heparin concentrations, measured using the Hepcon HMS, at T3 showed that the heparin concentration was 0 (0-0) U/mL in both groups (p = 0.941), whereas ACT was significantly longer in the ATAAD group (120 [114-127] s *v* 108 [102-115] s; p = 0.018). Twenty-four hours after surgery there was no significant difference between the groups and both groups demonstrated a median APTT below the lower reference boundary (25.5 [24.8-28.0] s *v* 25.5 [23.5-28.8] s; p = 1.000).

ATAAD patients had lower levels of antithrombin at anesthesia induction (0.81 [0.73-0.94] kIU/L *v* 0.96 [0.92-1.00] kIU/L; p = 0.003) (Fig 2, F). There was a significant decrease in P-antithrombin in the ATAAD group at T1 and a trend toward lower antithrombin levels in the elective group (0.65 [0.61-0.70] kIU/L *v* 0.89 [0.76-1.05] kIU/L; p = 0.010 and p = 0.099 for T0 *v* T1, respectively). The levels of antithrombin did not recover during surgery, and at T3, the levels of antithrombin were lower for both groups compared with the preoperative levels (p = 0.002 and $p < 0.001$ in the ATAAD group and elective group, respectively).

Bleeding, Transfusions, and Medical Management

Patients in the ATAAD group demonstrated larger intraoperative bleeding volumes (2,407 [1,804-3,209] mL *v* 1,212 [917-1,920] mL; $p < 0.001$), whereas 24-hour chest tube output was similar to that of the elective group (720 [585-963] mL *v* 695 [555-848] mL; p = 0.645) (Table 2). Patients undergoing surgery for ATAAD received significantly more transfusions of packed red blood cells (2.5 [0.25-4.75] U *v* 0 [0-2.75] U; p = 0.022), platelets (4 [3.25-6] U *v* 2 [2-4] U; p = 0.002), and plasma (2 [0-4] U *v* 0 [0-0] U; p = 0.004) and received significantly more recombinant factor VIIa (0 [0-1.5] mg *v* 0 [0-0]

Table 1
Baseline and Surgical Characteristics of the Study Populations

Characteristic	ATAAD (n = 25)	Elective (n = 20)	p
Age	62 (56-75)	59 (52-71)	0.248
Female sex	8 (32)	3 (15)	0.297
Hypertension	14 (56)	11 (55)	0.947
History of aortic aneurysm	7 (25)	20 (100)	< 0.001
Marfan	0 (0)	2 (10)	0.192
Bicuspid aortic valve	0 (0)	6 (32)	0.004
Diabetes mellitus type 2	0 (0)	1 (5)	0.444
Hyperlipidemia	1 (4)	6 (30)	0.034
History of stroke	1 (4)	0 (0)	1.000
Chronic kidney disease	1 (4)	0 (0)	1.000
COPD	0 (0)	1 (5)	0.444
History of smoking	8 (32)	4 (27)	1.000
Aspirin	3 (12)	2 (10)	1.000
Any organ malperfusion	16 (64)	-	-
DeBakey type 1	22 (88)	-	-
Proximal surgical technique			
Supracoronary graft only	22 (88)	3 (15)	<0.001
Supracoronary graft + AVR	1 (4)	1 (5)	
Root replacement	1 (4)	8 (40)	
Valve repair	0 (0)	8 (40)	
Not completed	1 (4)	0 (0)	
Distal surgical technique			
Ascending aorta	22 (88)	16 (80)	0.124
Hemiarch procedure	1 (4)	4 (20)	
Arch procedure	2 (8)	0 (0)	
Surgical time (min)	293 (263-332)	312 (286-381)	0.075
CPB time (min)	159 (130-185)	203 (173-250)	0.001
Cross-clamp time (min)	65 (51-92)	136 (110-178)	<0.001
HCA time (min)	19 (14-25.8)	0 (0-0)	<0.001
Antegrade SCP	5 (20)	4 (20)	1.000
Retrograde SCP	4 (16)	0 (0)	0.117
Antegrade SCP time (min)	30.5 (22.3-44)	0 (0-4.5)	0.001
Retrograde SCP time (min)	18 (13.5-27.8)	0 (0-0)	<0.001
Lowest core temperature (˚C)	19.4 (18-20.8)	32 (30-32)*	<0.001

NOTE. Values are expressed as number and percentage (%) or median and interquartile range.
Abbreviations: AVR, aortic valve replacement; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; SCP, selective cerebral perfusion.
* Median lowest core temperature of the 14 elective patients analyzed at T1 was 31˚C (25˚C-32˚C) (p *v* ATAAD group < 0.001).

mg; p = 0.018), fibrinogen concentrate (5.5 [4-8] g *v* 2.5 [1.25-5.50] g; p = 0.002), and PCC (2,000 [1,000-2,250] IU *v* 750 [0-1,000] IU; p = 0.004). Reexploration for bleeding occurred in only 1 patient, who was from the ATAAD group (4%).

Mortality and Complications

In the ATAAD group, 1 patient died intraoperatively (4%) owing to aortic rupture and another patient died during hospital stay owing to cerebral infarctions. No patients in the control group died during hospital stay.

Discussion

Aortic dissection is caused by an injury to the intimal layer of the aorta, causing blood to access the non-endothelialized false lumen. It has been hypothesized that the contact between blood and subendothelial tissue factor, collagen, and the adventitial layer of the aortic wall causes a consumption coagulopathy resembling disseminated intravascular coagulation.[4] This prospective, observational study using a control group of patients undergoing elective aortic surgery confirmed that aortic dissection causes a significant activation of the coagulation system. Surgery enhances the derangement of the hemostatic system and has adverse effects on coagulation in patients undergoing elective aortic procedures.

