LUND UNIVERSITY

Effects on coagulation and bleeding in acute and elective cardiac surgery

Larsson, Mårten

2025

Document Version:
Publisher's PDF, also known as Version of record

Effects on coagulation and bleeding in acute and elective cardiac surgery

MÅRTEN LARSSON
DEPARTMENT OF CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

Effects on coagulation and bleeding in acute and elective cardiac surgery

Effects on coagulation and bleeding in acute and elective cardiac surgery

Mårten Larsson

LUNDS UNIVERSITET

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 10th of January at 13.00 in Segerfalksalen, BMC, Lund

Faculty opponent
Associate Professor Jonas Holm

Linköping University, Linköping University Hospital, Linköping, Sweden

Organization: LUND UNIVERSITY

Document name: **Date of issue** January 10

Author: Mårten Larsson **Sponsoring organization:**

Title and subtitle: Effects on coagulation and bleeding in acute and elective cardiac surgery

Abstract:

Background:
Bleeding complications are common in cardiac surgery, and aortic dissection is no exception. The coagulation is of great importance, both during and after surgery, even in the long term.

Aims:
I: to investigate the impact of blood group and risk of bleeding after surgery for type A aortic dissection (ATAAD); II: to investigate if anticoagulation therapy impacts the false lumen, survival or late reoperations; III: to analyse changes in ROTEM in patients undergoing surgery for ATAAD; IV: to investigate differences in ROTEM in conventional or minimally invasive mitral surgery.

Methods:
All studies were single center observational performed at Skåne University Hospital, Lund. Study I and II were retrospective analyses of 336 and 156 patients respectively who underwent surgery for ATAAD. Study III and IV were prospective non-randomised studies. Study III compared ROTEM in 23 patients with ATAAD to 20 patients undergoing elective aortic surgery. Study IV compared 35 patients undergoing minimally invasive mitral valve surgery (MIMVS) to 36 patients undergoing mitral valve surgery through conventional sternotomy.

Results:
I: There were no differences in bleeding outcomes between different blood groups. Blood group O received more fibrinogen concentrate compared to non-O (6.1±4.0 vs. 4.9±3.3 g, p=0.023). II: False lumen patency was 81%, anticoagulation did not correlate with false lumen patency. Anticoagulation did not affect survival nor reintervention rate. III: ROTEM was significantly impacted by surgery, and the coagulopathy was more severe in ATAAD but no difference was found at the end of surgery. ATAAD received more transfusions and procoagulants. IV: No differences were found in ROTEM. MIMVS was associated with less bleeding and lower transfusion rate. The inflammatory response was lower in MIMVS during surgery (IL-6 38 ng/L [23-69] vs 61 ng/L [41-139], p=0.01) and the following day (CRP 0.50 µg/L [0.35-1.00] vs 0.30 µg/L [0.16-0.49], p=0.008).

Conclusions:
Blood group does not seem to affect bleeding in ATAAD surgery. Anticoagulation after ATAAD surgery does not affect clinical outcomes in medium term. ROTEM in ATAAD is severly impacted but cannot fully evaluate the transfusion requirements. MIMVS reduce bleeding and inflammation, possibly leading to faster recovery.

Key words:

Classification system and/or index terms (if any) Supplementary bibliographical information

Language English **Number of pages**:78

ISSN and key title: 1652-8220

ISBN: 978-91-8021-657-9

Signature Date 2024-12-04

Effects on coagulation and bleeding in acute and elective cardiac surgery

Mårten Larsson

LUNDS
UNIVERSITET

Lund University, Faculty of Medicine
Department of Clinical Sciences, Lund

ISBN 978-91-8021-657-9
ISSN 1652-8220

Tryckt i Sverige av Media-Tryck, Lunds universitet
Lund 2024

Pergite!

Livregementets husarers valspråk

Table of 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. Henrik Guné, **Mårten Larsson**, Shahab Nozohoor, Erik Herou, Cecilia Luts, Sigurdur Ragnarsson, Maria Samuelsson, Johan Sjögren, Peter J Svensson, Igor Zindovic. Impact of ABO blood group on bleeding complications after surgery for acute type A aortic dissection. Blood Coagul Fibrinolysis. 2021 Jun 1;32(4):253-258.

II. **Mårten Larsson**, Gracijela Bozovic, Johan Sjögren, Igor Zindovic, Sigurdur Ragnarsson, Shahab Nozohoor. The effect of postoperative anticoagulation on false lumen patency after surgery for acute type A aortic dissection. J Cardiothorac Surg. 2021 Sep 28;16(1):279.

III. **Mårten Larsson**, Igor Zindovic, Johan Sjögren, Peter J Svensson, Karin Strandberg, Shahab Nozohoor. A prospective, controlled study on the utility of rotational thromboelastometry in surgery for acute type A aortic dissection. Sci Rep. 2022 Nov 8;12(1):18950.

IV. **Mårten Larsson**, Shahab Nozohoor, Jacob Ede, Erik Herou, Sigurdur Ragnarsson, Per Wierup, Igor Zindovic, Johan Sjögren. Biomarkers of inflammation and coagulation after minimally invasive mitral valve surgery: a prospective comparison to conventional surgery. Scand Cardiovasc J. 2024 Dec;58(1)

Populärvetenskaplig sammanfattning (summary in Swedish)

Hjärtkirurgin har sedan dess tillkomst varit och förblivit förknippat med blödningskomplikationer. Den första dokumenterade lyckade hjärtoperationen genomfördes 1896 då Ludwig Rehn opererade en man som blivit knivhuggen i hjärtat. Sedan dess har utvecklingen gått framåt och introduktionen av hjärt-lungmaskinen under 50- och 60-talet möjliggjorde fler ingrepp och inkluderar de diagnoser som idag utgör grunden för den moderna hjärtkirurgin. Trots utvecklingen av nya metoder, bättre läkemedel och provtagningsmetoder återstår blödning som en av de vanligaste allvarliga komplikationerna till hjärtkirurgi. Detta beror på flera saker; en är kirurgins natur där ingreppen utförs på cirkulationssystemet men flera faktorer beror på diagnos, läkemedelsbehandling och faktorer kopplade till hjärt-lungmaskinen.

Det finns mycket forskning på de negativa effekterna av blödning i samband med hjärtkirurgi. Även om den akuta dödligheten vid blödning är liten finns det tydliga samband med ökad risk för sen dödlighet, bestående njursvikt, hjärtsvikt och kognitiv svikt som konsekvenser av allvarlig blödning.

Aortadissektion är ett akut livshotande tillstånd där det innersta lagret på aortan, eller kroppspulsådern, brister och blodet tar sig in i kärlväggen så att den skiktar sig -dissekerar. Den kategoriseras ofta i typ A eller B där typ A är allvarligare och kräver omedelbar hjärtkirurgisk åtgärd då dödligheten obehandlad räknas i procent per timme. I samband med att aortan dissekerar aktiveras kroppens system för att förhindra blödning och de proteiner och celler i blodet som står för den funktionen konsumeras i hög takt. Detta leder till en klart ökad blödningsrisk i samband med operation och användandet av blodtransfusioner och läkemedel som främjar blodets levringsförmåga, så kallade prokoagulantia, är stort. Detta är inte helt utan risk då transfusioner och prokoagulantia ger ökad risk för komplikationer som stroke och njursvikt.

När blodets koagulationsförmåga är nedsatt kan det behöva korrigeras vid hjärtkirurgi. Dock är det inte alltid självklart vilken del i koagulationen som är påverkad och av den anledningen har flera olika metoder för att bedöma koagulationssystemet utvecklats. Vissa metoder kräver utrustning som enbart finns på sjukhuslaboratorier men utvecklingen går mot allt fler patientnära metoder. Dessa metoder är ofta snabba och ger ett tillräckligt noggrant värde för att man ska kunna styra behandlingar. En av dessa metoder kallas tromboelastometri där man kan mäta olika funktioner i koagulationen med endast ett prov och får svar inom 5–15 minuter. Tromboelastometri-metoden utvecklades i Tyskland redan 1948 och har de senaste åren fått förnyad popularitet. Det finns två konkurrerande metoder där ROTEM® är den ena och TEG® den andra men konceptet är detsamma.

Denna avhandling består av fyra delarbeten där fokus ligger på aortadissektion med risker för blödning, hur koagulationen påverkas under kirurgi med användandet av ROTEM® och faktorer som påverkar efterförloppet för de som genomgått kirurgi för aortadissektion. Ett av arbetena fokuserar på planerad kirurgi riktad mot mitralklaffen och hur ROTEM® och inflammation påverkas av operationsmetod.

Delarbete I undersökte risken för blödning beroende på blodgrupp vid kirurgi för aortadissektion hos 336 patienter. I denna studie jämfördes patienter med blodgrupp 0 med övriga patienter (blodgrupp A, B eller AB) då skillnader i blödning vid kejsarsnitt visat ökad blödningsrisk vid blodgrupp 0. I denna studie kunde inga skillnader i blödning urskiljas, om än med förbehållet att det användes något mer prokoagulantia (fibrinogen) i blodgrupp 0.

Delarbete II var ett retrospektivt arbete som undersökte effekterna av antikoagulerande läkemedel efter operation för aortadissektion och hur det påverkar förekomst av kvarstående dissektionsmembran, överlevnad och behov av reoperation hos 156 patienter. Där kunde vi visa att behandling med antikoagulantia inte gav upphov till ökad risk för kvarstående dissektionsmembran, ökad dödlighet eller risk för reoperation.

Delarbete III undersökte skillnader i ROTEM® mellan patienter som opererades med aortadissektion eller planerad aortaoperation. Där kunde vi visa en påverkan på koagulationen i båda grupperna som var mer uttalad i dissektionsgruppen och att ROTEM® i många fall underskattade behovet av blodtransfusioner.

Delarbete IV undersökte ROTEM® och inflammationsmarkörer hos patienter som genomgick planerad mitralklaffkirurgi med minimalinvasiv teknik eller full sternotomi. Där kunde vi påvisa en lägre inflammatorisk aktivitet, blödningsvolym och transfusionsfrekvens i den minimalinvasiva gruppen men ingen skillnad i ROTEM®.

Sammantaget har denna avhandling utforskat olika faktorer som påverkar blödning och blödningsrelaterade variabler vid framför allt aortadissektion. Behandling med antikoagulantia efter aortadissektion förefaller inte ge negativa konsekvenser på överlevnad eller reoperation och bör därför inte avstås om indikation föreligger. Blodgruppen har ingen kliniskt relevant inverkan på risken för blödning vid aortadissektion och kan sannolikt bortses ur det perspektivet. Även om ROTEM® vunnit mycket popularitet är det fortfarande inte tillräckligt tillförlitligt för att använda som enda metod att kontrollera koagulationen vid aortadissektion. Minimalinvasiva metoder har något lägre blödningsrisk men skillnaden går inte att förklara med ROTEM®.

Abbreviations

ADP	Adenosine diphosphate
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ATAAD	Acute type A aortic dissection
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BAV	Bicuspid aortic valve
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CT	Clotting time
DAPT	Dual antiplatelet therapy
ECM	Extracellular matrix
FFP	Fresh frozen plasma
GP	Glycoprotein
IL	Interleukin
INR	International normalised ratio
IQR	Interquartile range
MCF	Maximum clot firmness
MIMVS	Minimally invasive mitral valve surgery
NOAC	New oral anticoagulant
OR	Odds ratio
PCC	Prothrombin complex concentrate
PT	Prothrombin time
RBC	Packed red blood cells
ROTEM	Rotational thromboelastometry
TEG	Thromboelastography
TF	Tissue factor
vWF	Von Willebrand Factor

1 Introduction

1.1 Bleeding in cardiac surgery

Bleeding has since the inception of cardiac surgery been a dreaded complication and even though progress has been made, it remains as one of the main severe complications. Significant bleeding requiring blood transfusion is seen with worse outcomes such as acute kidney injury, pulmonary dysfunction, and stroke, and both re-exploration for bleeding and cardiac tamponade also increase the risk of mortality. As such, bleeding has been well-studied, and many risk factors have been established. The underlying reasons are numerous and contain both innate and acquired conditions where the latter is more common. The acquired conditions include pharmacological, surgical procedural, surgical skill and conditions connected to the treated heart disease, as well as other acquired diseases.

Some cardiac procedures such as aortic surgery, redo procedures and endocarditis are at greater risk of bleeding than others, and acute surgery has also demonstrated increased risk. Longer use of cardiopulmonary bypass (CPB) is shown repeatedly to increase the risk of bleeding, and preoperative use of antiplatelet or anticoagulant drugs given within a few days of surgery is also well-established risk factor. Minimally invasive surgical technique is demonstrated to reduce the risk of bleeding and transfusion.

1.2 Coagulation

Haemostasis, the system which aims to reduce blood loss, is a prerequisite for human life and is proven by the fact that few innate diseases exist and are uncommon. It is tightly regulated and has several pathways of activation as well as inactivation and is dependent on quick reaction and amplifying circuits. In a simplified version it consists of two main steps, the primary and secondary haemostasis, but in reality, both steps interact with each other.

1.2.1 Primary haemostasis

Upon injury to the vessel wall, the primary haemostasis is activated by the exposure of subendothelial structures in the extracellular matrix (ECM), such as collagen and von Willebrand Factor (vWF) to circulating platelets. Depending on conditions, the platelet adheres to the damaged tissue in different ways. The GP1b-IX-V-receptor on the platelet surface binds to exposed vWF which slows the moving platelet down, particularly in high shear stress conditions. vWF is produced by endothelial cells and megakaryocytes, and is released to both the ECM and the blood[1]. In the event of damage with lower shear stress, another platelet surface complex called Integrin α2β1, whose α2 subunit have similar structure as vWF, seems to play a larger role. Integrin α2β1 binds directly to exposed collagen in the ECM and is stronger than the GP1b-IX-V to vWF-connection[2]. Other platelet surface receptors, such as GPVI, Integrin αIIbβ3 and other β1 integrins bind to collagen, vWF and fibronectin/laminin respectively, and further adheres the platelet to the subendothelial structure[3].

The binding of GP1b-IX-V to vWF and GPVI to collagen leads to conformation changes in the intracellular part of the receptors, which through multiple steps and amplifications, result in the release of intracellular Ca^{2+}. This in turn activates several processes in the platelet, which lead to the release of granulae, and conformational changes of both the platelet and its surface proteins. Arachidonic acid from the cell membrane is converted to Thromboxane A2 (TxA2) through COX-1 and thromboxane synthase. TxA2 is then released outside the platelet where it binds to receptors on the platelet surface which promotes additional Ca^{2+}-release and TxA2 production[4].

The increased intracellular Ca^{2+} also stimulates the release of granulae containing ADP, which in turn activates ADP receptors such as P2Y12 on the platelet surface. P2Y12 is G-protein coupled receptor which irreversibly aggregates the platelets. The GPIIbIIIa-receptor undergo conformational changes which enables it to bind to its ligands, fibrinogen and vWF. Ca^{2+}-release also leads to a shape shift in the platelet from a discoid to an irregular shape with filopodia to increase the surface area[5].

1.2.2 Secondary haemostasis

Secondary haemostasis, or often called coagulation, is classically divided into two separate pathways, the extrinsic and intrinsic, leading to a common pathway. The intrinsic pathway, also called contact activation pathway, is initiated by the exposure of factor XII (FXII) to negative charged surfaces or large molecules such as glass, RNA, DNA, or polyphosphates released from granulae in the platelet. FXII is activated (FXIIa) and converts FXI to FXIa which in turn activates FIX to FIXa.

FIXa and FVIIIa form a complex and catalyses the reaction of FX to FXa, which is the first step in the common pathway[6]. The importance of the intrinsic pathway has been questioned, as FXII deficient have no clinically increased risk of spontaneous, trauma associated, or surgical related bleeding[7].

The extrinsic pathway is activated by tissue factor (TF) exposed by the tissue damage. TF is a protein produced by subendothelial cells such as smooth muscle cells and fibroblasts[8]. Upon damage, circulating FVII encounters TF, and form a complex of TF and activated FVII (FVIIa)[9]. This complex in turn, activates FX in the common pathway.

After transforming to its activated state, FXa can cleave prothrombin (FII) to thrombin (FIIa) or bind to the surface of platelets and together with FVa (activated by thrombin) form a complex that greatly enhances the conversion rate of prothrombin to thrombin. Thrombin is a protease that cleaves circulating fibrinogen, a double-stranded glycoprotein, to individual fibrin strands, while also activating FXIII which serves as a link between the fibrin strands, creating an extensive network as the basis of a stable clot[9-11]. Thrombin also increases the conversion of FVIII and FXI, creating a positive feedback loop.[12]

This view of the haemostatic system is simplified, the primary and secondary haemostatic systems are intertwined and still far from fully understood. However, in the clinical setting it provides enough understanding to direct therapies and strategies.

