UNIVERSITY OF TURKU

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Registry-based Studies with Special Emphasis on Reoperations and Preoperative Cardiac Arrest

Emily Pan

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To my mum, dad and dearest brother, Luka

ABSTRACT

Emily Pan

OUTCOMES AFTER ASCENDING AORTIC SURGERY – Registry-based Studies with Special Emphasis on Reoperations and Preoperative Cardiac Arrest

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Surgical repair for ascending aorta regarding an aneurysm or an acute type A aortic dissection (ATAAD) share similar principals in techniques. ATAAD is highly lethal, and the appropriate extent of surgery at acute setting is an ongoing debate. Study I researched the evolution and outcome of ascending aortic surgeries from a single centre with 47 years' experience. Studies II and III utilized one of the world's largest ATAAD databases to investigate the outcome in surgically treated ATAAD patients, with a special interest in reoperations and patients that had preoperative cardiac arrest requiring cardiopulmonary resuscitation.

These studies showed that the numbers of ascending aortic surgeries were steadily increasing. Patients were older at the time of surgery, but the mortality rate has decreased over time. Freedom from reoperations was 95.0% after ATAAD surgery at 5 years. In ATAAD patients, isolated ascending aortic replacement without aortic arch involvement did not increase the incidence for a late reoperation, and the midterm survival did not differ between the two groups of ascending aortic replacement and aortic arch repair. Survival of patients with ATAAD and preoperative cardiac arrest was 50% at 3 years.

The results after ascending aortic surgeries have significantly improved over time. The reoperation rate in Nordic countries was found to be low, and a less extensive repair at the initial presentation of ATAAD is sufficient to ensure freedom from reinterventions with comparable mortality rates. In patients with preoperative cardiac arrest, the mid-term outcome was acceptable, suggesting this group of patients should not be contraindicated for surgery.

Keywords: ascending aortic surgery, type A aortic dissection, ascending aortic aneurysm, outcome, reoperations, preoperative cardiac arrest

TIIVISTELMÄ

LL Emily Pan

NOUSEVAN AORTAN KIRURGIAN HOITOTULOKSET –Rekisteritutkimuksia aiheesta, mielenkiinnon kohteena erityisesti uusintaoperaatiot sekä sydänpysähdyksen saaneet potilaat

Turun yliopisto, Lääketieteellinen tiedekunta, Kirurgia, Turun kliininen tohtoriohjelma; Sydänkeskus, Turun yliopistollinen keskussairaala, Turku, Suomi

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Leikkausmenetelmät nousevan aortan kirurgiassa sekä aneurysmalle että akuutille tyypin A dissekaatiolle (ATAAD) ovat pitkälti samanlaisia. ATAAD:ssa on hyvin korkea kuolleisuus akuutissa vaiheessa, ja siitä, mikä on sopiva leikkaustekniikka hätätilanteessa, väitellään jatkuvasti. Ensimmäisessä osatyössä esitetään erään keskuksen nousevan aortan kirurgian kehitys ja pitkäaikaistulokset 47 vuoden ajalta. Toisessa ja kolmannessa osatyössä hyödynnettiin yhtä maailman suurimmista ATAAD-rekistereistä. Näissä osatöissä tutkittiin Pohjoismaiden kirurgisia hoitotuloksia ATAAD-leikkausten jälkeen, keskittyen erityisesti uusintaoperaatiota vaatineisiin potilaisiin sekä potilaisiin, joilla oli elvytystä vaativa sydänpysähdys ennen leikkausta.

Nousevan aortan leikkausten määrät olivat tasaisessa nousussa. Leikkaushetkellä potilaiden ikä oli aiempaa korkeampi, mutta alkuvaiheen kuolleisuus vähentyi ajan myötä. Viiden vuoden kohdalla 95,0 % potilaista ei ollut tarvetta ATAAD-leikkauksen jälkeiselle uusintaoperaatiolle. Nousevan aortan rekonstruktio ilman aortan kaaren korjausta primaarissa ATAAD-leikkauksessa ei lisännyt uusintaoperaatioiden määrää aortan kaaren korjauksiin verrattuna. Kolmen vuoden seurannassa näiden kahden ryhmän välillä ei ollut eroa eloonjäämisessä. Puolet potilaista, joilla oli sydänpysähdys ennen ATAAD-leikkausta, olivat elossa kolmen vuoden kohdalla.

Hoitotulokset nousevan aortan leikkauksen jälkeen olivat selkeästi parantuneet ajan kuluessa. Uusintaoperaatioiden määrä Pohjoismaissa oli matala, ja suppeampi aortan rekonstruktio akuutissa tilanteessa oli riittävä takaamaan hyvät keskipitkän ajan tulokset ilman kuolleisuuden nousua. ATAAD-potilaiden, joilla oli sydänpysähdys ennen leikkausta, ennuste kolmen vuoden kohdalla oli kohtalainen. Näin ollen näiltä potilaita ei tulisi evätä kirurgisen hoidon mahdollisuutta.

Avainsanat: nousevan aortan kirurgia, tyypin A aortan dissekaatio, nousevan aortan aneurysma, hoitotulokset, uusintaoperaatiot, sydänpysähdys

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ABBREVIATIONS

ACC	the American College of Cardiology
AHA	the American Heart Association
AscAA	Ascending aortic aneurysm
ATAAD	Acute type A aortic dissection
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
CABG	Coronary artery bypass grafting
CI	Confidence interval
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
ECG	Electrocardiogram
ACM	Extracellular matrix
EDS	Ehler-Danlos syndrome
ESC	the European Society of Cardiology
FET	Frozen elephant trunk technique
GERAADA	the German Registry for Acute Aortic Dissection Type A
HCA	Hypothermic circulatory arrest
HR	Hazard ratio
IRAD	the International Registry of Acute Aortic Dissection
LDS	Loeys-Dietz syndrome
MMP	Matrix metalloproteinaise
MRI	Magnetic resonance imaging
MVR	Mitral valve repair
NORCAAD	the Nordic Consortium for Type A Aortic Dissection
OR	Odds ratio
PCI	Percutaneous coronary intervention
ROSC	Return of spontaneous circulation
TAAA	Thoracoabdominal aortic aneurysm
TAD	Thoracic aortic disease
TEVAR	thoracic endovascular aortic valve repair
TGF-β	Transforming growth factor-β
TGFBR	Transforming growth factor β receptor
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram

LIST OF ORIGINAL PUBLICATIONS

I. Pan E, Kytö V, Savunen T, Gunn J. Long-term outcomes after open ascending aortic surgery, 47-year experience in a single centre. Heart Vessels. 2018 Apr; 33: 427-433.

II. Pan E, Gudbjartsson T, Ahlsson A, Fuglsang S, Geirsson A, Hansson EC, Hjortdal V, Jeppsson A, Jarvela K, Mennander A, Nozohoor S, Olsson C, Wickbom A, Zindovic I, Gunn J. Low rate of reoperations after acute type A aortic dissection repair from The Nordic Consortium Registry. J Thorac Cardiovasc Surg. 2018 Sep; 156: 939-948.

III. Pan E, Wallinder A, Peterström E, Geirsson A, Olsson C, Ahlsson A, Fuglsang S, Gunn J, Hansson EC, Hjortdal V, Mennander A, Nozohoor S, Wickbom A, Zindovic I, Gudbjartsson T, Jeppsson A. Outcome after type A aortic dissection repair in patients with preoperative cardiac arrest. Submitted.

1 INTRODUCTION

The most common thoracic aortic diseases (TAD) are aneurysm and dissection, which have many similarities both in aetiology and in treatment. An acute type A aortic dissection (ATAAD), the most relevant acute complication of an ascending aortic aneurysm, is a life-threatening condition, and one of the most devastating surgical emergencies (Goldfinger et al., 2014). An enlarged aorta is a strong predictor for aortic complications (Davies et al., 2002; Elefteriades et al., 2015; Juvonen et al., 1997), but patients with an ascending aortic aneurysm (AscAA) are usually asymptomatic and ATAAD typically has an unexpected sudden appearance, which make TADs hard to predict or prevent, and therefore much feared. In a nationwide population-study including autopsy results, the incidence for TAD has been estimated at 12.7 per 100 000 per year with an increasing trend (Olsson et al., 2006).

Once the dissection has occurred, both mortality and morbidity are high (Chiappini et al., 2005; Pagni et al., 2013). The pressure of the blood flow tears apart the layers of the aorta and exposes the patient to severe organ malperfusions, such as myocardial ischemia and stroke. It is estimated that 22-53% of patients with ATAAD die before reaching hospital due to rupture of the aorta, pericardial tamponade and/or acute critical end-organ hypoperfusion that caused multi-organ failure (Augoustides et al., 2009; Melvinsdottir et al., 2016; Olsson et al., 2006; Spittell et al., 1993). Furthermore, up to 17% of patients succumb en route to surgery due to severity of the disease and sometimes due to misdiagnosis or diagnostic delay (Howard et al., 2013). Among operated patients, perioperative mortality (in-hospital or 30-day) varies between 14.4% to 25.1% (Chiappini et al., 2005; Conzelmann et al., 2016; Rylski et al., 2014; Trimarchi et al., 2005).

The current European Society of Cardiology guidelines from 2014 suggest a threshold of 55 mm in maximal aortic diameter for surgical intervention in order to avoid disastrous complications in the absence of elastopathy or bicuspid aortic valve (Erbel et al., 2014). Once the ATAAD has occurred, the standard treatment is an immediate surgery. The extent of the surgery depends on the scale of the disease, the risk profile of the patient and the experience of the operating surgeon (Augoustides et al., 2011). The immediate goal is to prevent cardiac tamponade and coronary artery ischemia, then restore and ensure systemic perfusion by resecting and replacing the diseased aorta with an artificial tube. Neurological dysfunctions along with pseudoaneurysms or redissections are the most dreaded long-term complications following ATAAD surgery. The reoperation rate has previously been reported at 8.7-13.5%, most commonly related to the formation of a pseudoaneurysm (Geirsson et al., 2007; Kobuch et al., 2012; Pugliese et al., 1998).

There are two notable large international ATAAD registries, the International Registry of Acute Aortic Dissection (IRAD) (Hagan et al., 2000) and the German Registry for Acute Aortic Dissection Type A (GERAADA) (Boening et al., 2017). Both registries have high volume of patients, but the participating centres vary in size, treatment protocols and patient materials. Moreover, the follow-up rate is low. Other studies on ATAAD have mostly been single-centre studies with largely varied results. Despite many studies been conducted, there is a lack of evidence of how the patients perceived as having the most dismal prognosis (e.g. those with cardiac arrest) fare and whether an operation is justified. In addition, the appropriate extent of primary ATAAD repair still remains controversial. These and other questions gave rise to the idea of a unified Nordic registry – the Nordic Consortium for Type A Aortic Dissection (NORCAAD) – that is not only large in volume but is also reliable in long-term follow-up and has an ethnically and socioeconomically remarkably homogenous population, participating societies with high standards of health care, comprehensive national identity registries and access to almost complete follow-up data (Geirsson et al., 2016).

The objective of this study is to utilise quality registry data from Finland and other Northern European countries to determine the incidence and characteristics of AscAA and ATAAD, to depict real-life results after TAD surgery, and to provide new evidence-based medicine for cardiac surgeons in decision-making process of whether to operate and which procedure to choose.

2 REVIEW OF LITERATURE

2.1 Anatomy of the thoracic aorta

Normal aortic wall consists of three layers: the tunica intima – a thin, single layer of endothelium, the tunica media – a thick layer of elastic and collagen fibres and smooth muscle cells, and the tunica adventitia – an outer layer of mostly fibroblasts and collagen fibres. Small capillaries called vasa vasorum supply blood to the aorta, and they form a vascular zone on the outer layer of the aortic media.

The aorta begins from the aortic annulus and continues as a conduit that gradually branches into smaller and smaller arteries, eventually into capillaries. The normal anatomy of the thoracic aorta is shown in Figure 1. The aortic root is defined as the part proximal to the sinotubular junction and consists of the aortic annulus, the aortic valve leaflets, the ostia of the coronary arteries and the sinuses of Valsalva. The ascending aorta comprises the segment between the aortic root and the right brachiocephalic artery. The descending thoracic aorta begins distal to the left subclavian artery and extends to the level of the diaphragm. The aortic arch is the segment between the ascending and the descending aorta, and is where the supra-aortic branches arise to the head and upper extremities.

2.2 Definition and classification of thoracic aortic diseases (TADs)

A thoracic aortic aneurysm is often defined as a segmental dilatation of > 50% compared to the normal diameter or size beyond 40 mm (Hiratzka et al., 2010; Johnston et al., 1991). The normal size of the aorta is influenced by age, gender, ethnicity and body surface area. The size also varies depending on the cardiac cycle, the segment of the aorta, the imaging modality, and the interpreter of the study. Therefore, an absolute uniform cut-off measurement to define an aortic aneurysm is not possible.

Aortic dissection occurs when the inner layer of the aortic wall, known as the intima, is perforated with a tear, and the blood flow dashes between the intima and adventitia creating a false lumen and dissects along the aorta. The dissection can progress both anterogradely and retrogradely. The site where the tear originates is called the primary or entry tear, and can often be visually identified on different imaging modalities by an intimal flap.

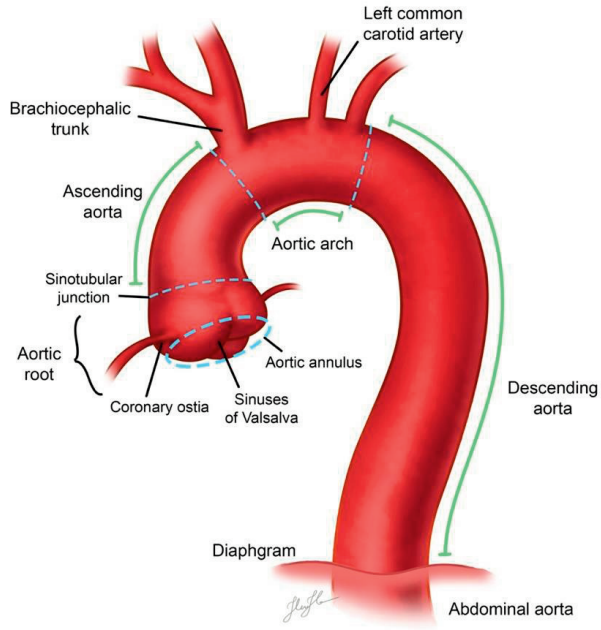

Figure 1. Anatomy of thoracic aorta.

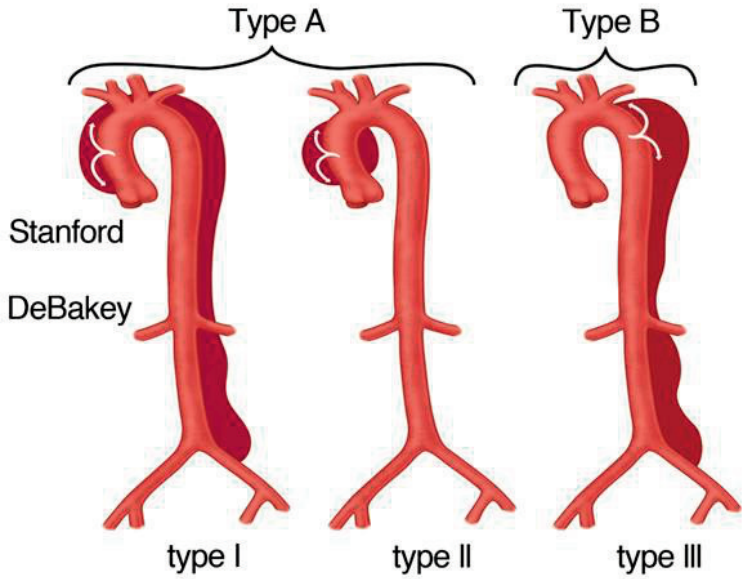

Figure 2. Stanford and DeBakey classifications of aortic dissection. Published with permission from the copyright holder, Professor Tomas Gudbjarttson.