To the best of the authors' knowledge, this is the first study comparing the coagulation system of ATAAD patients with a control group consisting of patients undergoing elective aortic surgery. Previous studies describing serial analyses of the coagulation system have demonstrated that ATAAD and associated surgery cause an increase in markers for activation of coagulation (eg, thrombin-antithrombin complex, prothrombin fragment 1+2 [F1+2], D-dimer, plasmin-antiplasmin complex, platelets, and platelet factor 4).[13–15] Furthermore, the reports demonstrated a consumption of platelets, fibrinogen, plasminogen, and antithrombin. The study conducted by Paparella

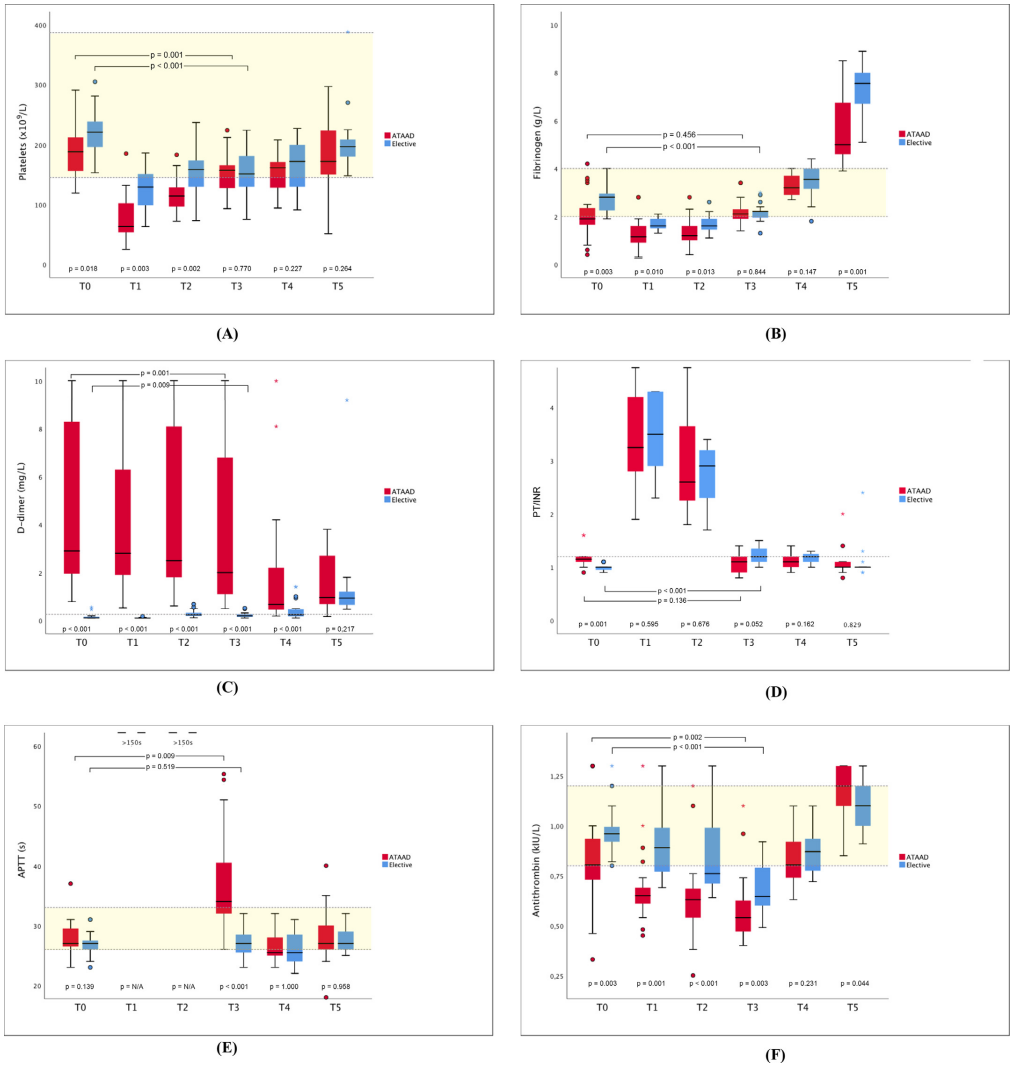

Fig 2. Box plots illustrating levels of platelets (A), fibrinogen (B), D-dimer (C), prothrombin time/international normalized ratio (D), activated partial thromboplastin time (E), and antithrombin (F). APTT, activated partial thromboplastin time; ATAAD, acute type A aortic dissection; PT/INR, prothrombin time/international normalized ratio; T0, anesthesia induction; T1, core temperature nadir; T2, before protamine reversal; T3, end of surgery; T4, 24 hours after surgery; T5, 5 days after surgery, stratified by group.

et al. was based on analyses for research purposes that are not accessible in standard patient care.[15] Guan et al. described a population of 87 patients undergoing aortic arch surgery after ATAAD; however, in similarity to the report by Paparella et al., the study did not include a control group. Nomura et al. compared the results of ATAAD patients with a control group[16]; however, the control group consisted of healthy control patients rather than patients undergoing equally or more complex surgery.

It has been shown that ATAAD causes a consumption of platelets owing to collagen exposure, and the degree of platelet consumption has been shown to affect survival after ATAAD surgery.[4,14,17] Furthermore, it has been shown that cardiopulmonary bypass leads to platelet consumption and activation of

Table 2
Early Mortality and Postoperative Data of the Study Populations

Characteristic	ATAAD (n = 25)	Elective (n = 20)	p
Intraoperative mortality	1 (4)	0 (0)	1.000
In-hospital mortality	2 (8)	0 (0)	0.495
Intraoperative bleeding (mL)	2,407 (1,804-3,209)	1,212 (917-1,920)	<0.001
Chest tube output (mL)			
12 h	480 (280-628)	480 (340-613)	0.786
24 h	720 (585-963)	695 (555-848)	0.645
PRBC (U)	2.5 (0.25-4.75)	0 (0-2.75)	0.022
Platelets (U)	4 (3.25-6)	2 (2-4)	0.002
Plasma (U)	2 (0-4)	0 (0-0)	0.004
rFVIIa (mg)	0 (0-1.5)	0 (0-0)	0.018
Fibrinogen concentrate (g)	5.5 (4-8)	2.5 (1.25-5.50)	0.002
Tranexamic acid (g)	4 (3-4)	4 (4-4)	0.040
PCC (IU)	2,000 (1,000-2,250)	750 (0-1,000)	0.004
Desmopressin (μg)	0 (0-30)	11.3 (0-30)	0.441
Antithrombin (IU)	0 (0-0)	0 (0-0)	0.371
Redo surgery for bleeding	1 (4)	0 (0)	1.000
Cardiac tamponade	1 (4)	0 (0)	1.000
Postoperative stroke	5 (21)	1 (5.9)	0.198
RRT	3 (13)	0 (0)	0.239
Ventilatory support >48 h	8 (32)	0 (0)	0.005
Length of ICU stay	4.5 (3-7.75)	1 (1-2)	<0.001