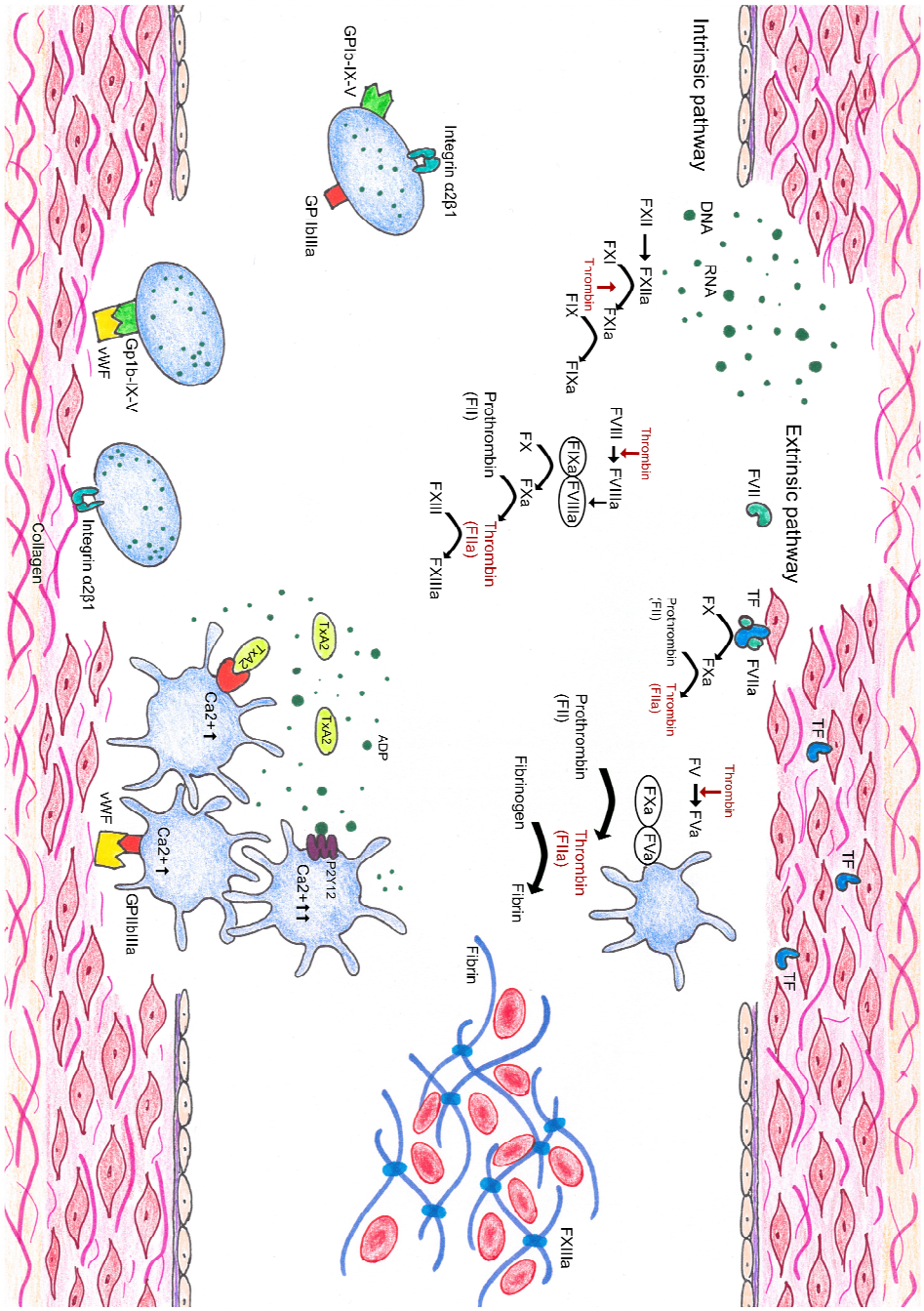

Figure 1. Schematic overview of the coagulation system.

1.2.3 Coagulation in cardiac surgery

As mentioned, bleeding is of considerable risk in cardiac surgery. The introduction of CPB revolutionized cardiac surgery by enabling many more procedures in a safe way. However, it has its drawbacks, and its effect on the coagulation system is one of them. The contact between blood and the surfaces of the CPB machine activates the coagulation system and is without any form of anticoagulation not possible to use for any significant time due to the risk of thromboembolism or poor oxygenation caused by clotting in the oxygenator. Heparinization of the blood in sufficient concentration solves this problem. Heparin is a polymer of sulphated disaccharide units with a molecular weight of 3-30kDa and is a member of the glycosaminoglycan family[13]. It has many effects on the coagulation system but the most important is its interaction with antithrombin. Antithrombin, a small plasma glycoprotein, is a protease inhibitor and regulates the coagulation system by inactivation of several activated coagulation factors, and in the presence of heparin its efficiency increases 500-1.000.000 times[14-16]. In contrary to early beliefs, the inactivation of the common pathway, thrombin (FIIa) and FXa, is most important to facilitate the use of CPB, and not the inactivation of FIXa of the intrinsic pathway[17].

Although heparin inhibits the coagulation during CPB, it does not inactivate it completely. Platelets are still activated, and its numbers reduced during CPB in a time dependent manner as well as reduction of factor V, VII, VIII, XI and fibrinogen[18-20]. In order to reduce the need of transfusions, haemodilution with crystalloid in combination with colloid solutions is used to prime the CPB[21]. Haemodilution is however linked to increased risk of bleeding, both in trauma and in cardiac surgery[22,23].

1.2.4 Anticoagulation and antiplatelet therapies

There are several pharmaceutical options available to anticoagulate a patient, with different mechanisms of action in the coagulation cascade. Warfarin is the most potent drug inhibiting the vitamin K dependent coagulation factors II (prothrombin), VII, IX and X, and its effect is monitored by measuring the prothrombin time which is normalized with to an international standard (INR). Warfarin is the only anticoagulant allowed after mechanical valve implantation. There are newer, direct oral anticoagulants available with the benefit of lower risk of bleeding complications, less interactions, and easier dosage. The three most common in Sweden are apixaban, rivaroxaban and dabigatran, where the latter is a direct thrombin (FII) inhibitor and the two former are both FXa inhibitors.

Antiplatelet therapies are designed to inhibit the platelet in different phases. The most common drug, acetylsalicylic acid (ASA), is an irreversible inhibitor of COX-1, thus blocking the production of Thromboxane A2, inhibiting platelet aggregation.

More potent platelet inhibitors include P2Y12-inhibitors, such as ticagrelor and clopidogrel which inhibit the ADP-dependent platelet aggregation. [24-30]

1.2.5 Blood group

Non-O blood group has been demonstrated increasing the risk of both venous and arterial thromboembolism, and increased levels of vWF and FVIII[31,32] has been suggested as potential explanation for this. This could indicate an increased coagulation activity which could reduce bleeding. A study of 877 patients in elective cardiac surgery undergoing coronary artery bypass grafting could however not demonstrate any significant differences in bleeding outcomes[33], but might be underpowered as bleeding in this context is less common compared to more extensive cardiac surgery.

1.3 Thromboelastometry

Thromboelastometry (TEM) is a method to test the coagulation in a functional way. It was first developed in 1948 by a German named Dr. Hartert and has since evolved to a point-of-care test method for coagulation. The first step is placing a small pin into a blood sample in which the coagulation is activated by different reagents. The pin is rotated by a spring in an oscillating movement inside the blood sample and as the blood clot forms on the pin, the oscillating movement is gradually reduced which is detected by an optical sensor. The original method described by Dr. Hartert instead oscillates the cup in which the blood sample is placed, and the measuring pin is suspended freely by a thin wire. As the clot forms, the pin starts to move and the force on the pin is measured. The method tests the time until the first clot starts to form, called clotting time (CT), and the strength of the clot, called maximum clot firmness (MCF). The CT is measured in seconds and MCF in millimetres.

The evolution of the method has come to include several channels to test different parts of the coagulation. There are two major competing distributors of point-of-care TEM; ROTEM® and TEG®, where both have similar setups and reagents. ROTEM® uses four channels in their standard setup and consists of INTEM, HEPTEM, EXTEM and FIBTEM.

INTEM is a test of the intrinsic pathway in the coagulation cascade and is activated by contact and is sensitive to heparin. A prolonged CT in INTEM is an indicator of coagulation factor deficiency or heparin effect and low MCF is more affected by low platelet count and/or low fibrinogen levels. HEPTEM uses the same activation of the coagulation with the addition of a heparinase which breaks down any heparin in the sample and comparing HEPTEM to INTEM gives a good indication if any

heparin effect is present in the patient. The INTEM/HEPTEM channels correlates with the activated partial thromboplastin time (aPTT) by using the same mode of activation, however the results are not explicitly comparable.

The EXTEM channel tests the extrinsic coagulation pathway and is activated by adding tissue factor to the sample, similar to the laboratory test of prothrombin time (PT) but is, unlike PT, insensitive to heparin. CT in EXTEM provides information on the coagulation factor levels, and MCF is more subject to influence of platelet count and fibrinogen levels. The FIBTEM channel is activated in the same way as the EXTEM channel but with the addition of a platelet inhibitor, and correlates well to plasma fibrinogen levels.

As described, ROTEM® has standard laboratory test equivalents and its role could therefore be questioned. The benefits lie in the quicker turnover time which enable serial testing and a more directed therapy to the underlying causes of clinical coagulopathy.

One drawback of TEM is the lack of platelet function test. Both EXTEM and INTEM MCF, when compared to FIBTEM, can provide information on platelet count, and have a strong correlation. However, even though TEM is a functional method, it does not provide useful information on platelet function. For this reason, a clinical coagulopathy can still be present with a normal ROTEM®. Also, even though the reference ranges for healthy individuals is well established, the question remains what targets are to be set in the event of bleeding.

1.3.1 ROTEM-based transfusion protocols

The evidence on the benefits of ROTEM®-based transfusion protocols have been published and studied in cardiac surgery[34-37]. The study by Lehmann et al[38], a randomised study comparing ROTEM based transfusion protocol to control in aortic surgery, shows a reduction in transfusions in patients with a ROTEM-directed transfusion strategy. Similarly, several retrospective studies comparing bleeding outcomes and transfusion rates before and after the introduction of a ROTEM®-based transfusion strategy show no increase in bleeding although the use of blood products and procoagulants decrease.

Although many protocols have been published, there is lack of data on what these protocols are based. The ROTEM reference ranges are often used as triggers for transfusions, but some use arbitrarily defined targets. There are no studies known to the author that have investigated the relationship between ROTEM and transfusions, with bleeding and thrombotic complications, to better establish what goals are to be set in the event of bleeding or severe coagulopathy, such as in aortic dissection.

The protocol employed at the author's centre is demonstrated in Figure 2 and is similar to others published. However, many published ROTEM protocols also include a platelet function test as this is not included in the traditional ROTEM method, but this protocol does not and is thereby solely dependent on platelet count.

1.4 Aortic dissection

1.4.1 The aortic anatomy

The aorta starts at the heart after the aortic valve with the aortic root, and leave the coronary arteries, and after the sinotubular junction the aorta transcends into the ascending aorta. The departure of the brachiocephalic trunk marks the start of the aortic arch which ends after the departure of the left subclavian artery and is thereafter called the descending aorta through the thoracic cavity and below the diaphragm called the abdominal aorta.

The aorta is normally 1-3mm thick and consists of three layers, tunica intima, media, and adventitia, defined by their properties. The intima is the thinnest innermost layer consisting of one layer of epithelial cells, called endothelium, and a thin layer of elastic fibres called the internal elastic lamina. The next layer, the media, is the thickest layer making up around 80% of the aortic wall and is made up of elastic fibres layered in-between circular smooth muscle cell layers. The outer layer, the adventitia, is thin and consists of collagen fibres and small vessels supplying blood to the aortic wall and has the highest tensile strength of the three layers.[39]

The aortic diameter is dependent on gender, and during adulthood increases approximately 5mm in diameter in the normal population over the course of 60 years[40]. Hypertension increase dilatation as well as smoking, and conditions affecting the collagen fibres such as Marfan, Loey-Dietz or Ehler-Danlos syndrome have a higher rate of aortic aneurysms[40-42]. Acute aortic events increase with aortic diameter and is often quoted to follow the physics of Young-Laplace Law, which state that the wall tension increases by the radius of the aortic wall, albeit an oversimplification.

1.4.2 Pathophysiology

Aortic dissection occurs when a tear in the intimal layer allows blood to flow into the aortic wall which dissects the tunica media along the aorta creating a false lumen. In the acute phase, aortic dissection has a high mortality and there are several different classification systems which depend on the extent of dissection, its localization, and effect on end-organs. The most used classification is Stanford

which has two classes, type A and B, where type A includes the ascending or aortic arch, and type B only involves the descending or abdominal aorta. Type B is usually treated with blood pressure control, but surgical strategies are not uncommon. Type A is a condition with high mortality, up to 50% never reach the emergency department and 50% of the remaining are dead within 48h if left untreated[43-46]. The mortality rate stems from either complete rupture of the aorta with subsequent fatal haemorrhage, rupture of the aorta with hemopericardium and subsequent cardiac tamponade, end-organ malperfusion such as myocardial infarction due to occlusion of the coronary ostiae, cerebral infarction due to occlusion of the carotid arteries or embolic events, abdominal ischemia, or cardiac failure due to massive aortic valve regurgitation. The treatment is emergent open-heart surgery with replacement of the damaged aorta and securing valve competency to restore blood flow in the true lumen, avoid haemorrhage into the pericardium and reverse potential end-organ malperfusion. However, the surgical treatment still come with a high mortality, with reported 30-day mortality in the range of 6-25% in smaller series and 16-18% in large databases, and a high morbidity with postoperative stroke rates of 13-18%[47,48] and renal failure requiring dialysis in 12-16%[49].

The long-term prognosis for patients surviving the initial 30-days is however quite good. Olsson et al reported similar midterm survival in ATAAD patients compared to background population with 95% 3-year survival and 76% in 8 years in the ATAAD group, compared to 95% and 86% respectively[50]. Remaining false lumen after ATAAD surgery has been reported impairing long-term survival[51-53], and as such, a desired goal in ATAAD surgery is to obliterate the false lumen. This have proven difficult as studies show 47-74% of patients have a residual false lumen after surgery[54-58] with lower rates where the surgical strategy has been more aggressive such as total arch replacement.

1.4.3 Surgical method

There are different methods used in ATAAD; however, the main procedure is replacing the ascending aorta with an aortic graft. Depending on the site of entry tear, extent of dissection, end-organ status, aortic diameter and aortic valve function, the operation method varies and is also centre-dependent. Some centres prefer a low-risk management at the cost of higher incidence of late reoperations, while others aim at minimizing risk of later events although at an initial higher risk, especially at lower volume centres. This text aims at describing the method employed at the author's centre while also providing some nuance in alternatives.

Normally, the femoral artery is cannulated as it is easily accessible and thereby enables quick cannulation in the event of hemodynamic instability and is one of the most employed cannulation sites. The right subclavian is a common alternative and has gained popularity after a recent meta-analysis demonstrated better survival and neurological outcomes[59]. However, large databases such as IRAD and GERAADA

have not shown any excess mortality or morbidity and the cannulation strategy is still debated[44,60].

After CPB is established, the patient is cooled to a hypothermic state around 20°C core temperature, after which the circulation is stopped and retrograde cardioplegia is administered. The aorta is opened and inspected for entry tears distally and if possible resected. If an entry tear is present in the arch the strategy is to repair it, after which the aortic graft is interposed into the proximal arch. This strategy has proven easy and reproducible even at lower volume centres. There are other methods using higher core temperature (28-30°C), often in combination with selective cerebral perfusion strategies, and has demonstrated favourable outcomes[61,62] but other high-profile centres such as Cleveland Clinic and Yale New Haven Hospital still use the simpler method with excellent results[63,64].

After the distal anastomosis has been completed, a cross-clamp is placed on the aortic graft, CPB is reinstated with reheating to normothermia, and the focus is diverted to the aortic root. Depending on the extent of dissection and aortic root diameter, a root replacement may be warranted, and the most common method is a Bentall procedure with a composite graft including a prosthetic valve and represent 20-25% of ATAAD patients[65,66]. The majority however does not require root replacement, and these patients are normally treated with resuspension of the aortic valve commissures to maintain aortic valve competency, after which the proximal anastomosis is sutured to the sinotubular junction, and the cross clamp is removed. CPB is weaned when the patient has reached normothermia, after which heparinization is reversed and the haemostasis is evaluated. Transfusions and procoagulants are usually needed to mitigate any coagulation deficiency present.

1.4.4 Coagulation in aortic dissection

The intimal damage and subsequent dissection of the aorta exposes the blood to large surface of collagen and TF initiating a massive activation of the coagulation system. This leads to a consumption and depletion of all major coagulation factors and platelets, similar to disseminated intravasal coagulopathy, and play an important role in the bleeding management in ATAAD surgery[67,68]. Beyond platelet depletion, aortic dissection also decreases platelet aggregability[69], and reduced platelet count has been associated with poorer outcome[70].

The operation itself aggravates the coagulopathy in multiple ways. The effects of the CPB circuit on the coagulation system is previously described, and the frequent use of hypothermia is also known to impair the coagulation system with increased platelet activation potentially enhancing platelet depletion, impaired vWF proteolysis resulting in improper recognition of FVIII and vWF, and reversible effects on aPTT and PT suggesting lower enzymatic activity at lower temperature[71].

The aortic graft introduces a new surface to which platelets can adhere, and this has been demonstrated to continue during several years[72].

1.5 Minimally invasive surgery

Surgical procedures are becoming less and less invasive in many fields. In cardiac surgery however, the adaptation has been slower although many methods have been described. The most common minimally invasive procedure in cardiac surgery is mitral valve repair and has equal results to conventional surgery through a median sternotomy in large meta-analysis studies, however randomized data is scarce[73].

The benefits of minimally invasive mitral valve surgery (MIMVS) are shorter recovery, better cosmetic result, and reduced pain[74-76]. There is also data indicating less blood loss and lower transfusion frequency[77,78]. The procedure, however, is more technically demanding, and both time on CPB and cross clamp are longer even in experienced centres in MIMVS. Increased time on CPB has been proven to exacerbate inflammation and coagulopathy[79-81], both of which are considered strong predictors of poorer outcomes[82-87].

1.6 Inflammation markers in cardiac surgery

There are many different markers of inflammation, where C-reactive protein (CRP) and leukocyte concentration are predominantly used in health care including cardiac surgery.

1.6.1 CRP

C-reactive protein was discovered in 1930 when Tillis and Francis demonstrated a substance that reacted with the capsule of pneumococcus bacteria in patients with inflammation. It is produced by the liver in the event of inflammation, and its production is mainly stimulated by rising levels of IL-6, amplified by the presence of IL- 1β[88]. By binding to damaged cell structures such as phospholipids from cell membranes, and histone and chromatin from cell nuclei, and presenting it to phagocytic cells it aids in recovery[89]. Following uncomplicated cardiac surgery, CRP peaks around 48h postoperatively, and is mainly used as an indicator for postoperative infection.

1.6.2 IL-6

Interleukin 6 (IL-6) is a small protein produced in the event of cellular damage or infection. IL-6 is involved in several aspects of inflammation including stimulation of CRP production in hepatocytes, stimulating B- and T-cell proliferation, megakaryocyte proliferation and platelet release, osteoclast activity, as well as play a role in metabolic control. IL-6 is, when pathologically elevated, linked to numerous chronic diseases such as rheumatoid arthritis, osteoporosis, and systemic sclerosis[90]. Its usefulness in the clinical setting is marginal due to its strong correlation with CRP at a higher cost, slower test result and lower availability.

In cardiac surgery, IL-6 has been linked to poorer outcomes such as need for dialysis, atrial fibrillation and respiratory problems[82-87].

1.6.3 Procalcitonin

Procalcitonin is a precursor to the hormone calcitonin and is produced in the thyroid gland. Upon bacterial infection, procalcitonin production is elevated by toxic byproducts from the bacteria, or by inflammatory molecules such as IL-6 or TNF-α, in a wide range of organs. As procalcitonin is not elevated in viral infection, it has proven itself useful to guide if antibiotic treatment is warranted[91].

