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BIOMECHANICAL AND MORPHOLOGICAL ASPECTS OF ABDOMINAL AORTIC ANEURYSM GROWTH AND RUPTURE

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Biomechanical and Morphological Aspects of Abdominal Aortic Aneurysm Growth and Rupture

Thesis for Doctoral Degree (Ph.D.)

By

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To
all persons
who suffered from
aneurysm disease and
contributed with their story,

and my parents
and friends;
thanks

Populärvetenskaplig sammanfattning

Kroppspulsåderbråck, eller aortaaneurysm, uppträder oftast på den del av aorta som är i buken och sjukdomen kallas där för bukaortaaneurysm. Aneurysm innebär att ett, vanligen cylinderformat blodkärl tappar sin form och börjar vidgas. Vidgningen i sig ger oftast inte upphov till några symtom men medför en risk för att aortan ska brista, s.k. ruptur. Ruptur är ett akut tillstånd som medför en hög risk för död och det mest effektiva tillvägagångssättet är att behandla patienter med bukaortaaneurysm innan ruptur inträffar. Då bukaortaaneurysm inte avger några symtom, upptäcks tillståndet oftast som ett bifynd vid radiologiska undersökningar av andra anledningar eller vid speciellt inriktade screeningprogram. Behandlingen av bukaortaaneurysm består antingen av öppen kirurgi eller kateterburen intervention. Ingen medicinsk behandling som skulle minska risken för ruptur finns beskriven, trots att många kliniska studier har genomförts. De nuvarande kirurgiska behandlingsalternativen är behäftade med ej försumbara risker för komplikationer och död. Nyttan med ingreppet måste således vägas mot riskerna. Nyttan består i att förebygga ruptur, och därmed öka den förväntade kvarstående livslängden hos patienten. I klinisk praxis används aneurysmets maximala diametern som ett mått på den förväntade rupturrisken. För män med aneurysm större än 55 mm, och kvinnor med aneurysm större än 50 mm, rekommenderar behandlingsriktlinjer att man bör överväga operation. Fram till dess att patientens aneurysm når dessa storleksgränser får patienten gå på regelbundna kontroller av aneurysmet storlek. Den nuvarande uppföljningen och behandlingen av patienter med bukaortaaneurysm är förhållandevis fungerande och säker på befolkningsnivå, men den är inte individanpassad.

Den första studien i avhandlingen inkluderade patienter med ett bukaorta-aneurysm som hade rupturerat och där datortomografiundersökning i samband med detta hade genomförts. I studien påvisas att en ej obetydlig andel av patienter vars bukaortaaneurysm har rupturerat, har så vid diametrar som är mindre än de nuvarande behandlingsrekommendationerna. Kvinnor och patienter med kronisk obstruktiv lungsjukdom utgjorde en speciellt stor andel av dessa patienter. De maximala diametrarna vid ruptur mellan könen närmade sig till varandra om man justerade dem för kroppsyta. Biomekaniska parametrar, dvs väggspänning eller väggspänning relaterat till väggstyrka, som kan simuleras från datortomografiundersökningar som inkluderar bukaorta-aneurysmet, visade sig vara högre hos patienter med små rupturerade aneurysm jämfört med patienteter med liknande ålder, kön och aneurysmstorlek men intakta aneurysm.

I den andra studien i denna avhandling studerades tillväxt av bukaortaaneurysm över tid, och patienter som hade genomfört tre eller fler datortomografiundersökningar inkluderades och analyserades med avseende på tredimensionella morfologiska och geometriska parametrar. Det visade sig att de flesta bukaortaaneurysm växte kontinuerligt

och vad som verkade linjärt, i motsats till vad som tidigare ofta föreslagits. Bukaortaaneurysm innehåller vanligen en sorts väggfast blodpropp (s.k. intraluminal tromb), och proportionen av denna ökade över tid. Proportionen av den intraluminala tromben var dock omvänt relaterad till ökande biomekaniska parametrar.

I den tredje studien studerades hur biomekaniska parametrar var relaterade med tid till aneurysmruptur, något som tidigare endast studerats i mindre patientmaterial. Patienter som hade genomgått åtminstone en datortomografiundersökning av sitt bukaortaaneurysm som senare hade rupturerat inkluderades i denna studie. Resultaten visade att även om man justerade för kända faktorer som påverkar risken för att ett aneurysm skall rupturera, i detta fall aneurysmets storlek och patientens kön, så var ett biomekaniskt rupurindex ändå associerat med tid till ruptur.

I den fjärde studien studerades om tvådimensionella mått kunde förutsäga vilka aneurysm som hade rupturerat och hur dessa mått var relaterade till biomekaniska parametrar. Detta i ett led att brygga från den mer komplicerade datoriserade analysen av biomekanisk stress, som kräver tredimensionella bildundersökningar som utsätter patienter för både strålning och injektion av intravenösa kontrastmedel, till ultraljudsundersökningar som är i princip oskadliga för patienten. Det visade sig att bland patienter som hade liknande ålder, kön och storlek av sina aneurysm, så var tvärsnittsarean av det blodförande lumen (den del av insidan av kärlet som ej upptas av den intraluminala tromben, och där blodet passerar) högre hos patienter med rupturerade bukaortaaneurysm. Arean av det blodförande lumen visade sig även korrelera med de biomekaniska parametrarna.

Sammantaget så styrker denna avhandling synen att de nuvarande behandlingsrekommendationerna för bukaortaaneurysm inte är individspecifika, och det finns utrymme för förbättring. Biomekaniska, tredimensionella och tvådimensionella morfologiska parametrar bidrar till beskrivningen av ett aneurysm, utöver dess maximala diameter, och kan i framtiden vara användbara för att skräddarsy vilka enskilda patienter som bör behandlas, eller på ett effektivt sätt utvärdera verkningsgraden hos potentiella läkemedelsbehandlingar för bukaortaaneurysm.

Abstract

Abdominal aortic aneurysms (AAAs) are dilatations of the abdominal aorta that pose a risk of rupture. The only effective treatment is intervention prior to rupture, but this is also associated with mortality and morbidity. It is therefore important to weigh the risks of intervention with the potential benefit. Current treatment guidelines recommend using the maximal aneurysm diameter (Dmax) as the indicator for rupture risk, and recommend considering intervention in men with AAAs > 55 mm, and >50 mm in women. Patients with small AAAs are put in surveillance, and the Dmax is followed until it reaches the threshold. The current policy is relatively efficient on a population-level but lacks specificity for individuals. Some patients rupture before this threshold, and many remain stable despite passing it. Aneurysm growth is often described as erratic, but measurements are affected by several levels of uncertainty. Biomechanical assessment, where 3D models of AAAs from computed tomography angiographies (CTAs) are analysed by finite element analysis, may improve risk prediction.

In the first study a population-based cohort of 192 patients with ruptured AAAs and CT imaging available at rupture were studied. A significant portion of patients ruptured with AAAs smaller than 60 mm, 10% of men and 27 % of women. When normalizing Dmax for body surface area (so-called aortic size index) there was, however, was not difference between the sexes. In an analysis of small, ruptured AAAs compared to Dmax, age and sex-matched asymptomatic AAAs, peak wall rupture index (PWRI), but not peak wall stress (PWS) was increased in the ruptured AAAs.

In the second study, a cohort of 100 patients with at least three computed tomography examinations were analysed with 3D morphological and biomechanical analysis. The growth pattern of AAAs appeared continuous and conferred well to a linear growth model. The evolution of the different analysed indices, Dmax, aneurysm volume and biomechanical stress did, however, not parallel each other. Intraluminal thrombus (ILT) grew faster than the lumen, but lumen volume growth was more closely related to increase in biomechanical stress.

In the third study, a cohort of 67 patients with 109 CTA examinations prior to rupture were identified. The relation between biomechanical variables and time-to-rupture was investigated. In small and medium sized AAAs (< 70 mm), PWRI, but not PWS, was associated with time-to-rupture, also when adjusting for potential confounders, aneurysm size and sex. The results further show that women have an approximately two-fold increased hazard ratio for AAA rupture, compared to men, when adjusted for AAA size.

In the fourth study lumen area is indicated as a potentially useful rupture risk marker. Ruptured AAAs, compared to Dmax-matched asymptomatic AAAs, have a larger luminal area, and the luminal area is related to biomechanical stress, even when adjusting for aneurysm size, or ILT area.

In conclusion, the results of this thesis indicate areas of potential improvement in the current care of patients with AAAs, explores the 3D growth of AAAs, and strengthens the potential role for biomechanical analysis. These results may in the future have relevance for personalizing timing of treatment for patients with AAAs, and the evaluation of pharmacological therapy for AAAs.

List of scientific papers

I. Siika A, Lindquist Liljeqvist M, Zommorodi S, Nilsson O, Andersson P, Gasser TC, Roy J, Hultgren R. A large proportion of patients with small ruptured abdominal aortic aneurysms are women and have chronic obstructive pulmonary disease. PLoS One. 2019 May 28;14(5):e0216558.

II. Siika A, Bogdanovic M, Lindquist Liljeqvist M, Gasser TC, Hultgren R, Roy J. Three-dimensional Growth and Biomechanical risk Progression of Abdominal Aortic Aneurysms under Serial Computed Tomography Assessment. Manuscript.

III. Siika A, Talvitie M, Lindquist Liljeqvist M, Bogdanovic M, Gasser TC, Hultgren R, Roy J. Peak Wall Rupture Index is Associated with Time-to-Rupture in Abdominal Aortic Aneurysms Independently of Size and Sex. Manuscript.

IV. Siika A, Lindquist Liljeqvist M, Hultgren R, Gasser TC, Roy J. Aortic Lumen Area Is Increased in Ruptured Abdominal Aortic Aneurysms and Correlates to Biomechanical Rupture Risk. J Endovasc Ther. 2018 Dec;25(6):750-756.

List of related peer-reviewed publications not included in the thesis

R. Mattila*, A. Siika*, J. Roy, and B. Wahlberg, A Markov decision process model to guide treatment of abdominal aortic aneurysms, in Proceedings of the IEEE Conference on Control Applications (CCA'16), pp. 436–441, 2016. * denotes equal contribution

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Contents

List of abbreviations

AAA	Abdominal Aortic Aneurysm
ADAM-trial	Aneurysm Detection and Management-trial
ASI	Aortic Size Index
BSA	Body Surface Area
CAESAR-trial	Comparison of Surveillance versus Aortic Endografting for Small Aneurysm Repair-trial
CI	Confidence Interval
CT	Computed Tomography
CTA	Computed Tomography Angiography
Dmax	Maximal aneurysm diameter
ESVS	European Society of Vascular Surgery
EVAR	Endovascular Aortic Repair
FEA	Finite Element Analysis
HR	Hazard Ratio
ILT	Intraluminal Thrombus
IQR	Interquartile Range
LMIC	Low-and-Middle Income
MEM	Mixed Effects Model
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
NICE	National Institute of Health and Care Excellence
OSR	Open Surgical Repair
PIVOTAL-trial	Positive Impact of Endovascular Options for Treating Aneurysms Early-trial
PWRI	Peak Wall Rupture Index
PWS	Peak Wall Stress
RAAA	Ruptured Abdominal Aortic Aneurysm
SD	Standard Deviation
STAR-cohort	Stockholm Aneurysm Rupture-cohort
SVS	Society of Vascular Surgery
UKSAT	UK Small Aneurysm Trial
US	Ultrasound

1 Introduction

ABDOMINAL AORTIC ANEURYSMS (AAAs) are focal dilatations of the abdominal aorta that pose a threat of rupture [1]. Rupture is a surgical emergency, and half of patients do not reach the hospital [2]. Even if a patient with a ruptured AAA reaches a hospital and is treated, the mortality is still high [3]. No effective medical treatment exists [4], and the only viable option is surgical intervention prior to rupture, by either endovascular aortic repair (EVAR) or open surgical repair (OSR). Both procedures are associated with a significant risk of mortality and morbidity. When deciding on a potential intervention, the risks of the procedure are weighed against the risk of having an un-operated AAA. Today, the recommended intervention limit is 55 mm for men, and 50 mm for women [5,6]. This intervention limit is, however, not patient-specific, which is made clear by the fact that some patients experience rupture below the threshold, and many patients rupture at considerably larger diameters [7]. Biomechanical analysis of AAAs with, so-called, *Finite Element Analysis* (FEA) has been suggested to aid the prediction of rupture and growth [8,9].

The Global Burden of Disease Study attributed 172 000 deaths in 2019 to aortic aneurysms [10]. Death rates from aortic aneurysms have decreased over the last decades in high-income countries but remain high in other parts of the world. In low-income countries, there is seldom access to qualified vascular surgery, and the true prevalence of disease is unknown [11,12]. The prevalence of AAAs in high-income countries has decreased, together with the decrease in cigarette smoking [13]. Low- and middle-income countries (LMICs) have not experienced equally beneficial changes in smoking habits, and other risk factors for vascular disease, such as high age are increasing also in high income countries [14]. The AAA panorama may be changing but will pose an increasing challenge especially to resource-scarce health care systems.

Health-care spending is increasing also in high-income countries [15], and it is important that resources are used in the most efficient way possible. AAA surveillance and treatment pose both monetary and logistic challenges to health-care systems, where patients need to be rigorously surveyed pre-operatively, and in the case of EVAR, life-long post-operatively [5,6]. Elective, and especially emergency, surgery is complex and takes up considerable resources from hospitals. The ageing population also presents challenges for AAA care, where older patients will have more comorbidities, and younger patients will expect to live longer. This will pose vascular surgeons and patients with new questions about when to treat an aneurysm. In turn, this will require more accurate prediction of AAA rupture and growth.

The rest of the thesis is structured in the following manner. In **Section 2** background is presented. **Section 3** presents the overall aims of the thesis, and in **Section 4** patient cohorts, relevant methods with some specific background information, and ethical considerations are described. **Section 5** is an extended overview of the results from the included studies, and in **Section 6** these results are discussed. **Section 7** presents conclusions and **Section 8** some points of future perspective. At the end of the printed book, the four papers that constitute the thesis are bound.

2 Background

2.1 Terminology and epidemiology

The term aneurysm comes from the ancient Greek word ἀνεύρυσμα, meaning widening [16]. In the aorta, aneurysms are most common in the infrarenal, abdominal, portion [17–19], and are there referred to as abdominal aortic aneurysms (AAAs). Most arteries may be affected by aneurysms, but in some locations, aneurysms are not seen or are exceedingly rare, such as the external iliac artery [17]. Aneurysms in the abdominal aorta that are above, or include the renal arteries, are referred to as supra- or juxta-renal [20]. Sometimes AAAs can be attributed to a specific aetiology, such as inflammation, trauma, or infection. Most AAAs, however, lack a specific readily identifiable triggering factor, and are termed as non-specific or degenerative. This thesis will mainly consider this last class of aneurysms. **Figure 2-1** shows a schematic illustration of the aorta and an AAA, and in **Figure 2-2** two images of computed tomography of AAAs, are shown.

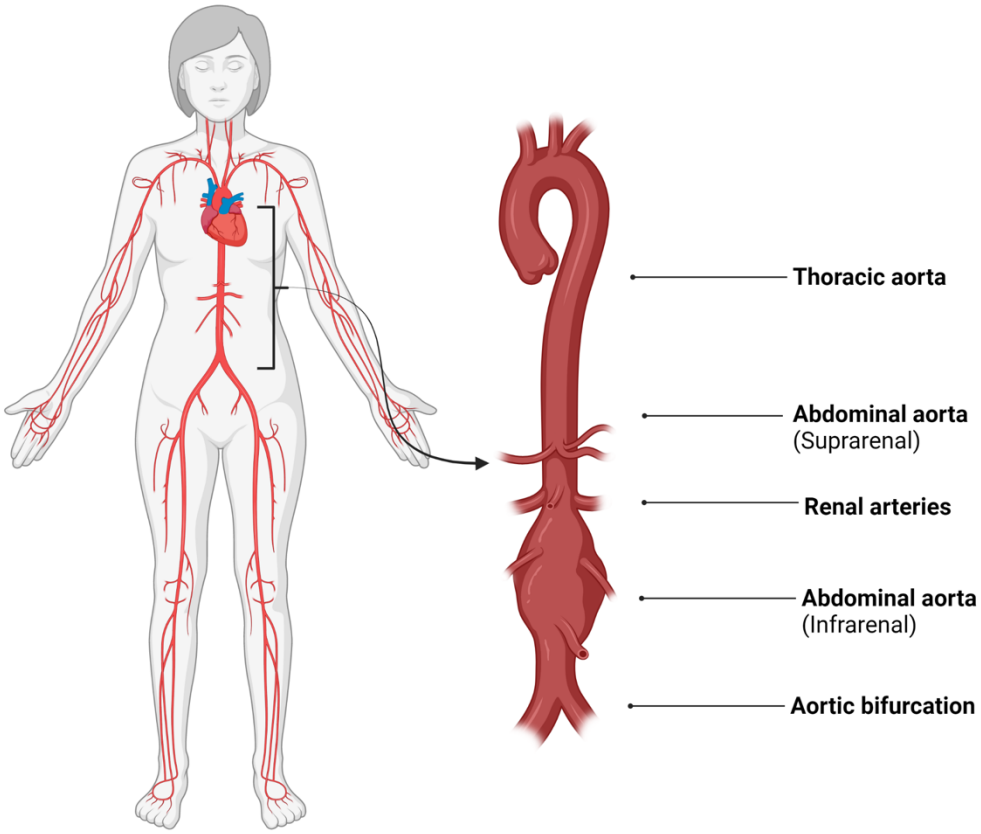

Figure 2-1: Schematic figure illustrating the aorta with an infrarenal abdominal aortic aneurysm. Created with biorender.com.