NOTE. Values are expressed as number and percentage (%) or median and interquartile range.
Abbreviations: ICU, intensive care unit; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; rFVIIa, recombinant factor VIIa; RRT, renal replacement therapy.

platelets, resulting in disturbed reactivity.[5,6] Finally, hypothermia, which is induced routinely during surgery for ATAAD, results in increased platelet activation and aggregation and a reversible thrombocytopenia caused by hepatic and splenic sequestration.[18] The present study confirmed these findings by demonstrating a trend toward lower preoperative platelet counts in ATAAD patients. During the hypothermic state, there was a significant consumption of platelets and a significant difference between ATAAD patients and elective control patients, indicating that platelet counts correspond to the degree of hypothermia.

The preoperative fibrinogen levels were significantly lower, and levels of D-dimer were significantly higher in ATAAD patients compared with those of elective control patients. The results of the present study indicate that these analyses were not affected by hypothermia. However, the elective group had significantly lower fibrinogen levels after surgery compared with their preoperative levels, indicating a substantial consumption of fibrinogen during elective surgery. Low fibrinogen concentration at admission has been shown to be an independent predictor of in-hospital mortality in patients undergoing ATAAD surgery.[19] In addition to its hemostatic function, fibrinogen is an acute phase reactant, and this study demonstrated that surgery causes fibrinogen concentrations to exceed normal levels 5 days after surgery. Interestingly, fibrinogen levels were similar between the groups on the first postoperative day, whereas the concentration was significantly higher in the elective group on the fifth postoperative day. This indicates an ongoing consumption of fibrinogen even after surgery in patients with ATAAD, presumably caused by persisting coagulation activity in the false lumen. Furthermore, aortic dissection is associated with a fibrinolytic state causing elevated D-dimer.[20] Consequently, D-dimer has been used at emergency departments as a test for ruling out aortic dissection, but the analysis does not discriminate between acute aortic events and pulmonary embolism (PE). Previous studies have shown that fibrinogen levels in patients with PE are normal or elevated.[21,22] In the present study, 12 of 23 patients with preoperative fibrinogen values had a fibrinogen level <2 g/L compared with 1 patient in the control group (1.9 g/L). Therefore, the combination of D-dimer and P-fibrinogen might provide a method of discriminating between aortic dissection and PE in an acute setting.

Cate et al. demonstrated that aortic dissection causes a decrease in factor II, V, VII, X, and XII levels with a significant elevation in fibrin/fibrinogen degradation products.[4] Therefore, it was not surprising that patients with ATAAD presented with significantly higher PT/INR in the present study. The postoperative PT/INR values of the ATAAD patients were not significantly different from the preoperative values, whereas surgery contributed to significantly higher PT/INR in the elective group. Cardiopulmonary bypass causes hemodilution; a decrease in platelet count; a decrease in factor V, VII, VIII, and XI levels; a decrease in fibrinogen; an increase of fibrin/fibrinogen degradation products; an increase in plasmin-antiplasmin-complex; and an increase in factor XIIa.[5–7] In addition, hypothermia impairs the function of von Willebrand factor.[8] Hypothermia also causes a prolongation of

prothrombin time independent of coagulation factor levels.[9] The present study demonstrated that the changes were not fully reversed in the elective group after cessation of cardiopulmonary bypass. Interestingly, the postoperative median APTT was above the upper reference limit in ATAAD patients, and along with ACT, significantly higher than that of the elective group. This indicates that the use of cardiopulmonary bypass or hypothermia has a non-heparin–dependent deleterious effect on the intrinsic system, which was more distinct in ATAAD patients than in elective control patients.

The present study found that patients undergoing ATAAD surgery had significantly larger intraoperative bleeding volumes; however, the postoperative chest tube outputs did not differ between the groups. This could be attributed to ATAAD patients receiving significantly more recombinant factor VIIa, PCC, and transfusions of platelets and plasma. There also was a trend toward more fibrinogen being administered to the ATAAD group. Only 1 patient in the ATAAD group underwent redo surgery for bleeding, which is considerably lower than the previously reported frequencies of reexploration, which range between 14% and 22%.[1,11,23] The low frequency suggests that the serial analyses provided continuous information about the hemostatic system, facilitating improved management of transfusions and medical correction of coagulopathy. However, it cannot be ignored that the present study excluded patients with ongoing anticoagulant and dual antiplatelet treatment, thus eliminating a patient group with considerably higher risk of bleeding complications.[24]

The 2 groups compared in this study were not identical with regard to baseline and surgical parameters, and hemostatic management was not strictly standardized. Most importantly, patients in the control group did not have aortic dissection and for patients to be completely matched with regard to surgical elements, it would require elective surgery at lower core temperatures than suggested in current guidelines. Furthermore, ATAAD patients were cooled to a lower body temperature, whereas elective patients underwent surgery with longer duration of cardiopulmonary bypass, both of which have significant effects on the coagulation system, and this might have skewed potential differences between the groups. Although there were differences between the groups, patients undergoing elective surgery of the ascending aorta or the aortic root represent the closest control group one can achieve in order to perform any type of comparison with ATAAD patients, and thus, the authors consider this to be the major strength of the present study. Still, one must bear in mind that the results of this report might be influenced by disparity in patient demographics and the presence of unreported confounders. Additional limitations include its small sample size and, consequently, the risk of type II errors. On the other hand, there is a greater chance that the statistically significant findings of this study represent true differences between the groups. Furthermore, the study relies on real life data. Consecutivity was desired, but owing to the urgent nature of the disease, surgeries occurred at all hours, and analyses for research purposes could not always be performed.