In cardiac surgery, procalcitonin has been demonstrated as a good indicator of bacterial infection in both elective surgery and heart transplants[92-94]. It has also been demonstrated to predict non-occlusive mesenterial ischemia in cardiac surgery patients, likely due to the translocation of bacteria in the affected bowel[95].

2 Aims

2.1 Study I

The aim of study I was to evaluate the impact of ABO blood group on bleeding complications following ATAAD repair.

2.2 Study II

The aim of study II was to investigate if anticoagulation treatment after surgery for ATAAD influence false lumen patency, and to study the effect of postoperative false lumen patency on survival, and the rate of reintervention in patients presenting with ATAAD DeBakey type I.

2.3 Study III

The aim of study III was to assess the performance of ROTEM during surgery for ATAAD and elective aortic surgery.

2.4 Study IV

The aim of study IV was to investigate differences in inflammation, bleeding, and ROTEM in patients undergoing mitral valve repair depending on surgical approach.

3 Materials and methods

3.1 Patients and study design

All studies were single centre retro- or prospective observational studies undertaken at Department of Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden.

3.1.1 Study I

This study was a retrospective study including patients who underwent surgery for ATAAD between 2004 and 2019. Pre-, peri- and postoperative variables from a database was used and supplementary data was collected by reviewing the medical records if needed. Patients were divided into groups by their AB0-blood type and outcomes were compared between patients with blood group 0 to non-0 (A, B or AB). Survival data was retrieved from the Swedish National Board of Health and Welfare (Socialstyrelsen, Sweden).

Primary endpoints were massive bleeding, reoperation for bleeding, total chest tube output at 12 hours, and administered transfusions. Secondary endpoints were in-hospital and 30-day mortality as well as remaining postoperative complications.

Massive bleeding was defined as the presence of any of the BART criteria as outlined in the Blood Conservation using Antifibrinolytics in a Randomized Trial study[96]: 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 10U of red blood cells within 24 h after surgery; or death from haemorrhage within 30 days.

3.1.2 Study II

This was a retrospective study designed to investigate the effects of postoperative anticoagulation therapy in patients operated for ATAAD performed at our centre. Data was collected from patients who underwent surgery between January 2005 to December 2018. 347 patients were screened for inclusion and pre-, peri-, and postoperative variables were analysed. Pre- and postoperative CT of the aorta was

examined and labelled into three categories depending on the state of the false lumen. Patients with intramural hematoma, DeBakey type II aortic dissection, patients who died within 30 days, or missing postoperative CT were excluded.

152 patients could be included in the study and their postoperative anticoagulation treatment (Warfarin or NOACs compared to no anticoagulation), or false lumen patency (patent false lumen or not) was used as grouping variables.

Primary endpoint was false lumen patency depending on anticoagulation treatment. Secondary outcomes were death or the composite of death and reoperation on the aorta due to a patent false lumen.

False lumen was considered patent if any contrast was found outside the true lumen in the thoracic aorta. All postoperative CT scans involving the chest with contrast enhancement within one year were evaluated. For patients with a limited number of examinations, the examination closest to one year with >30 days follow-up was chosen.

3.1.3 Study III

This study was a prospective study comparing patients who underwent surgery for ATAAD or elective aortic surgery. A total of 43 patients, 23 with ATAAD and 20 elective aortic surgery, was included in the study. Blood samples were collected and analysed with ROTEM® at six different time points; T0 anaesthesia induction, T1 at lowest core temperature, T2 prior to protamine administration, T3 end of surgery, T4 24h postop and T5 five days postop. Transfusion and bleeding variables were entered into a database as well as other pre-, peri- and postoperative variables.

The primary endpoints were ROTEM variables consisting of clotting time of EXTEM, INTEM and HEPTEM and maximum clotting firmness of EXTEM, INTEM and FIBTEM. Secondary outcomes were transfusion of blood products, procoagulants used, 30-day mortality, bleeding at 24h, and reoperation for bleeding.

3.1.4 Study IV

The final study was a prospective study investigating ROTEM and inflammation in patients who underwent elective mitral valve repair through either a right mini thoracotomy (MIMVS), or a conventional sternotomy. Inclusion criteria were patient over 18 who were scheduled for mitral valve repair, exclusion criteria were concomitant surgery (except closure of left atrial appendage and/or persistent foramen ovale), ongoing anticoagulation therapy, immunosuppressant therapy, active endocarditis, or redo-surgery.

Seventy-one patients were included (35 MIIMVS, 36 conventional sternotomy) between November 2017 and February 2022. Blood samples were collected at four

different timepoints; T1 before surgical incision, T2 at the end of surgery, T3 at postoperative day one, T4 at postoperative day four. Primary outcome was the release of specific inflammatory biomarkers (IL-6, CRP, and procalcitonin) and coagulation biomarkers (fibrinogen, platelet count, aPTT, PT INR, and ROTEM which included EXTEM, INTEM, HEPTEM and FIBTEM). Secondary outcomes were the need for any transfusion, reoperation for bleeding, and chest tube output.

3.1.5 Blood sample analysis

All blood samples were analysed at the Dept. of Clinical Chemistry, Division of Laboratory Medicine, Skåne University Hospital, Lund, Sweden. Procalcitonin levels were analysed using Atellica IM BRAHMS PCT (Thermo Fisher Scientific Inc, Waltham, Massachusetts, USA). IL-6 levels were analysed using ImmuliteVR 1000 (Siemens, München, Germany). The ROTEM variables analysed were clotting time (CT) measured in seconds (s) in EXTEM, INTEM and HEPTEM, and maximum clotting firmness (MCF) in millimetres (mm) in EXTEM and FIBTEM. ROTEM was analysed using ROTEM Delta 4000 (Tem Innovations GmbH, Munich, Germany).

3.2 Ethical aspects

All studies were performed according to the Declaration of Helsinki and were reviewed and approved by the regional Ethics Review Board at Lund University, Sweden (Study I-III ref ID: 2015/197, study IV ref ID: 2017/696). In study I and II, an informed consent was waivered, and in study III and IV, an informed consent was required prior to inclusion. In study III, an oral consent by either the patient or the next of kin was deemed sufficient in the ATAAD group due to the acute nature of the condition before inclusion, but formal written consent was always retrieved postoperatively. All other patients gave written informed consent prior to inclusion.

3.3 Surgical technique

3.3.1 Aortic dissection

Surgery was performed through a median sternotomy with cardiopulmonary bypass. Deep hypothermia (< 20℃) and circulatory arrest was used in most cases with open distal anastomosis after inspection of the ascending aorta and the aortic arch. Cerebral protection with steroids (500 mg methylprednisolone) and a barbiturate (thiopental or phenobarbital) was used routinely in deep hypothermic arrest. In some cases, cross-clamp was used in normothermia. After distal anastomosis was

completed, distal perfusion was re-established through a side branch in the vascular prosthesis, the patient rewarmed, and the proximal aorta, valve and root inspected for tears. If deemed necessary, the valve and/or or root was replaced. When the proximal anastomosis was completed and the patient was normothermic, cardiopulmonary bypass was terminated.

3.3.2 Mitral valve repair

Patients planned for MIMVS were preoperatively screened with angiographic imaging of the aorto-iliac vessels to rule out severe atherosclerotic disease. Relative exclusion criteria were advanced age, obesity, renal failure, previous cardiac surgery, extensive annular calcifications, and difficult vascular access. Patients in the MIMVS group were intubated with a single or double lumen endotracheal tube. Surgical access was obtained through a right anterior thoracotomy at the fourth intercostal space via a 5-6 cm skin incision. Cardiopulmonary bypass was installed through cannulation of the femoral artery and vein via guidewires under the guidance of transesophageal echocardiography. Cardioplegic arrest was achieved by antegrade administration of 1000ml cold crystalloid cardioplegia (Custodiol® HTK Solution, Essential Pharmaceuticals, Durham, USA) in the aortic root after aortic cross-clamping with a Chitwood clamp. Vacuum assisted venous drainage was utilized when necessary (max −40 mmHg). Ultrafiltration was utilized during CPB to remove excessive volume related to Custodiol® infusion.

The conventional group had median sternotomy with standard cannulation of the distal ascending aorta and bicaval cannulation. Cardioplegic arrest was achieved with intermittent cold blood cardioplegia (antegrade and retrograde in combination). Mitral valve repair techniques were similar in both groups with neo chords, leaflet preservation, and annuloplasty with semi-rigid or flexible ring.

3.3.3 ROTEM guided transfusion protocol

A ROTEM Delta (Tem Innovations GmbH, Germany) and standard lab test guided bleeding management protocol was used at our clinic, introduced circa 2015, and is presented in Figure 1. Red blood cell transfusions were given at B-Hemoglobin <90g/L. Platelets were administered at maximum clot firmness (MCF) EXTEM <50mm and MCF FIBTEM >10mm or platelet count $<100x10^9$/L. Fibrinogen and/or plasma were used at MCF FIBTEM <15mm or P-fibrinogen <2g/l. Plasma or prothrombin complex concentrate (PCC) were used at coagulation time (CT) EXTEM >100s, CT INTEM >240s, P-PT(INR) >1.5 or P-aPTT >1.5 x normal value. Additional Tranexamic acid was used when maximum lysis (ML) exceeded 15%. However, the final decision regarding transfusions was at the surgeon's discretion.

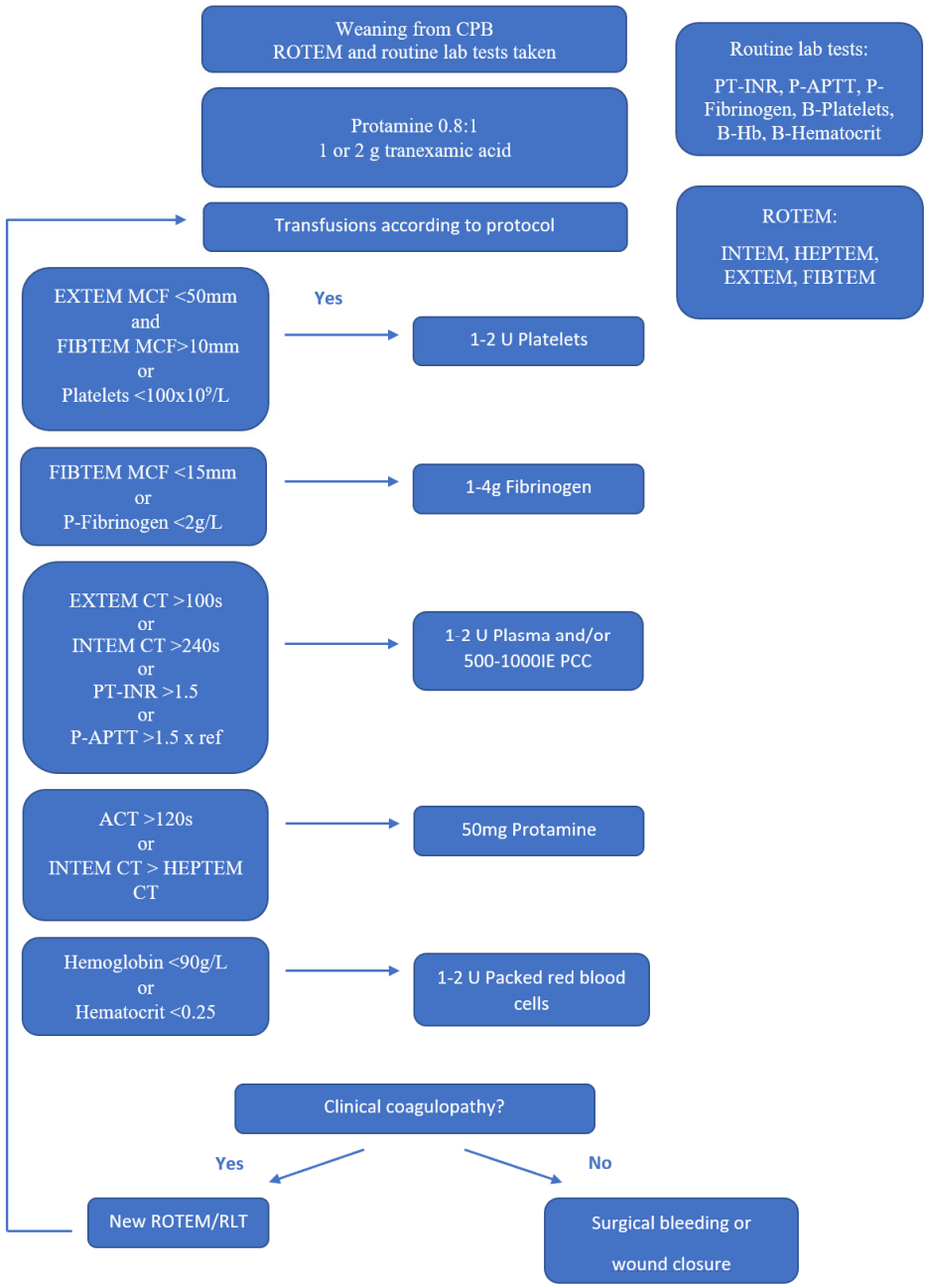

Figure 2. ROTEM guided transfusion protocol

3.4 Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean ±SD when normally distributed, otherwise as median [IQR]. [97]. Proportions were compared using the chi-square test. Fisher's exact test was used when the number of cases was less than 5, and continuous variables were evaluated using the Mann-Whitney test. Wilcoxon signed-rank test was used for analyzing related samples. Missing values were not analyzed. A *p*-value <0.05 was considered statistically significant and analyses were performed using standard software (SPSS software v25.0.0 to 28.0.0 (IBM, Armonk, NY, USA)). *P*-values of <0.05 were considered statistically significant.

In study II event rates during follow-up were estimated and survival was plotted using the Kaplan-Meier method, with the differences between groups compared using the log-rank test. Uni- and multivariable logistic regression analyses were performed to determine independent predictors of patent false lumen and relied on complete cases analysis. Variables that were considered to potentially impact false lumen status and with a *p*-value <0.1 were fitted to a multivariable regression model. Postoperative treatment with anticoagulation was forced into the analysis. The results of logistic regression analyses are expressed as odds ratio (OR) with 95% confidence intervals (CI).

In study III ROTEM variables were visualized using box plots. ROTEM reference values are illustrated as dashed lines and shaded areas, and are based on reference ranges by Lang et al[97].

4 Results

4.1 Study I

Study population and patient follow-up

Between January 2004 and January 2019, a total of 336 patients were surgically treated for ATAAD at the Department of Cardiothoracic Surgery of Skåne University Hospital (Lund, Sweden) of which, 152 had blood group O and 184 a non-O blood group. In-hospital follow-up was 100% complete. Late follow-up, performed in January 2019, was 99% complete (two patients with blood group O were lost to follow-up due to having emigrated) and included 1646 patient-years with a mean follow-up of 4.9±3.9 years (median 4.0, IQR 1.3–7.9).

Preoperative and surgical characteristics

There were no significant differences between the groups at baseline (Table I.1). Age was similar in both groups (64.3±10.6 vs. 63.6±11.8 years, blood group O and non-O patients, respectively, p=0.576), and the rate of preoperative DAPT (9.9% in blood group O patients vs. 9.2% in non-O, p=0.845). Furthermore, no between-group differences regarding surgical techniques employed were observed. CPB time was similar between blood group O and non-O patients (189 [152–234 min] vs. 191 min [158–241 min], p=0.430), as was circulatory arrest time (21.5 [17.3– 27.0] vs. 22 [17–29] min, p=0.153), and lowest core temperature (Table I.2).

Postoperative bleeding and complications

Rates of massive bleeding (27.0 vs. 25.5%, p=0.767) and of re-exploration for bleeding (16.4 vs. 13.0%, p=0.379) were similar between blood group O and non-O patients (Table I.3). Median bleeding volume collected by chest tubes 12 h after surgery was 520 ml [350–815 ml] in blood group O patients and 490 ml [278–703 ml] in those with a non-O blood group (p=0.229). Blood group O patients received significantly more fibrinogen concentrate (6.1±4.0 vs. 4.9±3.3 g, p=0.023) but there were no significant differences between the groups in amount of transfused PRBCs (5 [2–8] vs. 4 [2–9] U, p=0.736), platelets (4 [2–4] vs. 3 [2–5] U, p=0.521) and plasma (4 [1–7] vs. 4 [0–7] U, p=0.562) or the use of recombinant factor VIIa (38.6 vs. 40.2%, p=0.819). The need for renal replacement therapy (7.6 vs. 9.7%, in blood group O and non-O patients, respectively, p=0.514) and prolonged ventilatory support (44.4% vs. 43.7%, p=0.891) did not differ between the groups. Duration of

ICU stay (4 [3–7] days vs. 4 [3–7] days, p=0.679), and rates of postoperative stroke (27.1 vs. 26.3%, p=0.873) and deep sternal wound infection (2.8 vs. 1.7%, p=0.705) were also similar between the groups. Intraoperative mortality was 5.3% in blood group O patients and 4.9% in non-O (p=0.877), in-hospital mortality was 16.6 vs. 11.4% (p=0.174) and 30-day mortality was 14.7 vs. 9.5% in blood group O and non-O patients, respectively.

Table I.1 Preoperative characteristics

	O, *n*=152		**Non-O, *n*=184**		***p***
Age (years)	64.3	±10.6	63.6	±11.8	0.576
Female sex	50	(32.9)	72	(39.1)	0.237
BMI (kg/m²)	25.5	[22.5-28.2]	26.0	[23.5-30-0]	0.075
Symptom duration (h)	6.7	[4.2-11.0]	6.8	[4.9-15.0]	0.278
Smoking history	48	(32.2)	58	(33.0)	0.887
Marfan syndrome	12	(7.9)	14	(7.6)	0.922
Previous cardiac surgery	6	(4.0)	6	(3.3)	0.727
Hypertension	77	(50.7)	103	(56.0)	0.330
Hyperlipidemia	7	(4.6)	16	(8.7)	0.139
Diabetes mellitus	40	(26.3)	51	(27.7)	0.774
Coronary artery disease	9	(5.9)	16	(8.7)	0.335
Peripheral artery disease	2	(1.3)	6	(3.3)	0.248
Stroke	12	(7.9)	7	(3.8)	0.106
COPD	8	(5.3)	14	(7.5)	0.387
Dialysis	1	(0.7)	1	(0.5)	0.892
Organ malperfusion	52	(34.2)	76	(41.3)	0.183
Cardiac tamponade	24	(15.9)	25	(13.6)	0.552
DeBakey Type I	105	(69.1)	139	(76.4)	0.135
Intramural haematoma	18	(11.9)	30	(16.3)	0.254
Aspirin	40	(26.3)	51	(27.7)	0.774
DAPT	15	(9.9)	19	(9.2)	0.845
Warfarin	8	(5.3)	7	(3.8)	0.519
P-Creatinine (µmol/L)	89	[73-110]	86	[71-107]	0.304
P-Lactate (mmol/L)	1.7	[1.1-3.0]	1.7	[1.2-3.3]	0.726

Values expressed as number (%), mean ±SD, or median [IQR]. BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAPT, double anti-platelet therapy.