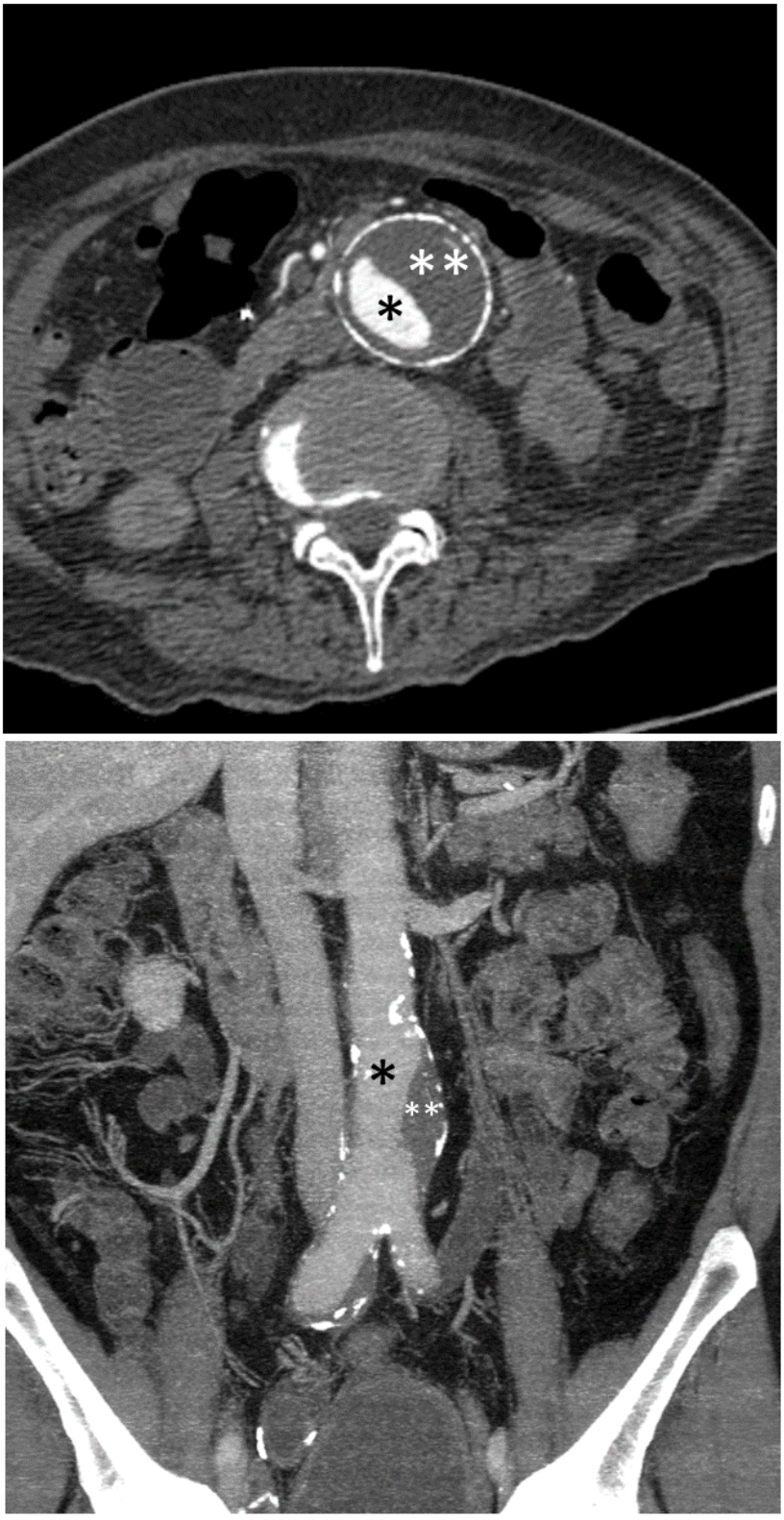

Figure 2-2. Computed tomography angiography (CTA) of two AAAs, (top) axial section, (bottom) coronal section. * Indicates the lumen of the AAA, and ** indicates the intraluminal thrombus (ILT).

In the literature, two principal definitions for AAA are used:

(i) A permanent widening of the aorta to 1.5 times its expected normal diameter or supra-renal diameter [5,20].

(ii) An abdominal aortic diameter >30 mm [5].

An aorta that is widened but does not meet the definition of an aneurysm is termed as sub-aneurysmal or ectatic, typically denoting patients that have an AAA diameter between 25 and 29 millimetres. In cohorts of men invited for AAA screening, it is reported that 30-66% of patients with a sub-aneurysmal aorta develop an aneurysm (>30 mm) within 3-5 years [21–23], and in 5-10 years more than one-tenth progress to >50 mm [23,24]. Data regarding the fate of women with abdominal aortic sub-aneurysms are scarce but indicate that a similar proportion of patients may progress to true aneurysms as in men [25].

2.1.1 The normal abdominal aortic diameter

The normal aorta tapers from the ascending aorta to the infrarenal portion and the aortic bifurcation [26]. The diameter varies both between different persons and within the same persons over their life course. It is generally larger in men, related to body surface area (BSA), and increases with age [27–29]. A recent meta-analysis combined data from almost 1 million participants where ultrasound had been used to measure abdominal aortic diameter. The mean abdominal aortic diameter in this population, with a mean age of 69 years, was 19.4 ± 2.0 mm, and the mean difference between men and women was 2.3 mm [30]. In a selection of the Framingham cohort participants who underwent computed tomography examinations, the mean abdominal aortic diameter was 16.0 mm for women below 45 years, to 17.8 mm for women above 65 years, and the respective numbers for men were 17.6 to 21.8 mm.

2.1.2 Prevalence

The overall prevalence of AAA in the modern population is known primarily from population-based screening with ultrasound. The prevalence estimates are based on the 30 mm threshold. The estimates vary over geographic regions, and over time. The prevalence detected in screening for 65-year-old men in Sweden is decreasing and is reported at 1.5 % or less [31–33], however appears unchanged in Denmark at 2.9% [34]. Global pooled prevalence is decreasing and estimated at 2.3% [30].

Screening-based estimates of prevalence are likely partially biased. Non-attendance to screening shares some common risk factors with AAAs, and already diagnosed or treated AAAs may not be included in the estimates, which leads to an underestimation of the total prevalence [35]. Further, most of these studies are conducted in men above 65 years of age. In Sweden, the prevalence among 70-year-old women is 0.5 % [36], and in a meta-analysis in women 60 years and older, combined prevalence was 0.74 %, but there was considerable heterogeneity of the estimates from the included studies (0.37-1.53%) [37]. The prevalence estimates for AAA are heavily biased to high income countries and to certain geographic regions. In LMICs the true rates of aneurysm disease may likely be underreported. There are, for instance, only a small number of studies that report on screening prevalence for AAA in Africa [38].

Moreover, prevalence is influenced by how an AAA is defined. The two definitions for AAA given previously do not always overlap, and if definition (i) for AAA is used, the prevalence in women increases more than two-fold and is similar to [39] or still lower [40,41] than that in men. The European Society for Vascular Surgery (ESVS) guidelines suggest that this definition may be more appropriate in women, and populations that have smaller normal aortae [5].

It should further be noted that the prevalence of patients with abdominal aortic sub-aneurysms, has been reported to be similar to that of AAAs > 30 mm [21,23,42]. As societal guidelines recommend considering to survey these patients (re-examine within 5-10 years), the number of patients under AAA-related surveillance is higher than the reported prevalence of AAAs > 30 mm.

2.1.3 AAA screening

AAAs are generally asymptomatic before rupture, and the only effective treatment is intervention prior-to-rupture. Specific screening programs to detect asymptomatic AAAs have therefore been evaluated and implemented [5]. Several randomized trials have evaluated the effects of screening. A reduction of aneurysm-related mortality, but not all cause mortality is reported [43], and screening is considered cost-effective [44]. Screening in women has not been deemed effective [45]. The Swedish screening-program was introduced for 65-year-old men in 2006 and reached nation-wide coverage in 2015 [32]. It has decreased aneurysm-specific mortality and is deemed cost-effective [32]. Nationwide screening programs have also been implemented in the United Kingdom [46].

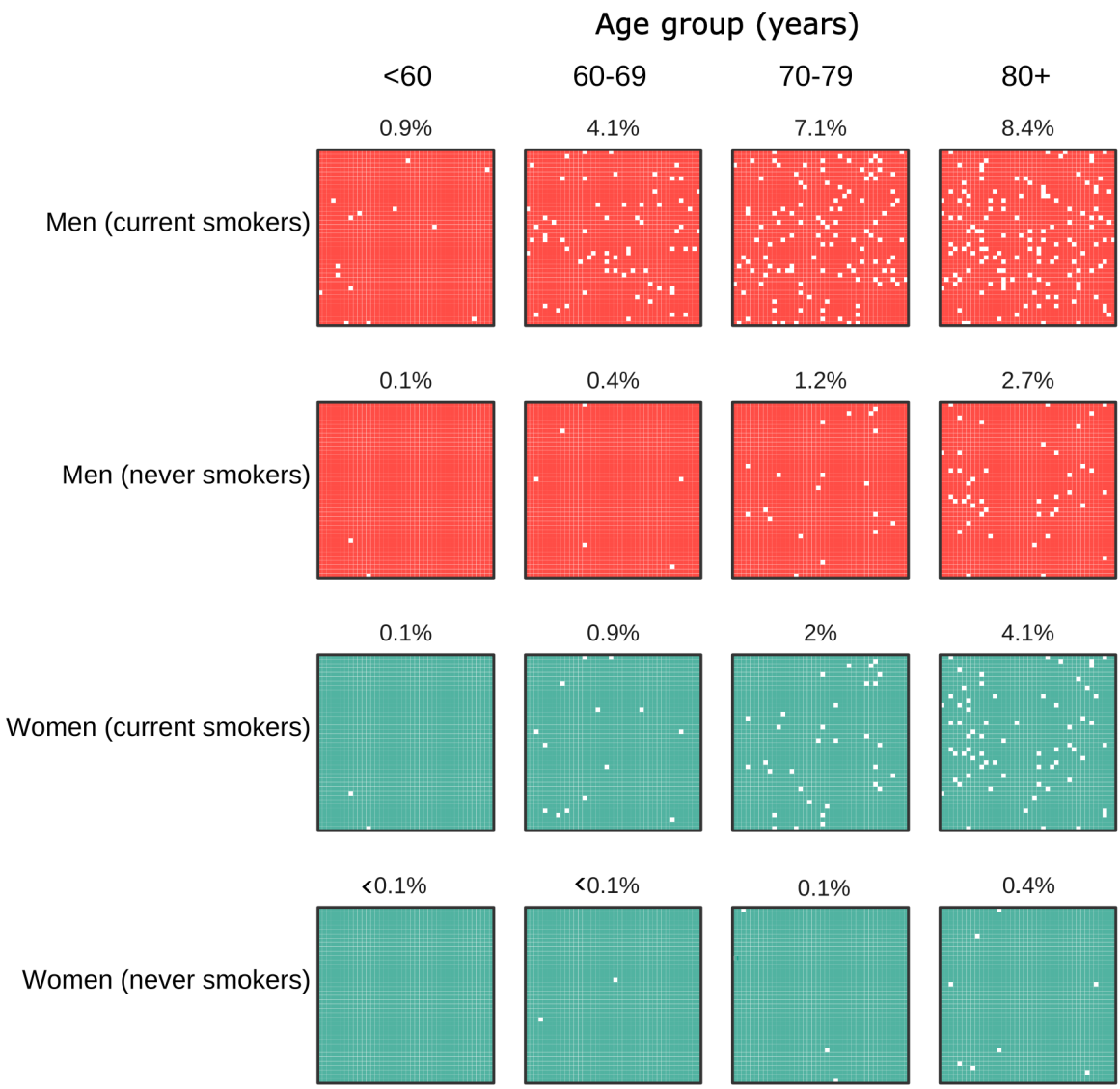

Figure 2-3: Prevalence, or risk, of having an AAA in different groups based on age, sex and smoking status. Data extracted from Carter et al [47]. Labels above facets show the reported prevalence in the respective group. Diagrams show representative illustrations for the respective prevalences, where the white squares represent a case of AAA.

2.1.4 Risk factors

AAAs share many common risk factors with other cardiovascular diseases. Some of the major risk factors that affect the prevalence of AAA are presented in **Figure 2-3**. Below is a short discussion on risk factors that affect the prevalence of AAA in the population.

Cigarette smoking is one of the major modifiable risk factors of many cardiovascular diseases, and in particular for AAA. Both the abdominal aortic diameter of patients without an AAA, and the prevalence of AAAs is associated with smoking [47–51]. The increased risk of having an AAA is more than ten-fold in those who smoke twenty or more cigarettes daily [52], and the risk increase is especially large in women [47]. Smoking also increases

both the rupture risk and growth rate of AAAs [53]. Smoking cessation reduces but does not normalize the increased risk of AAA [54]. While the global prevalence of smoking has decreased in recent decades, which is suggested as one reason for a decreasing prevalence of AAAs [55], it is still at approximately 20%, and the absolute number of smokers increases, especially in LMICs [56].

AAAs are more prevalent in men, commonly cited is approximately a 4:1 ratio, but as discussed previously this may in part be related to the aneurysm definition that is used [41,49,57]. Notably, women are more prevalent in cohorts consisting of patients with ruptured AAA and among untreated patients [58]. AAA prevalence is also strongly related to age, where AAAs are virtually non-existent in persons below 50 [59] or 60 [47] years of age, and the prevalence thereafter increases steeply. As smoking, age is also a dynamic risk factor on the population-level. The global population is becoming older, and the number of persons above the age of 65 is projected to more than double until 2050 [60].

Atherosclerotic diseases in general are associated with an increased prevalence of AAAs [49], but atherosclerosis itself, however, does not seem to be an independent risk factor for AAA [61], and may rather be linked by common risk factors. Diabetes is a common risk factor for many cardiovascular diseases [62], but appears instead a protective factor for AAA [63,64]. Similar inverse relationship between diabetes has been suggested for other types of aneurysms, such as thoracic [65] and intracranial [62,66]. Partly this relation may be explained by pharmacological activity of metformin [67]. Increased blood pressure is associated with an increased risk of AAA, and a causative link has been suggested especially for diastolic blood pressure [52,68,69].

Further, family history of AAAs is associated with an increased prevalence of AAAs. Siblings of patients with AAAs have a higher prevalence of AAAs and at younger ages [70–72], and twin studies have implied a high degree of heritability [73]. Co-existence of arterial aneurysms in other locations are common together with AAAs, and patients with other arterial aneurysms, such as popliteal [74], thoracic [75] and intracranial [76] have high prevalence of AAAs. Likewise, other arterial aneurysms are common in patients with AAAs [77–79]. Societal guidelines recommend screening for AAAs among patients with peripheral aneurysms [5,6].

2.2 Pathophysiology of AAA disease

2.2.1 The normal artery

The normal artery consists of three distinct layers. The inner most layer, *tunica intima*, is largely a single layer of endothelial cells that act as a semipermeable barrier for fluid, molecules, and cells to pass between the blood stream and the vessel wall. Endothelial cells also participate in regulation of haemostasis, and express several proteins that are active in the coagulation system, as well as a glycocalyx [80]. Further, the endothelial cells are an important mechano-sensing unit in the vessel of shear stress. An internal elastic lamina separates the *tunica intima* from the *tunica media*, where the majority of vascular smooth muscle cells are found. The smooth muscle cells give the artery the ability to regulate the vascular tone, especially in muscular arteries, whereas in elastic arteries the media is rich in elastic proteins. The external elastic lamina separates the tunica media from the tunica adventitia, which consist of extra cellular matrix that is rich in collagen, together with innervation and blood supply to the blood vessels through the so-called nervi and vasa vasorum.

The two main load bearing proteins in the vessel wall are collagen and elastin. They have different mechanical properties, which contribute to the non-linear stress-strain properties of the arterial wall. Collagen is the most abundant type of protein in humans and contributes with stiffness to vessels and other tissues. The stiffness provided by collagen had an important role in the development of a pressurized circulation and was key for the evolution of vertebrates [81]. Several subtypes exist, and the main ones that are in the vasculature are denoted Collagen I and III. In the vessel wall, during physiological conditions at low strain, collagen is mostly in an unloaded state [82]. The main mechanical properties when collagen is unloaded, is instead provided by elastin. Collagen is continually synthesized and degraded over the course of life [83], whereas elastin, is only expressed in the perinatal period [84] and is not renewed thereafter [85]. The amount of elastin and collagen in the aorta varies. In the ascending aorta, elastin is dominant, whereas the proportion decreases distally, and in in the abdominal aorta the proportion of collagen is higher than that of elastin [86,87].

2.2.2 Pathophysiology

Until the early 20th century, syphilis was the dominant aetiology for aortic aneurysms [88], and non-syphilitic aneurysms were denoted as atherosclerotic. The description of the atherosclerotic aneurysm was used due to an assumed common pathophysiology, due to the many common risk factors, such as age, smoking and high blood pressure, as previously discussed. This term has, however, been questioned [89], and is rarely used anymore. Transcriptomic studies have also supported the separation of these concepts [90].

Several different pathomechanisms have been implicated in AAAs. Typically, a loss of elastin and smooth muscle cells together with a thinning of the tunica media, and an infiltration of inflammatory cells is seen [91,92]. Elastin degradation leads to the aneurysmatic dilatation of a vessel, but experimentally collagenolysis is required for rupture [93]. In vivo, proteases, importantly matrix metalloproteinases (MMPs) contribute to degradation of collagen, and elastin [94]. Several MMPs have been suggested as causative in AAA pathogenesis, and as blood biomarkers for AAA [95,96]. Mechanically, AAAs are stiffer, especially in the circumferential direction, compared to normal aortic tissue [97].

A large proportion of all AAAs contain an intraluminal thrombus (ILT) [98]. The ILT is a highly heterogenous tissue that consists of fibrin, blood proteins and blood cells [99]. The thrombus appears to develop over time, and an evolution of the thrombus from a fresh blood clot consisting mostly of cells, to a more organized multi-layered tissue, has been described [100]. Disturbed hemodynamics, resulting from the aneurysmatic dilatation predispose to the formation of the thrombus [101]. The vessel wall under the thrombus is thinner and displays signs of more advanced degradation compared to the thrombus-free wall [102]. The ILT contains canaliculi or pores, which allow for pressure to be transmitted through the ILT to the aneurysm wall [99,103–105], but it still cushions the wall from stress [106,107].

Several genetic syndromes that involve aortic aneurysms have been described, these include Loeys-Dietz syndrome (involving the transforming growth factor β-related genes) [108], vascular Ehlers-Danlos syndrome (involving the collagen 3 alpha 1-gene) [109] and Marfan's syndrome (involving fibrillin-1 gene) [110]. These monogenic variants with high penetrance more commonly lead to thoracic aortic aneurysms or aortic dissections rather than AAA [111]. There are important differences between the thoracic and abdominal aorta. As described previously, the compositions and structure of the aorta varies in different locations [86,87]. The vasa vasorum is less dense in the abdominal portion of the aorta [112]. Further, the embryological origin of the abdominal aorta and the thoracic aorta are different [113]. The genetic basis of non-familiar AAA has also been studied, and genome wide association studies have implicated over 100 genetic loci including genes

that are related to proteins involved in lipid metabolism, vascular remodelling, inflammation, and extra cellular matrix dysregulation [68,114,115].

Animal models have been developed to study the disease process in AAAs. Widely studied models in small animals include the infusion or topical application of pancreatic porcine elastase (PPE-), calcium chloride (CaCl2) or Angiotensin II (Ang-II). These models capture different aspects of the aneurysm disease, the PPE- and CaCl2-models induce an inflammatory reaction in the aorta. Ang-II, in contrast to the aforementioned models, may rupture, but is primarily an aortic dissection model. These and other, also more recent models, have not succeed in replicating all important phenotypes from human AAAs such as growth, rupture and/or presence of an ILT [116,117].

2.2.3 Pharmacological therapy

Despite advances in the description of AAA pathophysiology, effective medical treatment to halt the progression of the disease has remained elusive. In animal models, many treatments have showed promise, and many of these have been tried in randomized clinical trials without success [118]. Telmisartan and perindopril, both targeting the renin-angiotensin system showed no effect on aneurysm growth [119,120]. Neither did ticagrelor, with the rational of modulating platelet activity [121], and propanolol instead appeared to increase mortality [122,123]. Anti-inflammatory therapies canakinumab and the mast cell inhibitor permirolast had no effect, as did neither lipid modification by fenofibrate [124–126]. Several antibiotics have also been trialled. Chlamydophilia pneumonia has been suggested to have a role in the pathogenesis of AAAs, but antibiotics including azithromycin and roxithromycin were unsuccessful [127,128]. Doxycycline, an antibiotic that has pleotropic effects that modulate the activity of MMPs [129], also failed to show an effect on aneurysm growth [130,131]. Several trials are ongoing to assess the effect of metformin [132–135]. The topic of pharmacological intervention in AAAs is discussed further in **Section 7.2.**

Regarding pharmacologic treatment for AAAs, it should be noted that persons with AAAs, and also persons with a normal but widened abdominal aorta are at an increased risk of overall mortality and cardiovascular events [136–139]. As such, it is important to treat these patients with optimal medical treatment to prevent non-aneurysm related cardiovascular disease and mortality [5,6,140].