There are two widely adopted classifications of aortic dissections, both based on anatomy; the Stanford and the DeBakey classifications (Figure 2). Stanford type A aortic dissection involves the ascending aorta, whereas in type B, the dissection solely affects the descending aorta (Miller et al., 1979). DeBakey type I accounts for both the ascending and the descending aorta, type II covers only the ascending part and type III the descending segment (Debakey et al., 1965). Aortic dissection can also be divided into acute and chronic phases. The morbidity and mortality rates are highest during the acute phase, which is defined as less than 14 days from the onset of the first symptoms. This thesis focuses on acute Stanford type A aortic dissection.

The Penn classification is based on ischemic presentation in ATAAD, and is used to stratify patients by operative mortality risk. Penn Class A applies to patients without any branch vessel malperfusion or ischemia, Penn Class B refers to localized ischemia with branch vessel malperfusion and signs of organ ischemia (e.g. stroke, renal failure, mesenteric ischemia) and Penn Class C stands for generalized ischemia with signs of circulatory collapse. When there are signs of both localized and generalized ischemia, Penn Class B&C is used. (Augoustides et al., 2009)

2.3 Aetiology, pathogenesis and predisposing factors for TADs

2.3.1 General

In TADs, it is known that the genetics plays an important role (Ahmad et al., 2017; Isselbacher et al., 2016). Despite similar manifestation during complications, the aetiology and pathogenesis of an AscAA is significantly different from a descending aortic aneurysm or abdominal aortic aneurysm that are predominantly related to acquired pathologies (Vapnik et al., 2016). Regardless of aetiology, the formation of an aneurysm is eventually caused by medial degeneration. The mechanism for this process is multifactorial and can be caused by genetic mutations, inflammatory changes, acquired conditions, or be purely sporadic. Predisposing factors for thoracic aortic aneurysm and ATAAD are listed in Table 1.

Table 1. Risk factors for acute type A aortic dissection. Apart from trauma and iatrogenic causes, the same risk factors are also valid for ascending aortic aneurysms.

Heritable causes
Heritable connective tissue diseases
Marfan syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome
Other familial thoracic aortic disease
Turner syndrome
Bicuspid aortic valve
Inflammatory causes
Vasculitis
Takayasu arteritis
Giant cell arteritis
Bechet disease
Syphilis
Tuberculosis
Acquired causes
Atherosclerosis
Hypertension
Increasing age
Smoking
Cocaine and other stimulant abuse
Repetitive heavy weight lifting
Trauma
Previous cardiac surgery
Iatrogenic
Cardiac catheterization
Insertion of intra-aortic balloon pump
Aortic cross-clamping

2.3.2 Medial degeneration

A histopathological examination of an aneurysmatic aortic tissue reveals degradation of the extracellular matrix (ECM) in the tunica media. This is often described as cystic medial necrosis that is characterized by fragmentation and loss of elastic fibres, degradation of collagen, depletion and atrophy of vascular smooth-muscle cell (SMC), and mucoid deposition. SMC and ECM proteins, like collagens and elastin fibres, give strength and integrity to the aortic wall so it can response to each cardiac pulsation with elasticity and flexibility. The degradation of these structural components causes the process of cystic media necrosis and weakening of the aortic wall, which eventually may lead to aneurysm formation and tear on the wall. (El-Hamamsy & Yacoub, 2009; Isselbacher et al., 2016; Milewicz et al., 2017)

The exact mechanism leading to medial degeneration is not fully understood. It is known, however, that regardless of the aetiology, the immune-inflammatory mechanisms significantly contribute to aortic wall degradation and remodelling. Activation of macrophages in the tunica media releases and regulates matric metalloproteinases (MMPs) and several pro-inflammatory cytokines that are pivotal in triggering and maintaining the ECM degradation and neoangiogenesis. The imbalance between MMPs and MMP tissue inhibitors is the key in the early process of aneurysm formation. (Cifani et al., 2015; Danyi et al., 2011; Ikonomidis et al., 2006; Tamarina et al., 1997)

2.3.3 Heritable causes

2.3.3.1 Heritable connective tissue diseases

Connective tissue diseases are a heterogeneous spectrum of heritable disorders that affect various organ systems including ocular, musculoskeletal, pulmonary, and cardiovascular systems. They all cause defects in the structure of ECM, and therefore have significant phenotypical overlapping (Bowen et al., 1987; Meester et al., 2017)

Marfan syndrome is an autosomal dominant heritable disorder that is caused by a variety of mutations in the FBN1 gene that encodes a large ECM protein called fibrillin-1. This protein forms elastic fibres and interacts with signalling cytokine called transforming growth factor-β (TGF-β), which in turn controls cell differentiation, motility and proliferation (Biery et al., 2002; Isselbacher et al., 2016;

Verstraeten et al., 2016). The increased activity of TGF-β, as well as increased MMP signalling, elastin fragmentation, vascular smooth muscle cell apoptosis, macrophage chemotaxis and inflammation lead to histopathological findings in the aortas of patients with Marfan syndrome (El-Hamamsy & Yacoub, 2009). The most typical cardiovascular abnormality in Marfan syndrome is a pear-shaped dilated aortic root, also referred to as annulo-aortic ectasia. It is reported that up to 5% of ATAAD patients have Marfan syndrome (Evangelista et al., 2018) and up to 80% of unexpected deaths in Marfan syndrome were caused by aortic complications, such as dissection or rupture (Groth et al., 2017; Murdoch et al., 1972). Although Marfan syndrome is a heritable disorder, 25% of patients present sporadic mutations without known family history (Milewicz et al., 2005).

Loeys-Dietz syndrome (LDS) is another type of connective tissue disorder that is caused by mutations in TGFBR1 or TGFBR2 (transforming growth factor beta receptor) genes, which are encoded by TGF-β. From the cardiovascular perspective, LDS is associated with arterial tortuosity, aneurysms, and dissections in the vascular system. Up to 98% of LDS patients have an aortic root aneurysm, and the most common cause of death is thoracic aortic dissection (Loeys et al., 2006).

Ehler-Danlos syndrome (EDS) is a diverse group of clinically and genetically heterogeneous diseases that are caused by mutations of COL3A1, which results in a defect in type III collagen synthesis. Up to 25% of these patients have an aortic aneurysm (Verstraeten et al., 2016) and up to 78% of EDS and their affected relatives die from aortic dissection or rupture (Pepin et al., 2000).

Apart from the above-mentioned, many patients who do not have connective tissue features are still discovered to have mutations in the TGF-β signalling pathway, suggesting there's much wider phenotypic variation in the manifestation of connective tissue diseases. In addition, up to 21.5% of these patients were found to have a first-degree family member with an arterial aneurysm (Albornoz et al., 2006).

2.3.3.2 Other familial TADs

Mutations in genes that encode smooth muscle myosins and actins, fibrillin-1, and MMP-17 are linked to familial TAD. These result in dysfunction of the vascular smooth muscle of the tunica media and will eventually lead again to medial degeneration. Familial TADs generally present at an earlier age (56.8 years) than patients with sporadic TADs (64.3 years) (Coady et al., 1999).

2.3.3.3 Bicuspid valve

A bicuspid aortic valve (BAV) is the most common congenital abnormality affecting the aorta, and it is a well-known risk factor for aortic aneurysm formation, dissection and rupture (Larson & Edwards, 1984). BAV is noted in 4.9-7.5% of patients with TAD (Roberts & Roberts, 1991; Trimarchi et al., 2005), while only in 1-2% in general population (Roberts & Elliott, 1968). A series of patients with BAV showed that the relative risk for developing an aortic aneurysm sized ≥ 50 mm was 26 times higher and aortic dissection occurred 8 times more frequently when compared to an age-adjusted general population (Michelena et al., 2011).

The association between a BAV and aortic dilatation or dissection has also been linked to genetic deficiencies of aortic fibrillin, apoptosis of vascular smooth muscle cells, and upregulation of MMP, which lead to medial degeneration and weakening of the aortic wall (Bonderman et al., 1999; Fedak et al., 2003; Verma & Siu, 2014). In addition, the morphology of a bileaflet valve makes it more prone to calcifications compared to trileaflet valves. This can lead to both aortic valve stenosis and aortic regurgitation, which may increase the aortic wall tension and thus cause dilatations (Siu & Silversides, 2010). According to the Sievers classification of BAV, the morphology of BAV with two raphes has a significantly higher proportion of aortic aneurysms compared to none or one raphe (Ridley et al., 2016; Sievers & Schmidtke, 2007). Irrespective of morphology, the tubular ascending aorta is the most commonly dilated segment of aorta in patients with BAV – up to 60% – and has the fastest growth rate in patients without Marfan syndrome. Patients with Marfan syndrome typically have the maximal aortic dilatation at the level of Valsalva sinuses. In contrast, the sinus of valsava is dilated in 27% of patients with BAV and it is associated with typical BAV morphology (Detaint et al., 2014). In the original Sievers and Schmidtke series that only included operated BAVs, 6% had aortic root involvement, 29% involved ascending aorta and ≤ 1% had aneurysms in the arch or descending aorta (Sievers & Schmidtke, 2007).

2.3.4 Inflammation

Any inflammatory aortic disease may result in aortic dilatation. It is typically characterised by various degrees of inflammation both in the media and the adventitia. This causes fibrous intimal thickening and medial injury that can sometimes evolve into medial infarction leading to laminar medial necrosis if the vasa vasorum are involved. Necrosis of the vasa vasorum may in turn cause bleeding inside the aortic wall, a condition that is known as intramural haematoma.

In vasculitis, especially in giant cell arteritis and Takayasu aortitis, adventitial fibrosis with inflammation of the vasa vasorum, medial necrosis and scarring, fibrous intimal thickening and a grossly tree-bark appearance can be found. Systemic diseases like sarcoidosis, lupus erythematosus, rheumatoid arthritis and ankylosing spondylosis may also affect the aorta, causing inflammation and predispose to aortic complications (Tavora & Burke, 2006) .

Infectious aortitis can be caused by syphilis and various haematogenically disseminated organisms (Roberts et al., 2015). Although very rare, these conditions may cause massive AscAAs which can erode the aortic wall leading to dissection or rupture (Tavora & Burke, 2006).

2.3.5 Acquired causes

In acquired diseases, the formation of AscAA is mostly caused by increased aortic wall stress. The tension on different parts of the aortic wall varies significantly as dictated by LaPlace's law; the larger the diameter, the higher the pressure against the wall (Hademenos et al., 1994).

Hypertension is the most significant condition that elevates wall stress. Higher systolic blood pressure has been shown to be linearly correlated to increased wall stress, and the increase is even more significant the larger the diameter of the aortic wall has (Rabkin & Janusz, 2013). Hypertension also indirectly cultivates aneurysm formation by triggering pro-inflammatory condition on the aortic wall. Enlarged arteries are in danger of a tear, as the tears usually occur at the point where the wall tension is the most prominent. Anatomically, the sinus Valsalva has the largest diameter of the aorta. Therefore, the tear often begins at the sinotubular junction or the root of ascending aorta.

Atherosclerosis is an acquired disease which has non-infectious inflammatory components that primarily affects the intima. Although it is more commonly related to the descending and abdominal aorta, it can be encountered in the ascending aorta. Endothelial injury caused by rupture of an atherosclerotic plaque may trigger a dissection (Maleszewski, 2015).

Being an elastic wall, the tensile limit can be reached by aneurysm formation, and a large aneurysm itself predisposes to greater increments in growth, increasing thus the risk for dissection or rupture (Elefteriades & Ziganshin, 2015). The median AscAA size at the time of rupture or dissection is 60 mm and < 50 mm for patients with Marfan syndrome (Coady et al., 1999). Yet, a dissection may occur without

a pre-existing aneurysm. In fact, up to 60% of ATAAD occurred at the aortic diameter of < 55 mm and 40% < 50 mm (Pape et al., 2007).

Increasing age, male gender and smoking are associated with ATAAD. Age increases the stiffness of the aorta and the formation of atherosclerotic plaques and is a significant risk factor for both aortic aneurysm formation and a dissection. Smoking may contribute to the inflammatory components of medial degeneration. Not only it increases the risk for dissection but it might also be responsible for more rapid growth of the aortic aneurysms (Kihara et al., 2017).

Cocaine or stimulants use, aortic coarctation, pheochromocytoma, stress and physical trauma (especially blunt trauma) to the chest can raise the aortic wall stress temporarily and predispose to dissection (Ahmad et al., 2017).

Other acquired causes for ATAAD include iatrogenic incidences due to invasive procedures, such as percutaneous coronary intervention (PCI), open cardiac surgery, arterial cannulation and other arterial manipulations, especially among older patients with cardiovascular risks (Ramanath et al., 2009). As many as 5% of all aortic dissections were found to be iatrogenic, most commonly related to cardiac surgical procedures (Januzzi et al., 2002). Previous cardiac surgery, chronic aortic dissection, and post-traumatic aortic transection are also risk factors for an aortic aneurysm. Diabetes and dyslipidaemia, which contribute to the formation of atherosclerotic plaque, do not seem to be directly associated with TAD (Achneck et al., 2005).

2.3.6 Vasa vasorum

Apart from medial degeneration, another hypothesis regarding the development of ATAAD suggests a progression from intramural haematoma (IMH). IMH is caused by bleeding into the aortic media due to small, spontaneous ruptures in the vasa vasorum. It has been suggested that the mass effect of IMH weakens the aortic wall by increasing the stress on the intima, and therefore exposes to an entry tear (Harris et al., 2012a). Although IMH does not have an intima tear, the progression, management and prognosis of the type A IMH is similar to ATAAD (Goldberg et al., 2014; Harris et al., 2012b)

2.4 Epidemiology of TADs

2.4.1 Incidence of TADs

A large population-based study reported an incidence of 16.3/100,000/year for male and 9.1/100,000/year for women in TADs. The incidence for thoracic aortic aneurysm alone is reported around 10.4/100,000/year (Clouse et al., 1998) and for ATAAD is estimated at 2.53-6/100,000/year (Howard et al., 2013; Yeh et al., 2015).

An increasing trend in the incidence of TADs has been noticed in several studies (Clouse et al., 1998; Olsson et al., 2006), albeit it is difficult to tell to what extend it can be attributed to incidental findings, better diagnostics, and aging of the population. TAD is a clinically predominantly silent disease, and while it is estimated that 22% of TAD patients end up with a complication (dissection or rupture) (Albornoz et al., 2006), up to 95% of patients are asymptomatic before a complication occurs (Kuzmik et al., 2012). On the other hand, one quarter of patients with ATAAD do not reach the hospital alive and their diagnosis is made at autopsy (Melvinsdottir et al., 2016; Olsson et al., 1993). In contrast, a whole-nation study that included autopsy results showed a stable incidence of ATAAD (Melvinsdottir et al., 2016). These elements make determining the true prevalence of AscAA and incidence of ATAAD challenging.

2.4.2 Demographics of ATAADs

The mean age of patients presenting with ATAAD is typically around 60 years, women being significantly older than men, but two-third of patients are male. Marfan syndrome is present in 5%, atherosclerosis in 23.8%, known aortic aneurysm in 12.7%, prior aortic surgery in 14.2% and previous acute aortic dissection in 4.0% of ATAAD patients (Evangelista et al., 2018).

2.5 Diagnosis of TADs

2.5.1 Clinical symptoms and findings

Dilatation of the ascending aorta is an indolent process, and patients with AscAA are most of the time asymptomatic. Nevertheless, depending on the size and location of the aneurysm, a wide range of very rare and nonspecific symptoms can be found, such as throbbing of deep chest pain that can spread to the back, shortness of breath, cough, dysphagia, and hoarseness due to laryngeal nerve palsy (Erbel et al., 2014).

The clinical manifestation of ATAAD is very diverse and up to 21% report not having any chest pain initially (Hagan et al., 2000). Typically, however, the onset of ATAAD is abrupt and dramatic. The most common presentation is severe pain that is often described as sharp, tearing or ripping retrosternal chest pain that radiates to the back (Pape et al., 2015). Some 13-19% are reported to have syncope during initial presentation (Nallamothu et al., 2002). Initially, patients tend to be hypertensive but often become hypotensive at later settings. Upon clinical examination, approximately 44% have aortic insufficiency or newly detected murmur, and pulse defect can be present in 31% of patients (Trimarchi et al., 2005).