Table I.2 Operative characteristics

	O, *n*=152		Non-O, *n*=184		*p*
Distal surgical technique[a]					0.524
Supracoronary graft	125	(82.8)	147	(80.3)	
Hemiarch procedure	18	(11.9)	24	(13.1)	
Aortic arch procedure	7	(4.6)	13	(7.1)	
Proximal surgical technique[a]					0.279
Supracoronary graft[b]	109	(71.7)	125	(68.3)	
Bentall or Yacoub procedure	32	(21.1)	45	(24.6)	
Aortic valve replacement	1	(0.7)	6	(3.3)	
CPB time (min)	189	[152-234]	191	[158-241]	0.430
Aortic cross-clamp time (min)	88	[62-129]	90	[62-132]	0.552
Circulatory arrest, *n*[c]	136	(89.5)	167	(91.3)	0.580
Circulatory arrest duration (min)	21.5	[17.3-27.0]	22	[17-29]	0.153
Lowest core temperature (°C)	18	[17-20]	18	[17-20]	0.759

Values expressed as number (%), or median [IQR]. [a]One patient died in group O prior to attempted repair. [b]With or without commissural resuspension. [c]Without the use of selective cerebral perfusion.

Table I.3 Postoperative data

	O, *n*=152		Non-O, *n*=184		*p*
Major bleeding	41	(27.0)	47	(25.5)	0.767
Re-exploration for bleeding	25	(16.4)	24	(13.0)	0.379
Postoperative bleeding (ml)					
12h	520	[350-815]	490	[278-703]	0.229
24h	690	[475-1073]	685	[450-955]	0.473
Red blood cells (U)	5	[2-8]	4	[2-9]	0.736
Platelets (U)	4	[2-4]	3	[2-5]	0.521
Plasma (U)	4	[1-7]	4	[0-7]	0.562
Fibrinogen concentrate (g)	6.1	±4.0	4.9	±3.3	0.023
Tranexamic acid (g)	4	[3-4]	4	[3-4]	0.977
rFVIIa	32	(38.6)	43	(26.3)	0.819
RRT	11	(7.6)	17	(9.7)	0.514
Stroke	39	(27.1)	46	(26.3)	0.873
DSWI	4	(2.8)	3	(1.7)	0.705
Ventilatory support >48h	64	(44.4)	76	(43.7)	0.891
ICU days	4	[3-7]	4	[3-7]	0.679
Postoperative atrial fibrillation	71	(49.3)	77	(44)	0.344
Creatinine at discharge (µmol/L)	119	[88.5-188.5]	116	[85.8-204]	0.843
Postoperative lactate (mmol/L)	2.4	[1.8-3.1]	2.4	[1.9-3.8]	0.466
Postoperative CKMB (µg/L)	30	[18-59]	30	[19-62.4]	0.937
Intraoperative mortality	8	(5.3)	9	(4.9)	0.877
In-hospital mortality	25	(16.6)	21	(11.4)	0.174
30-day mortality	21	(14.7)	16	(9.5)	0.161

Values expressed as number (%), mean ±SD, or median [IQR]. rVIIa, recombinant factor VIIa; RRT, renal replacement therapy; DSWI, deep sternal wound infection; ICU, intensive care unit; CKMB, creatine kinase isozym MB.

4.2 Study II

Study population and patient follow-up

Study II included 156 patients out of 347 patients screened during the study period (January 2005 to December 2018) at the Department of Cardiothoracic Surgery of Skåne University Hospital (Lund, Sweden). The mean follow-up for mortality was 6.5 ± 3.9 years (median 5.6 years [3.2–8.3]). Mean follow-up for the composite endpoint of mortality and reintervention was 5.2 ± 3.5 years (median 4.5 years [2.5–7.5]) and mean follow-up of the last computed tomography was 358 ± 184 days, (median 389 days [268-475]).

Patient characteristics

A patent false lumen was present in 81% of patients (n=127/156) at 1-year follow-up. In 7% of patients (n=10), the false lumen extent changed between 30-day and 1-year follow-up. At discharge, 36% of patients (n=56) received anticoagulation treatment; 18 patients were treated with NOAC, and 38 patients received warfarin of which one was treated 3 months postoperative due to biological valve prosthesis (institution protocol at the time) and all others were indefinite due to atrial fibrillation or mechanical valve prosthesis. The control group (n=100) consisted of patients who did not receive anticoagulation treatment (n=45), received low dose aspirin (75mg) (n=51), or received other treatments (n=4). Of these, one patient received aspirin and dipyridamole, one low dose low molecular weight heparin (LMWH), one aspirin and low dose LMWH, and one full dose LMWH. None of the patients on LMWH were treated for longer than 3 months postoperatively. During the inclusion period, the in-hospital mortality was 13.6% (n=39) and surgical mortality (30-day or in-hospital mortality) was 13.9% (n=40) for all patients undergoing surgery for ATAAD (n=287).

The perioperative patient characteristics in relation to anticoagulation therapy are presented in Table II.1 and Table II.2. Patients with anticoagulation treatment were younger (59.0 ±13.3 vs 61.9 ±9.3, p=0.01), less frequently treated with ACE-inhibitors preoperatively (14% vs 30%, p=0.03), and more often operated with aortic root replacement procedure (62% vs 10%, p<0.001).

Predictors of false lumen patency

Patient and operative characteristics in relation to closed or patent false lumen are presented in Table II.3 and Table II.4. The use of a hemiarch procedure (p=0.03) and preoperative treatment with betablocker (p=0.02) reduced the risk of patent false lumen in univariable analysis. The need for transfusion with platelets as well as fibrinogen supplement was higher in the patent false lumen group (p=0.03 and p=0.01, respectively). However, transfusion with red blood cells or plasma did not differ between groups nor did rates of reoperation for bleeding or massive bleeding.

The multivariable model showed that betablocker treatment (OR 0.24, CI 95% 0.08-0.68, *p*=0.007) and hemiarch replacement (OR 0.18, CI 95% 0.06-0.56, p=0.003) were associated with a reduced risk of false lumen patency whereas platelet transfusion was an independent predictor of false lumen patency (OR 1.30, CI 95% 1.03-1.64, *p*=0.03) (Table II.5).

Predictors of reintervention

During follow-up, 25 patients had surgical or endovascular reinterventions. Eighteen patients underwent open thoracic surgery, 12 on the distal aorta (6 on the aortic arch, 7 on the descending aorta) and 11 on the proximal aorta. Eight patients had endovascular surgery, three of whom were treated with thoracic endovascular aortic repair (TEVAR) and two with fenestrated endovascular aortic repair (FEVAR). The remaining three patients were treated with stents in the mesenteric artery, the renal arteries, or the internal iliac artery. There were two deaths associated with these reoperations, one of whom presented with rapid dilatation of the proximal descending aorta and suspected infection or aortitis and had open arch surgery, and one of whom had been operated initially for ATAAD with a biological valve and root replacement and was later reoperated with a homograft due to endocarditis and a proximal descending aortic aneurysm of eight cm requiring replacement with a frozen elephant trunk.

Survival and freedom of reintervention

The Kaplan-Meier estimates for survival in patients who were discharged and thus included in this study were 100% vs. 99%, 96% vs. 98%, and 88% vs. 85% at 1, 2, and 5 years, respectively (log rank *p*=0.43) in patients with or without anticoagulant treatment (Figure II.1). Corresponding estimates for the composite endpoint of survival and freedom of reintervention were 94% vs. 96%, 86% vs. 90%, and 76% vs. 75% at 1, 2, and 5 years, respectively (log rank *p*=0.76). Also, false lumen status did not have a significant impact on survival (97% vs. 100%, 97% vs. 98%, and 93% vs. 84%) at 1, 2, and 5 years, respectively in patients with a patent and occluded false lumen (log rank *p*=0.21) (Figure II.2). Neither did the composite endpoint of survival and freedom of reintervention (96 vs 94%, 90 vs 86% and 75 vs 76% at 1, 2, and 5 years, respectively, log rank *p*=0.09). Freedom from reoperation did not differ between groups (100 vs 98%, 95 vs 92% and 95 vs 87% at 1, 2, and 5 years, respectively, log rank *p*=0.25).

Predictors of missing

Unpublished data of predictors of missing computed tomography scans were performed post-publication. A logistic regression model including age, sex, year of surgery and civil registration address showed significant correlation with civil registration address outside Region Skåne (OR 10, CI95% 4.9-21, *p*<0.001).

Table II.1 Preoperative characteristics dependent on anticoagulation

	No anticoagulation (*n*=100)	Warfarin or NOAC (*n*=56)	*p*-value
Patent false lumen	79 (79%)	48 (86%)	0.39
Age (years)	61.9 ±9.3	59.0 ±13.3	0.01
Female	27 (27%)	17 (30%)	0.71
Hypertension	52 (52%)	23 (41%)	0.19
Thoracic aneurysm	9 (9%)	5 (9%)	1
Marfan	7 (7%)	5 (9%)	0.67
Other connective disease	1 (1%)	1 (2%)	1
BAV	2 (2%)	2 (4%)	0.62
PVD	1 (1%)	1 (2%)	1
DM	25 (25%)	8 (14%)	0.12
Hyperlipidemia	5 (5%)	2 (4%)	1
Stroke	4 (4%)	2 (4%)	1
CKD	1 (1%)	1 (2%)	1
COPD	7 (7%)	1 (2%)	0.26
CAD	6 (6%)	1 (2%)	0.42
Smoking history	30 (30%)	14 (25%)	0.48
BMI	26.1 ±3.9	27.1 ±4.5	0.18
Betablocker	18 (18%)	8 (14%)	0.52
ACE inhibitor	29 (30%)	8 (14%)	0.03
Systolic blood pressure (mmHg)	127 ±35	118 ±32	0.18
Diastolic blood pressure (mmHg)	72 ±21	65 ±17	0.08

Values are expressed as numbers (%) or mean ±SD. BAV, bicuspid aortic valve; PVD, periferal vascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; BMI, body mass index; ACE, angiotensin converting enzyme.

Table II.2 Intra- and postoperative characteristics dependent on anticoagulation

	No anticoagulation (*n*=104)	Warfarin or NOAC (*n*=52)	*p*-value
Proximal surgery			<0.01
-Supracoronary graft	85 (85%)	19 (34%)	
-Bentall procedure	9 (9%)	33 (59%)	
-Mechanical	0	28 (54%)	
-Bioprosthesis	9 (9%)	5 (9%)	
-David/Yacoub	4 (4%)	0	
-AVR and supracoronary graft	2 (2%)	4 (7%)	
Distal surgery			0.55
-Ascending aortic graft	77 (77%)	46 (82%)	
-Hemiarch	15 (15%)	5 (9%)	
-Arch	8 (8%)	5 (9%)	
Crossclamp	5 (5%)	3 (5%)	1
Primary tear excised	62 (62%)	36 (66%)	0.67
GRF Glue	65 (65%)	29 (52%)	0.11
CPB time (min)	192±54	218±60	0.28
HCA time (min)	24±10	23±10	0.39
Arterial cannulation			0.11
-Femoral	75 (75%)	50 (89%)	
-Subclavia	3 (3%)	2 (4%)	
-Ascending aorta or arch	19 (19%)	4 (7%)	
-Left ventricle	3 (3%)	0	
Reop bleeding	11 (11%)	1 (2%)	0.06
Plasma (units)	4.5 ±4.4	3.7 ±4.3	0.32
Platelets (units)	3.6 ±2.8	3.5 ±2.2	0.97
Red blood cells (units)	5.5 ±5.1	4.1 ±3.9	0.07
Fibrinogen[1] (g)	5.2 ±3.4	5.0 ±2.6	0.79
Recombinant FVII	23 (39%)	11 (30%)	0.39
Bleeding 24h (ml)	860 ±660	702 ±306	0.17
Massive bleeding[2]	23 (23%)	6 (11%)	0.06

Values are expressed as numbers (%) or mean ±SD. AVR, aortic valve replacement; GRF, Gelatin Resorcinol Formaldehyde; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest.
[1] 60 missing values (38%) [2] according to BART criteria

Table II.3. Preoperative characteristics dependent on false lumen status

	No false lumen (*n*=29)	Patent false lumen (*n*=127)	*p*-value
Age (years)	63.6 ±11.6	60.2 ±10.7	0.14
Female	12 (41%)	32 (25%)	0.08
Hypertension	15 (52%)	60 (47%)	0.70
Thoracic aneurysm	3 (10%)	11 (9%)	0.73
Marfan	3 (10%)	9 (7%)	0.55
Other connective disease	0	2 (2%)	
BAV	0	4 (3%)	
PVD	1 (3%)	1 (1%)	0.34
DM	8 (28%)	25 (20%)	0.35
Hyperlipidemia	2 (7%)	5 (4%)	0.62
Stroke	0	6 (5%)	0.59
CKD	0	2 (2%)	
COPD	4 (14%)	3 (3%)	0.04
CAD	3 (10%)	4 (3%)	0.12
Smoking history	7 (24%)	37 (29%)	0.57
BMI	25.8±4.8	27.1±4.9	0.20
Betablocker	9 (28%)	17 (14%)	0.02
ACE inhibitor	8 (28%)	29 (23%)	0.62
Systolic blood pressure (mmHg)	125 ±35	124 ±34	0.83
Diastolic blood pressure (mmHg)	73 ±20	69 ±21	0.38

Values are expressed as numbers (%) or mean ±SD. BAV, bicuspid aortic valve; PVD, periferal vascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; BMI, body mass index; ACE, angiotensin converting enzyme.

Table II.4. Intra- and postoperative characteristics dependent on false lumen status

	No false lumen (*n*=29)	Patent false lumen (*n*=127)	*p*-value
Proximal surgery			0.09
Supracoronary graft	23 (79%)	81 (64%)	
Bentall procedure	4 (14%)	38 (30%)	8
Mechanical	3 (10%)	25 (20%)	
Bioprosthesis	1 (3%)	13 (10%)	
David/Yacoub	1 (3%)	4 (3%)	1
AVR and supracoronary graft	1 (3%)	3 (4%)	
Distal surgery			0.03
Ascending aortic graft	19 (66%)	104 (82%)	
Hemiarch	8 (27%)	12 (9%)	
Arch	2 (7%)	11 (9%)	
Crossclamp	4 (9%)	4 (4%)	0.21
Primary tear excised	20 (69%)	78 (62%)	0.48
GRF Glue	19 (66%)	75 (59%)	0.52
CPB time (min)	191 ±43	204 ±60	0.28
HCA time (min)	21.5±8.8	23.5±11.0	0.28
Arterial cannulation			0.86
Femoral	24 (83%)	101 (80%)	
Subclavia	1 (3%)	4 (3%)	
Ascending aorta or arch	4 (14%)	19 (15%)	
Left ventricle	0	3 (2%)	
Reop bleeding	1 (3%)	11 (9%)	0.47
Plasma (units)	3.9 ±5.4	4.3 ±4.1	0.72
Platelets (units)	2.6 ±2.1	3.5 ±2.7	0.03
Red blood cells (units)	5.6 ±6.5	4.8 ±4.3	0.44
Fibrinogen[1] (g)	3.2 ±2.0	5.4 ±3.2	0.01
Recombinant FVII	3 (20%)	31 (38%)	0.24
Bleeding 24h (ml)	673 ±370	853 ±524	0.17
Massive bleeding[2]	5 (17%)	24 (19%)	0.84
Anticoagulation			
NOAC	19 (41%)	32 (30%)	0.18
Warfarin	8 (17%)	31 (29 %)	0.12

Values are expressed as numbers (%) or mean ±SD. AVR, aortic valve replacement; GRF, Gelatin Resorcinol Formaldehyde; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest.
[1] 60 missing values (38%) [2] according to BART criteria

Table II.5 Multivariable logistic regression analysis evaluating predictors of a patent false lumen

Multivariate logistic regression			
	OR	CI95%	*p*-value
Betablocker	0.24	0.08-0.68	0.007
Distal surgery:			
Supracoronary graft	1		
Hemiarch[1]	0.18	0.06-0.56	0.003
Arch[1]	0.83	0.16-4.3	0.82
Platelets (units)	1.30	1.03-1.64	0.03
Age			ns
Sex			ns
CAD			ns
Anticoagulation			ns

CAD, coronary artery disease.
[1]Compared to supracoronary graft

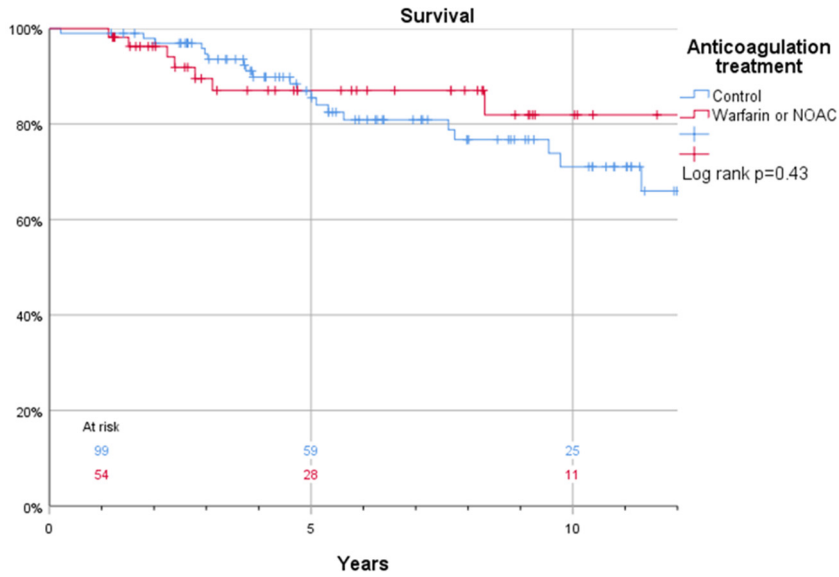

Figure II.1 Kaplan-Meier analysis of survival in patients with anticoagulation treatment

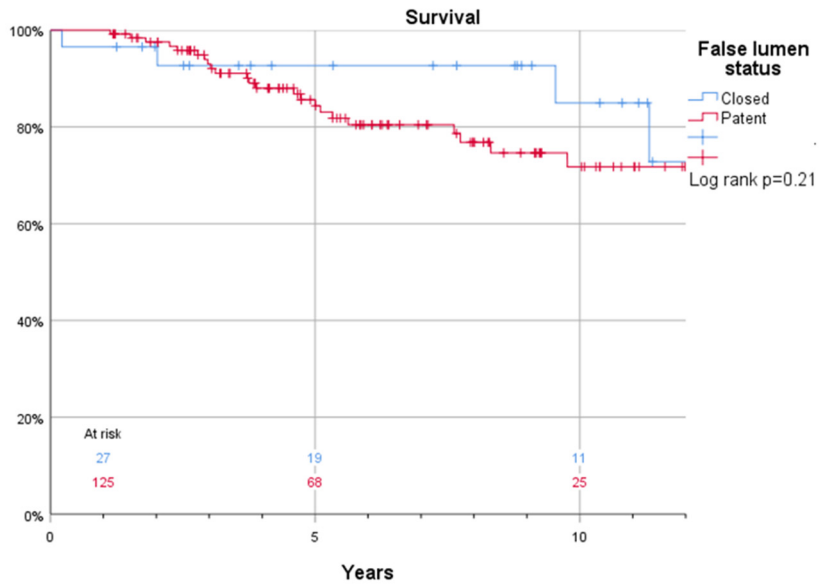

Figure II.2 Kaplan-Meier analysis of survival based on false lumen status

4.3 Study III

Patient characteristics

Patient characteristics are presented in Table III.1 and intraoperative data in Table III.2. Bicuspid aortic valve was less common in the ATAAD group (0% vs 32%, $p<0.01$), as was root replacements (4% vs 80%, $p<0.001$) compared to the control group. Cardiopulmonary bypass time was shorter in the ATAAD group (160 min ±36 vs 208 min ±60, $p<0.01$) as well as aortic cross-clamping (75 min ±31 vs 139 min ±44, $p<0.001$). The lowest core temperature was significantly lower in the ATAAD group (20.0°C ±2.8 vs 30.5°C ±3.1, $p<0.001$).