"The logical foundation of elective treatment of abdominal aortic aneurysms by resection and grafting is the assumption that aneurysmectomy restores to the patient the life expectancy he would have had without risk of a potentially lethal lesion."

Szilagyi et al. Annals of Surgery, October 1966 [141].

2.3 Surgical treatment for AAAs

The surgical era of AAA treatment was pioneered by Dubost in 1952, with the first reported replacement of an AAA with an aortic homograft [142]. Previous to this, Estes et al had reported that the 5-year survival after diagnosis of AAAs was 18.9%, where the cause of death was ascertained as rupture in 63.3% of cases [143]. Out of 102 patients, treatment had only been attempted in two. Prior treatment modalities included ligature of the aneurysm or wrapping it in cellophane [144,145] In 1964, DeBakey et al reported a series of 1 449 patients treated for AAA with noticeably superior survival compared to previous mostly untreated case series [146].

Today, two principally different treatment modalities for AAAs are used: open surgical repair (OSR) and endovascular aneurysm repair (EVAR). OSR has evolved since its introduction and today non-biological graft materials are used [5]. During the late 1980s, EVAR was developed in the Soviet Union, in current-day Ukraine [147,148], and Argentina [149], in parallel. A stent-graft is introduced through the femoral arteries into the lumen of the aneurysm and anchored proximally to the neck, and depending on anatomy, distally to the aorta or more commonly to the iliac arteries. Thereby the aneurysm sac is excluded from the circulation. If the exclusion is not complete, or fails, blood can flow between the aneurysm sac and the stent-graft (so-called endoleak). EVAR adoption has been widespread, and in Sweden almost 70 % of elective patients with AAAs are now treated by EVAR [150]. The proportion of patients treated by EVAR varies by country, and is reported even higher, approximately 80% in the US, but less than 50% in Denmark, Norway, and Hungary [151]. Manufacturers specify set instructions for use for use for each endovascular stent-graft, which limit treatment in some AAAs due to, e.g., unsuitable landing zones, neck angulation, or vessel dimensions [152]. Sac-growth preceeds rupture after EVAR [153], and guidelines recommend life-long surveillance post-operatively [5,6].

2.3.1 Mortality after AAA repair

In Sweden, the 90-day mortality after elective OSR and EVAR was 1.8% and 0.4% respectively in 2022 [150]. Several randomized trials have investigated the potential survival benefit of EVAR over OSR; the *UK endovascular aneurysm repair trial 1 (EVAR trial 1)* [154], *the Dutch randomized endovascular aneurysm management (DREAM)-trial* [155], *the Anevrysm de l'aorte abdominale: chirurgie versus endoprothese* (ACE)-trial [156], and the *open versus endovascular repair* (OVER)-trial [157]. All the trials show the same trend with an early survival benefit for EVAR, which is lost within the first few years of follow-up [158]. The 15-year follow up of the EVAR trial-1 showed that patients treated with EVAR had higher overall mortality, and in the late follow-up (>8 years) 7% of patients who died after EVAR-treatment succumbed to a secondary aneurysm rupture [154]. Re-intervention rates are in all trials considerable after EVAR. After a median 3 year follow up in the ACE-trial, the death or re-intervention rate after EVAR was 16%, compared to 3% for OSR. Real-world data have reported similar results as the randomized trials, and higher rupture rates after EVAR [159]. In light of the long-term results of EVAR, more recent guidelines from the UK National Institute for Health and Care Excellence have questioned the use of EVAR in the elective setting [160]. AAAs in women are less likely to be suitable for EVAR, and women suffer from an increased operative risk with both EVAR and OSR [161], and long-term mortality is especially poor for women after intervention [162].

The mortality after AAA rupture remains high despite modern treatment. In Sweden, the 90-day mortality in patients *treated* for ruptured AAA is 26 % [150]. Three larger trials have investigated the choice of EVAR over OSR in the setting of ruptured AAAs; the *endovasculaire versus chirurgie dans les anévrysmes rompus* (ECAR)-trial, the *Amsterdam acute aneurysm* (AJAX)-trial [163] and the *immediate management of the patient with ruptured aneurysm* (IMPROVE)-trial [164]. A patient-level meta-analysis of these three studies did not reveal a clear survival benefit for EVAR within 90 days but suggested that women may have an improved survival with EVAR [3]. The 3-year results of the IMPROVE trial, however, showed a lower overall mortality for patients treated with EVAR [164]. It should be noted that all ruptured aneurysms are not suited for a conventional infra-renal EVAR, in the AJAX-trial only 46% of AAAs were suitable [165].

The Hardman score is a risk-model developed to predict mortality after treatment of ruptured AAAs, and included clinical parameters such as: age, kidney function, cardiac ischemia, loss of consciousness and hemoglobin-levels [166]. Morphological parameters, such as neck length and angulation, are suggested to improve prediction of mortality compared to the Hardman score alone [167,168]. A recent attempt to externally validate risk-scores after AAA rupture did not show sufficient accuracy to base treatment decisions on for any risk-score, also including morphological variables [169].

2.4 A diameter-based policy for AAA intervention

Szilyagi et al reported already in 1966 [141] that size was a predictor for mortality among patients with untreated AAAs (**Figure 2-4**). Size, in this context, was determined by physical examination, X-ray, angiogram, during laparotomy or autopsy. Contemporary and modern autopsy studies also reported that the likelihood of finding a ruptured AAA, increased with the size of the aneurysm [170,171].

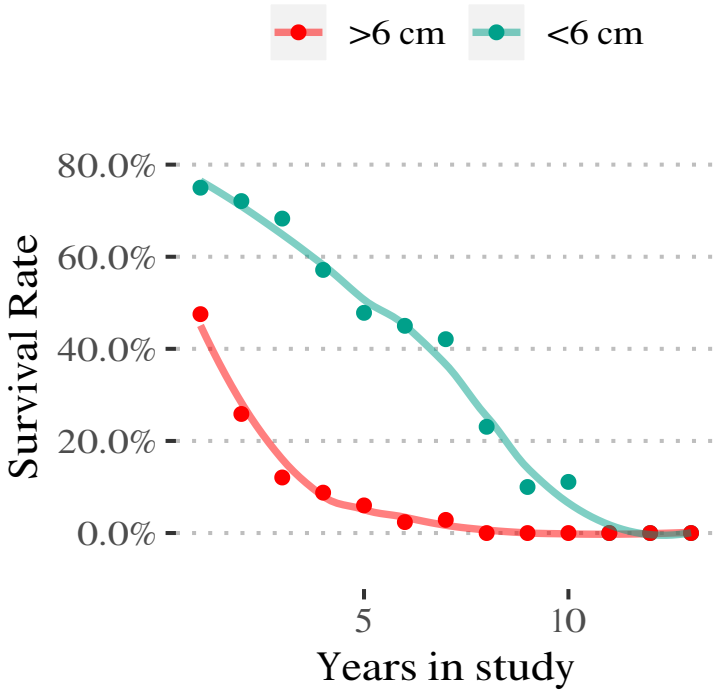

Figure 2-4. Cumulative 13-year survival rates for 105 non-surgically treated small (≤6 cm) and large (>6 cm) abdominal aortic aneurysms. Adapted from Szilyagi et al [141].

After the introduction of the OSR for AAA, the mortality associated with the procedure remained high for several decades, and it was clear that patients with small aneurysms might not benefit from treatment. This was the prelude to the trials conducted on intervention in small AAAs. To date, four randomized trials have investigated the benefit of Intervention on patients with small AAAs: the *United Kingdom Small Aneurysm Trial* (UKSAT), the *Aneurysm Detection and Management* (ADAM)-trial, the *Positive Impact of Endovascular Options for Treating Aneurysms Early* (PIVOTAL)-trial, and the *Comparison of Surveillance versus Aortic Endografting for Small Aneurysm Repair* (CAESAR)-trial. The UKSAT was the first of these trials, and the justification for choosing the 55 mm threshold for the UKSAT appears rather arbitrary. It was stated that all vascular surgeons would consider repair of a 60 mm aneurysm, but only some for a 40 mm aneurysm [172].

The study designs, and main results from these four studies are summarized in **Table 2-1**. The UKSAT and the ADAM trials compared OSR in patients with AAAs between 4.0 and 5.5 cm to surveillance and concluded that there was no support for early intervention. The PIVOTAL and CAESAR trials compared surveillance to EVAR, and similarly concluded that there was no benefit for early intervention. There is a discrepancy in the rupture rates between the studies, with the UKSAT reporting markedly higher rupture rates. This may partly be attributed to the use of ultrasonography for surveillance in the UKSAT, whereas the three other studies used CT. It is known that maximal aneurysm diameter of AAAs measured by ultrasonography is smaller compared to CT [173,174]. The low rupture rate in the PIVOTAL trial can be interpreted as a consequence of excluding patients with AAAs between 5.0 and 5.4 cm. Sub-group analysis in the UKSAT did not show any benefit from early intervention in women, or by age- or size-stratification, but the study was not powered to investigate such associations. At the 12-year follow-up of the UKSAT, 85 % of patients allocated to the surveillance arm were treated with AAA repair [175].

These studies have collectively led to recommendations in guidelines that men should be considered to be intervened upon once the diameter reaches 55 mm. For women, the recommendation is equally strong to consider intervention, but the diameter threshold is potentially lower, 50 mm. The recommendation in women is, however, not supported by trial data. A non-negligible proportion of patients with AAAs are still operated below the recommended diameter thresholds [176], and a non-negligible proportion rupture under surveillance [177]. Rapid expansion of AAA diameter (>0.5 cm / 6 months) was included in these randomized trials as an indication for repair, but this indication is judged to have weak evidence as is not recommended in the current societal guidelines as a repair indication [5,6].

It should further be noted that a strict diameter threshold-based policy is theoretically inferior to an optimal diameter-based policy [178,179]. The optimal policy, in the context of age and aneurysm diameter, should depend on both the maximal diameter and the remaining life expectancy of the patient, i.e., it may be beneficial to operate younger patients at smaller diameters, and surgery in patients with a low remaining life expectancy should be postponed. Naturally, this kind of policy is applied clinically today, where patients with a high operative risk are sometimes not intervened upon, or the surgical diameter threshold is postponed. The basis of the 55 mm diameter limit is, however, in this sense largely an arbitrary risk-threshold.

Table 2-1. Study design and results for the four studies conducted to evaluate of intervention in small AAAs.

	UKSAT [175]	**ADAM** [180]	**PIVOTAL** [181]	**CAESAR** [182]
N randomized (surveillance/ intervention)	1090 (527/563)	1136 (567/569)	728 (366/362)	360 (178/172)
Inclusion criteria	4.0-5.4 cm	4.0-5.4 cm	4.0-5.0 cm.	4.1-5.4 cm
Intervention		Repair for symptomatic AAAs or enlarged to 5.5 cm		Repair after defined threshold (diameter>5.5cm or enlargement >1cm/year).
Surveillence modality	US	CT	CT	CT
Diameter measurement	Antero-posterior (Outer-to-outer)	The maximum cross-sectional measurement in any plane but perpendicular to the vessel axis.§		
Main Endpoint	Crude HR 0.90 [0.77-1.04]	RR 1.21 [0.95-1.54]	HR 1.01 [0.49-2.07; p = 0.98]	HR 0.76 [0.30-1.93; p = 0.06]
Rupture rate	1.6% per year before June 1998 3.2% per year between July 1998-August 2001*	0.6 % per year. 2 (0.4 %) in immediate repair group, 11 (1.9%) in surveillance group.	0.6 % in both study arms.	2 (1.1%) ruptures in surveillance group

*Autopsy rate in the UKSAT was 26%. § Measurements were made on hard copies of CT scans with calipers and a magnifying glass.

2.4.1 Surveillance

As a consequence of the recommendations to postpone intervention until a diameter-limit is reached, a considerable number of patients with AAAs are put in surveillance. In screening programs, only approximately one tenth of men diagnosed with AAAs have a diameter > 55 mm, whereas 70 % are below 40 mm [33,183]. Societal guidelines recommend that patients with AAAs should undergo regular US examinations; every three years for a patient with an AAA between 3.0-3.9 cm, every year for a patient with an AAA between 4.0-4.9 cm, and every 3-6 months for a patient with an AAAs >5.0 cm [5,6]. A recent review from the screening program in the UK, reported that the annual incidence of rupture in men under surveillance (mean age 66.8 years) was estimated at 0.4% [184]. Other recent studies have reported much higher rupture rates in surveillance, e.g., 5% of patients ruptured in the MA3RS-trial [185], and others have reported that 3-4% of patients

rupture during surveillance, albeit with equally many or more deaths being of unknown cause or probable sudden death [186,187]. Among untreated patients in Sweden within a 5-year period 8% ruptured [58]. These cohorts perhaps better reflect clinical reality as patients were older and not all male.

Data does not support that surveillance itself has an impact on quality of life [188]. Low socio-economic status decreases the participation in screening programs [35,189], and increases the risk of presenting with a ruptured rather than an intact AAA [190]. In Stockholm, close to one-third of patients who rupture have previously known AAAs, of which almost half can be attributed to direct surveillance failure (other reasons are patients who are denied for elective surgery or by patient's choice) [191].

Table 2-2. Recommendations from Society for Vascular Surgery [6] and the European Society for Vascular Surgery [5] for the management of AAAs.

	Recommendation	Grading
Society for Vascular Surgery [6]		
Decision to treat	We recommend elective repair for the patient at low or acceptable surgical risk with a fusiform AAA that is ≥5.5 cm	1A
	We suggest repair in women with AAA between 5.0 cm and 5.4 cm in maximum diameter.	2B
Imaging	We suggest that the maximum aneurysm diameter derived from computed tomography imaging should be based on outer wall to outer wall measurement perpendicular to the path of the aorta	Good practice statement, ungraded evidence.
European Society for Vascular Surgery [5]		
Decision to treat	In men, the threshold for considering elective abdominal aortic aneurysm repair is recommended to be ≥5.5 cm diameter	IA
	In women with acceptable surgical risk the threshold for considering elective abdominal aortic aneurysm repair may be considered to be ≥5.0 cm diameter.	IIb C
Imaging	The antero-posterior measuring plane with a consistent caliper placement should be considered the preferred method for ultrasound abdominal aortic diameter measurement	IIa B
	Aortic diameter measurement with computed tomography angiography should be considered using dedicated post-processing software analysis in three perpendicular planes with a consistent caliper placement	IIa C
National Institute for Health and Care Excellence [160]		
Decision to treat	Consider aneurysm repair for people with an unruptured AAA, if it is: symptomatic; asymptomatic, larger than 4.0 cm and has grown by more than 1 cm in 1 year; asymptomatic and 5.5 cm or larger.	Consider
Imaging	Measured inner-to-inner maximum anterior-posterior aortic diameter on ultrasound	

2.4.2 Imaging

Several different techniques are used in clinical practice to evaluate patients with AAAs. Ultrasonography is the perhaps most prevalent method. It is used and recommended for screening and surveillance [5,6], as it is relatively inexpensive, widely available, and importantly does not expose the patient to radiation. CT is, after ultrasonography, the second most used technique for visualization of AAAs. CT-imaging is often accompanied by the injection of an intravenous contrast agent. Depending on the timing between the CT scan and the injection of the contrast agent, either the arteries (arterial phase) or also the veins (venous phase) are enhanced. CT is fast and able to visualize the entire aorta with good spatial resolution. The intravenous contrast, in either arterial or venous phase allows for the separation of the arterial lumen and the ILT in the AAA. CT does, however, expose the patient to radiation and while CT has a good spatial resolution, the discrimination of soft tissues, due to similar attenuation of x-rays, may be difficult. Magnetic resonance imaging (MRI) has clinically limited applications and is used most often when CT is contraindicated. MRI is, however, a potentially useful imaging method that may provide better description of the vessel wall and ILT compared to CT [192].

2.4.3 Maximal aneurysm diameter

Despite the numerous exact figures of AAA diameters cited in the literature no unified definition of the maximum AAA diameter has been developed and no general consensus exists. Guidelines give the recommendation to base the treatment decision of AAAs on the maximum diameter the highest level of evidence, with the strongest evidence grade. Yet, the suggested method to measure the maximal diameter is graded as a good practice statement, with an ungraded level of evidence (**Table 2-2**). Further, the four different studies on intervention in small AAAs did not use a unified definition of the maximum diameter (**Table 2-1**).

There are at least three principal degrees of freedom in the measurement of the aneurysm-diameter (**Figure 2-5**). CT-scans are acquired in a plane that is approximately axial relative to the body of the patient. A diameter can be measured in the native CT plane, but the today most accepted method to measure the diameter in a plane that is constructed perpendicular to the centreline of the vessel. Two principally different centrelines, however, exist; a line can be constructed through the centre of the aneurysm sac or through the centre of the lumen. The same is true for ultrasound, but it is difficult to preserve a plane between different examinations. A second degree of freedom is introduced in the cross-sectional plane where several different lengths can be defined; antero-posterior, transverse, maximum or perpendicular to the maximum, or area-derived. Yet another degree of freedom is introduced when deciding the position from where to measure, i.e., the external or internal wall of the vessel.

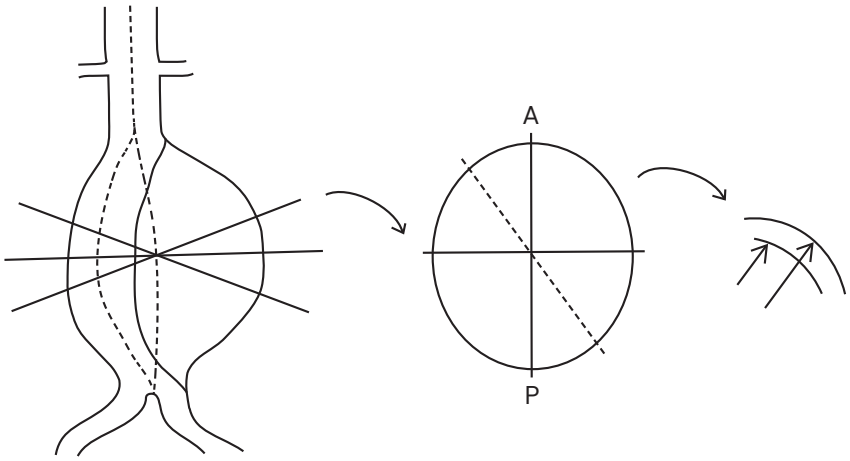

Figure 2-5. Three principal degrees of freedom in measuring the maximum diameter of an AAA. **Left:** the construction of a perpendicular plane varies according to the specification of the centreline. **Middle:** in a single cross-section several different diameters can be measured. **Right:** the location on the wall from which to measure. Illustration by Marko Bogdanovic.