Younger patients (< 40 years) tend to present without hypertension and are more likely to have a bicuspid valve, connective tissue disease, to have undergone prior aortic valve surgery, and the origin tends to be more proximal (Januzzi et al., 2004). Elderly patients are more likely to be hypertensive at presentation, to have a coexisting aneurysm, to have had a prior cardiac surgery and to have more comorbidities, such as atherosclerosis and diabetes (Mehta et al., 2002).

2.5.1.1 Complications

In ATAAD, preoperative malperfusion syndrome is a feared complication caused by obstruction or occlusion in arteries that can lead to end-organ failures. It is present among 30-40% of ATAAD patients and is a major risk factor for both in-hospital and long-term mortality (Czerny et al., 2015; Eusanio et al., 2013; Narayan et al., 2017; Zindovic et al., 2019).

Renal insufficiency is estimated to be present in 18% of ATAAD patients and associated with significantly increased in-hospital mortality. Acute limb ischemia was reported in 9.7% and major brain injury approximately in 10-20% of ATAAD

(Berretta et al., 2016; Eusanio et al., 2013; Weisberg et al., 2019). Patients with mesenteric ischemia, although rare, are noted to have highest mortality, up to two-thirds of cases (Evangelista et al., 2018).

When the dissection progresses retrogradely towards the aortic root and coronary arteries, it may cause coronary ischemia and severe aortic insufficiency that can lead to acute cardiac failure. Ruptures again may lead to cardiac tamponade, hypovolemic cardiogenic shock and eventually to cardiac arrest. Cardiogenic shock or pericardium tamponade can be registered in 13-18% of ATAAD patients before the surgery (Bossone et al., 2016; Evangelista et al., 2018).

2.5.2 Diagnostic imaging

A computed tomography (CT) with contrast agent is the golden standard for diagnosing TADs. It is fast, nowadays easily accessible, and both its sensitivity and specificity are nearly 100% (Mussa et al., 2016) (Figure 3). With 3D reconstruction, it can accurately show the measurements of aneurysms, an intimal flap, a penetrating ulcer and separate between an intramural haematoma and an aortic dissection. The downside of CT include exposure to radiation and the risks for contrast induced nephropathy.

Echocardiography provides a fast and easy way to get high-resolution, real-time images of cardiac function, anatomy of the valves, the aortic root, and the proximal aorta. It can be performed either transthoracically (TTE) or transesophagecally (TEE). TTE is non-invasive and can be done bedside, while TEE is a semi-invasive procedure but provides a better view of the entire thoracic aorta and is often routinely used during valve procedures to monitor cardiac function. The sensitivity of TEE in ATAAD approaches 86-100% with specificity of 90-100% (Mussa et al., 2016; Sobczyk & Nycz, 2015). However, they have limitations such as poor visualization of intramural haematoma, entry tear location and the aortic arch, and they often do not reveal the whole extent of the dissection.

Cardiac magnetic resonance imaging (MRI) shows the aortic valve and ventricular function, and provides precise measurements of the entire aorta, especially when combined with angiography. It is very accurate and does not emit ionizing radiation. On the other hand, it is time-consuming, more expensive, less readily available, contraindicated in patients with metallic foreign bodies and typically not suitable in the acute setting. It can also cause systemic nephrogenic fibrosis in patients with advanced renal failure (Mussa et al., 2016).

AscAA and ATAAD can be both revealed by a widened mediastinum on a standard chest X-ray. A plain chest X-ray is, however, not sensitive nor specific and certainly not diagnostic, but due to its simplicity and easy access, most patients end up having a chest x-ray first before the diagnosis is confirmed. A widened mediastinum can also lead to suspicion of a thoracic aortic pathology when not suspected before imaging.

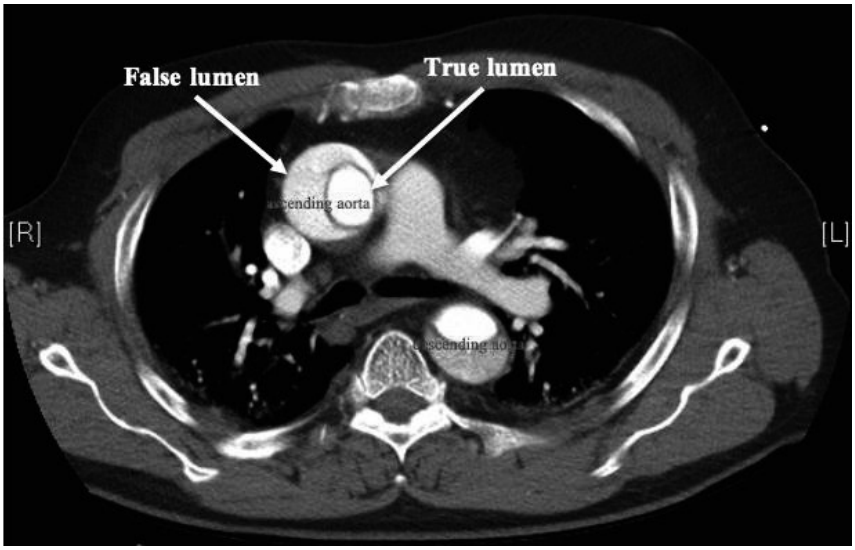

Figure 3. An axial plane of enhanced CT scan showing dissected aorta at the level of pulmonary truncus. Published with permission of the copyright holder, Professor Tomas Gudbjarttson.

2.5.3 Biomarkers and other diagnostic tools

D-dimer is a fibrin fragment found in coagulopathic disorders, such as in ATAAD. It has a high sensitivity for detecting ATAAD and is typically significantly elevated during the first hours after ATAAD, in contrast to other conditions where D-dimer elevates gradually. In low to intermediate suspicion of ATAAD, a negative D-dimer within the first 24 hours after symptom onset is most likely sufficient to rule out the disease (Rogers et al., 2011; Sobczyk & Nycz, 2015; Suzuki et al., 2009). A positive D-dimer, however, should raise suspicion for ATAAD but can

be related to many other conditions, including life-threatening pulmonary embolism (Nazerian et al., 2018). Several other biomarkers for AscAA and ATAAD are under investigation, but so far none of them are in clinical use (Suzuki et al., 2008)

An electrocardiogram (ECG) is not sensitive nor specific for aortic dissection. In the IRAD database, up to 40% of patients with thoracic aortic dissection have a normal ECG (Costin et al., 2018). Changes on ECG are secondary to dissection extending to the coronary arteries causing coronary ischemia and/or cardiac tamponade. Therefore, negative T-waves, ST-segment elevations or depressions, or low-voltage may be encountered (Kosuge et al., 2017). Correspondingly, a troponin raise is also secondary to myocardial ischemia and is elevated in 25% of ATAAD patients (Bonnefoy et al., 2005). Although neither ECG nor troponin are diagnostic for ATAAD, they are harbingers of poor outcomes in patients with ATAAD.

In 2010, the ACC/AHA guidelines proposed a risk assessment scoring tool for assessing the probability of acute aortic syndrome based on three features: predisposing conditions, pain features and clinical examination (Table 2) (Hiratzka et al., 2010). The scoring system was tested retrospectively using the IRAD database and stated as a highly sensitive clinical tool for detecting acute aortic dissection (Rogers et al., 2011). The key for diagnosing ATAAD is to keep it readily in mind and harbour a suspicion when patient is presented with one or more of the conditions listed in table 2.

Table 2. Risk assessment tool for detecting acute aortic dissection (Erbel et al., 2014).

High-risk conditions	**High-risk pain features**	**High-risk examination features**
Marfan syndrome (or other connective tissue diseases)	Chest, back, or abdominal pain described as any of the following:	Evidence of perfusion deficit:
Family history of aortic disease	• abrupt onset	• pulse deficit
Known aortic valve disease	• severe intensity	• systolic blood pressure difference
Known thoracic aortic aneurysm	• ripping or tearing	• focal neurological deficit (in conjunction with pain)
Previous aortic manipulation (including cardiac surgery)		Aortic diastolic murmur (new and with pain)
		Hypotension or shock

2.5.4 Differential diagnosis of TADs

Due to low incidence and diverse symptoms that often mimic other, more common disorders, such as myocardial ischemia or stroke, the diagnosis of ATAAD is often

delayed, mistaken or even missed (Luo et al., 2009). A prompt differential diagnosis between acute coronary syndrome and ATAAD is essential but can be very tricky. Sometimes congestive heart failure might be the only clinical finding and can be therefore often misleading. Moreover, it is not uncommon that these conditions occur simultaneously, which makes it even more complicated. Other important differential diagnoses include pulmonary embolism, myopericarditis, pneumothorax or hemothorax, dyspepsia, pneumonia, pleuritis, esophagitis, oesophageal spasm or perforation, ulcus perforation, Tieze's syndrome, and other musculoskeletal syndromes (Spittell et al., 1993).

2.6 Management of TADs

2.6.1 General principles

The only curative treatment for AscAA is surgery. The risks of complications, such as dissection or rupture, and possibly the progression of the aneurysm, however, can be reduced with medical therapy for the patients who do not yet meet the surgical criteria or are not eligible for an open surgery (Chun et al., 2013). Beta-adrenergic receptor blockade is considered the cornerstone of medical treatment of AscAA. It reduces the heart rate, decreases systolic pressure and the stress on the aortic wall (Shores et al., 1994). Some promising results in preventing aortic enlargement have been shown with angiotensin II receptor blocker in patients with Marfan syndrome (Brooke et al., 2008; Pees et al., 2013), however, larger clinical trials are still on the way (Mullen et al., 2013; Pitcher et al., 2015). Statins may also have beneficial effects against complications (Jovin et al., 2012). In terms of lifestyle, patients with TAD should also be cautious with intense, strenuous isometric activities (Hatzaras et al., 2007), avoid cocaine and other powerful stimulants, and quit smoking (Goldfinger et al., 2014).

The standard treatment for ATAAD is an immediate open cardiac surgery (Sutton et al., 1981). However, lowering blood pressure in the acute setting may limit the expansion of the dissection and thus likely reduces the extent of the disease, allowing more time for surgery (Kaji, 2019).

2.6.2 Surgical repair

2.6.2.1 Indications for surgical repair of TADs

Every patient presenting with ATAAD should be considered for surgery. There are few absolute contraindications for surgery, namely a background of terminal illness, global irreversible cerebral ischemia, and the patient's wish. Poor neurological response, coma, cardiogenic shock secondary to severe malperfusion are more relative and are at the discretion of the operating surgeon considering the patient's individual risk profile, life-expectancy and expectations.

Both the European (ESC) and the American (ACCF/AHA) guidelines on aortic diseases recommend elective surgery for AscAA when the maximal aortic diameter is ≥ 55 mm, regardless of aetiology, and when the aneurysm is symptomatic (class IIaC in ESC, class IC in ACCF/AHA) (Erbel et al., 2014; Hiratzka et al., 2010). Both guidelines also recommend a consideration for a concomitant repair of the aortic root or ascending aorta replacement with a size ≥ 45 mm when the patient is undergoing an open aortic valve repair or replacement, particularly if the valve is bicuspid (class IIaC in both ESC and ACC/AHA) (Erbel et al., 2014; Hiratzka et al., 2016).

According to ESC Guidelines on the diagnosis and treatment of aortic diseases (Erbel et al., 2014), patients with Marfan syndrome should have a lower threshold of ≥ 50 mm for aortic surgery (class IC). Marfan patients with additional risk factors including a family history of dissection, a size increase of > 3 mm/year on repeated examinations, severe aortic or mitral regurgitation, or the desire to become pregnant, the surgery should be considered already when the aortic diameter reaches ≥ 45 mm (class IIaC). There is not enough data available regarding patients with other connective tissue diseases. It is, however, generally recommended to treat them as Marfan patients but since patients with Loeyz-Diez syndrome or confirmed TGFBR1 or TGFBR2 mutation have higher risks for aortic complications, ESC guidelines proposed an intervention when aortic diameter reached > 42 mm (class IIaC). For patients with BAV, both ESC and ACCF/AHA guidelines recommend surgery when aortic diameter exceeds ≥ 55 mm (class IB in ACC/AHA, class IIaC in ESC), but 50 mm can be considered when there are additional risk factors, such as family history, systemic hypertension, coarctation of the aorta, or aortic diameter increase of > 3 mm / year according to ESC (class IIaC) and ≥ 5 mm/year in an aorta that is < 55 mm in size according to ACC/AHA (class IIaB) in repeated examinations (class IIaB) (Erbel et al., 2014; Hiratzka et al., 2016).

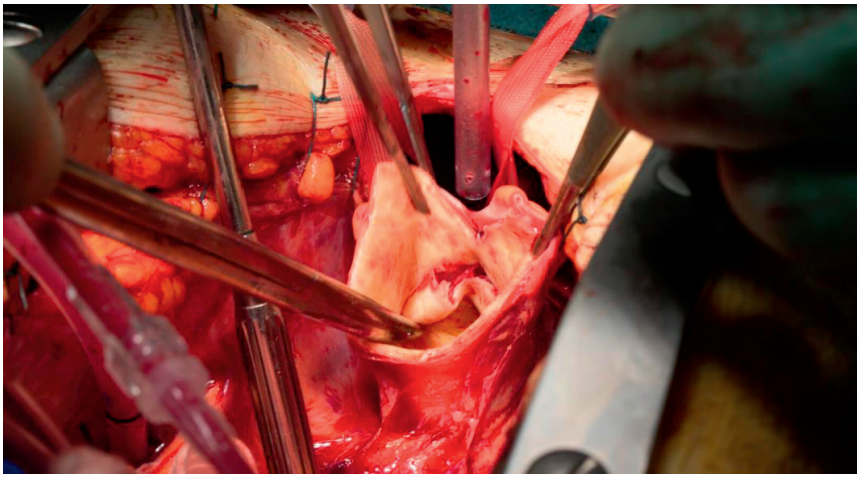

Figure 4. A photograph from an ATAAD operation showing a dissected aorta with a direct visibility to the primary tear site. The ascending aorta has been resected. Published with permission of the copyright holder, Professor Tomas Gudbjarttson.

2.6.2.2 Principles of surgical techniques

The goal of surgical intervention is to prevent further lethal complications, and to ensure adequate systemic perfusion by re-establishing blood flow to the true lumen of the aorta in the case of a dissection (El-Hamamsy et al., 2016).

Contemporary TAD surgery consists of standard median sternotomy and pericardiotomy, then arterial cannulation for initiating cardiopulmonary bypass (CPB). There are three major aortic cannulation strategies for CPB; through axillary or subclavian artery, using femoral artery, or direct aortic cannulation (Paulis et al., 2015). Less frequently used cannulation strategies include transapical cannulation and transatrial left ventricular cannulation through the right upper pulmonary vein (Schoeneich et al., 2015). The extent of the surgery, the accessibility and dissection of the cannulation site affect the decision on which site to choose.

Axillary artery or subclavian artery cannulation with a separate end-to-side anastomosed 6- or 8-mm Dacron graft is nowadays commonly used. This technique is time-consuming compared to other techniques but it provides antegrade perfusion, an easy accessibility for cerebral perfusion under hypothermic circulatory arrest (HCA), and has been proved safe (Rylski et al., 2016). Animal studies and retrospective studies have also suggested that axillary artery cannulation might reduce

embolic stroke events and thus early mortality (Etz et al., 2008; Hedayati et al., 2004; Kim et al., 2019; Svensson et al., 2004).