Table III.1

	ATAAD (*n*=23)	**Control (*n*=20)**	***p*-value**
Age (years)	64.6 ±11.1	59.2 ±14.2	0.17
Sex (Female)	7 (30%)	3 (15%)	0.29
Hypertension	14 (61%)	11 (55%)	0.70
Marfan	0 (0%)	2 (10%)	0.21
Other connective disorder	0 (%)	0 (0%)	1
Bicuspid valve	0 (0%)	6 (32%)	<0.01
Aortic aneurysm	6 (26%)	20 (100%)	<0.001
Diabetes	0 (0%)	1 (5%)	0.47
Smoking history	7 (30%)	4 (27%)	1
Chronic kidney disease	1 (4%)	0 (0%)	1
COPD	0 (0%)	1 (5%)	0.47
Stroke	1 (4%)	0 (0%)	1
Aspirin	3 (13%)	2 (10%)	1
Hyperlipidemia	1 (4%)	6 (30%)	0.04

Values are expressed as numbers (%) or mean ±SD. ATAAD, acute aortic dissection; COPD, chronic obstructive pulmonary disease.

Table III.2

	ATAAD (*n*=23)	Control (*n*=20)	*p*-value
Proximal surgical technique			<0.001
Supracoronary graft	21 (91%)	3 (6%)	
Supracoronary graft AVR	1 (4%)	1 (5%)	
Root replacement	1 (4%)	16 (80%)	
Valve sparing root replacement	0 (0%)	8 (40%)	
Bentall	1 (4%)	8 (40%)	
Distal surgical technique			0.04
Supracoronary graft	21 (91%)	16 (80%)	
Hemiarch	0 (0%)	4 (20%)	
Arch	2 (9%)	0 (0%)	
Arterial cannulation			<0.001
Femoral	18 (78%)	0 (0%)	
Arch	1 (4%)	17 (85%)	
Other	4 (17%)	3 (15%)	
Symptom duration (h)	7.0 (3.9)		
Operation time (min)	298 ±72	322 ±79	0.10
CPB time (min)	160 ±36	208 ±60	<0.01
Cx time (min)	75 ±31	139 ±44	<0.001
HCA time (min)	21.6 ±10.5	3.6 ±8.2	<0.001
SCP modality			<0.001
Circulatory arrest	14 (61%)	0 (0%)	
SABP	9 (39%)	4 (20%)	
SCP time		0	<0.001
Lowest core temp (°C)	20.0 ±2.8	30.5 ±3.1	<0.001
Circulatory arrest time (min)	17.9 ±5.8	0	<0.01
Intraoperative bleeding (ml)	2407 [1805-3204]	1410 [917-1920]	<0.001

Values are expressed as numbers (%), mean ±SD or median [IQR]. ATAAD, acute aortic dissection; AVR, aortic valve replacement; CPB, cardiopulmonary bypass; Cx, crossclamp; HCA, hypothermic circulatory arrest; SCP, selective cerebral perfusion; SABP, selective antegrade brain perfusion.

ROTEM

ROTEM data is presented in Figure III.3. At T_0 there was no significant difference in clotting time (CT) in INTEM (Figure III.3.a) or HEPTEM (Figure III.3.b) between groups (159s [140-170] vs 170s [159-180], p=0.08 and 156s [138-168] vs 163s [150-180], p=0.21). During CPB, HEPTEM CT increased markedly in both groups and was significantly higher in the ATAAD group at T_2 (212s [202-239] vs 198s [193-236], p=0.05). At the end of surgery (T_3), the HEPTEM CT recovered, although not to preoperative levels and was significantly higher in the ATAAD group (187s [166-203] vs 166s [151-173], p<0.01). The CT in INTEM and HEPTEM was significantly more prolonged in the ATAAD group at T_3 compared to T_0 (191s [179-211] vs 159s [140-170], p<0.01 and 187s [166-203] vs 156s [138-168], p<0.01). In the control group, INTEM CT was significantly longer at T_3 compared to T_0 (184s [162-196] vs 170s [159-180], p=0.03) but not HEPTEM CT (166s [151-173] vs 163s [150-180], p=0.93).

EXTEM

There was a significant difference in EXTEM CT (Figure III.3.c) at T_2 (87s [76-107] vs 76s [73-84], p=0.03) and a trend towards it at T_3 (59s [54-67] vs 64s [60-68], p=0.07). At the end of surgery, CT in the control group was significantly longer than preoperative levels (64s [60-68] vs 60s [56-65], p=0.05) and in the ATAAD group there was a trend towards shorter CT compared to preoperative (59s [54-67] vs 62s [56-71], p=0.06).

The maximum clot firmness (MCF) in EXTEM (Figure III.3.d) was lower in the ATAAD group compared to the control group at T_1, T_2, and T_5 (41mm [34-41] vs 55mm [51-61], p<0.001, 50mm [44-55] vs 57mm [54-62], p=0.001 and 69mm [66-72] vs 73mm [72-74], p=<0.01, respectively). EXTEM MCF was also lower in the control group at the end of surgery compared to preoperative levels (61mm [59-65] vs 64mm [58-68], p=0.02) but not in the ATAAD group (61mm [58-64] vs 59mm [56-65], p=0.15). Clot firmness at 10 minutes (A10) showed similar pattern and is presented in Figure III.3.e.

FIBTEM

The preoperative FIBTEM MCF (Figure III.3.f) was significantly lower in the ATAAD group compared to the control group (12.0mm [10.0-15.0] vs 16.5mm [13.5-20.0], p=0.03), and the pattern persisted during the operation (at T_1 9.0mm [5.5-11.5] vs 13.0mm [10.0-16.3], p<0.01 and at T_2 9.0mm [7.0-12.0] vs 13.5mm [11.3-15.0], p<0.01). There was no difference in FIBTEM MCF at T_3 or T_4 (p=0.91 and p=0.51, respectively), however at T_5, MCF was again lower in the ATAAD group (28.5mm [25.0-37.3] vs 37.0mm [35.0-38.0], p<0.01). A10 clot firmness followed the same pattern and is shown in Figure III.3.g.

Figure III.a-g

Bleeding, Transfusions and Medical Management

Data presented in Table III.3 reveal that patients in the ATAAD group received significantly more transfusions and procoagulants during surgery and the first 24 hours after surgery. Transfusion of packed red blood cells (3.3U ±4.0 vs 1.2U ±1.5, p=0.03), platelets (4.3U ±1.7 vs 2.5U ±1.6, p=0.001) and FFP (2.4U ±2.6 vs 0.6U ±1.2, p<0.01) was larger in the ATAAD group. The use of fibrinogen (6.0g ±3.4 vs 3.1g ±2.5, p<0.01), PCC (1780IU ±1050 vs 775IU ±896, p<0.01) and recombinant factor VIIa (5 (22%) vs 0 (0%) patients, p=0.03) also were significantly larger in the ATAAD group. No patient was reoperated for bleeding in both groups and postoperative bleeding volumes at 12h (492ml ±235 vs 498ml ±175, p=0.64) and 24h (810ml ±400 vs 740ml ±215, p=0.78) did not show any difference between groups.

Table III.3.

	ATAAD (*n*=23)	**Control (*n*=20)**	***p*-value**
Early mortality	1 (4%)	0 (0%)	1
Chest output (ml)			
12h	492 ±235	498 ±175	0.64
24h	810 ±400	740 ±215	0.78
Transfusions			
Packed red blood cells (U)	3.3 ±4.0	1.2 ±1.5	0.03
Intraoperative	1 [0-2]	0 [0-0]	0.003
Platelets (U)	4.3 ±1.7	2.5 ±1.6	0.001
Intraoperative	3.8 ±1.2	1.8 ±1.6	<0.001
Fresh frozen plasma (U)	2.4 ±2.6	0.6 ±1.2	<0.01
Intraoperative	0 [0-2]	0 [0-0]	0.70
Fibrinogen (g)	6.0 ±3.4	3.1 ±2.5	<0.01
Intraoperative	5.8 ±2.4	2.9 ±2.3	<0.001
Novoseven	5 (22%)	0 (0%)	0.03
Intraoperative	5 (22%)	0 (0%)	0.03
Antithrombin	2 (9%)	2 (10%)	1
Tranexamic acid (g)	3.5 ±0.9	3.9 ±0.4	0.03
Desmopressin (µg)	11.6 ±14.1	15.8 ±14.8	0.31
Intraoperative	11.6 ±14.1	15.8 ±14.8	0.31
PCC (IE)	1780 ±1050	775 ±896	<0.01
Intraoperative	1583 ±985	575 ±815	<0.001
Re-exploration for bleeding	0 (0%)	0 (0%)	1
Postoperative stroke	5 (22%)	1 (5%)	0.19
Dialysis (RRT)	3 (13%)	0 (0%)	0.24
Prolonged ventilation (>48h)	8 (35%)	0 (0%)	<0.01
ICU stay (days)	6.7 ±6.8	1.4 ±0.8	<0.001

Values are expressed as numbers (%) or mean ±SD. ATAAD, acute aortic dissection; PCC, prothrombin complex concentrate; RRT, continuous renal replacement therapy; ICU, intensive care unit.

4.4 Study IV

Patient and Operative Characteristics

Patient and operative characteristics are presented in Table IV.1. The MIMVS population had lower mean age (55 years ±11 vs 62 years ±12, p=0.02), a lower EuroScore II (0.7 8±0.36 vs 1.11 ±0.72, p=0.019), and a lower rate of preoperative treatment with aspirin (0 (0%) vs 8 (22%), p=0.005). One patient (3%) was converted to sternotomy and one patient (3%) in the sternotomy group had valve replacement due to repair failure. MIMVS had longer cardiopulmonary bypass times (127 minutes [115-146] vs 79 minutes [65-112], p<0.001), and were cooled to a lower body temperature (34°C vs 36°C, p=0.04), when compared to the sternotomy group. There was no in-hospital mortality in either group.

Coagulopathy and transfusions

Antithrombin levels were significantly higher in the minimally invasive group both preoperatively (0.90 IU/L ±0.10 vs 0.85 IU/L ±0.11, p=0.03) and at the end of the surgical procedure (0.76 IU/L ±0.10 vs 0.71 IU/L ±0.13, p=0.02), but no significant differences could be detected at postoperative day 1 or 3. No significant differences were observed in levels of D-dimer, PT-INR, aPTT, or platelets at any time point. ROTEM CT did not differ at any point in time between the groups, neither did MCF in EXTEM nor FIBTEM. The number of patients receiving transfusions before discharge was lower in MIMVS (14% vs 35%, p=0.04), and chest tube output was lower (395 ml [190-705] vs 570 ml [400-1040], p=0.04). Transfusion and bleeding data is presented in Table IV.2.

Inflammatory reaction

IL-6 was lower in the minimally invasive group compared to the conventional sternotomy group when measured at the end of the surgical procedure (38 ng/L [23-69] vs 61 ng/L [41-139], p=0.01), but no statistically significant differences were demonstrated at other time points. Procalcitonin was higher in the minimally invasive group compared to the conventional sternotomy group on postoperative day 1 (0.50 µg/L [0.35-1.00] vs 0.30 µg/L [0.16-0.49], p=0.008). CRP levels were reduced in the minimally invasive group compared to the conventional sternotomy group when measured on postoperative day 1 (38 mg/L [32-48] vs 61 mg/L [50-78], p<0.001). There were no differences in leukocyte counts between the two groups at any time.

Table IV.1 Patient and operative characteristics

	MIMVS (n=35)	Conventional group (n=36)	*p* value
Age (years)	56 ±11	62 ±12	0.02
Female gender	3 (9)	8 (22)	0.11
Heigth (cm)	178 ±8	177±10	0.67
Weight (kg)	76 ±9	83 ±16	0.07
Hypertension	11 (32)	17 (47)	0.20
Diabetes	1 (3)	1 (3)	0.98
COPD	0	1 (3)	0.32
Creatinine	80 ±13	84 ±16	0.21
Preoperative LVEF 30-50%	2 (6)	2 (6)	1
Preoperative LVEF <30%	0	0	
NYHA Class III-IV	6 (17)	1 (3)	0.11
Pulmonary hypertension (>60mmHg)	6 (17)	2 (6)	0.26
Previous AFib	2 (6)	6 (17)	0.15
Peripheral vascular disease	0	0	1
Previous cardiac surgery	0	0	1
EuroScore 2	0.78 ±0.36	1.11 ±0.72	0.019
Preoperative ASA	0	8 (22)	0.005
CPB time (min)	127 [115-146]	79 [65-112]	<0.001
Aortic cross clamp (min)	76 [58-82]	56 [42-90]	0.07
Lowest temperature (°C)	34 [33-36]	36 [35-36]	0.04
Conversion to sternotomy	1 (3)		NA
Mitral valve replacement	0	1 (3	0.43
Post operative MR			
None	28 (80)	24 (67)	
Trace	6 (17)	8 (22)	
Grade 1	0	1 (3)	

Values were expressed as number and percentage (%), mean ± SD, or median [IQR]. ASA: acetyl salicylic acid; CPB: cardiopulmonary bypass; MR: mitral regurgitation; Afib: Atrial fibrillation.

Table IV.2 Bleeding and transfusions

	MIMVS (n=35)	Conventional group (n=36)	*p* value
Bleeding/drain volume (ml)	395 [190-705]	570 [400-1040]	0.04
Revision bleeding	1 (3%)	1 (3%)	0.98
Any transfusion	5 (14%)	12 (35%)	0.04
Packed RBC	3 (9%)	8 (24%)	0.09
Plasma	1 (3%)	6 (17%)	0.11
Platelets	3 (9%)	7 (19%)	0.31

Values were expressed as number and percentage (%), or as median [IQR]. RBC: packed red blood cells.

5 Discussion

5.1 Study I

In this study, no significant association between patient blood group and postoperative bleeding complications in the setting of ATAAD surgery could be demonstrated. Additionally, there was no difference between blood group O and non-O patients with respect to blood components transfused, however blood group O patients received significantly more fibrinogen concentrate. It has been described that blood group O patients have 25% lower levels of vWF compared with non-O patients[98], with concurring decrease in risk for both venous and arterial thromboembolism, including perioperative myocardial infarction and cerebrovascular stroke[31]. Therefore, one could speculate that blood group O patients would be more inclined towards developing bleeding complications following surgical procedures, but previous reports have shown diverging results[33,99-101].

In cardiac surgery, a large retrospective study with 13 627 patients showed reduced RBC transfusion in AB blood group in patients operated with CABG[101]. Nevertheless, both the aortic dissection and deep hypothermia during CPB cause major additional changes to the coagulation system and therefore, results from routine cardiac procedures cannot be assumed applicable to ATAAD surgery. Our study did not demonstrate any effect of patient blood group on bleeding outcomes in surgery with an elevated risk of bleeding complications. Nonetheless, it did however show that blood group O patients received significantly more fibrinogen concentrate than non-O patients (6.1±4.0 vs. 4.9±3.3 g, p=0.023). Although the effect of blood group on vWF and factor VIII levels is well known, there is no established evidence to suggest that blood group would influence fibrinogen concentrations[102].

Although our centre utilizes a ROTEM-advised transfusion strategy, the final decision is always at the hand of the surgeon. Therefore, although the difference in fibrinogen administration was not driven by patient blood group directly, more fibrinogen might have been administered to patients with a more distinct bleeding pattern during the operation. However, as the decision-making is similar for all procoagulant drugs and transfusions, but fibrinogen was the only product that differed between the groups, the observation might be a chance finding.

Plasma vWF is crucial for primary haemostasis and it has been shown that blood group O is associated with reduced levels of vWF. However, aortic dissection causes an increase in vWF activity[103,104] and procedure-induced increment in vWF activity could counteract the effects of the reduced levels of VWF in blood group O patients[98]. This could possibly explain the absence of difference in major bleeding, transfusion requirements, chest tube output and procoagulants between type O and non-O patients in ATAAD surgery.

Earlier studies have suggested that the lowest activity of factor VIII and vWF is observed in genotype O/O, intermediate in A1O/BO and the highest activity in A1A/A1B/BB [98]. Furthermore, it has been demonstrated that VWF antigen levels correlate to the number of O1 alleles and that the O1 allele is responsible for the strongest reduction in risk for MI[105]. We only assessed the phenotype of patients, rather than their genotype and speculate that we could be failing to identify an effect of the O1 allele by looking at blood group rather than polymorphisms of the individual alleles.