A review of studies in the AAA imaging field showed that only a minority of studies rigorously specify the measured maximum diameters [193]. Aneurysm diameter is, in general, larger when measured by CT compared to US [173,194,195]. It has been reported that 75.0% of patients with an US diameter of 5.0-5.4 cm are larger than 5.5 cm on CT, and conversely 6.3% of patients who are larger than 5.5cm on US are smaller than 5.5 cm in CT [174]. The limits of agreement between CT and US are reported to exceed 1.0 cm, which must be considered clinically relevant [194,195].

There is also considerable variation within the same modality. In a single CT, the diameter varied between 49.8 mm and 60.2 mm depending on how it was measured [193]. Maximal diameters in the axial plane are significantly larger than ones measured in planes perpendicular to the blood flow [173,194,196]. In a meta-analysis conducted to investigate the reproducibility of US measurements, the limits of agreement ranged from 1.9 to 10.5 mm [197].

A further source of variability in the imaging of AAAs comes from the pulsations in the blood vessels. The difference between measurements in systole and diastole have been reported between 0.6 to 1.9 mm [198,199]. In US, in particular, since it is based on the reflection of ultrasound waves in the transition between different materials, three different methods, the inner-to-inner wall, the outer-to-outer wall and the leading edge-to-leading edge, have been described. The variation between the outer-to-outer wall and the inner-to-inner wall may be between 4-6 mm, with leading edge-to leading edge in between [200–202]. The leading edge-to-leading edge has been suggested as the most reproducible and is used in the Swedish screening program [32,201].

Diameter measurements, perhaps especially in clinical practice, may further be hampered by so-called terminal digit preference, where diameters are disproportionately rounded to measurements with terminal digits 0 or 5 [203]. As discussed in the previous paragraphs there is considerable heterogeneity in AAA diameters depending on measurement method, and this was also true for the studies conducted on the intervention limit of AAAs. These heterogeneities are not particularly easy to account for in clinical practice, where modalities, measurement methods and observers are often intermixed, and the reported differences may be even larger when compared to specialized imaging labs.

2.4.4 AAA growth

In light of the above-described variations and limitations in AAA measurements, it is perhaps not surprising that AAA growth has in the literature often been described as discontinuous and staccato, sometimes, with erratically diminishing maximal diameters [204–207], and it is suggested that AAA growth is best described as exponential [208]. Maximal diameter measures growth at one location in the AAA. The location of the maximal diameter, may however, theoretically change as the AAA grows, and growth may occur at locations that are not the maximal diameter region. This has empirically been corroborated by Martufi et al. who showed that the fastest diameter growth does not necessarily take place at the maximal diameter [209]. If another location in the aneurysm overtakes the maximum diameter, this could contribute to the appearance of staccato growth when only measuring the maximal diameter.

Due to this description and the perceived erraticity of the maximal diameter growth, aneurysm volume has been suggested as more sensitive measure of disease progression [210–212], and AAA baseline volume correlates stronger with future volume growth compared to the baseline maximal diameter [213]. Aneurysm volume, compared to diameter, may theoretically detect aneurysm growth that is longitudinal or growth not in the maximal diameter region. Volume has also been suggested to have a similar potential use in post-EVAR surveillance [214,215]. There is currently no clinical indication for the use of volume, in AAA surveillance, either pre or postoperatively.

The RESCAN initiative collected individual patient-level data for 15 471 patients from 18 studies that had reported on surveillance of small AAAs [53]. The majority of the studies included in RESCAN used ultrasonography for surveillance, but measurements were mixed between inner and outer wall, and some of the studies also used CT. Considerable heterogeneity between for growth rates between studies was also reported in RESCAN. A 3.0 cm AAA in men had an estimated growth rate of 1.28 [1.03-1.53] mm/y, and for each 5 mm increase in diameter, the growth rate was estimated to increase by 0.59 [0.51-0.66] mm/y (Figure 3). The growth rates for men and women were similar. Current

smoking was the only identified risk factor for faster aneurysm growth, whereas diabetes, an increased pulse pressure and BMI were found to be associated with slower growth.

Several growth studies using CT have also been published. In a meta-analysis in 2014 which included ten studies, only two reported using centreline-based measurements [216]. Further, only two of the included studies corroborated the dependence of diameter-growth rate on the maximum diameter [216], but also in newer studies the correlation has been weak [217,218]. For both CT and US, the relative and absolute amount of thrombus in the AAA is associated with maximum diameter-growth-rate [219–221]. Further, local diameter growth is also associated to thrombus thickness [222]. Calcification of AAAs in CT has been related to slower growth [223]. Dynamical changes in aneurysm morphology, such growth of the ILT is also suggested to precede rupture [224].

2.4.5 Maximal diameter-based rupture risk

As previously discussed, maximal diameter is the current clinical predictor of rupture risk in patients with AAAs, and the issues that pertain to its measurement are equally relevant in the discussion of rupture risk as in aneurysm growth.

In RESCAN study, rupture risk was estimated, and the rupture rate in men with a 50 mm aneurysm was 6.4 per 1000 person-years, and women with a similarly sized AAA had a considerably higher rupture rate of 29.7 per 1000 person-years [53]. Age, lower BMI, current smoking, high blood pressure and pulse pressure were all also associated with an increased risk of rupture [225].

Data for growth and rupture rates of aneurysms >55 mm, are limited in the literature, since most patients are treated at 55 mm if no contraindications to treatment, such as high age or comorbidities, are present. Smoking is a risk factor for AAAs in general, but also aneurysm growth and rupture. Other serious comorbidities that may influence treatment decision in patients with AAAs; such as respiratory disease, cancer and cardiovascular disease in general, are also increased by smoking. The data on large AAAs must therefore be viewed in context of these potential confounding factors, and it is not certain that they can be extrapolated to all patients with AAAs.

Lederle et al. reported on a cohort of 198 patients with AAAs that had a maximum diameter of at least 5.5 cm, and where no repair was expected (either because it was contraindicated or due to patient refusal) [226]. In one year, 9.4% of patients that had 5.5-5.9 cm AAAs had a probable rupture. For 6.0-6.9 cm AAAs and ≥7.0 cm AAAs, 10.2% and 32.5% had experienced probable ruptures [226]. Noronen et al, in a population with a high autopsy rate (76%), reported similar but slightly higher rupture risks within the first year [227]. The EVAR trial 2 investigated the benefit of EVAR intervention in patients deemed

unfit for open surgical repair with AAA ≥ 55 mm and concluded that while aneurysm-related mortality significantly decreased in the intervention group, there was no difference in all-cause mortality [228]. There was, however, a considerable crossover of patients from the non-treatment arm of the trial. The, was influenced by aneurysm size at baseline. The rupture rate in the no intervention group of the EVAR trial 2 was 12.4 [9.6-16.2] ruptures per 100 person-years, and AAAs had a mean size of 6.7±1.0 cm.

In retrospective series of ruptured AAAs, it is also reported that women rupture at smaller maximum diameters [7,229], but maximal diameter divided by body surface area (aortic size index, ASI) is similar for men and women [230]. The mean diameter of rAAAs is reported close to 80 mm in many series, and some aneurysm rupture well beyond 100 mm [7,229–231]. In Finland, where no specific screening program for AAAs is implemented, 21.4% of men, but only 3% of women who rupture were younger than 65 years [7], and rupture below 55 mm occurred in 6.6% of men, and 18 % of women [7].

2.5 Beyond the maximum diameter criterion

Structural failure of vascular tissue components, such that mechanical stress, exceeds tissue strength, represents the rupture event in aneurysms. Stress is the physical measure of the force which acts upon a material to deform it.

The law of Laplace is often cited in the literature as a justification for the use of maximum diameter in growth and rupture risk prediction of AAAs. It states that the wall stress is proportional to the diameter. Wall stress in aneurysms is, however, influenced by geometry [232–234] which is variable, and further complicated by the presence of an ILT [235,236]. The advent of modern thin-slice CT technology has made it possible to precisely extract the 3D geometry of an AAA. Patient-specific finite element analysis (FEA) was introduced by Fillinger et al, where they used a model of an AAA that did not take into account the presence of an ILT [237]. They reported that peak wall stress (PWS) was increased in ruptured AAAs [237] and in AAAs prior to rupture [238]. FEA, however, better discriminates between ruptured and non-ruptured AAAs when the ILT is accounted for, and it is included in most modern FEA implementations [235]. **Figure 2-6** shows a single aneurysm modelled at three different time points.

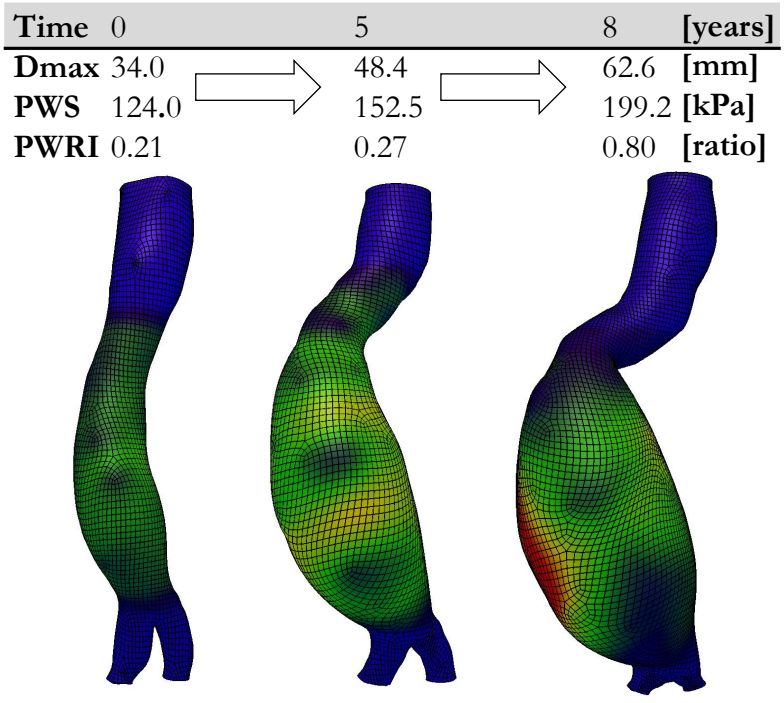

Figure 2-6. Three-dimensional models of an AAA from a patient at baseline, after 5 years and 8 years. Colours represent the distribution of peak wall rupture index (PWRI) in the aneurysm. Example includes data from patients included in Study II.

To further improve risk prediction of AAAs, Vande Geest et al. introduced a model to estimate the wall strength of an AAA from four characteristics; the local diameter normalized by age and sex (according to [29]), sex, family history and ILT thickness [239]. It is suggested that the wall strength of ruptured AAAs is lower [240,241], but this has not been confirmed [242]. The rupture potential index describes the ratio of wall stress to wall strength in a single point in the AAA [243], and is often referred to as peak wall rupture index (PWRI).

A recent systematic review and a meta-analysis concluded that PWS is increased in ruptured and symptomatic AAAs, compared to non-ruptured AAAs [8,244]. PWRI, is also increased in ruptured aneurysms [235,245,246]. It is, however, clear that ruptured AAAs are not the clinically relevant entity since prompt treatment is required regardless of biomechanical parameters. Instead, the true clinical question relates to non-ruptured AAAs, and it is not certain if an analysis of ruptured AAAs will accurately generalize also to non-ruptured AAAs. Erhart et al have showed that in pre-rupture AAAs, PWRI, but not PWS, is increased [245]. Despite a multi-centre design, the conclusions of the study are, however, limited by a small sample size, which consisted of 13 patients with imaging prior to rupture. Polzer et al. made similar conclusions with a cohort of 19 patients with imaging prior to rupture [247]. Some attempts to investigate the prediction of rupture location using FEA can be found in the literature. It is perhaps clinically irrelevant but would be convincing proof-of-concept for the method. Venkatasubramaniam et al [248] and Fillinger et al [237] reported perfect coherence of the rupture location and the maximal stress region, but this finding has later not been confirmed [245,249].

PWRI has also been shown to predict aneurysm related events, primarily progression to surgery [250–252]. Further, biomechanical indices are related to known rupture risk factors, such as sex and smoking [253,254]. It is reported that quickly expanding aneurysms have an increased baseline PWS and maximal AAA neck stresses [255], and that the diameter-growth rate of an AAA correlates to PWS [256]. Speelman et al found that AAAs with medium and high stress grew faster than aneurysms with low stress but could did not find any difference in growth rates between medium and high stress aneurysms [257]. Metaxa et al. also investigated the relation between biomechanical stress and aneurysm growth rate but, could not confirm the previous findings [258]. The time-dependent evolution of AAA biomechanics is largely unreported in the literature. In a single case report, wall stress was found to increase with linearly with time, but non-linearly with aneurysm size [259]. Another study, which included four aneurysms followed longitudinally, found that PWRI did not necessarily increase with time or diameter [260]. These studies are, however, statistically limited by a small sample size, and have not been able to examine the effect of patient characteristics on 3D-morphological or biomechanical change.

3 Research aims

The overarching aim of this thesis was to study growth and rupture of AAAs with specific focus on morphological and biomechanical aspects. Study I served as an exploratory study of the epidemiology of ruptured AAAs. Study II and III represent an analytic investigation of the growth of AAAs, and the relation between biomechanical parameters and AAA rupture. Study IV represents a potential simplified application of rupture risk prediction.

The specific aims of the included studies are described below.

Study I: examined a population-based cohort of patients with AAA rupture. The aim was to describes the morphology of AAAs at rupture, with specific focus on sex differences, and in a hypothesis-driven way investigates potential predictors of rupture.

Study II: aimed at describing the morphology of AAAs as they grow, with specific focus on semi-automatic diameter, 3D morphology, including the intraluminal thrombus and biomechanical parameters.

Study III: aimed at characterizing the relation between biomechanical parameters, PWS and PWRI, and time-to-rupture.

Study IV: aimed at characterising the relation between 2D geometric parameters, and rupture risk of AAAs, as characterized by rupture status and biomechanical parameters.

4 Materials and methods

Table 4-1. Overview of the study design of the studies included in the thesis.

	Study I	Study II	Study III	Study IV
Patient selection for main analysis	Patients with ruptured AAA and CT imaging at rupture	Patients with non-operated AAAs and at least 3 CTA examinations.	Patients with CTA imaging prior to rupture	Patients with ruptured AAA, and patients with asymptomatic AAAs
Study design	Retrospective	Retrospective	Retrospective	Retrospective
N patients	192 patients	100 patients	67 patients	30 + 60 patients
N CTs	192 CTs	384 CTAs	109 CTAs	90 CTAs
Methods used for image-analysis	Centreline-based morphological measurements.	Morphological and biomechanical analysis.	Morphological and biomechanical analysis.	Centreline-based morphological measurements and biomechanical analysis.
Main outcome	AAA morphology at rupture, and influence of patient characteristics.	AAA growth pattern with respect to maximal AAA diameter. Growth of ILT and its relation to biomechanical stress.	Relation between biomechanical variables PWS and PWRI and time-to-rupture	AAA lumen area in ruptured and asymptomatic AAAs
Additional cohorts	153 patients with asymptomatic AAA	-	97 patients with asymptomatic AAAs	-
Analysis including additional cohorts	Matched analysis of small asymptomatic and ruptured AAAs (40 vs 20).		Inclusion of matched patients into survival analysis	

4.1 Cohorts

All patient cohorts consisted of patients with AAA, where mycotic, traumatic, previously treated, or thoracic or iliac aneurysms were excluded.

4.1.1 Study I

The cohort in Study I was derived from the Stockholm Aneurysm Rupture Cohort (STAR). The STAR cohort is a population-based cohort of Stockholm and Gotland counties. All patients that presented with ruptured AAA (ICD 71.3), between the years 2009 and 2013 were considered for inclusion. Details about this cohort have been published previously [191,261]. Specifically, the subset that consisted of patients for whom CT-imaging (contrast or non-contrast) at rupture was available were used for Study I (n = 192). A cohort of asymptomatic AAAs was also included and used as a basis for matching against patients with small, ruptured AAA. This cohort consisted of 153 patients, mean age 73 years and 26 (17%) were female.

4.1.2 Study II

Study II consisted of patients with AAAs that had at least three contrast-enhanced CT examinations (will be referred to as CTA). All patients that were registered with the ICD code for AAA between the years 2012-2013 and who had presented to the Vascular Surgery outpatient clinic at Karolinska University Hospital were reviewed for inclusion (n = 884). Patients with at least three CTAs were included into the study, and for these patients all CTAs were included (100 patients, 384 CTAs).

4.1.3 Study III

This study was based on the above-described STAR-cohort (Study I), which was partially extended to 2018 by searching records for patients that presented and were treated for ruptured AAA at the Karolinska University Hospital. This yielded a total of 346 patients that were reviewed for inclusion. All patients that had at least one *CTA prior to rupture* were included into this study, and for these patients all CTAs were included (67 patients).

4.1.4 Study IV

Study IV consisted of patients from the STAR rupture cohort that had presented to Karolinska University Hospital and had a CTA available, at rupture, and an additional 60 patients with asymptomatic AAA and CT imaging available, during the same time.

4.2 Image and biomechanical analysis

Analysis of images was in this thesis based on solely on CT examinations. Contrast-enhanced examinations were treated similarly and included as such irrespective if they were recorded in arterial, venous, or any other phase so long as the lumen-intraluminal thrombus border was visible. Imaging analysis was undertaken with several different approaches. Below follows a short description of image segmentation, with regards to this thesis, a short description of biomechanical analysis of AAAs, and a description of the other imaging analysis methods used in this thesis.

4.2.1 Segmentation

CT is based on x-rays, which travel through the body. The detector measures the energy of the x-rays, and the attenuation of the x-ray energy between the emitter and detector is then used to estimate the properties of the material in-between. Hounsfield units are used to describe the attenuation (or brightness) of a CT image. CT images are typically stored in a standardized format (Digital Imaging and Communications in Medicine, DICOM) that consists of an array with defined spatial coordinates and a stack of such arrays constitutes a CT examination. Segmentation of a CT is the apportionment of individual voxels to annotated regions that represent anatomical structures. Segmentation can be entirely manual, where voxels are individually defined to belong to a certain class or structure. This type of segmentation has the potential to be arbitrarily accurate but is laborious and time consuming.

Several automated segmentation methods have been proposed. For instance, threshold segmentation, which usually refers to segmentation that is based on filtering individual voxels by their HU-value. This type of segmentation lends itself to structures that are clearly defined within a HU-range that is separate from the surrounding. In the case of AAAs this may be applied to the segmentation of the contrast-enhanced lumen of an AAA. The results of the segmentation are, however, contingent on the relative homogeneity of the contrast within the lumen. The ILT is difficult to segment using techniques based solely in thresholding, since the attenuation is similar to surrounding tissues. Other properties of the image may also be used for segmentation, such as the connectedness of pixels or the gradient of the image. Traditionally a common method to segment AAAs utilized some level of automation for the segmentation of the lumen, but the ILT was commonly segmented entirely manually [121,262].