Direct aortic cannulation into the true lumen is fast and therefore preferred when rapid initiation of CPB is needed. However, it has gained popularity in other situations as well as it provides faster access for an antegrade cerebral perfusion and there is increasingly amount of evidence showing that direct central cannulation might be as safe as peripheral cannulation (Kreibich et al., 2018 Accepted manuscript; Frederick et al., 2013; Gegouskov et al., 2018; Reece et al., 2007). Typically, the cannulation site is located under the lesser curvature of the arch, and it is performed using the Seldinger technique under ultrasound guidance (Gobolos et al., 2008; Kitamura et al., 2017). The cannulation does not leave any damage to the aortic wall as the cannulation site can be resected while performing the aortic anastomosis.

Femoral artery cannulation in TAD surgery has declined in popularity as it causes retrograde CPB perfusion, which may lead to inadequate flow distribution between true and false lumens, thus generating organ malperfusions, as well as possible retrograde embolization of atheromatous material (El-Hamamsy et al., 2016; Gulbins et al., 2007; Kim et al., 2019; Van Arsdell et al., 1998). There are no randomized prospective trials regarding cannulation techniques, but many retrospective studies have shown lower in-hospital mortality and lower incidence of permanent neurological deficit when using axillary artery cannulation compared to femoral artery cannulation (Benedetto et al., 2015; Gulbins et al., 2007; Ren et al., 2015).

After the venous cannula is placed into the right atrium, the aorta is cross-clamped and CPB is initiated. The heart is then stopped with intermittent cardioplegia. The operation consists of resection of the primary tear, when distinguishable, and replacement of ascending aorta with a Dacron tube graft (Figure 4). If there is aortic regurgitation, the aortic valve can be repaired by resuspension of the native valve, or replaced either using a valve-sparing technique performed by a surgeon familiar with the procedure or with a prosthetic valve (Beckmann et al., 2017). More often when the valve is compromised, aortic root replacement with coronary artery implantation, as well as aortic arch repair, when needed, will be carried out. Additional concomitant procedures like coronary artery bypass (CABG) or mitral valve repair (MVR) are also sometimes required.

In most contemporary centres, the distal anastomosis is sutured without aortic clamping (open-distal anastomosis) under direct vision, to enable visualization of the distal aorta and adequate resection of the compromised segment of the aortic wall. An open distal anastomosis also ensures precise placement and thereby a high quality of sutures, and it appears to be associated with better outcomes than a

clamped-on anastomosis, although there are not many comparative studies on the subject (Geirsson et al., 2018; Malvindi et al., 2016). Open-distal anastomosis requires discontinuing CPB, during which protection against organ ischemia is carried out by cooling the body temperature and thus decreasing the oxygen demand for metabolism. This is called hypothermic circulatory arrest (HCA), which can be moderate (24-28°C) or deep (18-20°C). There is no unequivocal consensus on the optimal temperature, but the recent literature tends to favour moderate hypothermia as deeper hypothermia is counterbalanced by a higher propensity for bleeding complications due to coagulopathy associated with lower temperature (Algarni et al., 2014; Keeling et al., 2017; Sun et al., 2018). A separate cerebral perfusion can be established during HCA to prolong the tolerated ischemic window. An antegrade cerebral perfusion, either through the right axillary artery or bilaterally through the right axillary and left carotid arteries, is often used as it is likely to provide longer ischemic time, possibly better brain perfusion and less cerebral complications compared to retrograde perfusion (Abe & Usui, 2017; Panos et al., 2006; Reuthebuch et al., 2004; Shimazaki et al., 2004). Alternatively, the supra-aortic branches may be selectively cannulated for cerebral perfusion. Retrograde cerebral perfusion through the superior vena cava is also used in many centres but may be associated with worse neurological outcomes and a higher incidence of prolonged ICU stay compared to antegrade cerebral perfusion, although there are studies demonstrating excellent outcomes with both techniques (Griepp et al., 1997; Okita et al., 2015; Spielvogel et al., 2013; Sugiura et al., 2012; Ueda et al., 1999).

2.6.2.2.1 Supracoronary aortic replacement

Isolated supracoronary aortic replacement typically means the ascending aorta between the coronary ostia and the brachiocephalic artery is resected and replaced with a vascular tube graft (Figure 5a). It is considered the “simplest” technique for both AscAA and ATAAD repair when the ascending aorta is affected without significant aortic root involvement and the valve is competent and not stenotic. However, more often TAD is associated with aortic valve disease as well (David et al., 2007). The decision to undertake supracoronary replacement alone is often a compromise when seeking to avert the increased risk of perioperative morbidity associated with more extensive repair, for example in a patient deemed to poorly tolerate extended operative and CPB durations, especially in ATAAD surgeries.

2.6.2.2.2 Aortic root surgery

Aortic root is often affected in TAD diseases. In ascending aortic aneurysms, the sinuses and the sinotubular junction area are often dilated, especially in patients with Marfan. In ATAAD with primary intimal tear located in the ascending aorta, the dissection often extends into the non-coronary sinus, less frequently into the left or right coronary sinus, causing aortic regurgitation.

Most of the time, even when the aortic valve is partially dissected, the native valve can be repaired and competency restored without replacement (Leshnower & Chen, 2016). Aortic root can be repaired with resuspension of the aortic valve by suturing from its three commissures. The "sandwich" technique – Teflon felt with or without biological glue is placed between the dissected layers of sinuses to support the media layer – may be applied (Rylski et al, 2014). If the aortic valve needs to be replaced, both ESC guidelines on valvular diseases and ACCF/AHA guidelines on thoracic aortic disease generally recommend valve-sparing procedures performed by experienced surgeons when technically feasible, and if not, aortic root replacement using a composite graft conduit prosthesis (Baumgartner et al., 2017; Hiratzka et al., 2016). A valve-sparing procedure is recommended in patients with aortic root dilation and tricuspid aortic valves according to ESC (class IC), and also in patients with aortic root dilation and valve regurgitation according to ACCF/AHA (class IC), provided that the surgeon is experienced in the technique. Patients with Marfan syndrome or other connective tissue disease undergoing an aortic surgery are typically younger and, therefore, a valve-sparing technique is particularly appealing. If the aortic root is severely dilated ($\geq$ 45 mm) or dissected, if the patient has a concomitant severe aortic valve disease, such as valvular stenosis, or has a history of a connective tissue disease, a valve-sparing root replacement or replacement with a mechanical or biological valve should be indicated (Leshnower & Chen, 2016).

The Bentall-de Bono procedure was first described in 1968 and has since been referred to as the golden standard for aortic root repair. The original Bentall and de Bono technique involves a tubular composite graft including a mechanical valve which is sutured to the aortic annulus and distal aorta. The coronary arteries are reimplanted into the graft and the aneurysm wall is not removed but wrapped tightly around the graft for hemostasis (Bentall & De Bono, 1968). This technique is associated with high coronary complications, such as coronary detachment, postoperative bleeding, and recurrent pseudoaneurysm formation at the coronary artery and around aortic anastomoses (Crosby et al., 1973; Inberg et al., 1985; Kouchoukos & Marshall, 1986). There were various modifications introduced to reduce these complications. Cabrol et al described a technique where the coronaries are sutured end-to-end to a separate small graft which is then anastomosed to

the aortic graft (Cabrol et al., 1981). This technique showed worse outcome compared to direct reimplantation and therefore has not been adapted. Inberg et al. from Turku University Hospital presented a modified root repair with a composite graft in 1985 (Inberg et al., 1985). In their technique, the aneurysm is entirely resected, and both the coronary ostia and the proximal parts of the coronary arteries were dissected free and mobilized before reimplantation to the graft, which reduces tension at the coronary anastomosis. This technique is similar to what has been later popularized by Kouchoukos and associates, who dissected the coronaries with a button of aortic tissue, known as the coronary button technique (Kouchoukos et al., 1991). Nowadays, in a typical modified Bentall procedure the aneurysm sack is resected and a composite Dacron graft containing either a mechanical or a bioprosthetic valve replaces the diseased valve and ascending aorta, and the coronary arteries are detached from the aortic sinuses and sutured to the graft using a button-technique (Figure 5b). The Bentall procedure using a composite graft shows excellent durability and low mortality, and the long-term results are excellent (Celiento et al., 2016; Ehrlich et al., 2001; Mookhoek et al., 2016; Nezafati et al., 2015). However, due to many adverse effects related to an artificial valve, such as life-long anticoagulation and increased risk of endocarditis and aortic stenosis, the native valve is preferably preserved whenever possible.

The first valve-sparing technique, known as Yacoub's procedure, was introduced by Sir Magdi Yacoub in the late 1980s (Yacoub et al., 2018). This procedure reconstructs the aortic root with remodelling technique, which means the graft is tailored to conform to the shape of aortic sinuses and the anastomoses is performed following the shape. However, this technique does not protect the annulus from the dilation (Rahnavardi et al., 2011).

Another valve-sparing technique, the David procedure, has become more and more common in recent years. In the David reimplantation procedure, introduced by Dr. Tirone David in 1992, the aortic sinus segments are excised leaving a 2-3 mm remnant of aortic tissue around the annulus. The ascending aorta is then replaced with a tubular graft that is seated at the level of the aortic annulus. The aortic valves are reimplanted by pulling the commissures upwards and securing them to the graft using sutures (David & Feindel, 1992) (Figure 5b). If the valve has prolapsing cusps, they can be shortened by plication along the nodule of Arantius (David, 2011). This technique protects and supports both the valve leaflets and the annulus, therefore conferring protection from subsequent dilatation (Beyersdorf & Rylski, 2012).

Although David's procedure is time-consuming, the results from large centres using valve-sparing technique in elective cases are superb. In David's procedure, the

results have shown excellent valve durability, low early and late mortalities, and low need for any reoperation (David et al., 2010; Paulis et al., 2010; Kallenbach et al., 2005; Leontyev et al., 2012; Svensson et al., 2013). The recurrence of severe aortic valve regurgitation, the need for a later reoperation, and the long-term mortality seem to be lower when using David's reimplantation technique compared to Yacoub's remodelling technique (Kallenbach et al., 2013). Especially in patients with Marfan syndrome or other connective tissue disease, the aortic tissue is weaker and therefore the David's technique is more justified, as it provides an extra fixation of the aortic annulus, whereas the Yacoub's technique does not (Benedetto et al., 2011; Flynn et al., 2017; Price et al., 2016).

2.6.2.2.3 Aortic arch repair

When the aortic dissection extends to aortic arch and beyond, or if the primary tear is located in the aortic arch, the arch is likely to be repaired. ESC guideline recommends aortic arch repair for patients with the maximal diameter of ≥ 55 mm or who present symptoms or signs of local compression (Erbel et al., 2014). The choice of operative technique depends on the clinical presentation and aortic anatomy of the patient, especially the size of the aorta and the location of the intimal tear, but not the least on the experience of the surgeon and the centre (El-Hamamsy et al., 2016). Most commonly used techniques are hemiarch replacement or total arch replacement with or without an intraluminal stent graft put into the proximal descending aorta (Poon et al., 2016b; Roselli et al., 2018; Shrestha et al., 2017).

Hemiarch replacement is the simplest and quickest technique when the aortic arch is partially affected (Figure 5c). In hemiarch replacement, a various length of the lesser curvature of the aortic arch is resected obliquely but the branch vessels and the downstream aorta are untouched (Sultan et al., 2016). The prosthesis is fashioned into a shape mimicking the aortic arch, and the distal anastomosis is then performed in an open-distal fashion under deep or moderate HCA preferably with selective cerebral perfusion. This technique mandates direct inspection of the distal aortic arch and the branch vessels.

Total arch replacement is a more aggressive approach for repairing a diseased arch (Figure 5c). An extended arch surgery enables resection of primary intimal tear beyond the ascending aorta and possibly excludes re-entry tears in the distal aorta and expands the distal true lumen, potentially reducing postoperative malperfusion and later reinterventions (El-Hamamsy et al., 2016; Smith et al., 2017). In the total arch replacement, both the ascending aorta and the aortic arch are completely resected, and the distal anastomosis extends distal to the left subclavian artery. The

supra-aortic vessels can be reimplanted as an island en bloc or each vessel separately with or without a branched graft (Shelstad et al., 2016a). In the island technique, the supra-aortic vessels are resected as a single aortic patch. This technique limits the number of anastomoses and may be the fastest technique, but in ATAAD, the tear might be present around the greater curvature of the aorta, and the dissected tissue is often problematic as it's fragile for sutures and potentially diseased aortic tissue remains after surgery. The technique is also difficult in reaching the posterior anastomosis in the case of bleeding. A variation of the island technique is the peninsula technique described by Itoh et al. They suggested for arch replacement, specifically in patients with BAV and arch dilatation, an operation in which a cleft is formed in the distal part of the arch prosthesis, leaving the island of supra-aortic vessels connected with the distal native aorta, thereby creating a peninsula (Itoh et al., 2010).

Kazui et al introduced a technique using an aortic arch graft that has three or four branches attached (Kazui et al., 2000). The branches of the graft were anastomosed to the brachiocephalic artery, the left common carotid artery and the left subclavian artery. The additional fourth branch is used for antegrade perfusion and will be later resected. Spielvogel et al developed a separate trifurcated graft in order to enable antegrade cerebral perfusion (Spielvogel et al., 2002). The graft serves itself as the brachiocephalic trunk and has two branch limbs which are anastomosed to the left common carotid artery and the left subclavian artery under the period of HCA while using a selective cerebral perfusion from the right axillary artery. The proximal prosthetic brachiocephalic trunk is then anastomosed graft-to-graft fashion to the aortic arch prosthesis. There are many variations of branched techniques which all enable the resection of the origin of arch vessels as they most frequently develop atherosclerotic lesions, and the distal anastomosis can be performed at the intact sites of branch vessels. The perfusion time may be reduced, especially in the Spielvogel's technique, when the corresponding branch may be opened after the previous branch anastomosis is performed.

Total arch replacement is technically challenging, especially with branch grafts, and significantly increases risk of morbidity and mortality compared to less aggressive procedures (Shelstad et al., 2016b). Therefore, it requires a great level of experience and expertise from the surgical team. The long-term outcomes are not well established, and there are mixed results based on retrospective studies (Preventza et al., 2015; Shi et al., 2014; Smith et al., 2017b). Unequivocal superiority for a single technique is difficult to ascertain, as the results are dependent upon many factors, such as the specifics of the patient and his/her unique pathology, as well as the experience of the surgical team in different approaches.

2.6.2.2.4 Endovascular treatment

The first successful endovascular repair of ATAAD was reported in 2000 (Dorros et al., 2000). Since then, endovascular technology has made leaps forward in the management of the aortic valve and the descending aorta, but the progress has not been significant for ascending aortic diseases. The reasons lie in the complexity of regional anatomy, technical difficulties and high complication rates. Nevertheless, endovascular techniques for ATAAD have been under active scrutiny, and a few small studies have shown appropriate results in carefully selected patients (Bernardes et al., 2014; Follis et al., 2016; Horton et al., 2016; Ronchey et al., 2013). Further research is warranted before endovascular techniques can be implemented in clinical use.

The frozen elephant trunk technique (FET) was first introduced in 1996 by Kato et al. (Kato et al., 1996), and it has undergone many modifications since then. FET is a hybrid technique that combines conventional ascending aortic surgery with an endovascular stentgraft that is placed in the proximal descending aorta and anastomosed to the aorta reminiscing an elephant's trunk, hence the name (Roselli et al., 2018). In ATAAD, when there is type I DeBakey dissection or aneurysm that involves descending aorta, the FET technique is thought to reduce later complications from the remaining dissection or aneurysm, as it helps to expand the true lumen in the proximal descending aorta and consequently reduces the false lumen, thereby promoting its thrombosis (Shrestha et al., 2015). The FET technique, however, is a complex procedure with long CPB time, and it is thought to be associated with a higher risk of postoperative complications, especially spinal injuries (Shrestha et al., 2015). However, in complex thoracic aortic pathologies, the results in the centres that have adopted this technique have been promising (Koizumi et al., 2018; Lin et al., 2015; Shrestha et al., 2015; Sun et al., 2011).