5.2 Study II

In this study, anticoagulation treatment had no significant impact on the incidence of a false lumen patency within the first postoperative year after surgery for ATAAD. Postoperative beta-blocker treatment reduced the risk of patent false lumen, but false lumen patency was neither associated with impaired survival nor the need for reintervention.

In the current study, we hypothesized that postoperative anticoagulation therapy maintains a patent false lumen. Data in the present study showed that anticoagulation treatment was not associated with a higher incidence of patent false lumen, in line with previous publications by Song et al[106] and von Kodolitsch[53], in contrast to the study by Gariboldi et al[52]. Song et al demonstrated better survival in the anticoagulation group, however we could not replicate these findings. Although there are no current recommendations regarding the use of anticoagulation following ATAAD repair, many physicians believe anticoagulation may have a negative effect on remodeling of the residual distal aorta. In this study, patients receiving anticoagulation were younger and primarily treated with warfarin due to implantation of a mechanical valve in a root replacement procedure, which intuitively should result in longer life expectancy.

The study in this thesis had a rather high rate of false lumen patency at 80% compared to 47-74% in previously published material and could possibly be impacted by the relatively low frequency of arch or hemiarch surgery. Suboptimal connection of the distal part of the graft implanted in the ascending aorta to the true lumen, or the presence of secondary tears in the arch or distal aorta may account for

the persistence of flow into the residual false lumen after complete surgical resection of the primary entry tear[107]. To decrease the incidence of residual patent false lumen, some authors suggest systematic extended or total arch replacement for the initial surgical management of ATAAD, irrespective of the site of entry[108,109]. Those supporting this method claim improved long-term survival[110], while others maintain no improvement in long term survival but rather increased early mortality[111]. In this study, 40% of the patients that had a hemiarch replacement had a patent false lumen compared to 84% for patients receiving a supracoronary graft. Hemiarch replacement seems to be protective against a patent false lumen at one year (OR 0.18, CI95% 0.06-0.56, *p*=0.003), which supports the increasing trend towards this surgical technique[108,109,112]. Interestingly, arch replacement did not show similar results but might be impacted by higher mortality (21% vs 15% for arch vs ascending/hemiarch replacement for all 283 patients with ATAAD) and the small number operated with this technique.

Hypertension is a known risk factor for developing aortic aneurysm and ATAAD, and the use of betablockers has been shown to reduce the growth rate of aortic aneurysm. This study shows that treatment with betablockers also is beneficial after surgery for ATAAD, reducing the risk of a patent false lumen (OR 0.24, CI95% 0.08-0.68, p=0.007), probably indicating the importance of strict postoperative blood pressure control.

The main hypothesis for this investigation was that anticoagulants increase postoperative false lumen patency. The reverse hypothesis could be that procoagulants reduce false lumen patency. Fibrinogen and recombinant factor VII have proved to reduce the need for transfusion in cardiac surgery [113,114] but neither the use of recombinant factor VII (OR 2.48, CI95% 0.65-9.49, *p*=0.19), nor the administrated dose (OR 1.09, CI95% 0.87-1.38, *p*=0.46) had a significant impact on the false lumen status. However, we did find a significant association between fibrinogen and a higher incidence of patent false lumen (OR 1.38, CI95% 1.07-1.79, *p*=0.02) in univariable analysis. Due to numerous missing values, fibrinogen was not included in the multivariable model. Moreover, transfusion of platelets was also increased in patients with patent false lumen (OR 1.30, CI95% 1.03-1.64, *p*=0.03). These contradicting findings may merely reflect a more severe coagulopathy, requiring larger doses of procoagulant products, with the severe coagulopathy maintained by the false lumen.

Late survival in 30-day survivors was 99%, 87%, and 74% at 1, 5, and 10 years, respectively, in this study, which is comparable to contemporary data from the NORCAAD registry[50]. Time from the index operation to reoperation has been reported to be approximately five years[56,57]. In the present study, both mortality and the need for surgical/endovascular treatment increased from the third year of follow-up after ATAAD in all patients with persistent patent false lumen, which suggests that structural and/or dynamic factors responsible for dissection complications require time to develop.

5.3 Study III

The results of this study demonstrate that there are predictable and quantifiable changes in ROTEM values during surgery in ATAAD and elective aortic surgery with CPB. Surgery significantly and negatively impacted all ROTEM values assessed in this study (EXTEM CT, INTEM CT, HEPTEM CT, EXTEM MCF, and FIBTEM MCF). The greatest impairment in coagulation parameters occurred consistently in patients with ATAAD. This study demonstrated that ATAAD caused an activation of the coagulation shown in ROTEM prior to surgery (T0), which developed to coagulopathy during CPB (T1 and T2) and was not fully recovered compared to elective controls at wound closure (T3) despite significantly greater use of procoagulants and transfusions. Our ROTEM-guided transfusion protocol does not seem to catch the full need of transfusions as most of our patients received more transfusions than what ROTEM would suggest. However, bleeding volumes and the need for re-exploration for bleeding or tamponade did not differ and had favorable outcomes in both groups.

Aortic dissection leads to blood being exposed to tissue factor, extracellular collagen, and other subendothelial structures that activate the coagulation process. This is evident by the decreased MCF in FIBTEM indicating consumption of fibrinogen. MCF in EXTEM was also decreased but did not reach the level of significance. Both EXTEM and INTEM CT showed a trend towards longer clotting time, indicating reduced amounts of clotting factors. Combined, this indicates an established activation of coagulation when ATAAD develops resulting in a consumption coagulopathy. During surgery, both groups showed similar trends in all ROTEM variables, but the ATAAD group had consistently more impaired values, which could indicate that the dissection consumed coagulation factors, platelets, and fibrinogen prompted by more profound hypothermia.

At the end of surgery, both groups showed similar ROTEM findings. The ATAAD group had longer HEPTEM CT than the control group, but not INTEM CT. This indicates a reduction of factors in the intrinsic pathway in the ATAAD group and a remaining heparin effect in the control group. In the ATAAD group, FIBTEM is normalized and equal to the control group. These findings are in line with similar work by Liu et al. and Guan et al. who did serial TEG analysis on patients with ATAAD[115,116]. Data in both studies demonstrated that ATAAD initiates a consumption coagulopathy, and surgery affects fibrinogen and clotting factors more than platelets. However, TEG is not able to detect differences between intrinsic and extrinsic pathways. The studies lacked either a control group or did not provide differences between samples with heparinase.

Postoperatively, the patient was hypercoagulable in both groups, primarily in terms of MCF in FIBTEM and EXTEM, which may be explained by an increase in fibrinogen levels caused by inflammation[117]. ROTEM at day 4-5 (T5) showed

normal CT in INTEM and a prolonged CT in EXTEM in both groups. The prolonged CT in EXTEM indicates a higher threshold for extrinsic pathway activation, likely induced by increased activity by inhibiting factors such as antithrombin, protein C, and protein S. This is supported by the normal PT-INR and increased antithrombin at day five as shown previously[118].

Point-of-care testing with thromboelastometry (ROTEM or TEG) has been proven to reduce the need for red blood cell transfusion and reduce bleeding in cardiac surgery[37]. One of the main benefits is its fast results compared to routine plasma-based laboratory coagulation tests (RLT). This enables serial testing of the coagulation and allows for faster response on changes in the coagulation during and after surgery. However, ROTEM reference values have a wide range, possibly driven by the design of a whole blood test. RLT have well-established quality assurance programs with imprecision results and coefficient of variation (CV%) <5%. As several factors affect each ROTEM value, it is harder to interpret, and in the setting of complex coagulopathy, the use of both RLT and ROTEM provides a more nuanced picture[119].

To be able to use ROTEM as a substitute for RLT in a transfusion protocol it needs to adequately identify differences in coagulation seen in RLT. When comparing our ROTEM data with RLT in the same cohort, we find that ROTEM does not detect as many pathologies as RLT does. ROTEM identified all cases with low levels of fibrinogen, a finding supported by previous studies[120,121]. However, low levels of clotting factors and platelets seem to be underdiagnosed by ROTEM. In this study, ROTEM suggests that 35% of the patients require PCC or FFP, but RLT indicates that all patients have decreased levels of coagulation factors. This is also demonstrated by Rugeri et al.[121] who showed poor correlation between CT and aPTT/PT-INR. Platelet levels were also underdiagnosed by ROTEM, where only one out of seven thrombocytopenic patients were detected compared to RLT. This could be because ROTEM is a functional test and does not specifically correspond to each step in the coagulation cascade.

Our ROTEM-guided transfusion protocol was introduced in 2015. It follows a similar structure to previously published protocols [35,37,122]. The adherence to protocol in this study, however, was not always optimal. When analyzing the transfusions, all patients in the ATAAD group received platelets, fibrinogen, and PCC and/or FFP. Compared to the transfusion protocol, all patients in the ATAAD group met the criteria for PCC/FFP substitution, >80% for fibrinogen, but only 50% met the criteria for platelets and RBC at T2. This could be interpreted in different ways: either pre-emptive transfusions were used to prevent coagulopathy, or the protocol was bypassed due to clinical coagulopathy not detected by the protocol. As mentioned earlier, ROTEM failed to identify the patients with low levels of coagulation factors or platelets indicating that the ROTEM-guided algorithm used in routine surgery may not be directly translated to ATAAD or other complex

surgery. Also, our ROTEM does not contain platelet function analysis, which may explain why the algorithm was not followed for platelet transfusion.

Although ROTEM has been proven to reduce transfusions in cardiac surgery, some studies show no predictive value of ROTEM [123-126]. One potential reason might be its imprecision. In elective surgery, a preoperative test enables the patient to act as its own control, and changes in ROTEM could better be interpreted in that context. However, in the acute setting of surgery for ATAAD, the patients' preoperative values are impaired, and preoperative levels have a limited value. This is supported by several studies of ROTEM and TEG showing that comparing pre- and post CPB levels is better at predicting bleeding rather than a post CPB ROTEM/TEG analyzed with predetermined cut-off values [123-126].

5.4 Study IV

This study shows that, despite longer duration of CPB, MIMVS is associated with reduced inflammatory response and a lower transfusion rate. Furthermore, there were no differences in coagulation activation detected by ROTEM or routine lab analyses.

Minimally invasive MV repair is an established and reproducible procedure, but still, the adoption of this technique is rather limited in the cardiothoracic community. This is partly due to the relatively long learning curve 15, which usually means longer time on CPB. Prolonged time on CPB has negative effects on both coagulation and inflammation. CPB has been shown to activate proinflammatory cytokines such as IL-8 and IL-10, complement factors, and neutrophile leukocytes [82]. The inflammatory response has been shown to increase the risk of poorer outcomes. The negative effects of CPB on coagulation have been thoroughly studied and are multifactorial. CPB induces consumptive coagulopathy, which leads to a decrease in coagulation factor V, VII, VIII, and IX levels as well as a decrease in fibrinogen and platelet number and function [18].

IL-6 and CRP are well-studied inflammatory response markers and have been linked to worse outcomes in cardiac surgery patients [84-86]. In this study, we could show that MIMVS reduces IL-6 and CRP compared to conventional sternotomy, which is in line with the study by Paparella et al. who compared conventional sternotomy with minimally invasive aortic valve replacement and mitral valve repair. Both these studies further confirm the conclusion by Asimakopoulos 16 that increased IL-6 and CRP are more a product of surgical trauma rather than CPB.

Procalcitonin is another marker for inflammatory response, most used to detect bacterial infections [127], but also is elevated in non-infectious inflammatory responses [128-130] and has been associated with poorer outcomes after cardiac surgery [85,131].

Kilger et al.[132] compared procalcitonin in patients undergoing coronary bypass with conventional sternotomy with minimally invasive off-pump coronary bypass (MIDCAB) and demonstrated lower procalcitonin in the MIDCAB group. Our results contrast with their findings, with higher procalcitonin in the MIMVS group on the first postoperative day. A possible explanation could be the increased CPB time in the MIMVS. This association has been supported by several studies [133-135], although the causality of CPB-effects on procalcitonin has been debated [136,137].

ROTEM is widely used to monitor coagulation disturbances in both elective and acute settings. To the best of our knowledge, this is the first study comparing ROTEM in MIMVS to CS. Despite the longer CPB time in the MIMVS group, this study could not identify any negative effects on ROTEM variables or in routine laboratory coagulation tests. This indicates that coagulation activation is similar between groups despite the longer CPB time in MIMVS. Consequently, this suggests that the reduced bleeding volume and transfusion requirement in MIMVS is an indicator of reduced surgical trauma rather than alterations of the coagulation system.

Our data demonstrated a reduced number of transfusions and lower chest tube output in patients undergoing minimally invasive surgery. A reduction in postoperative hemorrhage and transfusion requirements has been suggested as a potential advantage of minimally invasive valve surgery. This benefit is important given the significant morbidity and mortality associated with transfusions and re-exploration for bleeding [138].

5.5 General discussion

Bleeding in cardiac surgery is a wide topic and as such has many different root causes and plans of action. Procedural and surgical technical aspects can greatly affect the bleeding risk, including inducing coagulopathy, and as such should always be under consideration. New methods, such as ROTEM, provide more information on the coagulation system, faster than before. However, more information does not always equate better; a normal ROTEM is not equivalent of normal coagulation. Even though ROTEM is a functional test, it is not done under physiological conditions, thereby possibly bypassing important steps in the coagulation. This is evident by the lack of detecting the effects of antiplatelets, direct oral anticoagulants or vWF deficiency in normal ROTEM setups. This could possibly explain the poor negative predictive value of ROTEM.

In the clinical setting, this means that ROTEM cannot be used by itself, and the assumption that a normal ROTEM in a bleeding patient is indicative of a surgical bleeding is not true. While surgical bleeding is not uncommon, neither is coagulopathy, and the two are intertwined. This further emphasizes the importance

of preventative measures on both ends, and the need for close collaboration between anaesthesiologists and surgeons. ROTEM guided transfusion algorithms should be interpreted as “guided” and not directed, as the obvious drawbacks demonstrates.

6 Limitations

Study I:

Previous studies showing an effect of blood group on bleeding outcomes have all relied on study samples much larger than the one in the current study, giving them the possibility to detect weaker associations between blood groups and measured outcomes. The current study was potentially underpowered to detect a statistically significant effect of patient blood group on the risk of postoperative bleeding but given the observed bleeding volumes in our report it is not certain that any genuine differences between the groups would be of such dignity, that it would result in a modification of bleeding management based on patient blood group.

The study is also limited by its retrospective nature and therefore, we were not able to present data on some potentially important confounders such as history of abnormal bleeding. Furthermore, although we did use an algorithm for bleeding management, the final decision-making regarding administration of procoagulant drugs and transfusions was up to the surgeon in charge and thus not completely standardized.

Study II:

The present study had several limitations. The series was not that large thus increasing the risk of type II errors and biases. However, this study population was homogenous and excluded DeBakey type II ATAAD and intramural hematomas. The study was performed retrospectively, and the indications for using anticoagulation differed. Therefore, the sole effect of the drugs on the degree of thrombosis or false lumen patency after surgical repair of ATAAD may not be generalizable. The main reason for missing examinations were due to patients referred from other regions whose examinations postoperatively are not routinely made available to the investigators. Patients in need of reoperation were most likely referred to our center due to regional agreements, lowering the risk of underestimating the need for reoperation. A longer follow-up period could possibly detect events triggered further back in time, however, the limitation to the follow-up was the lack of older examinations.

During the study period of thirteen years, substantial changes in routinely imaging surveys and advances in imaging techniques improved morphological and functional assessment. Some computed tomography examinations were performed

only in the early arterial phase, which might have led to an underestimation of the actual incidence of residual patent false lumen. Moreover, enhanced computed tomography scanning was not routinely performed in all patients who were included, and no assessment of growth rate or partial thrombosis was performed. Additionally, the examiner was not blinded to anticoagulation however, a mechanical valve is not possible to blind, and the fate of the false lumen was rarely hard to determine.

Although our surgical approach may have led to a relatively high incidence of residual patent false lumen, the long-term outcomes were acceptable and did not differ according to the status of the residual false lumen.

Study III:

There are several limitations to this study. First, the sample size is not large leaving room for type II errors. However, including more subjects would require a longer inclusion period, and smaller differences found in a larger cohort may have questionable clinical value. The use of a control group undergoing aortic surgery is of benefit, but a better-matched surgical procedure with deep hypothermic circulatory arrest could possibly have given even more insights. Adherence to the transfusion protocol was impaired, and the true effect of a ROTEM-guided protocol could not be evaluated. However, the aim of this study was originally not intended for evaluating the ROTEM-guided transfusion protocol, and the results provided are merely indicative, requiring further studies.

Study IV:

The major limitation of this study is the lack of randomization. Our groups had a different preoperative clinical profile, and the conventional group was older and had more aspirin. However, randomization was not considered feasible and ethical during study conception because patients' preference and surgeon experience play a major role in the choice of the surgical approach. Hemofiltration was only used in MIMVS group and could potentially influence inflammatory markers in either direction although evidence suggest it does not [139]. Being an exploratory analysis, a formal sample size calculation was not performed but to reduce the risk of type 2 errors, we based our sample size on previous studies of our group with similar endpoints.

7 Conclusions

Study I:

Blood group O does not seem to impact bleeding in any significant manner in ATAAD although the effect could have been alleviated by more fibrinogen concentrate substitution.

Study II:

In study II, we hypothesized that postoperative anticoagulation therapy maintains a patent false lumen. In line with several other studies in similar material, we could not prove our hypothesis, and neither could we see any impact on long term survival or the need for reintervention. This study was the largest published at the time of publication, however in a matter of weeks a similar study with similar sample size was published. They could demonstrate a higher incidence of partial thrombosis in anticoagulated patients.

Study III:

ROTEM is significantly impacted in ATAAD surgery but can be reversed with adequate transfusion and procoagulation drug therapy. However, ROTEM is not fully able to replace RLT as the single determinant for transfusion.

Study IV:

MIMVS leads to less activation of the inflammatory system and has lower bleeding volumes and transfusion frequency. There is no indication that the prolonged CPB time in MIVMS have deteriorating effects on coagulation in ROTEM.