The software, A4Clinics, used in this thesis for segmentation of AAAs provides an interface for semi-automatic segmentation of an AAA. The segmentation process is detailed elsewhere [263]. It is based on a three staged approach where an active contour

model [264] is used for the pre-segmentation of the lumen, and deformable balloon models are thereafter initialized from the pre-segmented lumen to segment the lumen, and then from the lumen to segment the outer border. The user input consists of specification of a starting seed for the lumen segmentation, and manual adjustments of the prior information of segmentation parameters; including lumen and ILT attenuation and, borders between the lumen and the outer vessel wall. The segmentation theoretically has subvoxel accuracy [265].

Recently the image segmentation field has had a rapid evolution with neural network-based segmentation techniques, and this has also been applied for AAAs [266,267]. Extensions beyond only segmentation may be possible, using these novel techniques. It has for instance been suggested that such AI-based methods may be used to generate intra-arterial contrast enhancement in non-contrast images [268]. Such methods, have however, not been evaluated in this thesis.

4.2.2 Biomechanical analysis - finite element method

Early applications of methods in finite element analysis were described in aerospace engineering in the 1950s [269], and today the method is used to solve problems in many branches of engineering and mathematics [270]. For many problems of real-world interest, analytical solutions, or even descriptions, are not practical. In the case of AAAs, the vessel including the AAA is divided into a large number of finite elements which are then equipped with the material mechanical properties of the tissue. The set of such small elements is typically denoted as a mesh. The set of all finite elements forms then then a structural approximation, which is then pressurised with blood pressure. A large system of equations is then solved to calculate the wall stress. Several assumptions regarding the mechanical properties of the aneurysm must be made. The process is detailed elsewhere [235,271], and for more comprehensive reviews underlying the assumptions on the methods refer to e.g., [265,272] or [273]. In short, both the aneurysm wall and the ILT were modelled as hyperelastic, incompressible and isotropic. The stiffness of the ILT was decreased from the luminal to the abluminal side [274]. Wall strength was inhomogeneous and determined by the thickness of overlying ILT, the relative expansion of the aneurysmal to the normal aortic diameter, family history and sex.

The software used for biomechanical analysis in this thesis was A4Clinics Research Edition, (VASCOPS GmbH, Graz, Austria). The software runs on standard desktop computers and is commercially available. As previously described, biomechanical analysis has evolved over time, and in the beginning ILT was commonly disregarded, and time for analysis was described as 2-4 hours for human input, and 2-4 hours of computing time

[238,275]. The analysis is significantly faster using A4Clinics, which has been reported on average between 20-40 minutes including segmentation [276,277], which is also the experience of the author.

It should be noted that other also contemporary constellations of software have been described, for instance the BioPARR system [278], or others [279]. These typically use commercial general purpose finite element solvers. To the knowledge of the author, no entirely open-source system has been developed.

The output from the biomechanical analysis, that are discussed in this thesis are mainly peak wall stress (PWS) and peak wall rupture index (PWRI). PWS is the stress at the point in the aneurysm with the highest stress, and peak wall rupture index is the highest ratio of peak wall stress to wall strength in the aneurysm. The software also outputs other biomechanical parameters such as mean wall stress, ILT-stress among others, that are not further investigated in this thesis.

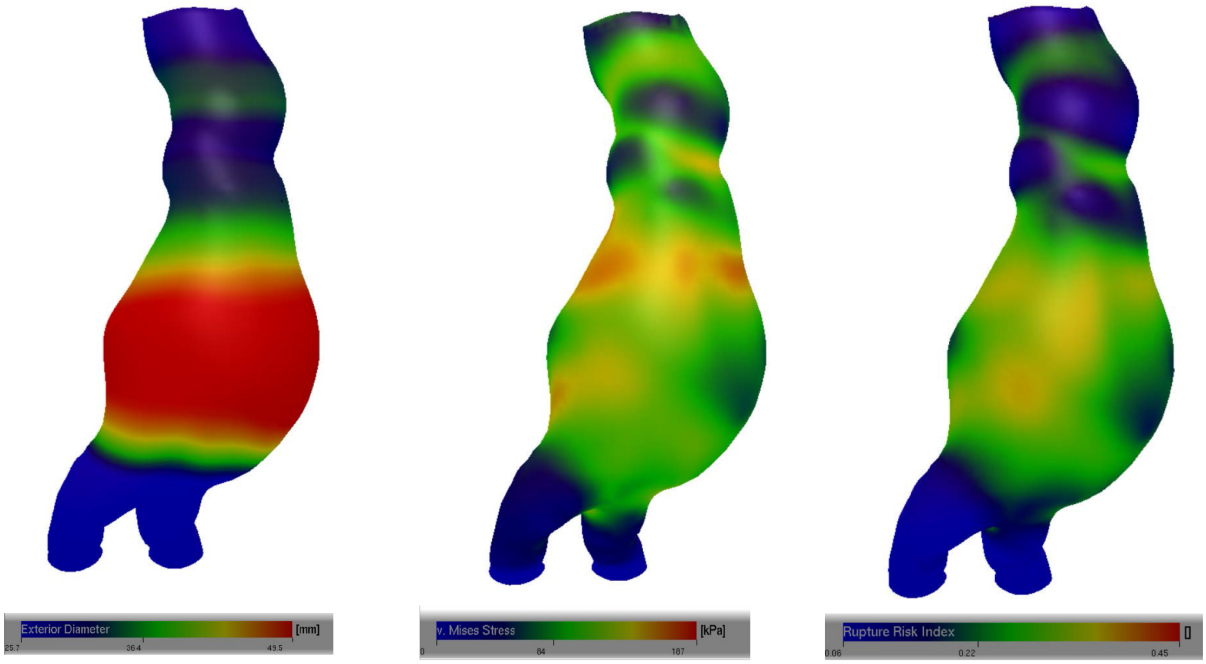

Figure 4-1. 3D models of an AAA, analysed by A4Clinics, VASCOPS GmbH. Aneurysms are coloured according to different properties, and the conversion between colour and value is shown in the scales below the facets. **Left:** Distribution of maximal aneurysm diameter, as measured along the centreline of the AAAs. **Middle:** von Mises stress values computed in the AAA wall. **Right:** Rupture Index in the Aneurysm wall.

4.3 Morphological analysis

In this thesis morphological analysis of AAAs was undertaken with several different computer programs, and the definitions of certain morphological parameters therefore differ between studies. Some universal definitions, however, relate to all the included studies.

The extent of the AAA was in all studies defined from the lowest, or most distal, renal artery (excluding accessory renal arteries) to the aortic bifurcation. The reasons for this definition are mainly practical; it has defined landmarks that denote the limits of the aneurysm that are theoretically easy to reproduce, both for different observers in the same examinations, and also for the same AAA across different examinations. It, however, may overestimate the extent of the true aneurysm, and include some normal aortic segments. This may specifically have relevance for computation of for instance mean stress in an aneurysm [280], but should not affect computation of PWS or PWRI. Further, while solitary iliac and thoracic aneurysms were not studied in this thesis, AAAs may, extend proximally and distally of the defined AAA limits, and involve an iliac or para-renal aneurysm.

The above-described process for AAA segmentation, which is necessary for the biomechanical analysis, is also used to extract parameters that describe the morphology of an AAA. Such parameters that are automatically extracted from the defied geometry in the A4Clinics software and include: maximal external diameter, the aneurysm volume, the intraluminal thrombus volume, and the lumen volume. The maximal external diameter in A4Clinics is based either on the centre-vessel line or the centre-lumen line. In this thesis the centre-vessel line diameter was used, and it represents a semi-automatic maximal diameter.

Morphological analysis in this thesis was further undertaken using also other available image analysis software, including 3Mensio Vascular (version 8.1, Pie Medical Imaging B.V, Maastricht, The Netherlands) and Sectra PACS IDS7 (Sectra AB, Linköping, Sweden). For Study I, aortic measurements were adapted from the St Georges Vascular Institute Protocol [281] (**Table 4-2**), and included: the neck length, neck diameter, alpha-angle, maximal external diameter (Dmax), maximal left and right common iliac artery diameters were measured. For study IV, the aortic luminal area and total vessel area were also measured perpendicular to the centreline.

Table 4-2. Definition of measurements used in Study I, definitions adapted from [236]. All measurements are based on centre lumen line.

Parameter	Definition
AAA neck	From the lowest renal artery, to the first point of significant aneurysmal dilatation
AAA neck length	Distance along the center lumen line, from the most distal renal artery to the point of significant aneurysmal dilatation
AAA neck diameter	Anteroposterior and transversal diameter measured distally to the most distal renal artery
α- angle	The angle between the center lumen points 20 mm above and below the proximal neck.
Maximal external AAA-diameter	The mean of the antero-posterior and transversal diameter at the point of maximal vessel widening, as assessed in the stretched vessel view.
Maximal common iliac artery diameter (left and right)	The mean of the antero-posterior and transversal diameter at the point of maximal vessel widening, as assessed in the stretched vessel view.
Supra-renal diameter	The mean of the antero-posterior and transveral diameters 1 mm proximal to the most proximal renal artery.

4.4 Statistical analysis

Several different statistical methods are used within this thesis. Descriptive statistics are presented with mean and standard deviation, or median and interquartile range.

For Study I and Study IV, hypothesis tests were undertaken to compare means, with either t-test or the non-parametric Mann-Whitney U -test, or to compare proportions with Chi-squared or Fisher's exact tests. For comparison of factors associated with ruptured, compared to intact AAAs, groups were matched for Dmax, age and sex using an automated matching algorithm in the R-package MatchIt [282].

For Study II, which includes data with repeated observations from the same individual, these data were analysed with mixed effects models (MEMs, see below **Section 4.4.1** for a short introduction). For the analysis of influence of patient characteristics on the growth rate of morphological and biomechanical variables, regression models were defined with an interaction term between the patient characteristic and time. Models were fitted with patient-specific random intercepts and random slopes for each patient. Simple linear regression models were also fitted to each patient, and the r-squared value of the fit was used as an indicator of the adequacy of a linear model, similar to what was used in [217].

For the descriptions of individual patient level growths of the included morphological and biomechanical variables the conditional patient-specific predicted values were used from a MEM with time as the only independent predictor and fitted with random slopes and random intercepts for each patient.

In Study III, data was analysed with survival analysis. The main analyses were performed in AAAs that were less than 70 mm, due to the material model used for PWRI not being validated in larger AAAs [283]. Univariable Cox proportional hazards models were fitted with time-to-rupture as the response variable, and Dmax, aneurysm volume, PWS or PWRI as the predictor variables. Further, in order to study the direct effect of the biomechanical variables, PWRI and PWS were investigated in multivariable models adjusted for aneurysm size (Dmax and PWRI), and aneurysm size and sex. Sensitivity analyses were conducted including AAAs of all sizes and including a cohort of patients with AAAs with known follow up time, that were censored at the end of follow-up.

4.4.1 Repeated measurements

An extension of ordinary linear regression models are so-called MEMs. Such models are typically specified in the case where observations are clustered within different strata, such as pupils in different schools, plants in different fields or repeated measurements within an individual. In these cases, observations are not independent of each other, and more precise statistical estimates can be evaluated when this interdependence is accounted for. MEMs are, in the statistical and medical literature, referred to by a multitude of different names, including random-effects models, *hierarchical models* and *multi-level models*. For a rigorous definition and discussion of the properties of these models see for instance [284–286]. Here follows a brief and non-formal introduction.

A linear regression, in the univariate case is the linear combination of a number of predictor variables that estimate a response. Here stated with one predictor:

$$y_i = \beta_0 + \beta_1 x_{1i} + \epsilon_i,$$

where y_i is the response variable for the i-th observation, β_0 is the intercept, x_{1i} is the value for the first predictor for the i-th observation, β_1 is the first regression coefficient, and ϵ_i is the error term. In the standard linear regression, observations are assumed to be independent. There are several possible specifications for MEMs, with so-called random intercepts and/or random slopes. A univariate MEM with both random intercepts and slopes, and a single predictor may be stated as:

$$y_{ij} = (\beta_0 + \beta_{0j}) + (\beta_1 + \beta_{1j})x_{1i} + \epsilon_i,$$

$$\beta_{0j} \sim Normal(0,\ \sigma_0^2),$$

$$\beta_{1j} \sim Normal(0,\ \sigma_1^2).$$

Here y_{ij} is the i-th observation for the j-th cluster, and β_{0j} and β_{1j} denote the random effects for the intercept and slopes for the j-th cluster. The random effects are from normal distributions with a mean of zero and some variance. The effect estimates from a MEM represent a partially pooled estimate, where clusters are expected to share some degree of similarity, i.e., one cluster of observations to some degree informs expectations of another cluster. It is therefore not expected that clusters are identical (completely pooled), or completely independent (no pooling). MEMs have been implemented in several programming languages, in the current thesis the lme4 and lmerTest - packages are used, which are implemented in the R programming language [287,288].

4.5 Ethical Considerations

All data collection and analysis within the studies included in this thesis was approved by the regional ethical review board in Stockholm. Informed consent was waived for all participants, where review of charts and access to imaging was without prior consent. This waiver of consent is ethically justifiable from several aspects. The intrusion itself may be considered limited, as it entailed only review of patient charts and imaging. All data was as soon as possible pseudonymized and the key was kept in a secure internal sever. Further, a requirement of informed consent would make these studies scientifically invalid as many patients are deceased or unable to give consent, whereby the research would not valuable due to a strong selection bias.

5 Results

5.1 Study I

5.1.1 Patient cohort and survival

In total, 283 patients who had presented with a ruptured AAA, were investigated. In the entire cohort, almost one-fourth of patients were women, and the mean age was 79 (SD = 9) years. Eighty-five patients (30%) had a previously known AAA, and 71 (25%) were not treated at rupture. The median survival-time for untreated patients with a rAAA was one day. Within two days 86% had died, and all had died within nine days. Median survival for treated patients was 736 days (**Figure 5-1**).

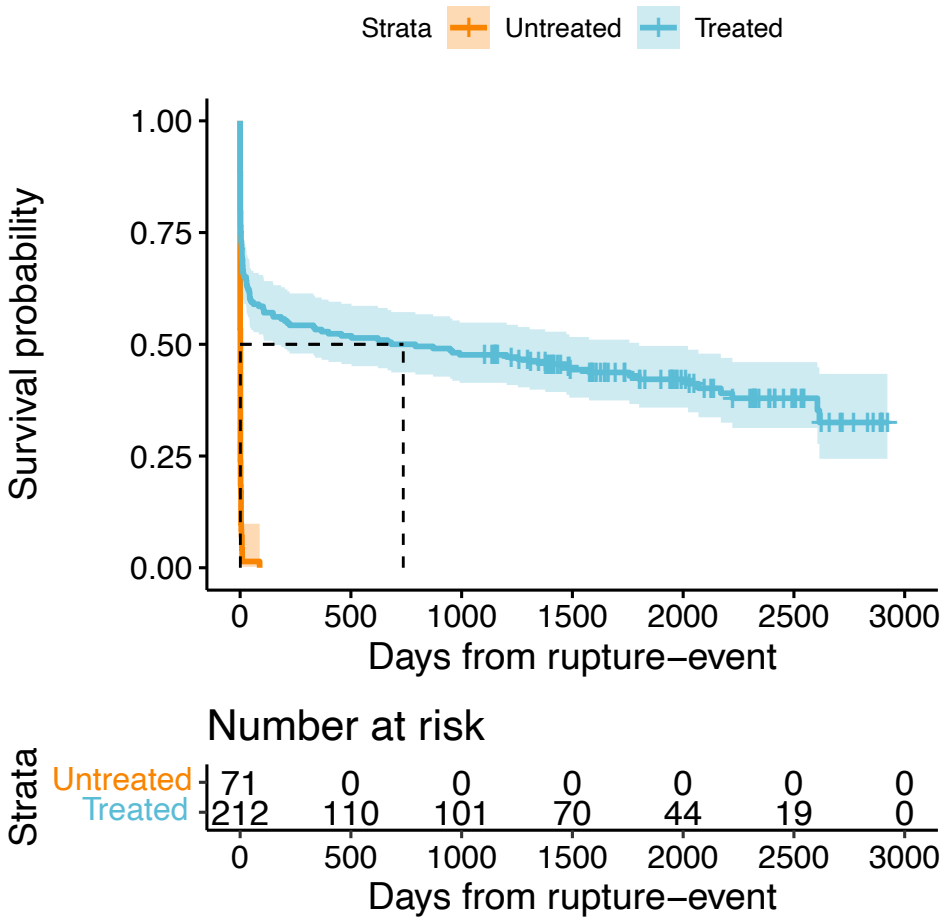

Figure 5-1. Survival for patients with ruptured AAA, treated and untreated, in the Stockholm Aneurysm Rupture Cohort,

Table 5-1. Characteristics for patients included in Study I, overall and grouped according to if CT imaging was available for analysis. Table adapted from Study I.

Characteristic	**Overall**, N = 283[1]	**CT available**		p-value[2]
		Yes, N = 192[1]	**No**, N = 91[1]	
Age at Rupture -yrs, Mean (SD)	79 (9)	79 (9)	79 (9)	0.80
Sex, n (%)				0.70
Female	69 (24)	45 (23)	24 (26)	
Male	214 (76)	147 (77)	67 (74)	
Height -m, Mean (SD)	1.73 (0.10)	1.73 (0.10)	1.72 (0.10)	0.72
Weight -kg, Mean (SD)	78 (19)	79 (19)	75 (18)	0.20
BSA - m2, Mean (SD)	1.91 (0.26)	1.92 (0.26)	1.89 (0.26)	0.68
Smoking, n (%)				0.92
Never	38 (26)	28 (26)	10 (29)	
Previous	49 (34)	38 (35)	11 (31)	
Current	57 (40)	43 (39)	14 (40)	
Diabetes, n (%)	35 (13)	31 (17)	4 (4.4)	**0.007**
Heart disease, n (%)	102 (37)	71 (39)	31 (34)	0.57
Hypertension, n (%)	175 (64)	120 (65)	55 (61)	0.60
Previously known AAA, n (%)	85 (30)	57 (30)	28 (31)	0.96
Treated, n (%)	212 (75)	153 (80)	59 (65)	**0.011**

[1] Mean (SD); n (%),[2] Welch Two Sample t-test; Pearson's Chi-squared test.
Abbreviations: BSA; body surface area.

CT imaging was available for 192 patients. Those who had CT imaging available more often had diabetes, and were more frequently treated for their rAAA, but other patient characteristics were similar to patients where there was no CT imaging available (**Table 5-1**).

5.1.2 CT imaging measurements at rupture

The mean Dmax at rupture was 81 (SD = 19, range 35.9 – 157.0) mm. Women had significantly smaller Dmax at rupture compared to men, 73 (SD = 18) mm vs. 83 (SD = 18) mm, p = 0.003 (**Figure 5-2**). The aneurysm neck length, neck diameter, and left and right common iliac artery Dmax were also smaller for women at rupture (**Table 5-2**).