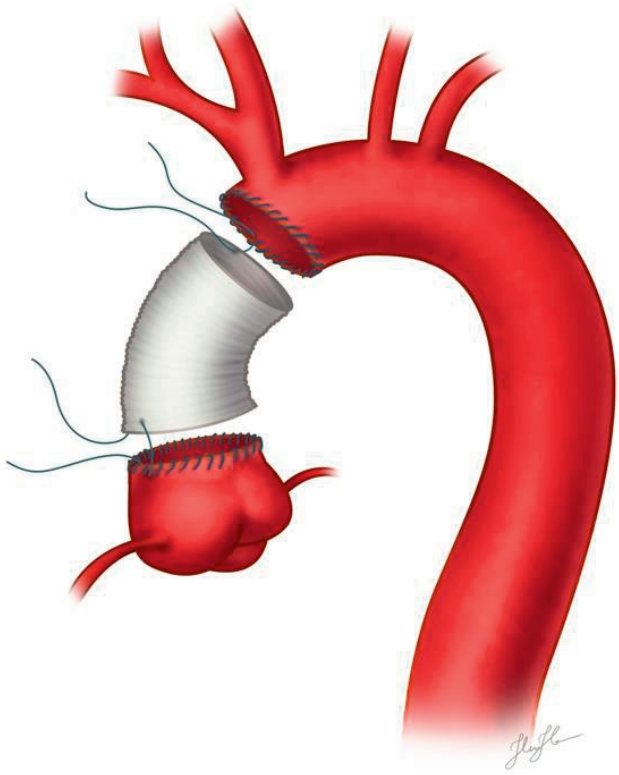

Figure 5a. Isolated supracoronary interposition technique.

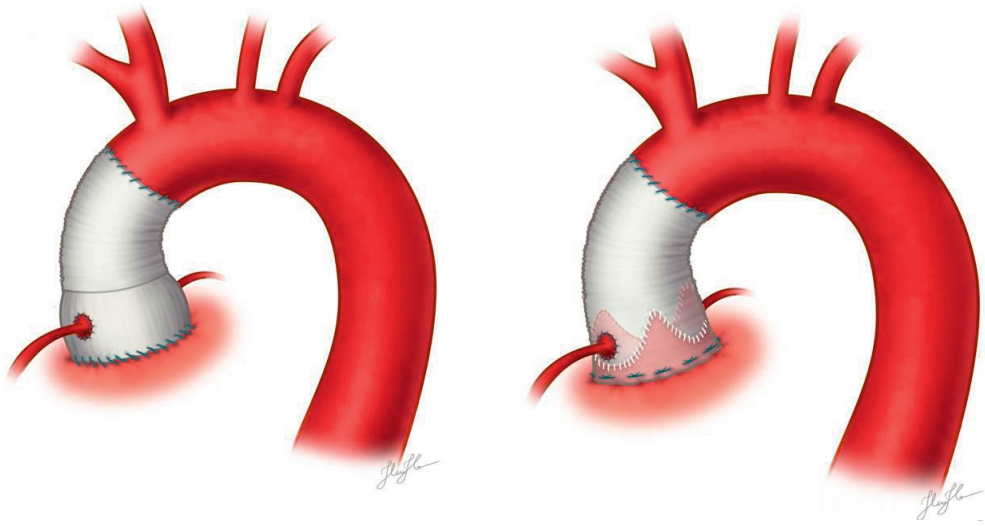

Figure 5b. Aortic root repair: Bentall's procedure on the left and valve-sparing technique with coronary artery implantation, also known as David's procedure, on the right.

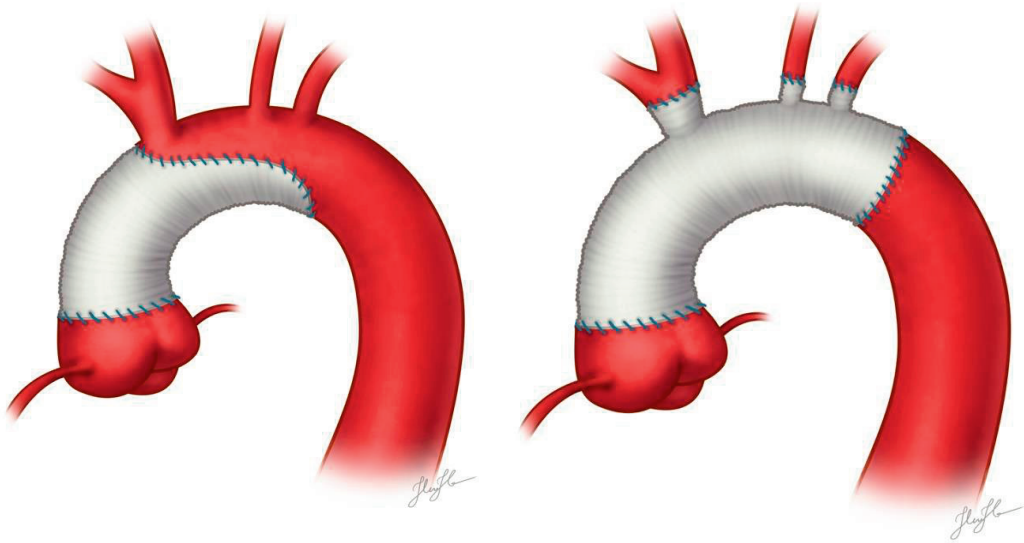

Figure 5c. Ascending aortic repair involving arch: hemiarch replacement on the left and total arch replacement using separate branch grafts on the right.

2.7 Outcomes after ascending aortic surgery

In unruptured TAD surgeries, the 30-day mortality varies between 3.8-7.6% (Achneck et al., 2007; Higgins et al., 2014; Olsson et al., 2006). Stroke is the most feared complication and 5.8% were reported to suffer from perioperative stroke (Achneck et al., 2007). A large American registry-based study that included all types of thoracic aortic surgeries reported a perioperative mortality (in-hospital or 30-day) of 8.67% for isolated ascending aortic replacement, 11.7% when the arch is involved and 7.6% when both the root and the arch were involved (Williams et al., 2012).

Hospital survival after ATAAD surgery is mostly related to patient's preoperative conditions and the worst results are reported in patients with cardiogenic shock, cardiac tamponade, cardiac arrest, and end-organ malperfusions, especially mesenteric malperfusion. The initial mortality rate varies a great deal between different studies and settings. In some high-volume single centres, the 30-day mortality was reported as low as 5% (Shi et al., 2014; Sun et al., 2011) but in most cases, the in-hospital or 30-day mortality were reported between 15.6% and 21% (Colli et al., 2016; Estrera et al., 2015; Narayan et al., 2008; Yeh et al., 2015). Large population studies have typically reported higher mortality rates; some as high as 37-45% for 30-day mortality (Howard et al., 2013; Olsson et al., 2006). On the other hand, these studies have unselected patient flow and may thus better represent of real-life situations. Two largest ATAAD registries, GERAADA and IRAD, have a 30-day mortality of 16.9% and an in-hospital mortality of 23.8%, respectively (Conzelmann et al., 2016; Trimarchi et al., 2010). The surgical mortality has dropped from 25% to 18% in two decades (Evangelista et al., 2018). Among patients discharged from the hospital, the estimated long-term survival at 1, 5, 10 and 20 years varies between 90.7%, 71.8-73%, 53.0-67.5% and 24.0% respectively (Bekkers et al., 2012; Concistre et al., 2012; Endlich et al., 2016; Geirsson et al., 2007; Wang et al., 2014).

Most frequent major complications after ATAAD surgery are bleeding problems, permanent neurological dysfunction, and organ failures. Bleeding leading to a resternotomy occurs in 19% (Olsson & Franco-Cereceda, 2013). During hospitalization, major brain injury occurs in approximately 7%, acute kidney failure in 17%, new myocardial infarction in 6% and cardiac tamponade in 5% (Eusanio et al., 2013). However, it is hard to differentiate to what extend the complication was developed postoperatively instead of being already present before the surgery.

There is scarce information in the literature regarding patients with ATAAD and preoperative cardiac arrest. However, preoperative CPB is a well-known independent risk factors for early mortality (Bekkers et al., 2012; Chiappini et al., 2005; Conzelmann et al., 2016; Hata et al., 2010). Other risk factors for in-hospital mortality include preoperative organ malperfusion, coma, cerebrovascular accident, hypotensive shock at presentation, ischemic peripheral neuropathy, and prior cardiac surgery (Trimarchi et al., 2010; Tsai et al., 2006). Longer CPB and HCA time were also associated with higher mortality (Bekkers et al., 2012; Hata et al., 2010; Tan et al., 2003).

The most common indications for a reoperation after ATAAD surgery are pseudoaneurysms that typically develop adjunct to suture lines (Kobuch et al., 2012). Freedom from proximal reoperation has been reported at 94.6%, 76.8-91.5%, and 79.3% at 5, 10, and 20 years, respectively, and 87.6%, 76.4-93.4%, and 83.3% at 5, 10, and 20 years from distal reoperation, respectively (Geirsson et al., 2007; Wang et al., 2014).

3 AIMS OF THE STUDY

The purpose of the study is to use large, comprehensive data registries to provide better understanding of thoracic aortic diseases and portray real-life outcomes after ascending aortic surgeries in a perspective of a single centre as well as in a multinational setting. In more detail, the aims are:

1. To describe the incidence and long-term outcomes after ascending aortic surgery in Southwest Finland during four decades;

2. To depict the incidence of reoperations after ATAAD surgery and to evaluate the relationship between the extent of primary aortic repair and its impact on later reoperations;

3. To evaluate outcomes after ATAAD surgery in patients with preoperative cardiac arrest.

4 MATERIALS AND METHODS

4.1 Study design and populations

4.1.1 Study I

The study cohort consists of 614 consecutive patients that underwent primary ascending aortic surgery in Turku University Hospital, Southwest Finland, between 1968 and 2014. Baseline data were retrospectively collected from patient records and surgical logs. Mortality data were obtained from Statistics Finland. For survival analysis, only patients surviving the index surgery were included. One patient was lost during follow-up.

Population data for incidence calculations were also retrieved from Statistics Finland. Patients ≥ 18 years were included, and the incidence calculation was standardized using the 2000 US Standard population with direct method. The current geographical catchment area for Turku University Hospital was established in 1984, therefore years 1984-2014 were used in the incidence calculation study.

To evaluate the impact of eras, the surgeries were categorized into four eras: 1968-1980, 1981-1990, 1991-2000, and 2001-2014. The characteristics of the population and surgical procedures were compared between the eras. Age was divided into five categories: ≤ 40, 41–50, 51–60, 61–70 and > 70 years. Surgical procedures were grouped as following: isolated supracoronary ascending aortic replacement, modified Bentall procedure (a composite graft with a mechanical or biological prosthetic valve and separately implanted coronary arteries), Bentall procedure with concomitant CABG or MVR, valve-sparing procedure (David or Yacoub procedure), hemiarch repair, or total arch repair. The indication for surgery was divided into two groups: 1) acute or chronic ascending aortic dissection, aortic rupture or intramural haematoma, and 2) elective indications, such as thoracic aortic aneurysms.

4.1.2 The Nordic Consortium for Acute Type A Aortic Dissection -registry

Collaborations between eight Nordic tertiary cardiothoracic centres resulted in a joint database, the Nordic Consortium for Acute type A Aortic Dissection (NORCAAD), to study acute type A aortic dissection (Geirsson et al., 2016). The centres

involved were Aarhus University Hospital, Skejby, Denmark; Karolinska University Hospital, Stockholm, Sweden; Landspitali University Hospital, Reykjavik, Iceland; Sahlgrenska University Hospital, Gothenburg, Sweden; Skåne University Hospital, Lund, Sweden; Tampere University Hospital, Tampere, Finland; Turku University Hospital, Turku, Finland, and Örebro University Hospital, Örebro, Sweden. The population catchment area for NORCAAD is estimated at 9,500,000.

The database consists of 1,159 consecutive surgically treated patients with ATAAD between January 1st, 2005, and December 31st, 2014, in the participating centres. The operation had to be performed within two weeks from the diagnosis or the first symptoms. The database was retrospectively collected from hospital records and mortality data obtained from each country's national population registries. Each centre was responsible for its own data collection.

A total of 194 variables were collected including demographics, past medical history, preoperative medications, clinical symptoms at presentation, diagnostic methods, operative variables, postoperative complications, bleeding and blood transfusions, laboratory test results, outcomes, follow-up echocardiography data, and reoperation data.

4.1.2.1 Study II

For study II, additional variables regarding reoperations (indications, urgency, date and type of surgery, and cause of death) were requested, and the information was collected retrospectively from patient logs of each centre. The data regarding the extent of primary surgery and/or reoperations was incomplete in 28 patients that were therefore excluded, leaving 1,131 cases for analysis.

Primary endpoints in the study were either reoperation or death. Reoperation was defined as any cardiac or aortic surgery that could be related to primary ATAAD surgery. Reoperations due to bleeding were excluded as they represent perioperative complications instead of directly reflecting the impact of different types of surgical approaches.

Each primary ATAAD repair and each reoperation procedure were classified according to both 1) proximal repair that is divided to either isolated supracoronary replacement group or aortic root group if the surgery included concomitant root replacement or valve-sparing procedure, and 2) the location of distal anastomosis that is further divided into ascending aorta, hemiarch, or total arch groups. Due to

low volume of both hemiarch and total arch groups, these two groups were combined for competing risk survival analysis. The patient selection and groups are presented in the flow chart (Figure 6).

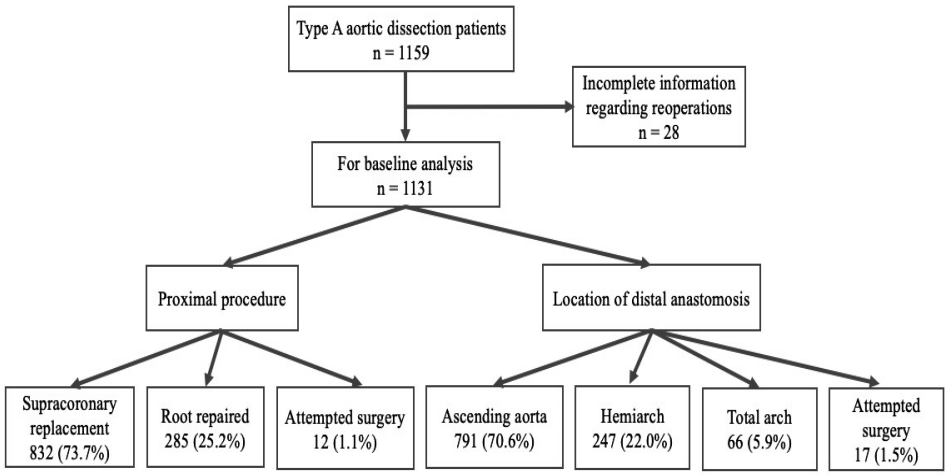

Figure 6. Flow chart of patient selection and types of primary ATAAD surgery in Study II.

4.1.2.2 Study III

In study III, 1,154 cases were included for analysis as 5 patients were excluded due to missing detailed information on preoperative cardiac arrest. Additional details regarding preoperative cardiac arrest and these patients' later daily functional ability were individually collected from each participating centre.

Preoperative cardiac arrest was defined as circulatory collapse that required a period of cardiopulmonary resuscitation (CPR) within 24 hours prior to ATAAD surgery. The location of cardiac arrest was divided into out-of-hospital, at the referring hospital, at the operating hospital, or in the operating room, and defined as the location when the first episode occurred. Unstable hemodynamics in the operating room was classified as systolic blood pressure < 90 mmHg, ventricular arrhythmia. or ongoing cardiac arrest.