8 Future perspectives

Bleeding is still a significant clinical problem in cardiac surgery and even though the underlying mechanisms are increasingly investigated, much remains to be explored. In some cases, such as the patient's blood group, the clinical impact might be of lesser magnitude. Coagulopathy is present in many patients, and ROTEM provides a good platform for transfusion strategy. However, in the context of severe coagulopathy as in ATAAD, the current evidence is scarce and to the author's knowledge, no studies have been conducted that explores which targets are to be met. In the meantime, new POC methods to test the coagulation have been developed, potentially reducing the need for ROTEM. ROTEM does not test platelet function, other methods have evolved to fill this gap, but the adoption has been lagging[140]. Future studies evaluating both ROTEM and platelet function tests in ATAAD could provide better algorithms for transfusions and procoagulants.

During the years of this thesis production, research on false lumen patency after ATAAD has progressed. A few weeks after the publication of the study presented in this thesis, a study with similar sample size was published in another paper. They demonstrated that partial false lumen thrombosis was more common with anticoagulation therapy. In 2023, a meta-analysis including this thesis study and four other studies, could show significant association between anticoagulation and false lumen patency (OR 1.82, CI 95% 1.22-2.71, p=0.003)[141]. No association between anticoagulation and late deaths or reinterventions could be detected. However, the causation is not determined, and future studies need to investigate the effect of underlying factors such as connective tissue diseases.

Another area that could be explored is postoperative atrial fibrillation after ATAAD surgery and treatment with anticoagulation medications. A common complication after open cardiac surgery is new-onset atrial fibrillation and many of these patients are put on anticoagulation treatment to prevent thromboembolic events. However, there are no studies investigating the risks and benefits of this treatment after ATAAD surgery. Also, there are remedies that could be made during surgery to reduce the risk of thromboembolic events in case of atrial fibrillation and could potentially tip the scale in favors of no anticoagulation treatment in postop atrial fibrillation.

Acknowledgements

This project has been a long undertaking and would not have seen the light of day without the contribution of so many. I would like to express my gratitude to all of you and hope to be able to repay you somehow.

Dr Shahab Nozohoor, you have been my senior supervisor for eight years. During this time, you have helped me with everything from big to small, in clinical practice and in research. You have been a true inspiration, with great surgical skill, clinical reasoning, and encouragement, setting a standard that I hope to achieve some day.

Dr Johan Sjögren, one of my co-supervisors. Together with Shahab, you hired me for my first job as a doctor and has since taught me so much; from performing my first sternotomy and my first cardiac procedure, to serious things such as the importance of reflection. I just wished we had the same sense of humour.

Dr Igor Zindovic, my second co-supervisor, who started out as a fellow PhD-student and during my thesis time have accomplished the stunning feat of becoming an associate professor, amongst much else. You are an inspiration in research productivity and results. I really appreciate our discussions on everything from surgical complications to managing family life. It is hard not to like you, even though I tried at first!

Dr Henrik Bjursten, you were the first to introduce me to the scientific community with the EPRICS trial. You have also been a great teacher in the cath lab, providing great skills to access the distal part of the aorta.

Dr Per Wierup, you have helped med tremendously in my surgical development and I am truly impressed by the way you make hard things look easy.

Dr Sigurdur Ragnarsson, colleague, I really appreciate our talks on clinical and personal difficulties. Some of them have been life changing.

Dr Jacob Ede and Dr Karl Terneau-Hermansson, two fellow PhD-students and colleagues, you provided me with a lot of the motivation to finish this thesis and its portifolio. It is always fun to be around you.

Dr Ronny Gustafsson, my clinical supervisor during the residency, I relish your stories about the “good” old days to put things in perspective and am thankful for the opportunities you have given me as supervisor and (now former) boss.

Dr Erik Herou, I really appreciate our discussions on everything from surgery to the best running shoes. I would also like to thank you for not finishing your thesis before me, it has been comforting to see someone with similar priorities as me.

I would also like to thank all the remaining co-authors to my papers. Dr Henrik Gunè, who contributed at least as much as me in the first paper and was an inspiration for my now early morning training sessions. Dr Gracijela Bozovic, a great radiologist, who guided me through the initially difficult to interpret CT scans.

Finally, I would like to thank those closest to me.

Mor, Kristina Helander, genom ständigt spännande kliniska berättelser fick du mig att söka in till läkarprogrammet utan att någonsin fråga om jag ville, och när jag berättade att jag skulle vikariera som underläkare på thorax omedelbart konstaterade "Mårten Larsson, thoraxkirurg" som om det redan då var bestämt. Jag har alltid uppskattat våra medicinska diskussioner, även om du ibland har svårt att avsluta dina meningar.

Min far, Kaj Larsson, du har själv disputerat inom ett långt svårare ämne bara ett år efter jag föddes vilket jag alltid har beundrat och som bara förstärkts under arbetet med min egen avhandling. Förhoppningsvis är jag nu lika djupt insatt i saker som inte så många andra förstår.

Mina syskon, Johan, Fredrik, Sara, Anna och Henrik, för att ni finns och låter mig vara er dryga bror. Och Fredrik, vi vet båda två att den hickan var på låtsas.

Sofie, jag är dig tacksam för så mycket. Du har gjort ypperliga illustrationer till denna avhandling och jag har verkligen uppskattat när vi arbetat med dem. Du har låtit mig driva genom mina projekt utan att tappa fotfästet hemma och du är en fantastisk mamma till våra två döttrar, Ninne och Agnes.

Ninne och Agnes, ni är mina ögonstenar.

Funding

The author received funding from Olle Dahlbäck's fund.

References

1 Cortes, G. A., Moore, M. J. & El-Nakeep, S. in *StatPearls* (2024).

2 Madamanchi, A., Santoro, S. A. & Zutter, M. M. in *I Domain Integrins* (ed Donald Gullberg) 41-60 (Springer Netherlands, 2014).

3 Tanaka, K. A., Key, N. S. & Levy, J. H. Blood coagulation: hemostasis and thrombin regulation. *Anesth Analg* **108**, 1433-1446 (2009). https://doi.org:10.1213/ane.0b013e31819bcc9c

4 Chaudhry, R., Usama, S. M. & Babiker, H. M. in *StatPearls* (2024).

5 Varga-Szabo, D., Pleines, I. & Nieswandt, B. Cell adhesion mechanisms in platelets. *Arterioscler Thromb Vasc Biol* **28**, 403-412 (2008). https://doi.org:10.1161/ATVBAHA.107.150474

6 Grover, S. P. & Mackman, N. Intrinsic Pathway of Coagulation and Thrombosis. *Arterioscler Thromb Vasc Biol* **39**, 331-338 (2019). https://doi.org:10.1161/ATVBAHA.118.312130

7 Long, A. T., Kenne, E., Jung, R., Fuchs, T. A. & Renne, T. Contact system revisited: an interface between inflammation, coagulation, and innate immunity. *J Thromb Haemost* **14**, 427-437 (2016). https://doi.org:10.1111/jth.13235

8 Drake, T. A., Morrissey, J. H. & Edgington, T. S. Selective cellular expression of tissue factor in human tissues. Implications for disorders of hemostasis and thrombosis. *Am J Pathol* **134**, 1087-1097 (1989).

9 Hoffman, M. A cell-based model of coagulation and the role of factor VIIa. *Blood Rev* **17 Suppl 1**, S1-5 (2003). https://doi.org:10.1016/s0268-960x(03)90000-2

10 Besser, M. W. & MacDonald, S. G. Acquired hypofibrinogenemia: current perspectives. *J Blood Med* **7**, 217-225 (2016). https://doi.org:10.2147/JBM.S90693

11 Dickneite, G. *et al.* Coagulation factor XIII: a multifunctional transglutaminase with clinical potential in a range of conditions. *Thromb Haemost* **113**, 686-697 (2015). https://doi.org:10.1160/TH14-07-0625

12 Posma, J. J., Posthuma, J. J. & Spronk, H. M. Coagulation and non-coagulation effects of thrombin. *J Thromb Haemost* **14**, 1908-1916 (2016). https://doi.org:10.1111/jth.13441

13 Connolly, G. C. & Francis, C. W. in *Williams Hematology, 9e* (eds Kenneth Kaushansky *et al.*) (McGraw-Hill Education, 2015).

14 Jordan, R. E., Oosta, G. M., Gardner, W. T. & Rosenberg, R. D. The kinetics of hemostatic enzyme-antithrombin interactions in the presence of low molecular weight heparin. *J Biol Chem* **255**, 10081-10090 (1980).

15 Griffith, M. J. Kinetics of the heparin-enhanced antithrombin III/thrombin reaction. Evidence for a template model for the mechanism of action of heparin. *J Biol Chem* **257**, 7360-7365 (1982).
16 Olson, S. T. & Bjork, I. Predominant contribution of surface approximation to the mechanism of heparin acceleration of the antithrombin-thrombin reaction. Elucidation from salt concentration effects. *J Biol Chem* **266**, 6353-6364 (1991).
17 Gray, E., Hogwood, J. & Mulloy, B. in *Heparin - A Century of Progress* (eds Rebecca Lever, Barbara Mulloy, & Clive P. Page) 43-61 (Springer Berlin Heidelberg, 2012).
18 Gelb, A. B. *et al.* Changes in blood coagulation during and following cardiopulmonary bypass: lack of correlation with clinical bleeding. *Am J Clin Pathol* **106**, 87-99 (1996). https://doi.org:10.1093/ajcp/106.1.87
19 Grossmann, R. *et al.* Changes in coagulation and fibrinolytic parameters caused by extracorporeal circulation. *Heart Vessels* **11**, 310-317 (1996). https://doi.org:10.1007/BF01747190
20 Linden, M. D. The hemostatic defect of cardiopulmonary bypass. *J Thromb Thrombolysis* **16**, 129-147 (2003). https://doi.org:10.1023/B:THRO.0000024051.12177.e9
21 Hall, T. S. The pathophysiology of cardiopulmonary bypass. The risks and benefits of hemodilution. *Chest* **107**, 1125-1133 (1995). https://doi.org:10.1378/chest.107.4.1125
22 Moore, E. E. *et al.* Trauma-induced coagulopathy. *Nature Reviews Disease Primers* **7**, 30 (2021). https://doi.org:10.1038/s41572-021-00264-3
23 Habib, R. H. *et al.* Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? *J Thorac Cardiovasc Surg* **125**, 1438-1450 (2003). https://doi.org:10.1016/s0022-5223(02)73291-1
24 Dubois, E. A. & Cohen, A. F. Dabigatran etexilate. *Br J Clin Pharmacol* **70**, 14-15 (2010). https://doi.org:10.1111/j.1365-2125.2010.03644.x
25 Agrawal, A., Kerndt, C. C. & Manna, B. in *StatPearls* (2024).
26 Arif, H. & Aggarwal, S. in *StatPearls* (2024).
27 Beavers, C. J. & Naqvi, I. A. in *StatPearls* (2024).
28 Iqbal, A. M., Lopez, R. A. & Hai, O. in *StatPearls* (2024).
29 Patel, S., Singh, R., Preuss, C. V. & Patel, N. in *StatPearls* (2024).
30 Singh, R. & Emmady, P. D. in *StatPearls* (2024).
31 Vasan, S. K. *et al.* ABO Blood Group and Risk of Thromboembolic and Arterial Disease: A Study of 1.5 Million Blood Donors. *Circulation* **133**, 1449-1457; discussion 1457 (2016). https://doi.org:10.1161/CIRCULATIONAHA.115.017563
32 Wu, O., Bayoumi, N., Vickers, M. A. & Clark, P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost* **6**, 62-69 (2008). https://doi.org:10.1111/j.1538-7836.2007.02818.x
33 Welsby, I. J. *et al.* ABO blood group and bleeding after coronary artery bypass graft surgery. *Blood Coagul Fibrinolysis* **18**, 781-785 (2007). https://doi.org:10.1097/MBC.0b013e3282f1029c

34 Gorlinger, K. *et al.* First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* **115**, 1179-1191 (2011). https://doi.org:10.1097/ALN.0b013e31823497dd

35 Weber, C. F. *et al.* Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology* **117**, 531-547 (2012). https://doi.org:10.1097/ALN.0b013e318264c644

36 Nakayama, Y. *et al.* Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. *Br J Anaesth* **114**, 91-102 (2015). https://doi.org:10.1093/bja/aeu339

37 Gorlinger, K. *et al.* The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol* **72**, 297-322 (2019). https://doi.org:10.4097/kja.19169

38 Haensig, M. *et al.* Thrombelastometry guided blood-component therapy after cardiac surgery: a randomized study. *BMC Anesthesiol* **19**, 201 (2019). https://doi.org:10.1186/s12871-019-0875-7

39 Komutrattananont, P., Mahakkanukrauh, P. & Das, S. Morphology of the human aorta and age-related changes: anatomical facts. *Anat Cell Biol* **52**, 109-114 (2019). https://doi.org:10.5115/acb.2019.52.2.109

40 Wu, J. *et al.* Aortic size distribution among normal, hypertension, bicuspid, and Marfan populations. *Eur Heart J Imaging Methods Pract* **1**, qyad019 (2023). https://doi.org:10.1093/ehjimp/qyad019

41 DePaolo, J. *et al.* Relationship Between Ascending Thoracic Aortic Diameter and Blood Pressure: A Mendelian Randomization Study. *Arterioscler Thromb Vasc Biol* **43**, 359-366 (2023). https://doi.org:10.1161/ATVBAHA.122.318149

42 Zuo, X. *et al.* Proximal aorta dilatation in hypertension. *J Hypertens* **41**, 1511-1520 (2023). https://doi.org:10.1097/HJH.0000000000003518

43 Nienaber, C. A. & Clough, R. E. Management of acute aortic dissection. *Lancet* **385**, 800-811 (2015). https://doi.org:10.1016/S0140-6736(14)61005-9

44 Conzelmann, L. O. *et al.* Mortality in patients with acute aortic dissection type A: analysis of pre- and intraoperative risk factors from the German Registry for Acute Aortic Dissection Type A (GERAADA). *Eur J Cardiothorac Surg* **49**, e44-52 (2016). https://doi.org:10.1093/ejcts/ezv356

45 Gudbjartsson, T. *et al.* Acute type A aortic dissection - a review. *Scand Cardiovasc J* **54**, 1-13 (2020). https://doi.org:10.1080/14017431.2019.1660401

46 Teurneau-Hermansson, K. *et al.* Mortality after non-surgically treated acute type A aortic dissection is higher than previously reported. *Eur J Cardiothorac Surg* **65** (2024). https://doi.org:10.1093/ejcts/ezae039

47 Evangelista, A. *et al.* Insights From the International Registry of Acute Aortic Dissection: A 20-Year Experience of Collaborative Clinical Research. *Circulation* **137**, 1846-1860 (2018). https://doi.org:10.1161/CIRCULATIONAHA.117.031264

48 Geirsson, A. *et al.* Differential outcomes of open and clamp-on distal anastomosis techniques in acute type A aortic dissection. *J Thorac Cardiovasc Surg* **157**, 1750-1758 (2019). https://doi.org:10.1016/j.jtcvs.2018.09.020

49 Wang, Z. *et al.* Acute kidney injury in patients operated on for type A acute aortic dissection: incidence, risk factors and short-term outcomes. *Interact Cardiovasc Thorac Surg* **31**, 697-703 (2020). https://doi.org:10.1093/icvts/ivaa164

50 Olsson, C. *et al.* Medium-term survival after surgery for acute Type A aortic dissection is improving. *Eur J Cardiothorac Surg* **52**, 852-857 (2017). https://doi.org:10.1093/ejcts/ezx302

51 Bernard, Y. *et al.* False lumen patency as a predictor of late outcome in aortic dissection. *Am J Cardiol* **87**, 1378-1382 (2001). https://doi.org:10.1016/s0002-9149(01)01556-9

52 Gariboldi, V. *et al.* Long-term outcomes after repaired acute type A aortic dissections. *Interact Cardiovasc Thorac Surg* **6**, 47-51 (2007). https://doi.org:10.1510/icvts.2006.136606

53 von Kodolitsch, Y. *et al.* Warfarin anticoagulation in acute type A aortic dissection survivors (WATAS). *Cardiovasc Diagn Ther* **7**, 559-571 (2017). https://doi.org:10.21037/cdt.2017.07.01

54 Takahara, Y., Sudo, Y., Mogi, K., Nakayama, M. & Sakurai, M. Total aortic arch grafting for acute type A dissection: analysis of residual false lumen. *Ann Thorac Surg* **73**, 450-454 (2002). https://doi.org:10.1016/s0003-4975(01)03422-1

55 Castaner, E. *et al.* CT in nontraumatic acute thoracic aortic disease: typical and atypical features and complications. *Radiographics* **23 Spec No**, S93-110 (2003). https://doi.org:10.1148/rg.23si035507

56 Hirotani, T., Nakamichi, T., Munakata, M. & Takeuchi, S. Routine extended graft replacement for an acute type A aortic dissection and the patency of the residual false channel. *Ann Thorac Surg* **76**, 1957-1961 (2003). https://doi.org:10.1016/s0003-4975(03)01325-0

57 Holloway, B. J., Rosewarne, D. & Jones, R. G. Imaging of thoracic aortic disease. *Br J Radiol* **84 Spec No 3**, S338-354 (2011). https://doi.org:10.1259/bjr/30655825

58 Evangelista, A. *et al.* Long-term outcome of aortic dissection with patent false lumen: predictive role of entry tear size and location. *Circulation* **125**, 3133-3141 (2012). https://doi.org:10.1161/CIRCULATIONAHA.111.090266

59 Ren, Z. *et al.* Which cannulation (axillary cannulation or femoral cannulation) is better for acute type A aortic dissection repair? A meta-analysis of nine clinical studies. *Eur J Cardiothorac Surg* **47**, 408-415 (2015). https://doi.org:10.1093/ejcts/ezu268

60 Elbatarny, M. *et al.* Axillary vs Femoral Arterial Cannulation in Acute Type A Dissection: International Multicenter Data. *Ann Thorac Surg* **117**, 1128-1134 (2024). https://doi.org:10.1016/j.athoracsur.2024.02.026

61 Panos, A., Murith, N., Bednarkiewicz, M. & Khatchatourov, G. Axillary cerebral perfusion for arch surgery in acute type A dissection under moderate hypothermia. *Eur J Cardiothorac Surg* **29**, 1036-1039 (2006). https://doi.org:10.1016/j.ejcts.2006.03.032

62 Zierer, A. *et al.* Fifteen years of surgery for acute type A aortic dissection in moderate-to-mild systemic hypothermiadagger. *Eur J Cardiothorac Surg* **51**, 97-103 (2017). https://doi.org:10.1093/ejcts/ezw289

63 Geube, M., Sale, S. & Svensson, L. Con: Routine Use of Brain Perfusion Techniques Is Not Supported in Deep Hypothermic Circulatory Arrest. *J Cardiothorac Vasc Anesth* **31**, 1905-1909 (2017). https://doi.org:10.1053/j.jvca.2017.02.024