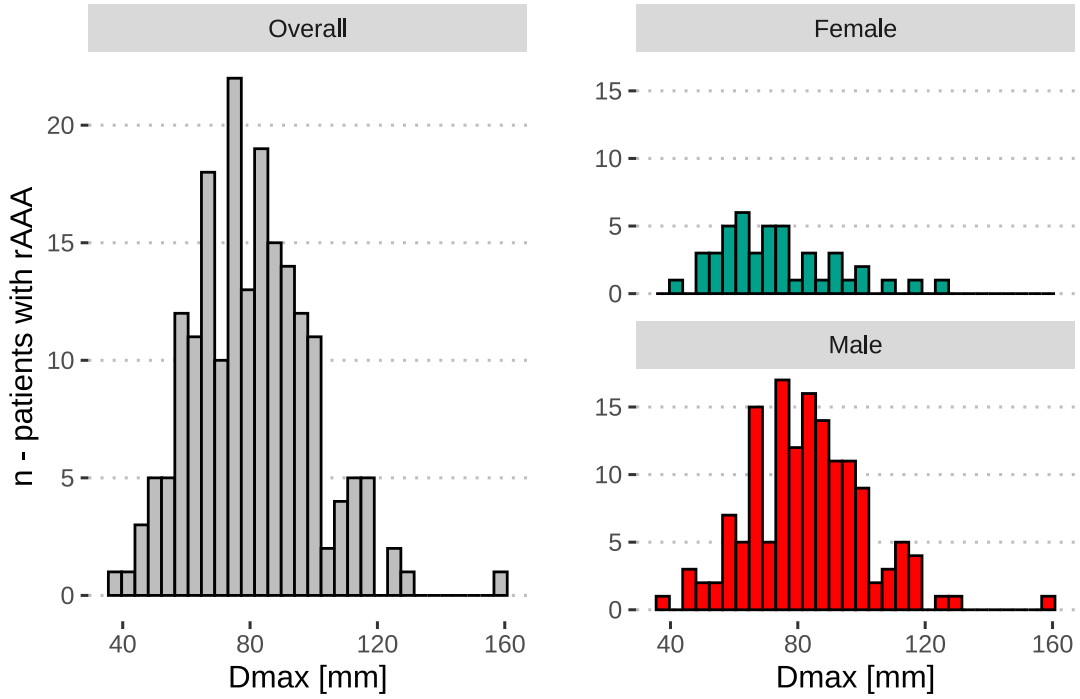

Figure 5-2. Histogram showing the maximal AAA diameter (Dmax) at rupture, overall and stratified by sex.

Table 5-2. Morphological characteristics of ruptured AAAs, overall, and stratified by sex. Table adapted from study I.

		Sex		
Characteristic	**Overall**, N = 192[1]	**Female**, N = 45	**Male**, N = 147	**p-value**[2]
Dmax -mm, Mean (SD)	81 (19)	73 (18)	83 (18)	**0.003**
Neck diameter -mm, Median (IQR)	26 (22 – 31)	23 (20 – 26)	27 (24 – 32)	**<0.001**
Neck length -mm, Median (IQR)	14 (1 – 27)	14 (6 – 29)	15 (1 – 25)	0.64
Alpha-angle -degrees, Median (IQR)	19 (11 – 34)	22 (12 – 36)	19 (10 – 34)	0.35
Dmax left common iliac -mm, Median (IQR)	18 (15 – 21)	15 (13 – 19)	18 (16 – 21)	**<0.001**
Dmax right common iliac -mm, Median (IQR)	17 (15 – 22)	16 (14 – 19)	18 (15 – 23)	**0.041**

[1] Mean (SD); Median (IQR), [2] Welch Two Sample t-test; Wilcoxon rank sum test. **Abbreviations:** Dmax; maximal aneurysm diameter.

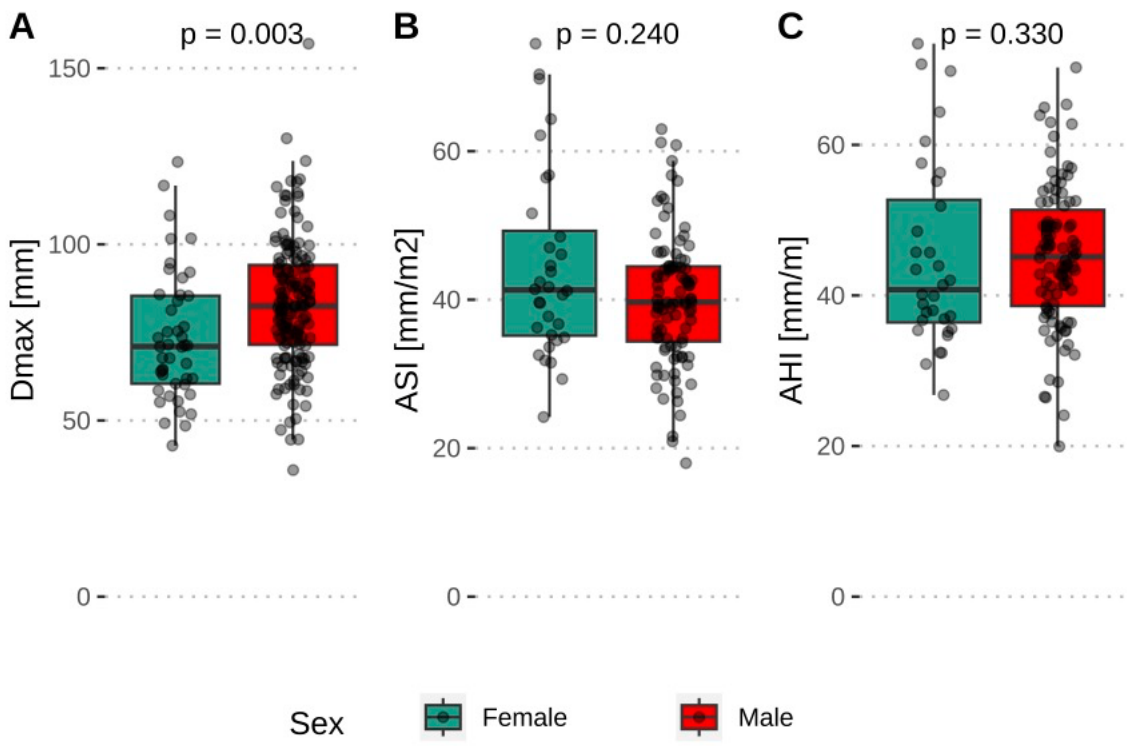

Figure 5-3. (A) Maximal aneurysm diameter (Dmax), **(B)** Aortic Size Index (ASI), **(C)** Aortic Height Index (AHI), for patients with ruptured AAAs stratified by sex.

Nearly one third of women (27%) had Dmax smaller than 60 mm at rupture, compared to 10% of men, p = 0.005. When comparing ASI at rupture there was, however, no statistically significant difference between the sexes. Distribution of an aortic height index (AHI, Dmax normalized by height), were also not statistically different (p = 0.330) (**Figure 5-3**). Patients with COPD were also likely to rupture at smaller diameters (35 vs 15%, p = 0.022). There was no difference in proportions between small and large ruptured AAAs in patients with diabetes, hypertension, heart disease or among smokers.

5.1.3 Comparison of small ruptured and asymptomatic AAAs.

For the small (<60 mm) ruptured AAAs, 3D segmentation and biomechanical analysis was attempted. In 15 / 27 cases FEA was possible, and in 20 / 27 cases 3D segmentations was possible. **Figure 5-4** shows the morphology of the 20 small AAAs where 3D segmentation was possible. The small AAAs were matched 1:2 by Dmax, sex and age to patients from the included asymptomatic cohort (**Table 5-3**). Patients that belonged to the ruptured cohort had shorter aneurysm necks, larger suprarenal ASI, and higher PWRI. PWS did not differ between the groups.

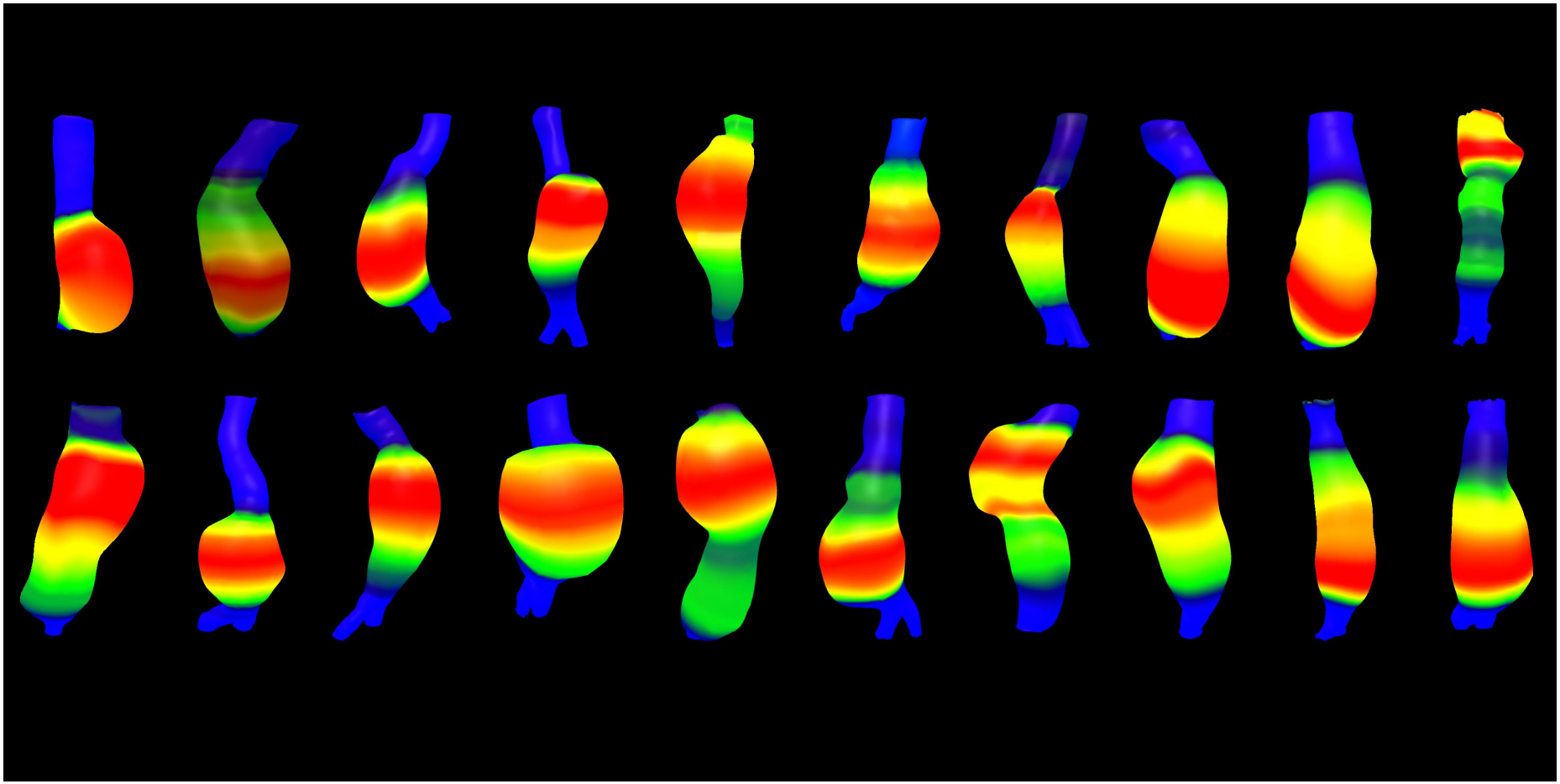

Figure 5-4. 3D morphology of twenty small (≤ 60 mm) ruptured abdominal aortic aneurysms. Colours indicate relative diameter.

Table 5-3. Characteristics, morphological and biomechanical variables for matched small ruptured asymptomatic AAAs.

Characteristic	AAA		p-value[1]
	Asymptomatic, N = 40	**Ruptured**, N = 20	
Dmax -mm, Mean (SD)	53.0 (5.7)	54.5 (5.2)	0.30
Sex -female, n (%)	16 (40)	9 (45)	0.71
Age -yrs, Median (IQR)	79 (74 – 83)	78 (77 – 82)	0.82
BSA -m2, Mean (SD)	1.89 (0.19)	1.79 (0.27)	0.17
Neck length -mm, Median (IQR)	32 (14 – 44)	12 (7 – 32)	0.054
Suprarenal diameter -mm	24.4 (22.0 – 26.1)	24.9 (23.3 – 27.0)	0.31
Aneurysm volume -cm3, Mean (SD)	156 (49)	144 (32)	0.28
ASI -mm/m2, Mean (SD)	28.3 (4.3)	31.4 (6.2)	**0.066**
Suprarenal ASI -mm/m2, Median (IQR)	12.79 (11.44 – 13.98)	13.96 (13.33 – 15.29)	**0.025**
PWS -kPa, Mean (SD)	197 (40)	216 (45)	0.16
PWRI -ratio, Mean (SD)	0.35 (0.08)	0.43 (0.11)	**0.016**

[1] Welch Two Sample t-test; Pearson's Chi-squared test; Wilcoxon rank sum test. **Abbreviations:** BSA; body surface area, ASI; aortic size index, PWS; peak wall stress, PWRI; peak wall rupture index.

5.2 Study II

In Study II, 384 CTAs from 100 patients were included. They were mostly male (78%), mean age at baseline was 70 years. Dmax at baseline was 43.9 mm, the mean total follow up was 5.2 years, and the mean number of CTs per patient was three (**Table 5-4**). The crude growth rate of AAAs was 2.64 (1.18) mm/year, and PWS increased 7.39 (SD = 4.95) kPa/year, and PWRI increased 2.38 (SD = 2.14) %/year.

Table 5-4. Patient characteristics and basic morphological and geometric parameters for patients included in Study II.

Patient Characteristics (n = 100)		
Age at Baseline -yrs	70.0 (8.5)	
Sex = Male	78 (78%)	
Current Smoker	36 (36%)	
Ever Smoker	86 (87%)	
Height -cm	174.0 (8.8)	
Weight -kg	82.6 (16.6)	
BSA -m^2	1.97 (0.22)	
BMI -kg/m^2	27.1 (4.5)	
CTAs (n = 384)		
Median No. of CTAs per patient –n	3.0 (3.0-4.0)	
Mean time between CTAs -years	2.7 (1.5)	
Mean total follow-up time -years	5.2 (2.5)	
Measurements (n = 100)	**Baseline** Mean (sd)	**Crude Growth Rate**– Estimate (/year) (sd) †
Dmax -mm	43.9 (6.8)	2.64 (1.18)
Aneurysm Volume -cm^3	94 (33)	14.28 (10.24)
Lumen Volume -cm^3	53 (19)	5.05 (6.04)
ILT Volume -cm^3	53 (19)	8.00 (7.24)
Peak Wall Stress -kPa	169 (44)	7.39 (4.95)
Peak Wall Rupture Index -%	30 (8)	2.38 (2.14)

Values denote n (%), mean (standard deviation) or median (interquartile range). † Estimates refer to estimates from mixed effects models, where the variable is a function of time with random intercepts and slopes. Standard deviation refers to the variability in the random slopes. **Abbreviations** BSA; body surface area, BMI; body mass index, CTA; computed tomography angiography, Dmax; maximal aneurysm diameter, ILT; intraluminal thrombus.

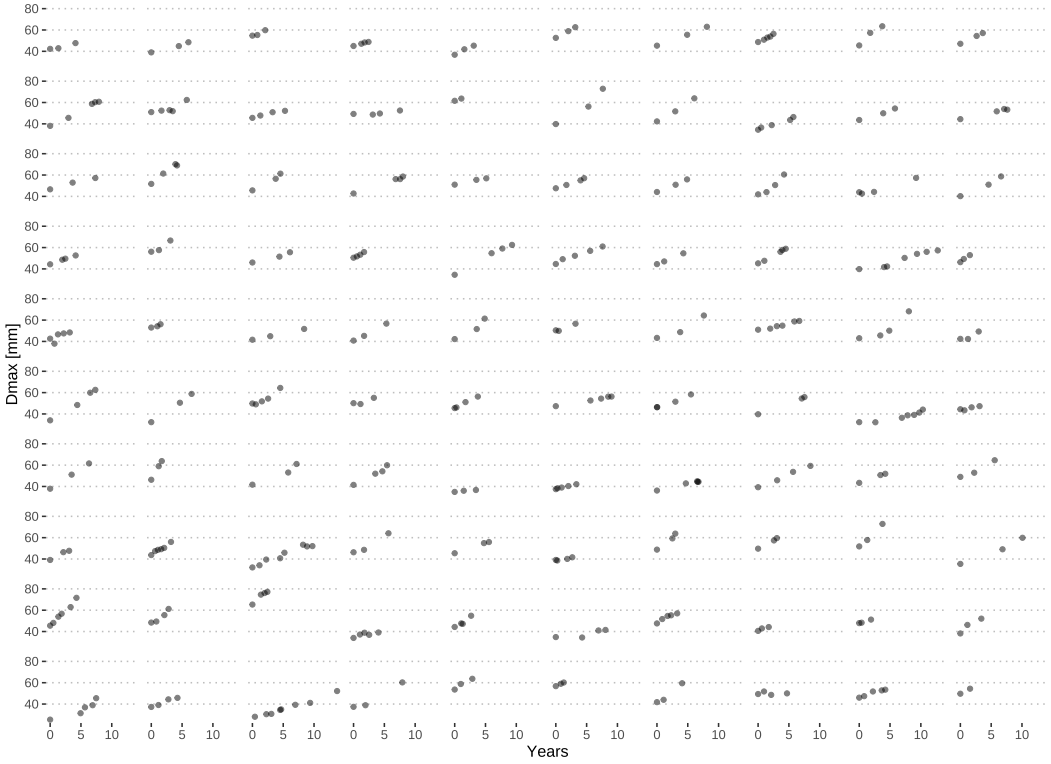

Figure 5-5. Maximal aneurysm diameter (Dmax) over time for patients included in Study II.

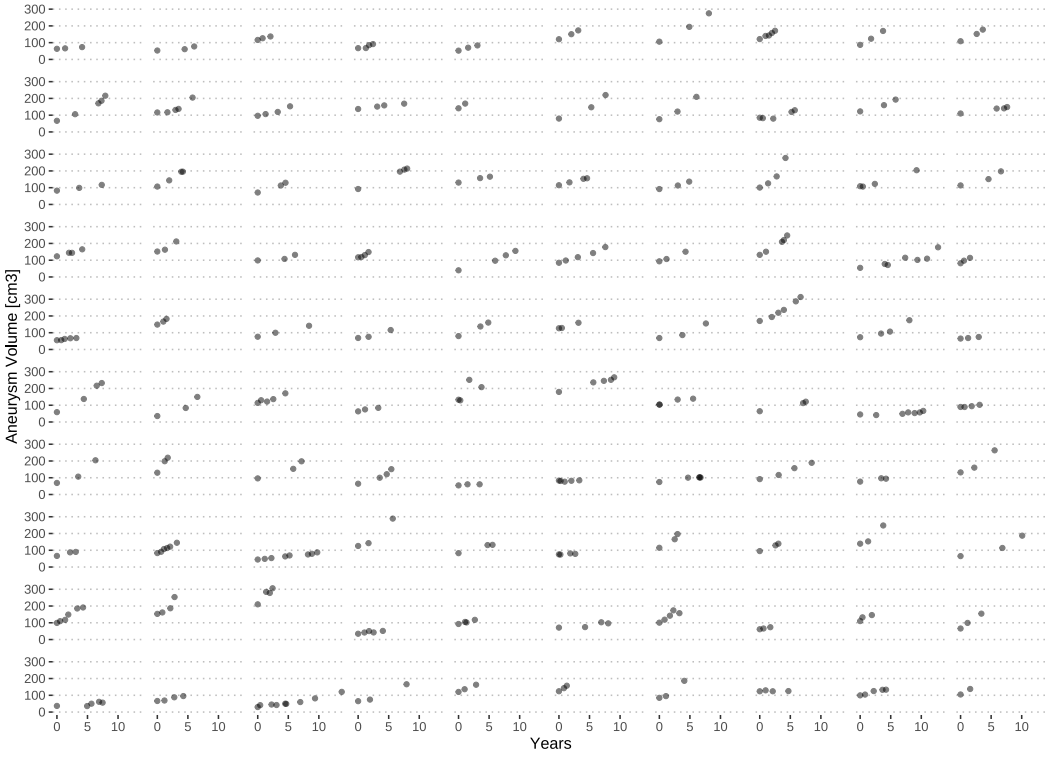

Figure 5-6. Aneurysm volume over time for patients included in Study II.