Conclusions

This prospective, control-matched, observational study demonstrated that aortic dissection causes a significant activation of the coagulation system and that surgery causes further derangement of the hemostatic system in patients undergoing acute and elective aortic surgery.

Conflicts of Interest

The authors declare no conflicts of interest.

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Full Length Article

The role of von Willebrand factor in acute type A aortic dissection and aortic surgery

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ABSTRACT

Introduction: Massive bleeding is a serious complication associated with impaired survival after surgery for acute type A aortic dissection (ATAAD). There are no previous reports evaluating the effect of ATAAD and associated surgery on von Willebrand factor (VWF). The aim of the present study was to analyze VWF activity (VWF:GPIbM) and thus the potential of Factor (F) VIII/VWF concentrate as a treatment for refractory bleeding in surgery for acute type A aortic dissection.

Material and methods: We prospectively compared serial measurements of VWF:GPIbM in 25 patients with ATAAD to 20 control patients undergoing elective surgery of the ascending aorta or the aortic root. In 10 of the ATAAD patients, high molecular weight multimer distribution was measured.

Results: Preoperatively, ATAAD patients demonstrated significantly higher VWF:GPIbM (1.58 (1.40–2.05) kIU/L vs 1.25 (1.02–1.42) kIU/L, $p = 0.003$). In the ATAAD group, VWF:GPIbM significantly decreased to 1.24 (0.98–1.44) kIU/L at lowest core temperature (T0 vs T1 $p < 0.001$), but remained unchanged in the elective group (1.25 (1.04–1.43) kIU/L, T0 vs T1 $p < 0.625$). Neither aortic dissection nor hypothermia caused any changes to the proportion of high molecular weight multimers when compared to control patients. Both groups demonstrated supernormal VWF:GPIbM on the first and fifth day after surgery.

Conclusions: This report showed that patients with acute aortic dissection had increased levels of VWF:GPIbM before surgery that decreased slightly during surgery. Our study could not provide evidence that would encourage administration of FVIII/VWF concentrate for major bleeding in patients undergoing surgery for ATAAD as well as elective aortic procedures.

1. Introduction

Acute type A dissection (ATAAD) is caused by a breach of the innermost layer of the aortic wall, the intima. Consequently, blood flow causes a separation of the aortic layers, exposing the blood to the non-endothelialized false lumen. In turn, the primary hemostasis and the coagulation system are activated, resulting in consumption of platelets and coagulation factors [1–5]. This causes a deterioration of the hemostatic system and consequential excessive bleeding in ATAAD surgery, which is associated with decreased survival [6,7]. Still, the pathophysiology of ATAAD related disorders of the coagulation has not been fully investigated.

The von Willebrand factor (VWF) is a multimeric glycoprotein produced in endothelial cells and megakaryocytes. Its key functions include the bridging of collagen to platelets by promoting adhesion to the site of injury and activation and aggregation of platelets as well as its role as a carrier molecule of factor VIII (FVIII) [8,9]. In cardiac surgery, mechanical circulatory support, aortic valve stenosis and congenital heart disease have been shown to cause acquired von Willebrand disease (VWD) type 2a, characterized by a loss of high-

Abbreviations: ATAAD, acute type A aortic dissection; ACT, activated clotting time; AUC, area under the curve; AVR, aortic valve replacement; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CT, computed tomography; F, factor; HDR, heparin dose response; HMWM, high molecular weight multimers; HCA, hypothermic circulatory arrest; ICU, intensive care unit; IQR, interquartile range; LMWM, low molecular weight multimers; MI, myocardial infarction; RRT, renal replacement therapy; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:GPIbM, GPIb binding activity of VWF

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molecular-weight multimers (HMWM) [10–14], whereas the use of cardio-pulmonary bypass (CPB) has been shown to increase the levels of VWF antigen as well as the number of HMWM [15].

Studies of disturbances of the hemostatic system associated with ATAAD may provide leads in how to treat surgical bleeding, and to our knowledge, VWF activity has not been studied in the coagulopathic setting of aortic dissection.

Therefore, the aim of this prospective, observational study was to assess the activity of VWF in patients undergoing surgery for ATAAD compared to patients undergoing elective surgery for diseases of the ascending aorta or the aortic root.

2. Material and methods

This study was approved by the Ethics Committee for Clinical Research at Lund University, Sweden (ref. 2015/197).

2.1. Study design

This was a single-center, prospective, observational study comparing patients with ATAAD to controls undergoing elective surgery of the ascending aorta or the aortic root. The design, objectives and methods of this study have been described previously as this was one of several sub-studies designed to evaluate different aspects of the coagulation system in ATAAD patients [5]. Inclusion criteria for the ATAAD group were ATAAD confirmed by computed tomography with symptom duration < 48 h in adult patients (18 years or older) who then underwent surgery for ATAAD using deep hypothermic circulatory arrest. Patients were excluded if they took anti-coagulants or anti-platelet drugs other than aspirin, if imaging showed an intramural hematoma and if the routine surgical approach (described below) was deviated from. Inclusion criteria for the elective group were adult patients (18 years or older) with an aortic aneurysm or severe aortic regurgitation requiring surgery, including replacement of the ascending aorta or the aortic root. Patients on anti-coagulants or anti-platelet therapy other than aspirin were excluded from the study. All patients with acute aortic syndromes (i.e. type A aortic dissections and intramural hematomas) referred to our clinic during the inclusion period were registered and are presented in Fig. 1.

2.2. Endpoints

The primary endpoints of the present study were measured GPIb-binding activity of VWF (VWF:GPIbM) at predefined timepoints, intraoperative bleeding and 24 h chest-tube output. Secondary endpoints were re-exploration for bleeding and transfusion of red blood cells, platelets and plasma in relation to VWF:GPIbM.