Patients with preoperative cardiac arrest were compared with those who did not experience preoperative arrest. In addition, survivors and non-survivors in the preoperative cardiac arrest group were compared. (Figure 7)

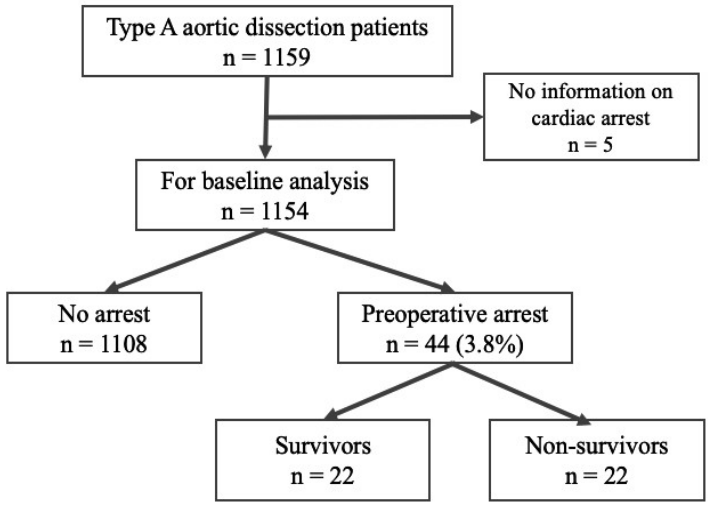

Figure 7 Flow chart of patient selection for Study III.

4.2 Ethical considerations

Study I was approved by the local institutional review board of Southwest Finland Hospital District, and a waiver of informed consent was granted due to the retrospective nature of the study.

In the NORCAAD studies, the study subjects were given randomly an identification number, and all potential patient identifiers were blinded. Each centre obtained approval from their data protection committees or commissions. As in Study I, individual patient consent was not needed in the NORCAAD studies, given the retrospective registry-based nature.

4.3 Statistical analyses

4.3.1 Study I

All statistical analyses were performed with SPSS IBM Statistics version 22.0 (IBM, Armonk, NY, USA). Chi-squared test was used to compare categorical variables and Mann-Whitney U-test was used for continuous variables. Kaplan-Meier survival curves were used to depict long-term survival for 30-day survivors, and the groups were compared using log-rank test. Clinically relevant variables were chosen for Cox proportional hazard regression analysis. First, the univariable Cox

regression analysis was used, and then the same variables were included in multivariable Cox regression analysis to identify predisposing factors for mortality. Hazard ratio (HR) was reported with 95% confidence interval, and p-value < 0.05 was considered statistically significant.

4.3.2 Study II

IBM SPSS Statistics version 24 (IBM-SPSS Inc, Armonk, NY) was used for baseline analyses. Continuous variables were reported as mean ± standard deviation. Chi-square test was used to compare categorical variables between the groups. All tests were two-sided. Stata/IC15.0 for Windows (StataCorp, College Station, Tex) was used to perform the following analyses: a cumulative survival, a cumulative incidence, and Fine-Gray competing risk regression analyses. The reoperation incidence curves after ATAAD surgery were stratified by the classification of DeBakey and the type of surgery (ascending aorta or arch involvement). These groups were then compared using Pepe-Mori test with death as a competing risk event. Fine-Gray competing risk regression model was used to identify independent risk factors for reoperation. The model was adjusted for connective tissue disease and DeBekey classification, and both types of proximal surgeries (supracoronary repair or aortic valve inclusive) and the types of distal anastomosis (ascending aorta, hemiarch, or total arch) were entered into the regression model. HR was reported with 95% confidence interval, and p-value < 0.05 was considered statistically significant.

4.3.3 Study III

The statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA). For comparisons between non-ordered categorical variables Chi-squared test was used, and between dichotomous variables Fisher's exact test was used. Continuous variables were reported as median with interquartile range (IQR). Mann-Whitney U-test was used to compare continuous variables. Logistic regression and univariable Cox regression analysis were performed to identify predisposing factors for overall mortality. Both odds ratios (OR) and HR were reported with 95% confidence interval. The proportional hazard was found satisfied in both groups for the time period of the events by visually reviewing the log(-log(Survival)) vs log(time) figures. Kaplan-Meyer survival curves were used to depict mid-term survival, and log-rank test was used to detect statistical differences between the groups. P-value < 0.05 were considered statistically significant. All tests were two-sided.

5 RESULTS

5.1 The operative incidence and characteristics of ascending aortic surgeries (Study I, II, III)

The population calculation study showed that the incidence of surgically treated TADs was 1.68/100,000 inhabitants/year in 1984-1990 and 4.80/100,000 inhabitants/year in 2011-2014. During the last decade, 2010-2014, the incidence was 7.76/100,000 inhabitants/year for males and 1.95/100,000 inhabitants/year for females.

The number of surgically treated TADs increased steadily in both sexes. Figure 8 shows an average of 3.8 operations per year in 1968-1990 and 32.5 operations per year in 2010s. Male gender was over-represented throughout the time (n=491, 80% vs n=123, 20%, $P < 0.001$) but females tended to have proportionally more dissections and ruptures (n=51, 41.8% vs n=155, 31.7%; $P = 0.04$).

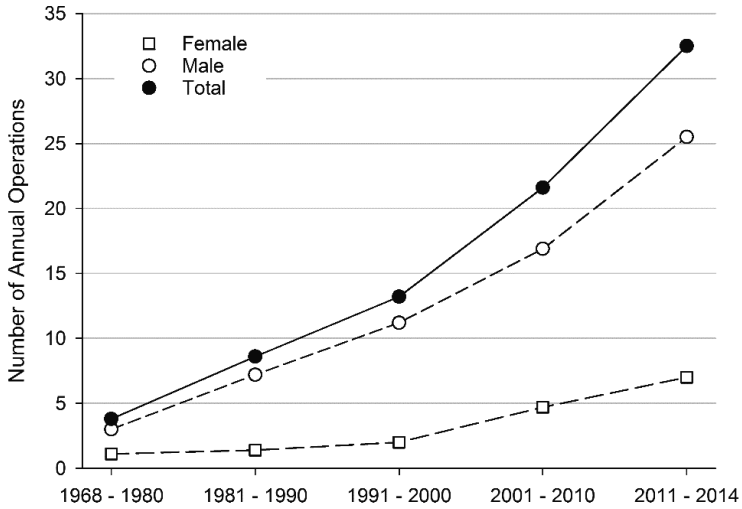

Figure 8. Number of surgically treated ascending aortic diseases per decade. Reproduced from the original publication I with the permission of the copyright holders.

Table 3 shows the evolution of patient selection and surgical procedures over time. Average age at the time of surgery was 56.0 ± 14.4 years. There were significant changes in the distribution of age over the study period. The proportion of younger

patients decreased significantly, and correspondingly, the proportion of elderly patients increased. The first patient above 70 years old was operated in the 90's and within two decades, the proportion of ≥ 70 years olds grew into more than 25% of all operated patients.

Table 3. Baseline characteristics and types of surgery stratified by time of ascending aortic surgery. Modified from the original publication I.

Variable	1968-1980	1981-1990	1991-2000	2001-2010	2011-2014	Total	P-value
Sex							0.259
male	36 (72.0%)	72 (83.7%)	112 (84.8%)	169 (78.2%)	102 (78.5%)	491 (80.0%)	
female	14 (28.0%)	14 (16.3%)	20 (15.2%)	47 (21.8%)	28 (21.5%)	123 (20.0%)	
Age							< 0.001
≤ 40	24 (48.0%)	25 (29.1%)	18 (13.6%)	9 (4.2%)	13 (10.0%)	89 (14.5%)	
41-50	7 (14.0%)	16 (18.6%)	28 (21.2%)	25 (11.6%)	9 (6.9%)	85 (13.8%)	
51-60	13 (26.0%)	28 (32.6%)	40 (30.3%)	57 (26.4%)	32 (24.6%)	170 (27.7%)	
61-70	6 (12.0%)	17 (19.8%)	39 (29.5%)	77 (35.6%)	43 (33.1%)	182 (29.6%)	
≥ 70	0 (0.0%)	0 (0.0%)	7 (5.3%)	48 (22.2%)	33 (25.4%)	88 (14.3%)	
Number of operations	49 (8.0%)	87 (14.2%)	132 (21.5%)	216 (35.2%)	130 (21.2%)	614 (100%)	
Indication							0.003
Dissection/ rupture	8 (16.3%)	34 (38.4%)	55 (42.3%)	77 (35.6%)	343(25.4%)	207 (33.7%)	
Others (aneurysms)	41 (83.7%)	53 (61.6%)	75 (57.7%)	139 (64.4%)	97 (74.6%)	404 (66.3%)	
Procedure							< 0.001
Bentall	22 (44.0%)	57 (66.3%)	70 (53.0%)	144 (66.7%)	74 (56.9%)	367 (59.8%)	
Valve-sparing	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.3%)	14 (10.8%)	19 (3.1%)	
Interposition	26 (52.0%)	21 (24.4%)	36 (29.5%)	20 (9.3%)	19 (14.6%)	122 (19.9%)	
Arch repair	1 (2.0%)	3 (3.5%)	6 (4.5%)	24 (11.1%)	10 (7.7%)	44 (7.2%)	
Bentall + CABG/MVR	1 (2.0%)	5 (5.8%)	20 (15.2%)	23 (10.6%)	13 (10.0)	62 (10.1%)	
Reoperation due to bleeding	0	5	1	13	1	20	

CABG = coronary artery bypass grafting; MVR = mitral valve repair

Two-third of the operations were elective procedures, mainly ascending aortic aneurysms. The rest (33.7%) were ATAADs or ruptures. The modified Bentall procedure was the most frequently used approach almost throughout the study period, in average of 59.8% of all surgeries.

In the NORCAAD database that included only surgically treated ATAADs, the mean age at the time of operation was 61.6 ± 12.1 years, and 66.9% of the patients were male. The details of patient characteristics are summarized in Table 4. Types

and distribution of primary ATAAD surgeries are illustrated in Figure 6. Connective tissue disease (9.9% vs. 3.0%; P < 0.01) and bicuspid aortic valve (14.8% vs. 3.0%; P < 0.01) were significantly more often present in the root repaired group, while open distal anastomosis technique was less used in comparison to supracoronary group. (95.4% vs. 88.3%; P < 0.01).

Table 4. Characteristics of patients with surgically treated ATAAD from the NORCAAD registry. (Studies II and III)

Variables	N	**Median ± IQR / N (%)**
Age	1159	61.6 (54.0-70.7)
Male gender	1159	784 (67.6%)
Active smoking	1091	259 (22.3%)
Family history of		
Aortic dissection	835	64 (5.5%)
Thoracic aortic aneurysm	835	40 (3.5%)
Clinical background		
Bicuspid aortic valve	1147	69 (6.0%)
Connective tissue disease	1099	56 (4.8%)
Marfan syndrome	1155	49 (4.2%)
Known thoracic aortic aneurysm	1154	111 (9.6%)
Previous cardiac or aortic surgery		64 (5.5%)
Coronary artery disease	1159	48 (4.2%)
Hypertension	1157	599 (51.7%)
Chronic obstructive pulmonary disease	1155	69 (6.0%)
Initial presentation		
Sudden pain	1152	981 (84.6%)
Hypotensive shock	1073	254 (21.9%)
Extent of Dissection	1151	
DeBakey Type I		842 (73.0%)
DeBakey Type II		304 (26.3%)
Organ malperfusion		
Cardiac malperfusion	1029	89 (7.7%)
Cerebral malperfusion	1031	90 (7.8%)
Gastrointestinal malperfusion	1030	35 (3.1%)
Penn classification*	1049	
Class A		709 (23.4%)
Class B		246 (21.2%)
Class C		126 (10.9%)
Preoperative lactate in serum (mmol/l)	628	1.6 (1.0-2.7)
Pericardial tamponade	911	222 (24.4%)

IQR = interquartile range; Penn Class A = no ischemia, Class B = localized ischemia, Class C = generalized ischemia

5.2 Outcomes after ascending aortic surgery (Study I, II, III)

The median follow-up time in study I was 11.8 years (range 0-46.8 years). In this study, intraoperative mortality was 7.5% and 30-day mortality 16.0% for the entire cohort. Among those who survived the operation, the postoperative 30-day mortality was 9.2% for all TADs, 18.3% for ATAADs or ruptures and 5.5% for other indications ($P < 0.001$).

The cumulative survival for those who survived the index operation was 86.8%, 79.5%, 70.3%, 47.1%, 34.6%, and 24.2% at 1, 5, 10, 20, 30, and 40 years, respectively. After the first 30 days, the Kaplan-Meier analysis showed no statistically significant difference in long-term survival between emergent dissection/rupture group and electively operated group (P=0.096) (Figure 9).

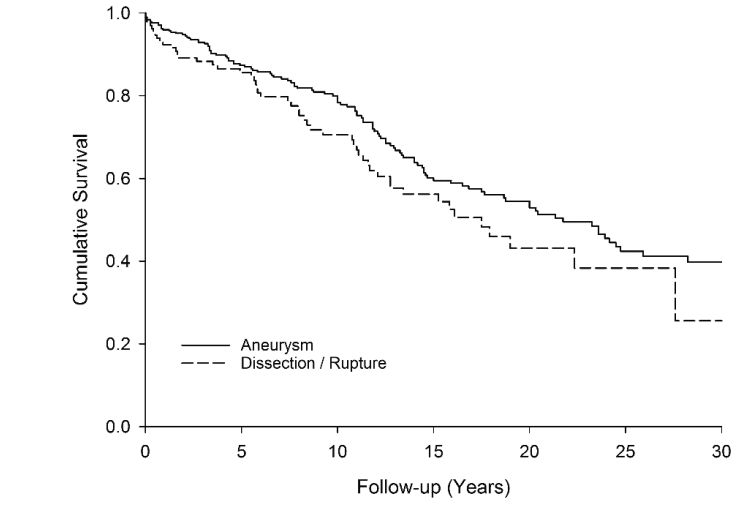

Figure 9. The cumulative survival after ascending aortic surgery in 30-day survivors, stratified by aneurysm and dissection/rupture groups. No statistically significant difference was detected (P=0.096). Reproduced from the original publication I with the permission of the copyright holders.

In NORCAAD studies, the mean follow-up time was 3.3 years (median 2.7, IQR 0.5-5.5) in overall and 4.0 years (median 3.8, IQR 1.6-6.1) for 30-day survivors. For the entire cohort (n=1159), the intraoperative death occurred in 7.4%, hospital mortality rate was 15.9% and 30-day mortality 17.6%. Estimated survival at 1, 5 and 8 years were 79.0%, 72.0% and 64.4%, respectively. For operative survivors, the estimated survival was 95.4%, 86.4%, and 76.5%, respectively.

The survival rates from different sub-groups are summarized in table 5.

Table 5. Cumulative survival after ascending aortic surgery in different sub-groups.

Variables	N	1 year	3 years	5 years	10 years	20 years
Elective ascending aortic surgery	405	87.2%	87.2%	82.0	75.0	51.6%
ATAAD in a single centre	208	60.0%	57.4%	56.2	46.6%	29.4%
ATAAD in NORCAAD	1159	79.7%	76.1%	72.1%		
Patients with preoperative cardiac arrest	44	49.2%	49.2%			
Patients that were reoperated*	51	96.0	93.4%	90.2%		

***bleeding reoperations were excluded**

5.3 Predictors of mortality after ascending aortic surgery (Study I, II)

In study I, the results of the multivariable Cox proportional hazard analysis are shown in Table 6. Increasing age was an independent risk factor for both 30-day and long-term mortality. ATAAD or rupture were associated with 4-fold, and the earliest era of TAD surgery compared to the latest era predicted 6-fold higher risk of 30-day mortality (1968-1980 vs. 2010-2014, HR 6.0, P = 0.002). Aortic arch involvement, aortic root repair and other concomitant procedures (CABG/MVR) did not have a significant impact on long-term mortality for 30-day survivors compared to isolated ascending aortic replacement procedures.

Table 6. Mortality assessed with multivariable Cox proportional hazard analyses after ascending aortic surgery. Modified from the original publication I.