64 Ziganshin, B. A. *et al.* Straight deep hypothermic circulatory arrest for cerebral protection during aortic arch surgery: Safe and effective. *J Thorac Cardiovasc Surg* **148**, 888-898; discussion 898-900 (2014). https://doi.org:10.1016/j.jtcvs.2014.05.027

65 Chemtob, R. A. *et al.* Stroke in acute type A aortic dissection: the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD). *Eur J Cardiothorac Surg* **58**, 1027-1034 (2020). https://doi.org:10.1093/ejcts/ezaa197

66 Kallenbach, K. *et al.* Treatment of the Aortic Root in Acute Aortic Dissection Type A: Insights from the German Registry for Acute Aortic Dissection Type A (GERAADA) Registry. *Eur J Cardiothorac Surg* (2022). https://doi.org:10.1093/ejcts/ezac261

67 Scott, J. & Humphreys, D. R. Dissecting aortic aneurysm and disseminated intravascular coagulation. *Br Med J* **1**, 24 (1977). https://doi.org:10.1136/bmj.1.6052.24

68 ten Cate, J. W., Timmers, H. & Becker, A. E. Coagulopathy in Ruptured or Dissecting Aortic Aneurysms. *Am J Med* **59**, 171-176 (1975). https://doi.org:10.1016/0002-9343(75)90351-4

69 Tanaka, M., Kawahito, K., Adachi, H. & Ino, T. Platelet dysfunction in acute type A aortic dissection evaluated by the laser light-scattering method. *J Thorac Cardiovasc Surg* **126**, 837-841 (2003). https://doi.org:10.1016/s0022-5223(03)00734-7

70 Huang, B. *et al.* Low admission platelet counts predicts increased risk of in-hospital mortality in patients with type A acute aortic dissection. *Int J Cardiol* **172**, e484-486 (2014). https://doi.org:10.1016/j.ijcard.2014.01.001

71 Van Poucke, S., Stevens, K., Marcus, A. E. & Lance, M. Hypothermia: effects on platelet function and hemostasis. *Thromb J* **12**, 31 (2014). https://doi.org:10.1186/s12959-014-0031-z

72 Wakefield, T. W. *et al.* Platelet reactivity in human aortic grafts: a prospective, randomized midterm study of platelet adherence and release products in Dacron and polytetrafluoroethylene conduits. *J Vasc Surg* **9**, 234-243 (1989). https://doi.org:10.1067/mva.1989.vs0090234

73 Sa, M. *et al.* Mitral valve repair with minimally invasive approaches vs sternotomy: A meta-analysis of early and late results in randomized and matched observational studies. *J Card Surg* **35**, 2307-2323 (2020). https://doi.org:10.1111/jocs.14799

74 Casselman, F. P. *et al.* Mitral valve surgery can now routinely be performed endoscopically. *Circulation* **108 Suppl 1**, II48-54 (2003). https://doi.org:10.1161/01.cir.0000087391.49121.ce

75 Glower, D. D. *et al.* Mitral valve operation via Port Access versus median sternotomy. *Eur J Cardiothorac Surg* **14 Suppl 1**, S143-147 (1998). https://doi.org:10.1016/s1010-7940(98)00123-7

76 Walther, T. *et al.* Pain and quality of life after minimally invasive versus conventional cardiac surgery. *Ann Thorac Surg* **67**, 1643-1647 (1999). https://doi.org:10.1016/s0003-4975(99)00284-2

77 Grant, S. W. *et al.* Propensity-matched analysis of minimally invasive approach versus sternotomy for mitral valve surgery. *Heart* **105**, 783-789 (2019). https://doi.org:10.1136/heartjnl-2018-314049

78 Modi, P., Hassan, A. & Chitwood, W. R., Jr. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* **34**, 943-952 (2008). https://doi.org:10.1016/j.ejcts.2008.07.057

79 Missault, S. *et al.* Analysis of clinical outcome and postoperative organ function effects in a propensity-matched comparison between conventional and minimally invasive mitral valve surgery. *J Card Surg* **35**, 3276-3285 (2020). https://doi.org:10.1111/jocs.15010

80 Speziale, G. *et al.* Results of mitral valve repair for Barlow disease (bileaflet prolapse) via right minithoracotomy versus conventional median sternotomy: a randomized trial. *J Thorac Cardiovasc Surg* **142**, 77-83 (2011). https://doi.org:10.1016/j.jtcvs.2010.08.033

81 Hall, R. I., Smith, M. S. & Rocker, G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. *Anesth Analg* **85**, 766-782 (1997). https://doi.org:10.1097/00000539-199710000-00011

82 Asimakopoulos, G. Systemic inflammation and cardiac surgery: an update. *Perfusion* **16**, 353-360 (2001). https://doi.org:10.1177/026765910101600505

83 Bartoszko, J. & Karkouti, K. Managing the coagulopathy associated with cardiopulmonary bypass. *J Thromb Haemost* **19**, 617-632 (2021). https://doi.org:10.1111/jth.15195

84 Bauer, A. *et al.* EuroScore and IL-6 predict the course in ICU after cardiac surgery. *Eur J Med Res* **26**, 29 (2021). https://doi.org:10.1186/s40001-021-00501-1

85 Brocca, A. *et al.* Elevated Levels of Procalcitonin and Interleukin-6 are Linked with Postoperative Complications in Cardiac Surgery. *Scand J Surg* **106**, 318-324 (2017). https://doi.org:10.1177/1457496916683096

86 Ucar, H. I. *et al.* Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. *Heart Surg Forum* **10**, E131-135 (2007). https://doi.org:10.1532/HSF98.20061175

87 Zhang, W. R. *et al.* Plasma IL-6 and IL-10 Concentrations Predict AKI and Long-Term Mortality in Adults after Cardiac Surgery. *J Am Soc Nephrol* **26**, 3123-3132 (2015). https://doi.org:10.1681/ASN.2014080764

88 Ganter, U., Arcone, R., Toniatti, C., Morrone, G. & Ciliberto, G. Dual control of C-reactive protein gene expression by interleukin-1 and interleukin-6. *EMBO J* **8**, 3773-3779 (1989). https://doi.org:10.1002/j.1460-2075.1989.tb08554.x

89 Nehring, S. M., Goyal, A. & Patel, B. C. in *StatPearls* (2024).
90 Tanaka, T., Narazaki, M. & Kishimoto, T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* **6**, a016295 (2014). https://doi.org:10.1101/cshperspect.a016295
91 Vijayan, A. L. *et al.* Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care* **5**, 51 (2017). https://doi.org:10.1186/s40560-017-0246-8
92 Baykut, D., Schulte-Herbruggen, J. & Krian, A. The value of procalcitonin as an infection marker in cardiac surgery. *Eur J Med Res* **5**, 530-536 (2000).
93 Klingele, M., Bomberg, H., Schuster, S., Schafers, H. J. & Groesdonk, H. V. Prognostic value of procalcitonin in patients after elective cardiac surgery: a prospective cohort study. *Ann Intensive Care* **6**, 116 (2016). https://doi.org:10.1186/s13613-016-0215-8
94 Jebali, M. A. *et al.* Assessment of the accuracy of procalcitonin to diagnose postoperative infection after cardiac surgery. *Anesthesiology* **107**, 232-238 (2007). https://doi.org:10.1097/01.anes.0000271871.07395.ad
95 Klingele, M. *et al.* Elevated procalcitonin in patients after cardiac surgery: a hint to nonocclusive mesenteric ischemia. *Ann Thorac Surg* **99**, 1306-1312 (2015). https://doi.org:10.1016/j.athoracsur.2014.10.064
96 Fergusson, D. A. *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* **358**, 2319-2331 (2008). https://doi.org:10.1056/NEJMoa0802395
97 Lang, T. *et al.* Multi-centre investigation on reference ranges for ROTEM thromboelastometry. *Blood Coagul Fibrinolysis* **16**, 301-310 (2005). https://doi.org:10.1097/01.mbc.0000169225.31173.19
98 Jenkins, P. V. & O'Donnell, J. S. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? *Transfusion* **46**, 1836-1844 (2006). https://doi.org:10.1111/j.1537-2995.2006.00975.x
99 Drukker, L. *et al.* The association between ABO blood group and obstetric hemorrhage. *J Thromb Thrombolysis* **42**, 340-345 (2016). https://doi.org:10.1007/s11239-016-1360-5
100 Komatsu, R. *et al.* Blood Type O is not associated with increased blood loss in extensive spine surgery. *J Clin Anesth* **26**, 432-437 (2014). https://doi.org:10.1016/j.jclinane.2014.01.019
101 Welsby, I. J. *et al.* ABO blood group influences transfusion and survival after cardiac surgery. *J Thromb Thrombolysis* **38**, 402-408 (2014). https://doi.org:10.1007/s11239-013-1045-2
102 Wang, Z. *et al.* Influences of ABO blood group, age and gender on plasma coagulation factor VIII, fibrinogen, von Willebrand factor and ADAMTS13 levels in a Chinese population. *PeerJ* **5**, e3156 (2017). https://doi.org:10.7717/peerj.3156
103 Blann, A. D. Plasma von Willebrand factor, thrombosis, and the endothelium: the first 30 years. *Thromb Haemost* **95**, 49-55 (2006).

104 Zindovic, I. *et al.* The role of von Willebrand factor in acute type A aortic dissection and aortic surgery. *Thromb Res* **178**, 139-144 (2019). https://doi.org:10.1016/j.thromres.2019.04.018

105 von Beckerath, N. *et al.* ABO locus O1 allele and risk of myocardial infarction. *Blood Coagul Fibrinolysis* **15**, 61-67 (2004). https://doi.org:10.1097/00001721-200401000-00010

106 Song, S. W. *et al.* Effects of early anticoagulation on the degree of thrombosis After repair of acute DeBakey type I aortic dissection. *Ann Thorac Surg* **92**, 1367-1374; discussion 1374-1365 (2011). https://doi.org:10.1016/j.athoracsur.2011.04.111

107 Uchida, N. *et al.* Operative strategy for acute type a aortic dissection: ascending aortic or hemiarch versus total arch replacement with frozen elephant trunk. *Ann Thorac Surg* **87**, 773-777 (2009). https://doi.org:10.1016/j.athoracsur.2008.11.061

108 Colli, A. *et al.* Acute DeBakey Type I aortic dissection without intimal tear in the arch: is total arch replacement the right choice? *Interact Cardiovasc Thorac Surg* **26**, 84-90 (2018). https://doi.org:10.1093/icvts/ivx229

109 Di Bartolomeo, R., Leone, A., Di Marco, L. & Pacini, D. When and how to replace the aortic arch for type A dissection. *Ann Cardiothorac Surg* **5**, 383-388 (2016). https://doi.org:10.21037/acs.2016.07.07

110 Ohtsubo, S. *et al.* Surgical results of hemiarch replacement for acute type A dissection. *Ann Thorac Surg* **74**, S1853-1856; discussion S1857-1863 (2002). https://doi.org:10.1016/s0003-4975(02)04133-4

111 Kim, J. B. *et al.* Total arch repair versus hemiarch repair in the management of acute DeBakey type I aortic dissection. *Eur J Cardiothorac Surg* **40**, 881-887 (2011). https://doi.org:10.1016/j.ejcts.2010.12.035

112 Brase, J. *et al.* Analysis of Outcomes Using Low-Dose and Early Administration of Recombinant Activated Factor VII in Cardiac Surgery. *Ann Thorac Surg* **102**, 35-40 (2016). https://doi.org:10.1016/j.athoracsur.2016.01.004

113 Poon, S. S. *et al.* Hemiarch versus total aortic arch replacement in acute type A dissection: a systematic review and meta-analysis. *Ann Cardiothorac Surg* **5**, 156-173 (2016). https://doi.org:10.21037/acs.2016.05.06

114 Lansman, S. L., Goldberg, J. B., Kai, M., Malekan, R. & Spielvogel, D. Extended Arch Procedures for Acute Type A Aortic Dissection: A Downstream Problem? *Semin Thorac Cardiovasc Surg* **31**, 17-20 (2019). https://doi.org:10.1053/j.semtcvs.2018.07.013

115 Guan, X. L. *et al.* Changes in the Hemostatic System of Patients With Acute Aortic Dissection Undergoing Aortic Arch Surgery. *Ann Thorac Surg* **101**, 945-951 (2016). https://doi.org:10.1016/j.athoracsur.2015.08.047

116 Liu, Y. *et al.* Consumption coagulopathy in acute aortic dissection: principles of management. *J Cardiothorac Surg* **12**, 50 (2017). https://doi.org:10.1186/s13019-017-0613-5

117 Castell, J. V. *et al.* Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* **12**, 1179-1186 (1990). https://doi.org:10.1002/hep.1840120517

118 Zindovic, I. *et al.* The Coagulopathy of Acute Type A Aortic Dissection: A Prospective, Observational Study. *J Cardiothorac Vasc Anesth* **33**, 2746-2754 (2019). https://doi.org:10.1053/j.jvca.2019.02.013
119 Sahli, S. D. *et al.* Point-of-Care Diagnostics in Coagulation Management. *Sensors (Basel)* **20** (2020). https://doi.org:10.3390/s20154254
120 Ogawa, S. *et al.* A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. *Transfusion* **52**, 14-22 (2012). https://doi.org:10.1111/j.1537-2995.2011.03241.x
121 Rugeri, L. *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* **5**, 289-295 (2007). https://doi.org:10.1111/j.1538-7836.2007.02319.x
122 Girdauskas, E. *et al.* Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg* **140**, 1117-1124 e1112 (2010). https://doi.org:10.1016/j.jtcvs.2010.04.043
123 Davidson, S. J., McGrowder, D., Roughton, M. & Kelleher, A. A. Can ROTEM thromboelastometry predict postoperative bleeding after cardiac surgery? *J Cardiothorac Vasc Anesth* **22**, 655-661 (2008). https://doi.org:10.1053/j.jvca.2008.07.002
124 Lee, G. C. *et al.* Does rotational thromboelastometry (ROTEM) improve prediction of bleeding after cardiac surgery? *Anesth Analg* **115**, 499-506 (2012). https://doi.org:10.1213/ANE.0b013e31825e7c39
125 Tanaka, K. A., Bolliger, D., Vadlamudi, R. & Nimmo, A. Rotational thromboelastometry (ROTEM)-based coagulation management in cardiac surgery and major trauma. *J Cardiothorac Vasc Anesth* **26**, 1083-1093 (2012). https://doi.org:10.1053/j.jvca.2012.06.015
126 Wasowicz, M. *et al.* The incremental value of thrombelastography for prediction of excessive blood loss after cardiac surgery: an observational study. *Anesth Analg* **111**, 331-338 (2010). https://doi.org:10.1213/ANE.0b013e3181e456c1
127 Cleland, D. A. & Eranki, A. P. in *StatPearls* (2024).
128 Carsin, H. *et al.* Evolution and significance of circulating procalcitonin levels compared with IL-6, TNF alpha and endotoxin levels early after thermal injury. *Burns* **23**, 218-224 (1997). https://doi.org:10.1016/s0305-4179(96)00124-6
129 Mimoz, O. *et al.* Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome. *Intensive Care Med* **24**, 185-188 (1998). https://doi.org:10.1007/s001340050543
130 Nylen, E. S., Al Arifi, A., Becker, K. L., Snider, R. H., Jr. & Alzeer, A. Effect of classic heatstroke on serum procalcitonin. *Crit Care Med* **25**, 1362-1365 (1997). https://doi.org:10.1097/00003246-199708000-00024
131 Chen, X. *et al.* Procalcitonin, Interleukin-6 and C-reactive Protein Levels Predict Renal Adverse Outcomes and Mortality in Patients with Acute Type A Aortic Dissection. *Front Surg* **9**, 902108 (2022). https://doi.org:10.3389/fsurg.2022.902108

132 Kilger, E. *et al.* Procalcitonin as a marker of systemic inflammation after conventional or minimally invasive coronary artery bypass grafting. *Thorac Cardiovasc Surg* **46**, 130-133 (1998). https://doi.org:10.1055/s-2007-1010209

133 Beghetti, M., Rimensberger, P. C., Kalangos, A., Habre, W. & Gervaix, A. Kinetics of procalcitonin, interleukin 6 and C-reactive protein after cardiopulmonary-bypass in children. *Cardiol Young* **13**, 161-167 (2003). https://doi.org:10.1017/s1047951103000301

134 Franke, A. *et al.* Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? *Eur J Cardiothorac Surg* **28**, 569-575 (2005). https://doi.org:10.1016/j.ejcts.2005.07.007

135 Meisner, M. *et al.* Early increase of procalcitonin after cardiovascular surgery in patients with postoperative complications. *Intensive Care Med* **28**, 1094-1102 (2002). https://doi.org:10.1007/s00134-002-1392-5

136 Aouifi, A. *et al.* Effect of cardiopulmonary bypass on serum procalcitonin and C-reactive protein concentrations. *Br J Anaesth* **83**, 602-607 (1999). https://doi.org:10.1093/bja/83.4.602

137 Clementi, A. *et al.* Procalcitonin and Interleukin-6 Levels: Are They Useful Biomarkers in Cardiac Surgery Patients? *Blood Purif* **43**, 290-297 (2017). https://doi.org:10.1159/000454672

138 Murphy, G. J. *et al.* Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* **116**, 2544-2552 (2007). https://doi.org:10.1161/CIRCULATIONAHA.107.698977

139 Geisler, D. *et al.* Impact of CytoSorb(R) on interleukin-6 in cardiac surgery. *Front Cardiovasc Med* **10**, 1166093 (2023). https://doi.org:10.3389/fcvm.2023.1166093

140 Vendramin, I. *et al.* Do oral anticoagulants impact outcomes and false lumen patency after repair of acute type A aortic dissection? *J Thorac Cardiovasc Surg* **166**, 38-48 e34 (2023). https://doi.org:10.1016/j.jtcvs.2021.09.009

141 Gong, X., Lang, Q., Qin, C., Meng, W. & Xiao, Z. The effect of postoperative anticoagulation on acute aortic dissection: a systematic review and meta-analysis. *Front Cardiovasc Med* **10**, 1173945 (2023). https://doi.org:10.3389/fcvm.2023.1173945

Printed by Media-Tryck, Lund 2025 NORDIC SWAN ECOLABEL 3041 0903

"Not the fastest, not the greatest, but I made it!"

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2025:4
ISBN 978-91-8021-657-9
ISSN 1652-8220