2.3. Biomarker measurements

Blood samples were collected at T0- anesthesia induction, T1- lowest core temperature (only collected in elective patients with core temperature $\leq 32\,^{\circ}C$, $n = 14$), T2- before protamine reversal, T3 - immediately after surgery, T4 - 24 h after surgery and T5- five days after surgery (four days if elective patient was transferred to local hospital). Samples at T0, T3, T4 and T5 were collected using a central venous line, whereas the arterial line of the cardiopulmonary bypass circuit was used at T1 and T2.

Plasma analyses were performed at the Dept. of Clinical Chemistry, Division of Laboratory Medicine, Skåne University Hospital, Sweden. The activity of von Willebrand factor was analyzed with an immunoassay based on the spontaneous binding of VWF to a gain-of-function mutant glycoprotein Ib (GPIb) fragment (VWF:GPIbM) (Innovance VWF:Ac; Siemens, Marburg, Germany) on a BCS instrument (Siemens). This method is used as a screening method for von Willebrand disease (VWD) in the bleeding panel. Reference interval established locally was 0.5–2.0 kIU/L. VWF multimeric sizing (VWF:MS) was performed with SDS agarose gel and Western-blotting technique. Optical density values representing the concentrations of VWF antigen and multimers of different molecular weights were analyzed using the open-source software ImageJ (v.1.52 k, National Institute of Health, Bethesda, MD, USA). Area under the curve (AUC) representing the protein-loading was quantified for the five top bands and five bottom bands of the Western Blot and results were presented as ratio between the protein-loading of study samples compared to the protein-loading of a pooled plasma control sample analyzed on the

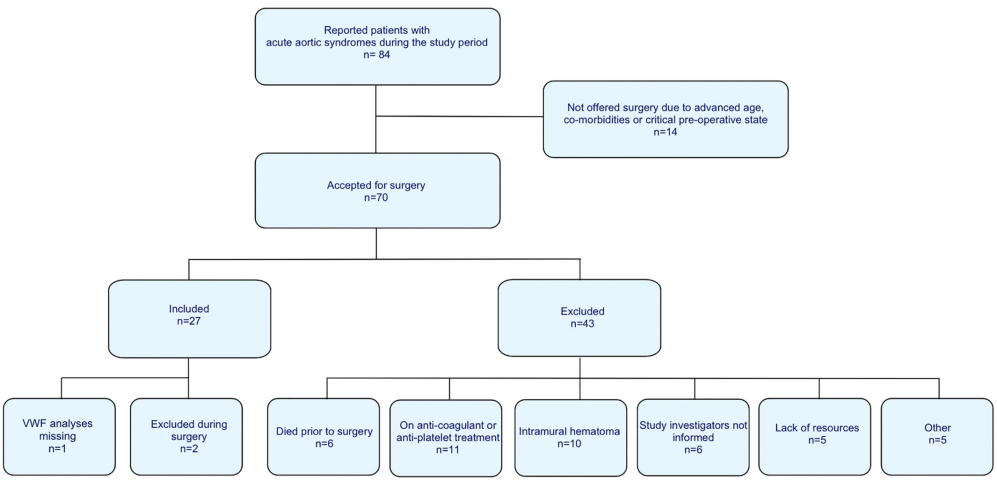

Fig. 1. Flow chart of patients with acute aortic syndromes referred to the Department of Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden during the inclusion period.

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2.4. Definitions

Acute aortic dissection was defined as an intimal tear with the presence of a true and a false lumen, presenting within 14 days of symptom onset. In-hospital mortality was defined as death prior to hospital discharge. Intraoperative bleeding was defined as blood-loss collected and quantified between the cessation of cardiopulmonary bypass and end of operation using intraoperative cell salvage and surgical gauze swabs. Postoperative stroke was defined as an ischemic neurologic deficit with or without confirmation using computed tomography (CT). Renal Replacement Therapy (RRT) was defined as need for postoperative continuous venovenous hemofiltration or hemodialysis and cardiac tamponade as pericardial effusion that required pericardial drainage or re-exploration. Transfusions were reported as units (U) of packed red blood cells (PRBC), platelets or plasma per patient, administered perioperatively.

2.5. Surgical procedures

The surgical technique of ATAAD used at our clinic has been described previously [5,16]. Resection of the dissected ascending aorta and inspection of the aortic arch was performed under deep (< 20 °C) hypothermic circulatory arrest, whereas elective aortic procedures were performed at temperatures between 25 °C and 36 °C. Hepcon HMS Plus system (Medtronic, Minneapolis, MN, USA) was used for estimation of heparin dose necessary to achieve a target activated clotting time (ACT) of > 480 s. If the heparin dose response (HDR) slope was < 70 s/U/ml, 1000 U of antithrombin was administered, and 10 min later a new HDR measurement was conducted. Two patients in the elective group and two patients in the ATAAD group received 2000 U of antithrombin before cardiopulmonary bypass was initiated. Patients routinely received 4 g of tranexamic acid, typically 2 g before surgery and 2 g after termination of cardiopulmonary bypass.

2.6. Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as medians and quartiles and visualized using box-plots. Reference values are illustrated as dashed lines or shaded areas and are based on 95% confidence intervals of the Swedish population. Proportions were compared using the chi-square test, and continuous variables were evaluated using the Mann-Whitney *U* test. Fisher's exact test was used when the number of cases was < 5. A *p*-value < 0.05 was considered statistically significant and analyses were performed using standard software (IBM Corp. Released 2017. IBM SPSS Statistics for Mac, Version 25. Armonk, NY: IBM Corp).

3. Results

3.1. Study population and follow-up

Between September 2015 and October 2017, 24 ATAAD patients were included in the present study. Twenty control patients undergoing elective aortic surgery were enrolled between December 2016 and April 2018 (Fig. 1). Data was 100% complete up to patient discharge.

3.2. Baseline and intraoperative data

There were no significant differences between groups in preoperative characteristics, with the exception of ATAAD patients, who less often presented with a history of aortic aneurysm (29% vs 100%, $p < 0.001$), bicuspid aortic valve (0% vs 32%, $p = 0.004$) and hyperlipidemia (4% vs 30%, $p = 0.035$) (Table 1).