Dmax and aneurysm volume, over time is displayed for individual patients in **Figure 5-5** and **Figure 5-6**. Qualitatively, the growth of both Dmax and aneurysm volume, for most part appeared continuous and not erratic. To assess the appropriateness of a simple time linear model, individual linear regression models were fit to each patient (no pooling of co-efficients). For Dmax and aneurysm volume, 87 and 77 % respectively had a r-squared over 0.90. For seven selected patients, Dmax measurements collected from medical records are presented (**Figure 5-7**). There is substantial variation, depending on which modality is used for measuring. In some cases, such as the fourth patient, the clinical CT diameter appears stagnant, until it suddenly increases, in contrast to the semi – automatic diameter, which continually increases.

Among the third of patients with the slowest diameter growth (<2.11 mm/year), 22 (67%) were in the slowest volume increase (<9.6 cm^3/year), 17 (52%) also displayed PWS increase in the slowest tertile (<5.38 kPa/year), and 18 (55 %) to the slowest PWRI increase (<0.01%/year).

Table 5-5. Goodness of Fit for individual linear regression models.

	R-squared		
	Mean	SD	> .90 (n)†
Dmax	0.94	0.12	87
Aneurysm Volume	0.91	0.16	77
Lumen Volume	0.72	0.29	39
ILT-Volume	0.81	0.26	60
Peak Wall Stress	0.66	0.33	38
Peak Wall Rupture Index	0.72	0.30	35

Abbreviations: SD; standard deviation, Dmax; maximal aneurysm diameter, ILT; intraluminal thrombus. †The number of patients where the r-squared value for the model exceeds 0.90.

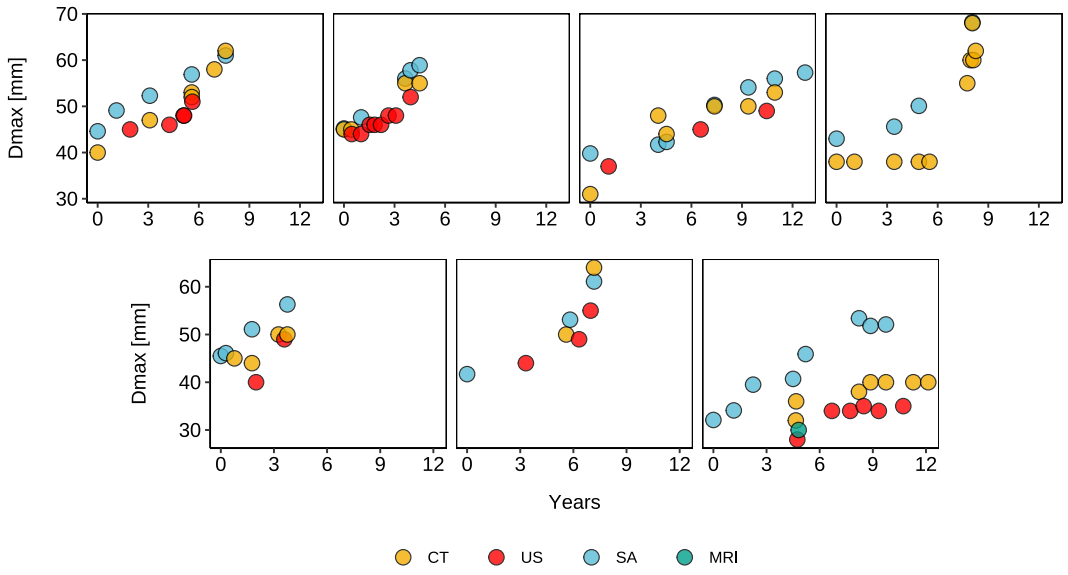

Figure 5-7. Figure shows patient-level plots for seven selected patients for whom Dmax measurements were collected from the clinical medical records. Colors indicate modality, computed tomography (CT), ultrasound (US), semi-automatic (SA, measured from CT), and MRI (magnetic resonance imaging).

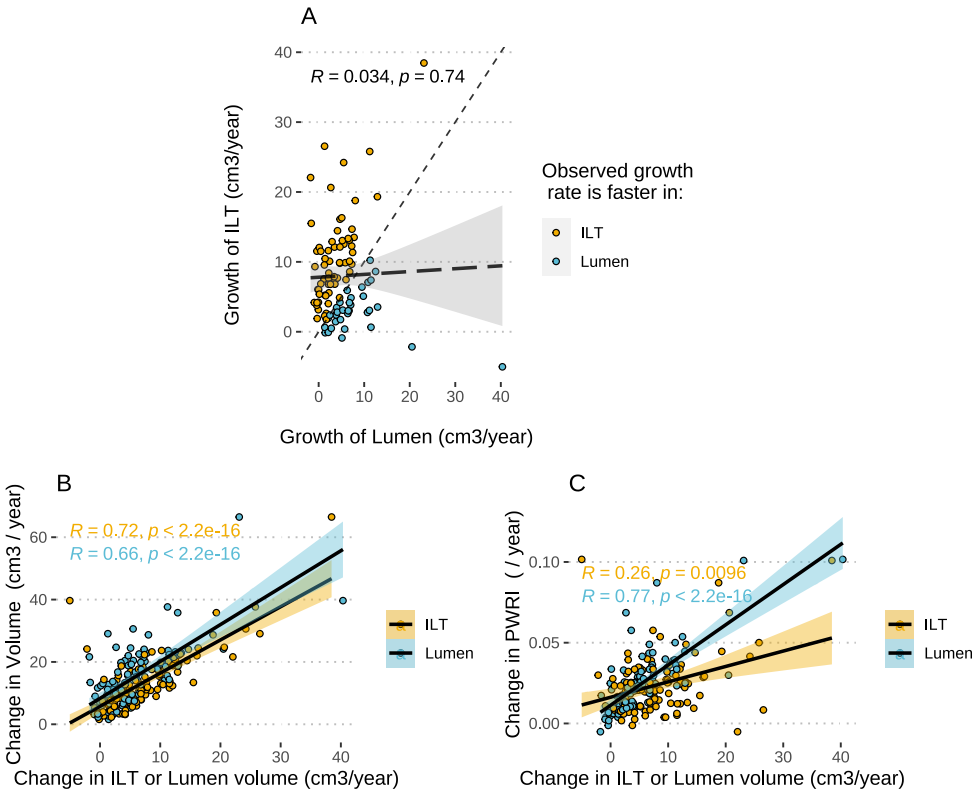

Figure 5-8. Scatter plots where each dots represents a patient, showing the relation between **(A)** growth of the lumen and the intraluminal thrombus (ILT), **(B)** the change in ILT or lumen volume, and the change in total aneurysm volume, and **(C)** the change in ILT or lumen volume and the change in peak wall rupture index (PWRI). Note in B and C patients appear twice, once for ILT and once for lumen volume.

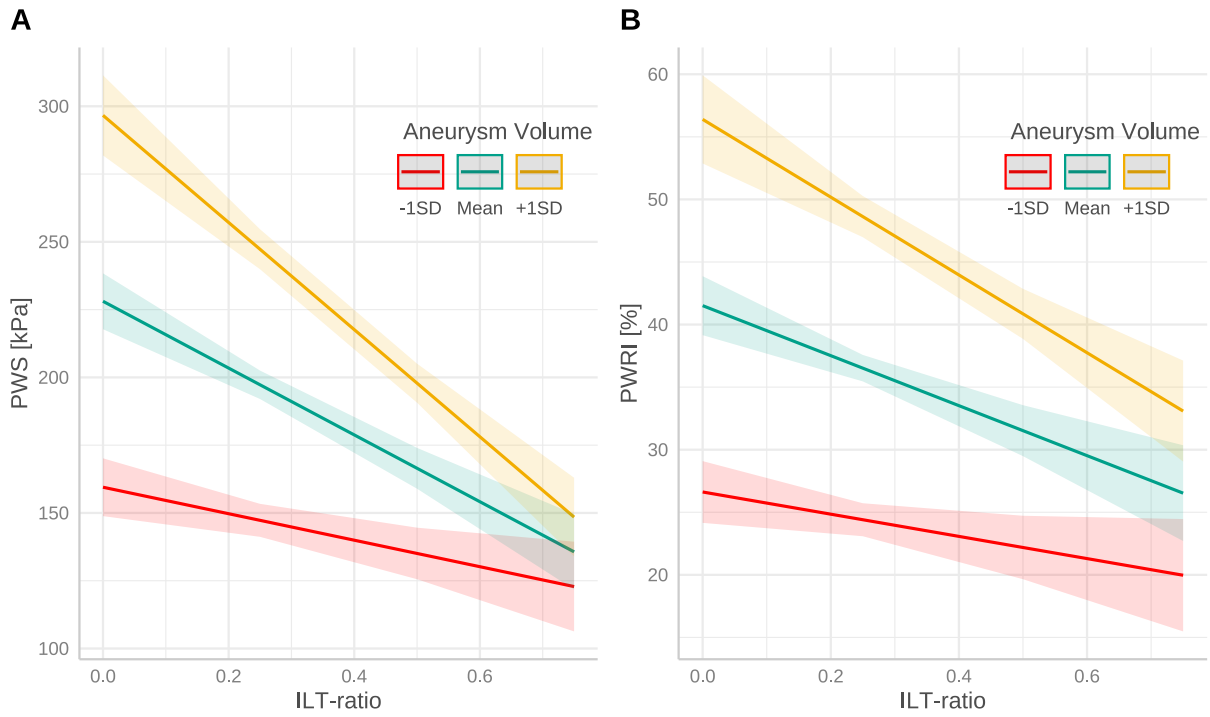

Figure 5-9. Counterfactual plot showing mixed effects regression models with either peak wall stress (PWS) or peak wall rupture index (PWRI) as the response variable, with aneurysm volume, intraluminal thrombus (ILT)-ratio and their interaction as predictors.

To investigate the relation between growth of the different morphological and biomechanical indices, patient level values for these indices were extracted. There was no correlation between ILT growth and lumen volume growth ($R = 0.034$, $p = 0.74$) (**Figure 5-8 A**), but for most patients ILT grew faster than the lumen and consequently and the proportion of ILT (ILT-ratio) increased over time (2.36 % / year, model not shown).

Both the growth of the ILT and lumen, however, correlated with change in overall aneurysm volume ($R = 0.72$, $p < 0.001$, and $R = 0.66$, $p < 0.001$), but the correlation was numerically stronger for ILT (**Figure 5-8 B)**. Lumen volume change correlated significantly stronger to change in PWRI compared to ILT volume change ($r = 0.77$, $p < 0.001$ vs. $R = 0.26$, $p = 0.001$, p for difference in correlations < 0.001).

As the results indicated that the proportion of ILT increased with aneurysm size, this was assumed as a potential confounder between the relation of the proportion of ILT and biomechanical stress. Therefore, a model that accounted for the interaction of proportion of ILT (ILT – ratio) and aneurysm size was used. This showed that the proportion ILT, in fact correlated negatively with increasing biomechanical stress (PWS and PWRI) when accounting for AAA volume (**Figure 5-9**). In other words, for any given volume, the biomechanical stress decreased as the ILT ratio increased.

5.3 Study III

In Study III, to investigate how biomechanical factors relate to time-to-rupture, a cohort of patients with CTAs and a known time to rupture was identified. A total of 67 patients with 109 CTAs prior-to-rupture were included. They were mostly male (70%), and the mean age was 77 (71-82) years (**Table 5-6**). The median time to rupture was 2.1 (0.6 – 4.7) years. A control cohort including 97 patients with asymptomatic AAAs were also included, these patients were younger, and more likely to be male compared to the pre-rupture cohort.

The mean Dmax of the pre-rupture examinations was 56 (46 – 65) mm. In the pre-rupture group those CTs that were within half a year from rupture, 9% (2) were smaller than 55 mm, and within half a year – to one year 36% (4) were smaller than 55 mm (**Figure 5-10**).

Table 5-6. Patient characteristics, morphological and biomechanical factors for the pre-rupture cohort and stable cohort.

	Pre-rupture cohort, N (patients) = 67	**Stable cohort**, N = 97	**p-value**[1]
Age -yrs	77 (71 – 82)	72 (66 – 77)	**0.004**
Sex -n (%)			**0.027**
Female	20 (30)	15 (15)	
Male	47 (70)	82 (85)	
	Pre-rupture cohort, N (of CTs) = 109	**Stable cohort**, N = 97	
Time-to-rupture/ censoring -yrs	2.1 (0.6 – 4.7)	6.4 (4.9 – 8.9)	**<0.001**
Dmax -mm	56 (46 – 65)	46 (43 – 47)	**<0.001**
Aneurysm volume -cm3	168 (104 – 236)	94 (83 – 114)	**<0.001**
Peak Wall Stress -kPa	193 (155 – 238)	172 (149 – 186)	**<0.001**
PWRI -ratio	0.39 (0.28 – 0.50)	0.31 (0.27 – 0.36)	**<0.001**

[1]; Pearson's Chi-squared test; Wilcoxon rank sum test. Continuous variables presented as median (IQR). **Abbreviations**: Dmax; Maximal aneurysm diameter, PWRI; Peak wall rupture index, PWS; peak wall stress

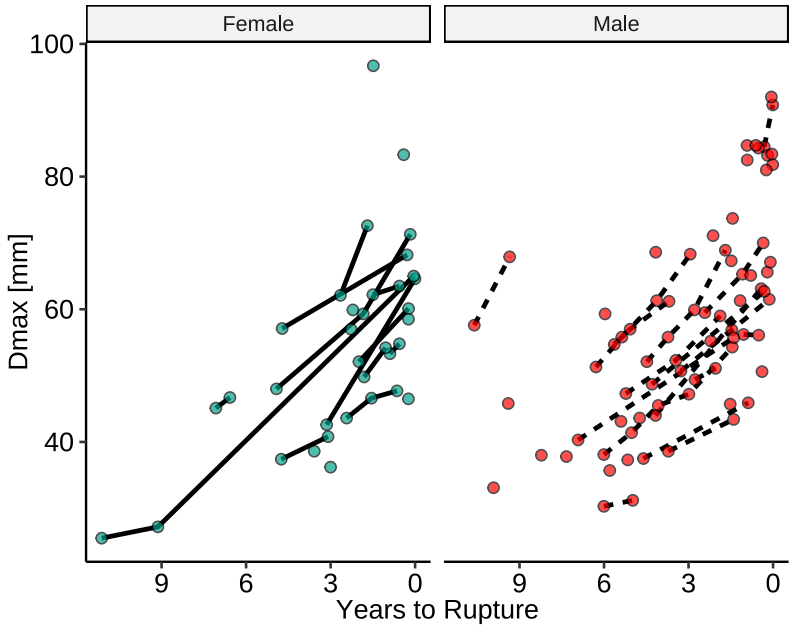

Figure 5-10. Maximal aneurysm diameter for women (left) and men (right) in computed tomography angiography (CTA) examinations prior to rupture. Circles represent a pre-rupture CTA examination, and lines join the same patient with multiple examinations. The vertical axis represents maximal aneurysm diameter (mm) and the horizontal axis represents time to rupture (years).

To assess the relation between biomechanical markers (PWS and PWRI) and time-to-rupture, several analyses were performed. The main analysis was conducted in patients with AAA < 70 mm at pre-rupture CTA. As discussed previously, the material model used in the calculation is not validated in AAAs with maximal diameters beyond 70 mm, why they were excluded for the main analysis.

In this cohort, in the univariable analysis Dmax, aneurysm volume, PWS and PWRI were all significantly associated with time-to-rupture (p for all < 0.001) (**Table 5-7**). When adjusting the univariable models with PWRI and PWS for aneurysm size (either Dmax or aneurysm volume), PWRI was associated with time to rupture (HR 1.04, 1.02 – 1.06), and (HR 1.04, 1.01 – 1.06) respectively for Dmax and aneurysm volume (**Table 5-7**). For PWS, no statistically significant association was seen. The results remained similar if adjusted for sex, but the estimates were slightly smaller (not shown). As a sensitivity analysis, a cohort of patients with asymptomatic AAAs were included into the survival analysis, this did not influence the overall results, even if point estimates were affected. Further, in analysis of AAAs of all sizes, PWRI and PWS was not significantly associated with time-to-rupture.

Table 5-7. Univariable and multivariable association between time-to-rupture and geometric and biomechanical indices of intact abdominal aortic aneurysms less than 70 mm, with a known time-to-rupture.

	Univariate		Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)[1]	**p-value**	**HR (95% CI)[1]**	**p-value**	**HR (95% CI)[1]**	**p-value**	**HR (95% CI)[1]**	**p-value**	**HR (95%CI)[1]**	**p-value**
PWRI (%)	1.05 (1.04-1.07)	**<0.001**	1.04 (1.02-1.06)	**<0.001**	1.04 (1.01-1.06)	**<0.001**				
PWS (kPa)	1.01 (1.01-1.01)	**<0.001**					1.00 (1.00-1.01)	0.18	1.00 (1.00-1.01)	0.12
Dmax (mm)	1.05 (1.02-1.09)	**<0.001**	1.03 (0.99-1.07)	0.12			1.04 (1.00-1.09)	0.051		
Aneurysm vol (cm3)	1.01 (1.00-1.01)	**<0.001**			1.00 (1.00-1.01)	**0.032**			1.01 (1.00-1.01)	**0.006**

[1]HR = Hazard Ratio, CI = Confidence Interval. PWRI = peak wall rupture index, PWS = peak wall stress, Dmax = Maximal Aneurysm Diameter.

5.4 Study IV

Study IV was conducted to assess the potential utility of 2D area-based measurements of ILT and lumen to differentiate ruptured from asymptomatic AAAs, and thereby investigate their potential utility as rupture risk markers.

Thirty patients with ruptured AAA, and 60 patients with asymptomatic AAA were included in Study IV. Patient characteristics are summarised in **Table 5-8**. Patients with ruptured AAAs had larger Dmax, larger total vessel area, lumen area, lumen volume, ILT volume, and higher PWS and PWRI.

Table 5-8. Patient Characteristics, AAA morphology and biomechanics for patients included in study IV.