	30-day mortality		Long-term mortality for 30-day survivors	
	HR (95.0% CI)	P-value	HR (95.0% CI)	P-value
Sex (male vs. female)	0.97 (0.49-1.92)	0.93	1.23 (0.81-1.86)	0.327
Age (per one year)	1.05 (1.02-1.08)	0.002	1.05 (1.03-1.06)	0.000
Indication*	3.95 (2.16-7.23)	<0.001	1.16 (0.80-1.68)	0.442
Era (vs. 2011-2014)		0.002		
1968-1980	6.00 (1.60-22.53)	0.008	2.16 (0.83-5.59)	0.113
1981-1990	0.89 (0.23-3.46)	0.870	1.58 (0.66-3.82)	0.306
1991-2000	0.37 (0.10-1.41)	0.147	1.37 (0.58-3.21)	0472
2001-2010	1.90 (0.90-4.01)	0.094	1.12 (0.48-2.63)	0.786
Surgical approach (in addition to ascending aortic replacement)				
+Arch	2.09 (0.98-4.45)	0.056	0.83 (0.38-1.78)	0.625
+Aortic valve	1.56 (0.76-3.22)	0.225	1.11 (0.67-1.48)	0.976
+CABG/MVR	2.18 (0.97-4.93)	0.060	1.11 (0.66-1.85)	0.697

*Indication = dissection/rupture vs elective surgery

5.4 The relationship between the extent of ATAAD surgery and re-operation (Study II)

In study I, a total of 18 patients (cumulative incidence of 3.2%) had a reoperation during the same treatment period. Thirteen patients (cumulative incidence 2.3%) had a reoperation that was related to index ascending aortic surgery during another hospital admission, and four of these patients died due to reoperation. Indications for reoperations are listed in Table 7.

In NORCAAD study (II), we found out that the incidence of reoperation was low. In total, 51 (4.5%) individual patients underwent 53 separate reoperations. Five patients had both proximal and distal aorta repaired, 3 of them simultaneously. Most of the reoperations were elective (69.8%), the rest were either urgent or emergent (30.2%).

Table 7. Indications for a reoperation in Study I.

Indications for reoperation after ascending aortic surgery	Numbers of patients
Thoracic aortic aneurysm	3
Abdominal aortic aneurysm	2
Aortic dissection	2
Chronic pericarditis	2
Arrhythmia	2
Thoracic aortic rupture	1
Abdominal aortic rupture	1
Mechanical valve infection	1
Aortic valve stenosis	1
Mitral valve regurgitation	1
Coronary artery disease	1
Coronary artery aneurysm	1
Unknown	13

Reoperation details regarding the indications and type of procedures in 51 patients are presented in Table 8. There was no significant difference in the risk for distal reoperation between the type of distal anastomosis during primary surgery at 1, 5, and 8 years (ascending aorta vs. arch involvement; 99.2%, 97.5%, and 95.3% vs 99.3, 94.8%, and 92.4%, respectively, P = 0.22) (Figure 10). Nor was there significant difference in the risk for proximal reoperation between the primary root replacement group and isolated supracoronary graft technique (98.6%, 97.5%, and 97.4% vs 98.7%, 97.2%, and 93.8% at 1, 5, and 8 years, respectively; P = 0.84). Statistical differences between the distributions of DeBakey type I or II and later distal reoperations were not observed either.

Table 8. The indications for reoperations and the procedures performed in 51 individual patients. Secondary indication or procedures were shown in brackets. Modified from the original publication II.

Proximal reoperation (n=26)				Distal reoperation (n=30)			
Indications		**Procedures**		**Indication**		**Procedures**	
Severe aortic valve insufficiency	12	Composite graft	16	TAAA	18	TAAA repair	19
+ Graft infection	(2)	Valve sparing root replacement	4	Pseudo-aneurysm	9	-TEVAR	(4)
Root dilatation or pseudoaneurysm	9	Supracoronary repair	3	Graft infection	1	-Combination of TEVAR and open repair	(3)
+ Severe aortic valve insufficiency	(1)	Isolated aortic valve replacement	1	Others	2	Hemiarch repair	3
+ Endocarditis	(2)	Repair of anastomosis	1			Total arch repair	7
Graft infection	2	Unknown	1			+Frozen elephant trunk	(3)
Endocarditis	1					Traditional elephant trunk	(1)
+ Root dilatation	(1)					Other	1
Anastomotic rupture	1						
Root dissection	1						
+ severe aortic valve insufficiency, graft infection	(1)						

TAAA = thoracoabdominal aneurysm; TEVAR = thoracic endovascular aortic valve repair

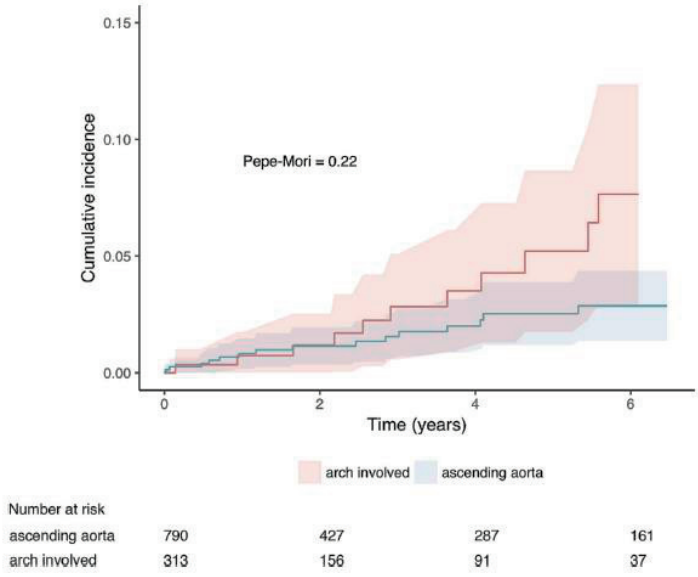

Figure 10. The cumulative incidence of reoperations after ATAAD surgery according to the initial extent of distal surgery. No significant differences were detected (P=0.22). Reproduced from the original publication II with the permission of the copyright holders.

The mean follow-up time was 3.3 years (median 2.7; range 0-10 years). Freedom from any reoperation was 98.2%, 95%, and 92.3% at 1, 5, and 8 years, respectively. Freedom from proximal reoperation was 98.9%, 97.8%, and 96.1% and freedom from distal reoperation were 99.2%, 96.9%, and 94.7%at 1, 5, and 8 years, respectively.

The cumulative survival of patients who underwent a reoperation was 98.0%, 92.8%, and 88.2% at 1, 5, and 8 years, respectively. Overall, 5 deaths (9.8%) occurred in reoperated patients during follow-up period. The cause of death and indications and procedures for earlier reoperation are presented in Table 9.

Table 9. Details regarding five patients that died after reoperation. Modified from the original publication II.

	Proximal reoperation		Distal reoperation		Cause of death
	Indication	**Procedure**	**Indication**	**Procedure**	
Patient 1.	Graft infection	Valve sparing root replacement	None	None	Aortic rupture
Patient 2.	None	None	TAAA	Total arch replacement	Postoperative stroke
Patient 3.	None	None	TAAA	Combination of TEVAR and open repair	Sepsis
Patient 4.	None	None	TAAA	Combination of TEVAR and open repair	Postoperative multiorgan failure
Patient 5.	Root aneurysm, endocarditis	Valve sparing root replacement	TAAA	TEVAR	Aortic rupture

TAAA = thoracoabdominal aortic aneurysm; TEVAR = thoracic endovascular aortic valve repair

In Fine-Gray multivariable regression model with death as a competing risk, the extent of the proximal or distal surgery was not associated with the risk of a reoperation. A history of connective tissue disease increased 5-folds the risk for a proximal reoperation (HR 4.99; 95% CI 1.80-13.85; $P < 0.01$) and was the only independent risk factor for a reoperation.

5.5 Characteristics and outcome in patients with ATAAD and preoperative cardiac arrest (Study III)

Forty-four (3.8%) patients with ATAAD experienced cardiac arrest less than 24 hours before surgery, and four of them had recurrent episodes of cardiac arrest. Unstable hemodynamics was present in 52.3% (n=23) at the beginning of the surgery, and 9 of them had ongoing CPR during initiation of cardiopulmonary bypass.

Comparisons between the cardiac arrest group and the non-arrest group are presented in Table 10. Patients with cardiac arrest had significantly higher intraoperative, in-hospital, and 30-day mortality than those without arrest (Figure 11). In logistic regression analysis, arrest patients had 5.3-fold risks for having perioperative myocardial infarction (24.3% vs. 5.7%; OR 5.3; P <0.001). Early complications, like stroke (48.4% vs. 18.2; OR 4.2; P < 0.001) and new-onset of atrial fibrillation (55.9% vs. 38.1%; OR 2.1; P = 0.04), occurred also significantly more often in the arrest group.

Table 10. Surgically treated type A aortic dissection patients (n=44) compared with non-arrest patients (n=1110). Modified from the manuscript of study III.

	Preoperative arrest group		Non-arrest group		
	N	**Median IQR / n (%)**	**N**	**Median IQR / n (%)**	**P-value**
Age (years)	44	66.6 (52.5-71.25)	1100	63.0 (54.0-70.8)	0.67
Male gender	44	31 (70.5%)	1110	750 (67.6%)	0.75
Hypotensive shock	44	24 (54.5%)	1026	227 (22.1%)	<0.001
Preoperative cardiac malperfusion	44	12 (27.3%)	1020	76 (7.5%)	<0.001
Penn classification					
Class A	44	12 (27.3%)	1101	693 (62.9%)	<0.001
Class B	44	2 (4.5%)	1101	244 (22.2%)	0.003
Class C	44	19 (43.2%)	1101	107 (9.7%)	<0.001
Class B&C	44	11 (25.0%)	1101	57 (5.2%)	<0.001
Preoperative lactate in serum (mmol/l)	30	5.5 (2.4-8.7)	598	1.5 (1.0-2.6)	<0.001
Pericardial tamponade	43	26 (60.5%)	1086	172 (15.8%)	<0.001
Perioperative myocardial infarction	37	9 (24.3%)	1084	62 (5.7%)	<0.001
Stroke	31	15 (48.4%)	1088	198 (18.2%)	<0.001
New-onset atrial fibrillation	34	19 (55.9%)	1078	411 (38.1%)	0.04

IQR = interquartile range; Penn Class A = no ischemia, Class B = localized ischemia, Class C = generalized ischemia, Class B&C = localized and generalized ischemia

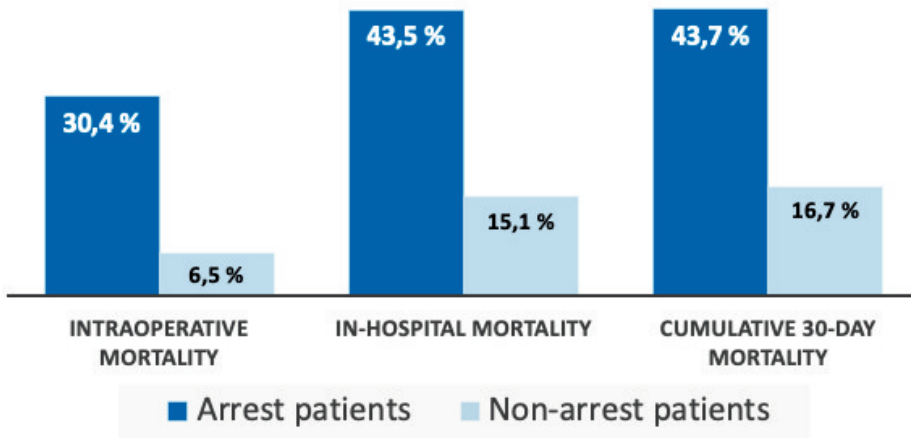

Figure 11. Patients with ATAAD and preoperative cardiac arrest have significantly higher intraoperative, in-hospital and 30-day mortality (all P < 0.001).

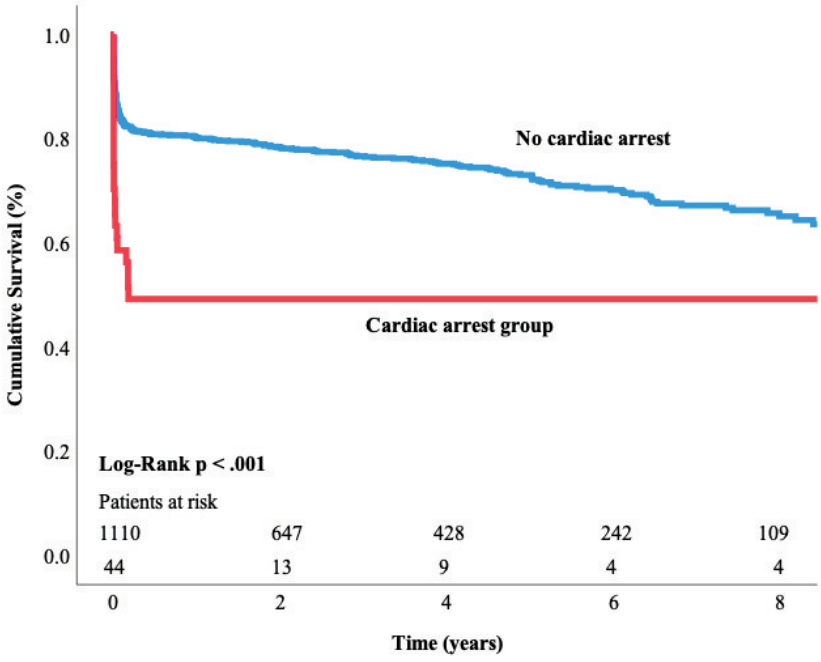

Figure 12. Kaplan-Meier curves from Study III showing cumulative survival in surgically treated ATAAD with or without preoperative cardiac arrest (P < 0.001).

In total, 50% (n=22) of cardiac arrest patients survived the follow-up period. Daily functional ability at the end of the follow-up period was grossly assessed using patient records in 15 of the 22 surviving arrest patients. Twelve (80%) of the 15 cardiac arrest patients were independent in their daily life, and the rest 3 (20%) had neurological dysfunctions: one had impaired vision, one had lower limb paresis and one was not able to write for unknown reasons. The cumulative survival at 1, 3 and 5 years was 49.2%, 49.2%, and 49.2% in the cardiac arrest group, and 79.7%, 76.1%, and 72.1% in the non-arrest group, respectively (Figure 12).

The characteristics of ATAAD patients with preoperative cardiac arrest are presented in Table 11. Type I DeBakey is associated with 6.2-times and preoperative cardiac tamponade with 4.9-times higher hazard of death in patients with preoperative cardiac arrest. Non-survivor were more frequently presented with cardiac malperfusion and a higher preoperative lactate level in serum during initial presentation. Survivors in the cardiac arrest group experienced relatively more often an out-of-hospital cardiac arrest than non-survivors, although this was not statistically significant (Table 12).

Table 11. The characteristics of ATAAD patients with preoperative cardiac arrest. Modified from the manuscript of study III.

	Number of patients N (%)
Location of the first cardiac arrest episode (n=44)	
Outside hospital	22 (50.0%)
At the referring hospital	7 (15.9%)
At the operating hospital	7 (15.9%)
In the operating room	8 (18.2%)
Rhythm (n=33)	
Shockable	14 (42.4%)
Non-shockable	19 (57.6%)
ROSC (n=32)	
ROSC achieved	25 (78.1%)
No ROSC before operation	7 (21.9%)
Unstable haemodynamics* in operating room (n=40)	23 (52.3%)
Ongoing CPR	9 (22.5%)

ROSC = return of spontaneous circulation; CPR = cardiopulmonary resuscitation; Unstable haemodynamics = systolic pressure < 90 mmHg or ventricular arrhythmia or ongoing CPR suring cardiopulmonary bypass initiation

Table 12. The characteristics between the survivors and the non-survivors in the cardiac arrest group were compared using univariate Cox regression analysis. Modified from the manuscript of study III.