ATAAD patients underwent less extensive proximal and distal aortic surgery ($p < 0.001$ and $p = 0.039$, respectively) with significantly shorter duration of cardiopulmonary bypass (161 (133–187) min vs 203 (173–250) min, $p = 0.002$), cross-clamping (65 (50–95) min vs 136 (110–178) min, $p < 0.001$) and hypothermic circulatory arrest (19 [15–26] min vs 0 (0–0) min, $p < 0.001$). Patients with ATAAD had significantly lower body temperature nadir when compared to elective patients analyzed at T1 (19 [18–21] °C vs 31 (25–32) °C, $p < 0.001$).

Table 1
Baseline and surgical characteristics of the study populations.

Characteristic	ATAAD ($n = 24$)	Elective ($n = 20$)	*p*
Age	63 (58–75)	59 (52–71)	0.179
Female gender	8 (33)	3 (15)	0.162
Hypertension	14 (58)	11 (55)	0.824
History of aortic aneurysm	7 (29)	20 (100)	< 0.001
Marfan	0 (0)	2 (10)	0.201
Bicuspid aortic valve	0 (0)	6 (32)	0.004
Diabetes mellitus type II	0 (0)	1 (5)	0.455
Hyperlipidemia	1 (4)	6 (30)	0.035
History of stroke	1 (4)	0 (0)	1.000
Chronic kidney disease	1 (4)	0 (0)	1.000
COPD	0 (0)	1 (5)	0.455
History of smoking	8 (33)	4 (27)	0.734
Aspirin	3 (13)	2 (10)	1.000
Any organ malperfusion	15 (63)	0 (0)	< 0.001
DeBakey type 1	21 (88)	NA	NA
Proximal surgical technique			
- Supracoronary graft only	21 (88)	3 (15)	< 0.001
- Supracoronary graft + AVR	1 (4)	1 (5)	
- Root replacement	1 (4)	8 (40)	
- Valve repair	0 (0)	8 (40)	
- Not completed	1 (4)	0 (0)	
Distal surgical technique			
- Ascending aorta	21 (88)	16 (80)	0.039
- Hemiarch procedure	1 (4)	4 (20)	
- Arch procedure	2 (8)	0 (0)	
Operating time (min)	291 (260–327)	312 (286–381)	0.100
CPB time (min)	161 (133–187)	203 (173–250)	0.002
Cross-clamp time (min)	65 (50–95)	136 (110–178)	< 0.001
HCA time (min)	19 (15–26)	0 (0–0)	< 0.001
Lowest core temperature (°C)[a]	19 (18–21)	32 (30 – 32)	< 0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). COPD: chronic obstructive pulmonary disease; AVR: aortic valve replacement; CPB: cardio-pulmonary bypass; HCA: hypothermic circulatory arrest.

[a] Median lowest core temperature of the 14 elective patients analyzed at T1 was 31 (25–32) °C (*p* vs ATAAD group < 0.001).

3.3. Von Willebrand factor activity (VWF:GPIbM)

The VWF:GPIbM at the predefined timepoints is plotted in Fig. 2. ATAAD patients demonstrated a significantly higher preoperative VWF:GPIbM compared to the control group (1.58 (1.40–2.05) kIU/L vs 1.25 (1.02–1.42) kIU/L, $p = 0.003$). The VWF:GPIbM significantly decreased in the ATAAD group (1.24 (0.98–1.44) kIU/L, T0 vs T1 $p < 0.001$) at lowest core temperature but remained unchanged in the elective group (1.25 (1.04–1.43) kIU/L, T0 vs T1 $p < 0.625$). When compared to preoperative levels, the postoperative VWF:GPIbM was unchanged in the ATAAD group (1.55 (1.22–1.72) kIU/L, T0 vs T3 $p = 0.438$), whereas there was a significant increase in VWF:GPIbM in the control group (1.83 (1.43–2.13) kIU/L, T0 vs T3 $p = 0.001$). Although supernormal, VWF:GPIbM in ATAAD patients was significantly lower at T4 (2.32 (1.71–2.74) kIU/L vs 3.11 (2.57–3.56) kIU/L, $p < 0.001$) and on the fifth postoperative day there was no between-group difference in VWF:GPIbM (3.72 (2.76–4.51) kIU/L vs 3.66 (3.01–4.45) kIU/L, $p = 0.729$). The VWF:MS was performed in four randomly selected ATAAD patients at all intraoperative timepoints and did not show any change in multimer distribution throughout the operation (Supplementary Fig. 1A and B). Therefore, we limited the

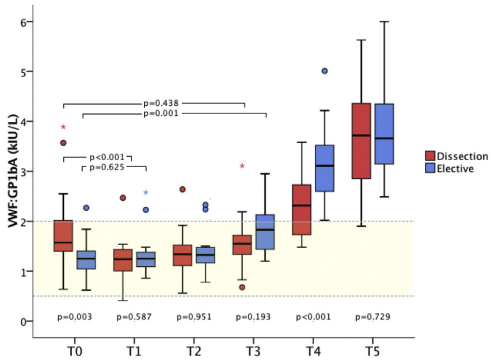

Fig. 2. Box-plot illustrating VWF:GPIbM at T0 - anesthesia induction; T1 - core temperature nadir; T2 - prior to protamine reversal; T3 - end of operation; T4 - 24 h after surgery; T5 - five days after surgery, stratified by group. VWF:GPIbM: GPIb binding activity of von Willebrand factor.

analysis to a total of 10 patients (the five patients with the largest drop in VWF:GPIbM from T0 to T1 and an additional five patients randomly selected) to T0 and T1 (Fig. 3). Semi-quantification of VWF antigen showed that the ratio of protein-loading of study samples compared to pooled normal plasma was similar between high molecular weight multimers (HMWM) and low molecular weight multimers (LMWM) at T0 (1.49 (1.23–2.70) vs 1.53 (0.76–2.03), $p = 0.721$) and T1 (1.67 (1.24–3.06) vs 1.55 (0.76–2.10), $p = 0.953$) (Supplementary Table 1). Thus, we found no indication of an acquired VWD type 2 multimer pattern.

3.4. Bleeding, transfusions and medical management

Patients with ATAAD demonstrated significantly larger intraoperative bleeding volumes (2415 (1780–3219) mL vs 1212 (917–1920), $p < 0.001$) but there was no significant between-group difference in 24-hour chest tube output (700 (580–940) mL vs 695 (555–848) mL, $p = 0.779$) (Table 2). ATAAD patients received

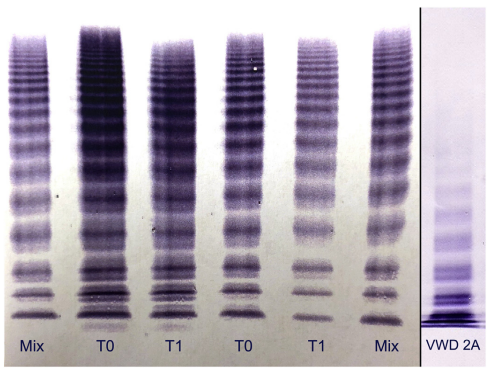

Fig. 3. Multimeric composition in two ATAAD patients showing typically normal proportion of high molecular weight multimers at T0 and T1. Pooled control samples from the normal population constitute mixed-samples and typical multimeric composition in von Willebrand disease 2A (VWD 2A), showing the lack of several top bands presented as additional reference.

Table 2
Early mortality and postoperative data of the study populations.

Characteristic	ATAAD ($n = 24$)	Elective ($n = 20$)	p
Intraoperative mortality	1 (4)	0 (0)	1.000
In-hospital mortality	2 (8)	0 (0)	0.493
Intraoperative bleeding (mL)	2415 (1780–3219)	1212 (917–1920)	< 0.001
Chest tube output (mL)			
- 12 h	450 (280–620)	480 (340–613)	0.635
- 24 h	700 (580–940)	695 (555–848)	0.779
PRBC (U)	2 (0–5)	0 (0–2.75)	0.028
Platelets (U)	4 (4–6)	2 (2–4)	0.006
Plasma (U)	2 (2–4)	0 (0–0)	0.001
rFVIIa (mg)	0 (0–0)	0 (0–0)	0.029
Fibrinogen concentrate (g)	5 (4–8)	2.5 (1.25–5.5)	0.003
Tranexamic acid (g)	4 (3–4)	4 (4–4)	0.034
PCC (IU)	2000 (1000–2375)	750 (0–1000)	0.004
Desmopressin (μg)	0 (0 − 30)	11 (0–30)	0.509
Antithrombin (IU)	0 (0–0)	0 (0–0)	1.000
Reoperation for bleeding	0 (0)	0 (0)	NA
Cardiac tamponade	0 (0)	0 (0)	NA
Postoperative stroke	5 (22)	1 (5)	0.192
RRT	3 (13)	0 (0)	0.236
Ventilatory support > 48 h	8 (35)	0 (0)	0.004
Length of ICU stay	5 (3–7.5)	1 (1–1.5)	< 0.001

Values were expressed as number and percentage (%) or median and interquartile range (IQR). PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; PCC: prothrombin complex concentrate; RRT: renal replacement therapy; MI: myocardial infarction; ICU: intensive care unit.

significantly more transfusions of PRBC (2 (0–5) U vs 0 (0–2.75) U, $p = 0.028$), platelets (4 [4–6] U vs 2 [2–4] U, $p = 0.006$) and plasma (2 [2–4] U vs 0 (0–0) U, $p = 0.001$) and were treated with significantly more recombinant factor VIIa (0 (0–0) mg vs 0 (0–0) mg, $p = 0.029$), fibrinogen concentrate (5 [4–8] g vs 2.5 (1.25–5.50) g, $p = 0.003$), tranexamic acid (4 [3,4] g vs 4 [4] g, $p = 0.034$) and prothrombin complex concentrate (2000 (1000–2375) IU vs 750 (0 − 1000) IU, $p = 0.004$).

Table 3 illustrates ATAAD patients and control patients divided into two groups, depending on preoperative GPIb activity levels. The 12 ATAAD patients that presented with the lowest preoperative VWF:GPIbM demonstrated a trend towards higher volumes of intraoperative bleeding (2742 (2084–4183) mL vs 1900 (1741–3000) mL, $p = 0.079$) and chest tube output, primarily driven by blood loss during the first 12 h after surgery (540 (398–720) mL vs. 280 mL, $p = 0.051$). The trends seen in ATAAD patients were not detected in the elective group.

3.5. Mortality and complications

Two patients in the ATAAD group (8%) died during hospital stay, one due to intraoperative aortic rupture and one due to cerebral watershed infarctions on the seventh postoperative day (Table 2). ATAAD patients more often required prolonged ventilatory support (35% vs 0%, $p < 0.001$) and had a longer stay in the intensive care unit (5 (3–7.5) days vs 1 (1–1.5) days, $p = 0.004$). None of the patients required reoperation for bleeding.

4. Discussion

This prospective, observational, matched control study, to our knowledge the first of its kind, demonstrated that aortic dissection causes an initial increase in VWF:GPIbM whereas deep hypothermia causes a significant decrease in VWF:GPIbM. Both acute surgery for ATAAD and elective aortic surgery cause supernormal postoperative VWF:GPIbM.

The von Willebrand factor plays a key role in the coagulation system, facilitating the bridging of platelets to collagen and serving as a

Table 3
Early mortality and postoperative data of the study populations, stratified per preoperative VWF:GPIbM and group.