	Non-Survivors n = 22	Survivors n = 22	Univariate Cox regression HR (95% CI)	P-value
DeBakey type I	89.5%	50.0%	6.21 (1.20-22.67)	0.02
Pericardial tamponade	81.0%	40.9%	4.94 (1.45-16.85)	0.01
Cardiac malperfusion	40.9%	13.6%	2.51 (1.06-5.94)	0.04
Preoperative lactate level in serum (mmol/l)	6.3 (IQR 4.8-11.8)	3.4 (IQR 1.7-7.6)	1.13 (1.01-1.27)	0.04
Out-of-operating hospital cardiac arrest	36.4%	63.6%	2.16 (0.93-5.00)	0.11

HR = hazard ratio

6 DISCUSSION

6.1 Operative incidence and characteristics of TADs

The number of surgically treated thoracic aortic diseases has been steadily increasing. In our study, the increase was 4.3-fold in women and 2.6-fold in men between 1968 and 2014, while in a Swedish nationwide registry study, the gender distribution was similar, but the increase was more significant – 15-fold in women and 7-fold in men between 1986 and 2002 (Olsson et al., 2006). Instead, the absolute operative incidence per 100,000 inhabitants per year was not that different between the studies. The trend was also rising when it comes to exclusively operated ATAAD. In the NORCAAD registry, the number of operations increased linearly from 85 per year in 2005 to 150 per year in 2014 (Geirsson et al., 2018). It is noteworthy, however, that our studies did not reflect the overall incidence of thoracic aortic diseases in general population as we did not have access to clinical data of non-operated patients or autopsy results.

The characteristics of patients with TAD were mostly similar to the results from the world's largest ATAAD registry, IRAD (Tsai et al., 2006). There was a rather steady male-female ratio of 3:1 for ATAAD and 4:1 for combined TADs throughout the study period, and females were typically older at the time of operation. Both registry studies in this thesis showed that the peak of age for undergoing an ATAAD surgery was in the patients' early sixties, and that the patients undergoing aortic surgery were significantly older than decades before. This is not surprising as not only the understanding of the disease and surgical techniques have evolved but, perhaps even more importantly, the perioperative care has taken great leaps allowing sicker and older patients to be treated postoperatively (Stevens et al., 2009). Moreover, better availability and a striking increase in diagnostic imaging (Smith-bindman et al., 2009) contribute to not just faster and more accurate diagnosis, but also to many incidental findings of indolent aneurysms. These improvements, in turn, directly affect the number of thoracic aortic operations.

6.2 Outcomes after ascending aortic surgery

6.2.1 Survival

The long-term survival after TAD surgery was markedly better in study I than in a previous study with a nearly identical setting (Olsson et al., 2006). Notably, our

results combine both elective and emergent aortic repairs, which differ considerably from each other in the initial presentation, the time for surgical preparation, the quality of the tissues and in particular, the risks that the surgery carries. Study I showed that an ascending aortic dissection or rupture indicated a nearly 4-fold risk for 30-day mortality compared to elective procedures. What was interesting, however, was that the very long-term survival did not significantly differ between electively and emergently repaired TAD groups in 30-day survivors. This indicates that even if ATAAD has a dramatic initial presentation with high mortality, once the aorta is repaired and the patient has survived the first critical month postoperatively, the survival stabilizes and is reasonably satisfying.

The survival after ATAAD surgery in the NORCAAD registry was comparable to other notable large registries in recent years (Conzelmann et al., 2016; Pape et al., 2007). Compared to older studies, however, the survival was better throughout the current study period (Ehrlich et al., 2000; Knipp et al., 2007). From 2005 to 2014, the 30-day mortality has significantly decreased within the NORCAAD registry (Geirsson et al., 2018). In one of the NORCAAD sub-studies, the survival of 30-day survivors was compared to a large normal age- and gender-matched population in Sweden, and a worse survival was noted within ATAAD group compared to matched population (Olsson et al., 2017). Same finding has been noted before (Bekkers et al., 2012), albeit in a NORCAAD study, where the difference between the groups was modest and seemed to be effaced and stabilized over time, which also supports the survival findings that was noted in Study I. In study I, however, the era of surgery did not have an effect on very long-term mortality. These findings suggest that the acute management and perioperative care of ATAAD have significantly improved in the 21st century which has resulted in both better short and mid-term results. Nonetheless, longer follow-ups in large registries are needed before assumptions regarding long-term survival can be made.

6.2.2 Predictors for mortality

For 30-day mortality after TAD surgery, the era of surgery and increased age were found to be independent predictors. For those who survived 30 days after TAD surgery, the only independent predictor for mid-term mortality was increasing age. In the NORCAAD registry, 30-day mortality was highest among those that experienced cardiac (32.8%), gastrointestinal (30.8%), or cerebral (26.4%) malperfusion (Zindovic et al., 2019). Increased age, a history of chronic renal disease, cardiac malperfusion and previous aortic surgical repair were independent predictors of mid-term mortality, whereas a heritable condition, open distal anastomosis, and

a surgery at a later year/later period were independently associated with better medium-term survival (Olsson et al., 2017). Although higher age seems to be an independent predictor in both registries, previous studies have shown that in-hospital complications did not differ between ≥ 70 and < 70 years old. In fact, within ≥ 70 years, the survival was superior in the surgically treated group compared to the medically treated, and over 75 years were noted to have acceptable early and intermediate survival after ATAAD surgery as well (Malvindi et al., 2015; Mehta et al., 2002). Therefore, although risks might be higher, patients with advanced age alone should not be considered less suitable for surgical repair.

6.3 The relationship between the extent of primary ATAAD surgery and reoperations

The reoperation rates from both Turku University Hospital and the NORCAAD study were notably lower than in most previous studies (Bekkers et al., 2012; Geirsson et al., 2007; Trimarchi et al., 2005), yet early and mid-term mortality after primary ATAAD surgery, and mortality after reoperations were still comparable with other large registry studies.

The extent of primary repair of ATAAD is an ongoing debate among aortic surgeons. There are many studies that speak on behalf of a more aggressive surgical approach during initial ATAAD repair in order to reduce risks for later aortic dilatations and reinterventions (Bartolomeo et al., 2015; Moon et al., 2001; Sun et al., 2011; Weigang et al., 2010). Equally, there are studies that were more cautious and would favour a more conservative approach (Poon et al., 2016a; Rylski et al., 2014; Wang et al., 2017). Our studies support the latter one. In addition to low overall reoperation rates, the NORCAAD registry also showed that the extent of proximal or distal primary surgery did not affect the incidence of reoperations, nor did the extent of the dissection (DeBakey type I vs. II). Moreover, in Study I, there was a tendency towards a more aggressive approach, such as arch involvement or concomitant CABG/MVR, increasing the risk for 30-day mortality. In general, the surgical approaches in our studies were rather conservative compared to other studies (Conzelmann et al., 2016; Geirsson et al., 2007). The distribution of DeBakey type I and II (73% and 26%, respectively) was similar to others, albeit the proportion of total arch replacement (5.9%) was less frequent than other studies have reported (Conzelmann et al., 2016; Eusanio et al., 2013; Geirsson et al., 2007). Nevertheless, the median follow-up time is limited to 3.3 years in the NORCAAD registry, which is shorter than in many other studies. The need for reinterventions may emerge many years after primary surgery and, therefore, longer follow-ups are still warranted, and our results cannot be interpreted directly.

Isolated supracoronary aortic replacement with intimal tear resection is considered the simplest and safest way to repair ATAAD (Westaby et al., 2002). More aggressive initial approaches, like total arch repairs with or without frozen elephant trunk (a hybrid prosthesis that consists of a distal endovascular stent graft and a proximal conventional surgical graft), are not only highly demanding procedures but also very time-consuming, associated oftentimes with a much longer operating time, CPB time, aortic cross-clamp time, HCA time, and requiring selective cerebral perfusion, which are all associated with higher postoperative complications and early mortality (Bekkers et al., 2012; Hata et al., 2010; Schoenrath et al., 2016; Tan et al., 2003). As our studies have shown, early mortality is still remarkable despite having significantly improved over time. In short, the operative risk increases steadily with complexity and duration, and therefore, the primary objective and ultimate goal during surgery would be to do only what is absolutely necessary to repair the aorta and restore perfusion in order to come out of the operating room with a stable, alive patient.

It is worth noting that a reoperation after ascending aortic surgery is also a complex and challenging procedure due to variations in clinical and anatomical features, and abundant scar tissue that has formed after primary surgery. Naturally, another risky open cardiac surgery is also an undesired setback for the patient. Study II showed that most indications for distal reoperations were pseudoaneurysms due to progressive enlargement of the persistent false lumen or suture dehiscence which is in accordance with previously reported results (Hsu & Chen, 2014; Kobuch et al., 2012). It has been suggested that by treating the residual false lumen at the index operation when the dissection extends to the aortic arch or beyond (DeBakey type I), long-term prognosis may be more favourable as the risk for reoperations might be lower. In recent years, acceptable early results have been presented after a more extensive initial repair during ATAAD (Omura et al., 2016; Poon et al., 2016a; Smith et al., 2017b) suggesting that an extensive primary repair can be safely performed to avoid late reoperations. Some centres have even introduced total arch repair with frozen elephant trunk as the standard treatment for aortic arch repair (Geirsson et al., 2007; Sun et al., 2011). Nevertheless, these results are from high-volume centres with expertise in aortic surgeries, and long-term outcomes are yet not well established.

The incidence of ATAAD is fairly low, but when it occurs, it almost always results in an emergent surgery. High-volume aortic centres might have a separate acute aortic syndrome team but most centres in the world are small-to-medium sized, thus annual number of encountered ATAAD per surgeon in these centres remains limited, and these operations are often performed by on-call cardiac surgeons who might not be the most experienced aortic surgeons in the centre. Therefore, it remains at the surgeon's discretion to evaluate his or hers and the team's competence

and to choose the procedure they feel comfortable in safely performing, while considering in the decision-making the patient's comorbidities and presentation.

The only independently significant risk factor for a late proximal reoperation was a history of connective tissue disease. Therefore, in the presence of aortic root enlargement in patients with known connective tissue disease, the threshold for concomitant root operation should be lower.

All in all, there is little evidence for advocating routine adoption of complex extensive primary surgical strategies for ATAAD in low- to medium-volume centres. Based on the existing literature and studies I and II, there is little to be gained by choosing an unfamiliar and complex but definitive repair over a simpler, more conservative approach. However, the findings based on our studies are encouraging: good surgical results with low reoperation rate and acceptable reoperation survival can be achieved in non-aortic centralized cardiothoracic centres with moderately simple approaches.

6.4 Surgically treated ATAAD in patients with preoperative cardiac arrest

Study III focused on ATAAD patients that experienced a cardiac arrest < 24 hours before the surgery. Our study revealed a novel finding that, despite perceived dismal prognosis in these patients, up to 50% survive in the long-term and experience an acceptable functional recovery.

In the NORCAAD registry, the incidence of preoperative cardiac arrest was 3.8% (44/1154) among surgically treated patients with ATAAD. Most previous studies reviewed the incidence and outcome of ATAAD among all cardiac arrest patients, which is essentially a different population to that of Study III. A retrospective study from an emergency department in a single centre reported that 1.0% out of all in- or out-of-hospital cardiac arrests were caused by non-traumatic thoracic aortic dissections (Meron et al., 2004). However, the incidence of aortic dissection/rupture is significantly higher among those that died after out-of-hospital cardiac arrests, and studies involving either post-morten CT or autopsies have higher rates of aortic dissection/rupture than the studies without them (Tanaka et al., 2016; Virkkunen et al., 2008). Previous studies with post-mortem CT analysis revealed that up to 7-8% of all out-of-hospital cardiac arrest patients were caused by ATAAD, and 51% of these patients died pre-hospital (Moriwaki et al., 2013; Tanaka et al., 2016). It is therefore plausible that the incidence of patients with ATAAD and preoperative cardiac arrest in the general population is much higher than study III has reported.

In the present study, half of the patients experienced a cardiac arrest out-of-hospital, which means the diagnosis was made post hoc. Ironically, survival after out-of-hospital cardiac arrest seems to be better than after in-hospital arrest, although the difference was not statistically significant (63.6% vs. 36.4%, p=0.11). Instead, non-survivors in cardiac arrest group had more often malperfusion syndrome and DeBakey type I dissection, which is in line with other studies on ATAAD in general (Eusanio et al., 2013; Narayan et al., 2017; Zindovic et al., 2018). It is also noteworthy that one-third of patients (3/9) that had ongoing CPR during cardiopulmonary bypass initiation did actually survive till the end of follow-up. However, the number of patients with ongoing preoperative CPR was so small that it is not reasonable to make further extrapolations.

Having no deaths among cardiac arrest patients after the 65th postoperative day might be coincidental, yet it still alludes to the same findings noticed in all three sub-studies: the initial mortality is high in ATAAD, but survival stabilises substantially after the first months. Cumulative survival in ATAAD patients with preoperative cardiac arrest at 5 years being 49.2% is acceptable. In particular, recovery among survivors was notably better than expected; only one patient needed daily assistance for independent living. These results were substantially better than the findings of a previous study with a similar design which reported only a 13% hospital survival after surgically treated ATAAD in patients with preoperative cardiac arrest (Godon et al., 2001).

Although these survival results might be encouraging, one should bear in mind that there already was a patient selection process before the decision to operate. Patients with prolonged arrest time or otherwise assessed as having no chance of neurological recovery were most likely already denied surgery. From a surgeon's point of view, however, it is important to rationally understand how the patient selection was made and to have objective data regarding long-term survival in patients with ATAAD and preoperative cardiac arrest, instead of making decisions based on intuition. As the number of these patients is very limited, a large database such as the NORCAAD registry, adds valuable details to the literature. Nonetheless, due to limitations of the study, prospective studies are needed to better understand the course of ATAAD with preoperative cardiac arrest and to determine when surgery adds value and when it only prolongs suffering.

6.5 Limitations and strengths

A study can only be as good as the data it is based on. All studies were based on variables collected from patient records which have many limitations due to the retrospective observational nature. There were some data that were missing and

could not be tracked subsequently. Moreover, only surgically treated patients were included which may cause selection bias since the patients that did not survive to the hospital or were denied surgery were unaccounted for. There is a risk of statistical analyses being underpowered and entangled by unknown confounders. In NORCAAD multicentre studies, the protocols of each centre differ to some extent. At the end, the decision to operate and the procedure to be performed always depends on the experience and preference of the surgeon, the perioperative team and the facilities the centre provides. In study I, the exact indications for elective ascending aortic operations were not known, although it is presumable that other indications than ascending aortic aneurysm were very marginal. Study II was also limited by a relatively short follow-up time, the paucity of radiologic data and limited number of reoperated patients. In addition, there's a possibility for false negatives as some patients may succumb before a reoperation is needed. In study III, the study sample of preoperative cardiac arrest patients was small making multivariable regression model unreliable to conduct. In addition, although we have a complete mortality data, the exact cause of death was unknown and therefore, the causality from the results should be interpreted with caution.

The strength of these studies is the completeness of the data. In NORCAAD studies, all the centres involved were low-to-medium sized academic institutions. The Nordic countries are similar in many ways, including electronic medical records, high standards of health care, similar universal health care systems, equivalent cardiothoracic surgical training programs, homogenous populations, and similar geographical population distributions. Above all, nearly complete mortality data were provided by each country's government-funded national registries. Furthermore, Study I depicted comprehensively the trend and evolutions as it had a very long follow-up spanning over six decades. The study also covered all consecutive TADs ever operated in Turku University Hospital, and the centre remained the only tertiary cardiothoracic centre throughout the study period in this region. These elements together provide prerequisites for comprehensive and reliable data registries that mirror the real-life challenges, and yield results that can be applied to daily clinical work.

7 CONCLUSIONS

The following conclusions can be drawn from the present study:

I. The number of TAD operations has significantly increased and the surgical results have improved in 47 years. After the initial critical 30-days, the long-term survival did not significantly differ between the group treated for ATAAD/rupture and the group treated for ascending aortic aneurysm.

II. The risk for reoperation after ATAAD surgery was low in the Nordic countries. Isolated ascending aortic replacement during the primary ATAAD repair did not increase the cumulative incidence for a later reoperation in comparison to arch involvement.

III. Surgically treated ATAAD with preoperative cardiac arrest had high rates of complications and early mortality rates. However, mid-term outcome was acceptable. A preoperative cardiac arrest in patients with ATAAD should not be considered as an absolute contraindication for a surgical repair.

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