Characteristic	ATAAD lowest VWF:GPIbM (n = 12)[a]	ATAAD highest VWF:GPIbM (n = 11)[b]	p	Elective lowest VWF:GPIbM (n = 10)[c]	Elective highest VWF:GPIbM n = 10	p
Preoperative VWF:GPIbM (kIU/L)	1.40 (1.02–1.50)	2.02 (1.68–2.49)	< 0.001	1.05 (0.88–1.21)	1.41 (1.32–1.62)	< 0.001
Intraoperative bleeding (mL)	2742 (2084–4183)	1900 (1741–3000)	0.079	984 (826–2027)	1293 (947–1791)	0.353
Chest tube output (mL)						
- 12 h	540 (398–720)	280 (250–510)	0.051	480 (318–570)	510 (375–723)	0.579
- 24 h	905 (625–1030)	620 (440–770)	0.059	725 (530–780)	685 (605–995)	0.631
PRBC (U)	2.5 (1.25–4.75)	2 (0–5.0)	0.608	0 (0–1.5)	2 (0–3.25)	0.218
Platelets (U)	4 (3.25–6)	4 (4–6)	1.000	2 (1.5–4)	4 (1.5–4)	0.393
Plasma (U)	2.5 (0–3.75)	1 (0–4)	0.695	0 (0–0.75)	0 (0–0.5)	0.912
rFVIIa (mg)	0 (0–0)	0 (0–4)	0.235	0 (0–0)	0 (0–0)	1.000
Fibrinogen concentrate (g)	4.5 (4–9.5)	6 (4–8)	0.880	2.5 (0–6.3)	2.5 (1.8–4.5)	1.000
Tranexamic acid (g)	4 (3–4)	4 (2–4)	0.786	4 (4–4)	4 (4–4)	0.481
PCC (IU)	1750 (1125–2375)	2000 (1000 – 3000)	0.799	500 (0 – 2000)	750 (0–1000)	0.853
Desmopressin (μg)	0 (0–28)	23 (0–30)	0.551	11 (0–30)	15 (0–30)	0.739
Antithrombin (IU)	0 (0–0)	0 (0–0)	1.000	0 (0–0)	0 (0–0)	1.000
Reoperation for bleeding	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000

Values were expressed as number and percentage (%) or median and interquartile range (IQR). VWF:GPIbM: GPIb binding activity of von Willebrand factor; PRBC: packed red blood cells; rFVIIa: recombinant factor VIIa; PCC: prothrombin complex concentrate.
[a] VWF:GPIbM ≤1.55 kIU/L.
[b] Patient that died intraoperatively is not reported in this table.
[c] VWF:GPIbM ≤1.25 kIU/L.

carrier protein of FVIII [8,9]. It has previously been demonstrated that shear stress caused by aortic stenosis and mechanical circulatory support is associated with acquired von Willebrand disease type 2A, with loss of high molecular weight multimers (HMWM) and thus decreased VWF activity [10–13]. The present study could not show an association between acute type A aortic dissection and the loss of HMWM. In fact, the contact between blood and subendothelial tissue caused a significant increase in VWF:GPIbM compared to elective control patients, most likely due to platelet activation, and thus release of VWF from α-granules and from Weibel-Palade bodies of endothelial cells. This supports the findings of previous reports showing aortic dissection to cause an activation of the coagulation system [2–5]. The presence of the HMWMs is important for GPIb and collagen binding activity, whereas all multimers take part in FVIII binding. This study was unable to demonstrate any change in vonn Willebrand multimer patterns. Therefore, platelet adhesion and aggregation by this mechanism does not seem to be impaired in ATAAD and aortic surgical patients [17].

Previous reports have shown hypothermia to have an adverse effect on the coagulation system [18]. It has also been shown that exposure to low temperatures causes VWF to lose the ability to form long cell-surface strings. Instead, VWF forms globular deposits with poorer hemostatic properties. In addition, Hewlett et al. showed that a decrease in temperature significantly slows down the release of VWF from endothelial cell Weibel-Palade bodies [19]. This study demonstrated that deep hypothermia, employed in surgery for ATAAD, caused a significant decrease in VWF:GPIbM. No change was seen in elective patients undergoing surgery in a moderate hypothermic state, implying that only dramatic changes in temperature have an impact on VWF:GPIbM.

In the present study, VWF:GPIbM reached supernormal levels in both ATAAD patients and elective controls one and five days after surgery. Nossent et al. have previously demonstrated the association between increased VWF secretion and venous thromboembolism [20] and Sonneveld et. al have shown a relationship between elevated VWF levels and the occurrence of arterial thrombosis [21]. Furthermore, it has been shown that ATAAD and related surgery causes decreased levels of antithrombin, and it has been speculated that this renders the patients in a pro-coagulative state [22]. It cannot be overlooked that the supernormal levels of VWF demonstrated in this study would enhance the pro-coagulant effect of low antithrombin levels in an early postoperative state. In theory, this could cause postoperative organ failure by means of thromboses in the micro- and macro vascular beds [22], but the sample size of this study is too small to draw any such conclusions.

In anecdotal cases of major trauma and surgery for acute type A aortic dissection, FVIII/VWF concentrate has been used as an off-label, last-resort treatment for massive bleeding, but reports on the use of FVIII/VWF concentrate in these settings are scarce. However, FVIII/VWF concentrate has been used as a successful prophylactic treatment for bleeding in patients with von Willebrand disease [23]. In recent years, the use of recombinant factor VIIa has been shown to be a safe and effective treatment for refractory bleeding in ATAAD [24,25]. Therefore, it has been appealing to speculate that FVIII/VWF concentrate could be used as a last resort treatment for massive bleeding in cardiac surgery and Icheva et al. recently reported that FVIII/VWF concentrate was well tolerated when used for treatment of surgical bleeding in infants undergoing surgery for congenital cardiac disease [14,26]. However, our results show normal or supernormal perioperative VWF:GPIbM and thus, based on the present data, there is no indication that patients undergoing ATAAD surgery would benefit from the use of FVIII/VWF concentrate or desmopressin acetate [27].

This study is limited by its small sample size and the consequent risk of type II errors. Furthermore, although desired, consecutive inclusion of study objects was not achieved. Instead, the study relies on a "real-life" cohort of patients. The two groups were not identical with regard to baseline and surgical characteristics, but it is our opinion that regardless of differences between the groups, the comparison between ATAAD patients to elective controls is a major strength of this study.

5. Conclusions

This prospective, observational, matched control study demonstrated that ATAAD causes an increase in VWF:GPIbM, counteracted by deep hypothermia. Surgery for ATAAD and elective aortic surgery both cause supernormal postoperative VWF:GPIbM and based on this, we cannot provide evidence that administration of FVIII/VWF concentrate would improve the management of major bleeding associated with surgery for ATAAD.

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