Characteristic	**AAA**		**p-value**[1]
	Asymptomatic, N = 60	**Ruptured**, N = 30	
Age -yrs	76±8	77±10	0.665
Men, n (%)	46 (77)	23 (77)	0.791
Smoking, ever, n(%)	39 (65)	23 (77)	0.377
Blood pressure - mmHg			
Systolic	144±15	149±16	0.148
Diastolic	82±9	86±9	0.095
AAA morphology			
Dmax, mm	62±13	77±15	**<0.001**
ILT area ratio	61±25	53±25	0.169
Lumen area, mm^2	1059±674	2281±1964	**<0.001**
ILT area, mm^2	1883±1244	2406±1383	0.089
Total vessel area, mm^2	2942±1137	4687±1952	**<0.001**
Lumen volume, cm^3	84.8±41.2	201.7±206.2	**<0.001**
ILT volume, cm^3	102.4±78.6	180.1±110.8	**<0.01**
Relative ILT volume, %	43±19	48±19	0.161
Total sac volume, cm^3	213.5±103.2	381.8±243.7	**<0.001**
Biomechanical measurements			
PWS, kPa	210.9±53.4	292.6±53.9	**<0.001**
PWRI, ratio	0.41±0.11	0.87±0.54	**<0.001**

[1] Welch Two Sample t-test; Pearson's Chi-squared test. **Abbreviations:** Dmax; maximal aneurysm diameter, ILT; intraluminal thrombus, PWS; peak wall stress, PWRI; peak wall rupture index.

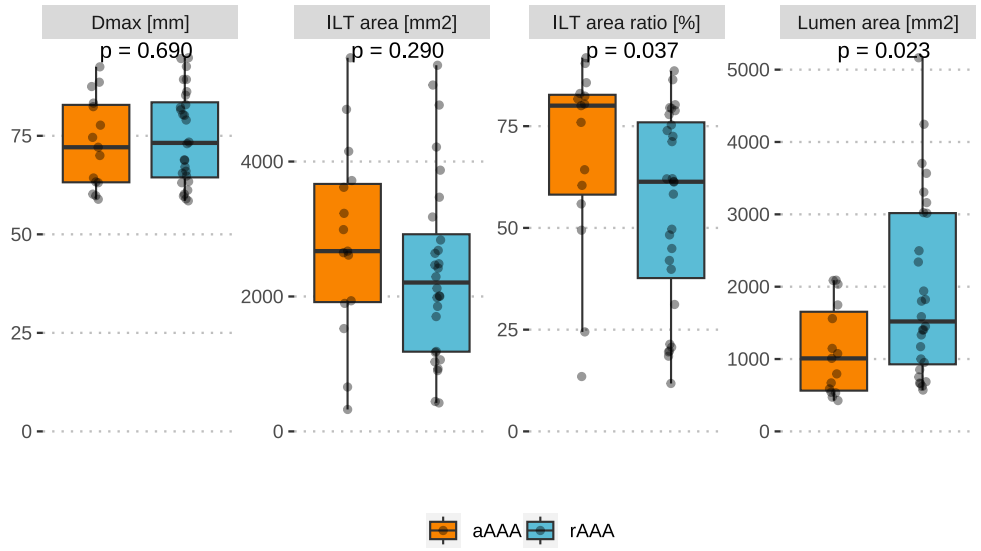

Figure 5-11. Boxplots showing 2D morphological measurements in 28 ruptured AAAs matched by Maximal diameter (Dmax), age and sex to 15 asymptomatic AAAs.

Patients included in the study were matched according to Dmax, age, and sex, which yielded 28 patients with ruptured AAA and 15 patients with asymptomatic AAA. In this matched analysis, there was no difference in Dmax (p = 0.690), or ILT area (p = 0.290). The ILT area ratio was, however decreased in the ruptured AAA group, and the lumen area was increased (p = 0.037 and p = 0.023, respectively) (**Figure 5-11**).

To assess the relation between the 2D parameters and biomechanical markers, finite element analysis was performed for all 60 patients with asymptomatic AAAs in addition to 2D measurements. Multivariable regression models with PWS or PWRI as the response variable and Dmax, lumen area and ILT area were fitted. Lumen area was associated with both PWS and PWRI, whereas the association with ILT area was weaker for PWS and not statistically significant for PWRI (**Table 5-9**).

Table 5-9. Linear multivariable regression, with PWS or PWRI as response variables, and Dmax, lumen area and ILT-area as predictors.

	PWS		PWRI	
	Beta (95% CI)[1]	**p-value**	**Beta (95% CI)**[1]	**p-value**
Dmax	-0.28 (-1.0 to 0.45)	0.45	-0.33 (-1.2 to 0.51)	0.44
Lumen area	0.95 (0.47 to 1.4)	**<0.001**	0.90 (0.34 to 1.5)	**0.002**
ILT area	0.89 (0.10 to 1.7)	**0.028**	0.77 (-0.14 to 1.7)	0.10

[1] CI = Confidence Interval. All variables are scaled to mean zero and unit variance. Beta represents coefficients from the corresponding linear multivariable regression model with PWS or PWRI as response variable. **Abbreviations:** PWS; peak wall stress, PWRI; peak wall rupture index, Dmax; maximal aneurysm diameter, ILT; intraluminal thrombus.

6 Discussion and conclusions

6.1.1 Maximal aneurysm diameter – as a surgical threshold and surveillance variable

Today the clinical management of patients with AAAs is largely based on diameter measurements. In the first study it is evident that a certain proportion of patients will rupture under the current treatment thresholds. This has been also reported by others, and a recent study based on the Vascular Quality Initiative-registry of almost 4000 ruptured AAAs, the proportions of small AAAs (less than 5.0 cm for women, and less than 5.5 cm for men) was 12.2 % [289]. The mean diameter at rupture, conversely, was in Study I 81 mm, which has been reported between 76 - 84 mm by others [290,291]. This altogether indicates that the use of diameter in a dichotomous way is associated with surgery too late for same patients, and for some perhaps needlessly early. It should be noted that in Study I, patients who do not rupture are not included, and it is therefore not possible to estimate the rupture risk of an AAA with a certain size.

Further, as noted in study I women appear to be affected by rupture at small diameters. The smaller rupture Dmax in women may be normalized by BSA, which confirms previous findings [292]. Other mechanisms may be important where female sex itself confers increased biomechanical stress, as well as decreased wall strength [254,283,293]. This is strengthened by results in Study III where women have an approximately two-fold hazard for rupture for an aneurysm of a given size.

Dmax in patients with AAAs is also used for surveillance. Previously growth of the Dmax has oftentimes been described as erratic and discontinuous [204,205]. As discussed in the background section of the thesis (**Section 2.4.2**), the measurement of Dmax is complicated by its imprecise definition and varies widely between different methods. This is likely to be especially apparent in the clinical setting as this represents a combination of many different factors that affect the measurements. Recently, Olsen et al investigated a cohort of 257 patients with serial CT examinations during 2 years and measured in a core laboratory, as a part of the Non-Invasive Treatment for AAAs Clinical Trial (NTA3CT) [217]. They reported that only a small number of AAAs displayed staccato growth (3%), and linear growth was evident in 70% cases [217]. From the few examples in Study II, where semi-automatic Dmax is contrasted to clinically recorded Dmax, discrepancies are evident. The diameters that are compared as clinical may not be all of them measured for the purpose of AAA surveillance, and therefore the method and absolute accuracy with which those are measured is unknown. Altogether these results indicate

that previously assumed unpredictable nature of AAA growth may in fact for many patients be rather predictable with accurate and unified measurements.

6.1.2 Biomechanical analysis

As previously described, the use of the diameter as a rupture risk predictor is sometimes justified by the law of Laplace, whereby its assumed to relate directly to the wall stress of the aneurysm. As stated previously, the biomechanical hypothesis states that a vessel ruptures when the stress acting to deform the vessel exceeds its material strength.

PWS, which represents the maximal stress in the AAA, has previously been indicated to be increased in ruptured AAAs compared to stable [8,244], but a recent meta-analysis has suggested that PWRI, but not PWS is increased when comparing AAAs that are matched for Dmax [9]. This does not represent the clinical situation, where instead the prediction of rupture in AAAs prior to rupture is of interest. Previously others have investigated the predictive performance of biomechanical analysis for future AAA rupture, [245,247]. Both studies which use a case-control design indicate that PWRI may be a marker for rupture risk, but were partially limited by small sample size. Also, in a study of consecutive small AAAs, PWRI, PWS and lumen diameter were associated with the development of symptomatology or rupture [252]. In Study III a larger cohort of AAAs with CTA prior to rupture is presented, and even adjusting for AAA size, in the form of Dmax or aneurysm volume, and sex, PWRI is still associated with time-to-rupture in small and medium sized AAAs. Further The limit of 70 mm is introduced as the wall strength model that is used in the calculation of PWRI is not validated in AAAs beyond that. Further, the clinical decision to perform or postpone surgery in such a cohort would likely not depend on the rupture risk, but rather other patient related factors.

These biomechanical quantities are not measured directly, but instead obtained from patient-specific models. There are many levels of complexity that can be theoretically stated in association to this modelling problem, all of which are not possible to account for. Some salient features that are not included in the current implementations of biomechanical analysis in this thesis are discussed below.

As previously alluded, the rupture mechanism in, at least, some AAAs may be a fissure in the thrombus that suddenly transmits blood pressure to the aneurysm wall and may stimulate rupture. However, this kind of mechanism is not currently implemented in any of the current biomechanical analytical packages. While it may not be feasible to implement a detailed simulation of thrombus dissection, future studies may investigate the inclusion of biomechanical parameters that relate to the ILT, such as ILT stress Other possible venues of investigation are the analysis of the attenuation of the ILT on CT-im-

aging, and the distribution of these values (so-called radiomics), which may give information on thrombus integrity [294], or the use of other methods, such as MRI, which may enhance the characterization of the ILT [192].

Another factor which is not considered in the current biomechanical analysis is calcification, although readily visible in CT imaging. It has associated been with an increased rupture risk, but a decreased AAA growth rate [295–297] Calcification may give rise to stress concentrations, but the overall impact on biomechanical properties is uncertain [272,298,299]. Material properties of the wall are extrapolated from population-level data [283], but possibly could be improved by additional modalities, e.g., radioisotopes or other biologically meaningful radiological markers [300,301].

Patient characteristics are used to inform the biomechanical simulations. Blood pressure, which affects both the stress and wall strength calculations, varies over time, in both short and longer timespans [302]. The optimal blood pressure measurement to use is not known and may depend on the purpose of the analysis. A peak blood pressure is perhaps more adequate for rupture prediction, whereas mean blood pressure may be more adequate for aneurysm progression, this is however not studied within the thesis. This thesis constitutes retrospective data, and it was not possible to acquire structured blood pressure data.

Biomechanical analysis, as proposed in thesis, requires a CTA, which exposes the patient to radiation and potentially nephrotoxic contrast agents. Other potential implementations that that use other methods such as MRI or 3D-US are theoretically possible. The application of such technologies potentially limited due to cost, availability, and the need for specialized equipment.

Additionally, all AAAs are surveyed by ultrasound as a first-hand option, and more simple rupture risk parameters, such as the lumen area, which is analysed in Study IV, therefore may still have impact. While the efficiency of 2D markers such as luminal area is not directly contrasted to the full 3D analytical methods in the thesis, it is important to put the results into a wider context, where implementation of such methods may be challenging due to scarcity of health-care resources, or patient-related factors.

Another aspect, which may be useful with regards to 2D area measurements is that only one such measurement exists in a plane. For a diameter, there are, as previously discussed, several possible definitions in a single plane: antero-posterior, transversal, maximal in any direction or their combinations.

6.1.3 The role of the intraluminal thrombus

The role of the ILT in AAAs has been widely investigated. As described in the introduction it has been proposed to be involved in both AAA growth and rupture. The ILT appears to be a source of proteolytic enzymes and the vessel wall that is covered by ILT is hypoxic and thinner, compared to the non-thrombus covered wall [303]. In study II, in a longitudinal follow-up of AAAs the proportion of ILT increases as the AAAs grow. This fact may confound studies that do not account for the size of the AAA when investigating the relation of ILT, to any also size-related outcome, such as rupture risk. Further, also in a longitudinal follow-up of AAAs, the increase of biomechanical stress is related to the increase in lumen size. For a given AAA size, biomechanical stress appears inversely related to the proportion of thrombus. These data in context with previous studies, suggesting that ILT promotes AAA growth [220], may indicate a complex role for the ILT in AAAs, with perhaps opposite influence on growth and rupture.

6.2 Limitations

In addition to the limitations discussed above, some specific points merit consideration. All studies included in this thesis suffer from potential selection bias. This is inherent in retrospective work, but is also a consequence of the way the cohorts are constructed.

In Studies I and IV, patients with ruptured AAAs are included. Conclusions are drawn from analysis of this patient cohort. However, the large majority of patients, who do not rupture, are not included in this study. Conclusions regarding the rupture rates at specific diameters, or the number of patients with small AAAs that do not rupture are not investigated. Further, large AAAs may be more unstable at presentation, and may therefore be underrepresented in the cohort [289].

The analysis of imaging studies in ruptured AAAs is complicated by sometimes suboptimal imaging conditions, and very likely a disruption of the geometry of the aneurysm at the moment of rupture. The rupture event therefore may affect both morphological and biomechanical measurements in the AAA. It has been suggested that AAA diameter may increase markedly at rupture [304], which would influence also biomechanical simulations.

Study III represents an attempt to counter this limitation by investigating AAAs prior to rupture. However, the main cohort represents only AAAs that do rupture at some point in time. This may or may not represent a true selection bias, in the sense that these patients may suffer from a more rupture prone phenotype of AAA that eventually actually ruptures, which may not be the case for all patients with AAA disease.

In Study II, where patients are selected on the bases of the availability of three or more CTAs, this also represents a heterogenous cohort. Patients in Sweden do not generally undergo serial CTA examinations for the purpose of AAA surveillance, this is instead performed with US, but for many patients CT examinations are performed for other reasons, and the AAA is visualized *en passant*. The selection of patients on the basis of number of examinations may leave out patients with a fast-growing AAA, and may specially include patients that are examined with CT frequently for other reasons.

6.2.1 Statistical treatment

Many of the studies may reveal more insightful data from a more sophisticated statistical treatment. There are several outstanding features in AAA data that allow for specific consideration. Central to the treatment of aneurysm disease today is the idea of surveillance, which implies a longitudinal data model. Imaging and biomechanical modelling yield many variables that are followed over time. Multivariate modelling approaches, which model several variables simultaneously may be used to fit a unified model for AAA growth, that in turn may be more appropriate and informative compared to standard univariate models. Implementations of these models have in many cases combined a survival function and a parameter change function, which both are dependent on time but could also incorporate multiple morphological and biomechanical parameters. This class of models are typically referred to as joint-models [53,305]. For prediction of AAA-related outcomes (growth or rupture) using MEMs in out of sample patients only population level effects are available, since no patient specific effect estimates for these patients are obtained. Dynamic models, that incorporate previous observations for a specific patient and update the predictions thereafter have been described and are likely key to make fully informed predictions [306,307].

6.3 Conclusions

The four studies included in this thesis examine different aspects of AAA growth and rupture.

- In Study I the results indicate that a non-significant portion of all AAA ruptures occur in patients with small AAAs, especially in women. The AAAs in women are, in general, smaller at rupture, with smaller aneurysm necks and iliac diameters. Normalizing Dmax for BSA, however, levels the differences between the sexes. The analysis of small, ruptured AAAs compared to diameter, age and sex-matched asymptomatic AAAs suggests that PWRI may be a biomechanical variable that differs in the case of rupture.

- In Study II, which analyses CTAs of AAAs under surveillance, it appears that the diameter growth pattern of AAAs is continuous and confers well to a linear growth model, but the evolution of the different analysed indices, Dmax, aneurysm volume and biomechanical stress, do not necessarily follow each other. ILT grows faster than the lumen, but lumen volume growth is more closely related to increase in biomechanical stress.

- In Study III, the relation between biomechanical variables and time-to-rupture is investigated. In small and medium sized AAAs (< 70 mm), PWRI, but not PWS, is associated with time-to-rupture, also when adjusting for aneurysm size or sex. The results again show that women have a two-fold increased hazard ratio for AAA rupture, compared to men.

- In Study IV, lumen area is indicated as a potentially useful rupture risk marker. Ruptured AAAs, compared to diameter-matched asymptomatic AAAs, have a higher luminal area, and the luminal area is related to biomechanical stress, even when adjusting for aneurysm size, or ILT area.

Overall, the work in this thesis underlines areas of improvement in the current care of patients with AAAs, explores the 3D growth of AAAs, and strengthens the potential role for biomechanical analysis in the care of patients with AAAs.

7 Points of perspective

Despite several randomized trials that have investigated the best way to select patients for surgical treatment of their AAA, it is clear that the singular diameter-threshold criterion is not patient-specific. The usefulness of these today used thresholds may further be questioned by the reported inter-observer accuracy of maximum diameter measurements, and the potentially future changing epidemiology of AAA disease. Importantly, no medical treatment exists that can influence the outcome of patients with AAAs, despite many trials to this end. In this section some further points of perspective in the AAA field are discussed.

7.1 A new treatment policy

The decision to treat a patient for AAA is contingent on both the estimated rupture risk, and the risk associated with the treatment. The aspect of treatment risk is not investigated in this thesis but is an equally important contributor to the treatment policy of patients. The diameter-based policy, currently used in clinical practice, has several attractive properties. The maximum diameter is used to predict both the rupture-rate and the diameter-growth (i.e., the expected growth of the rupture risk) of AAAs. Thus, a single maximum diameter measurement informs the surveillance intervals and the intervention limit. An optimal policy for the selection of patients for surgical treatment cannot, however, conceivably rely on a singular diameter threshold, as this would represent a distinct discontinuity in the rupture risk around this threshold. Data that is observed in the current treatment paradigm, however, may show such influence due to selection bias that is introduced from treatment of certain patients [308].

The inclusion of novel markers for rupture risk requires new current treatment guidelines. Such guidelines should not be based solely on expert opinion and can instead be synthesized by a decision model [178]. That is, based on the time-change of the included parameters and their relation to rupture risk, and the risk associated with the surgery, an optimal time to intervene can be estimated. In order to construct a policy that includes biomechanical determinants, the rupture rate and the time-evolution of these biomechanical determinants must be known, and these parameters should be sought in larger prospective clinical trials.

It should be noted, that for a novel policy to be truly effective, at least in all patient populations, it may not be enough to predict rupture for patients with small AAAs, but

benefit may largely come from the postponement of treatment in patients with larger AAAs who have a minimal risk of rupture.

7.2 Outcome measures in pharmacological studies for AAA treatment

As previously discussed, studies of many pharmacological agents have failed to show any effect in the treatment for AAAs. The studies have investigated primarily the attenuation of AAA growth. The choice of endpoint has been largely unanimous, perhaps since it is a striking feature of AAA disease. It is however a surrogate endpoint in the sense that AAA growth is subordinate to rupture risk. Rupture risk can be considered a latent state, that is estimated by morphological and biomechanical markers (**Figure 7–1**). These markers may be considered as surrogate markers of the true underlying state, which cannot be observed. While, for instance Dmax is generally assumed to be progressive, this is not necessarily true of the underlying rupture risk, and it is unlikely that a singular marker can unequivocally define it.

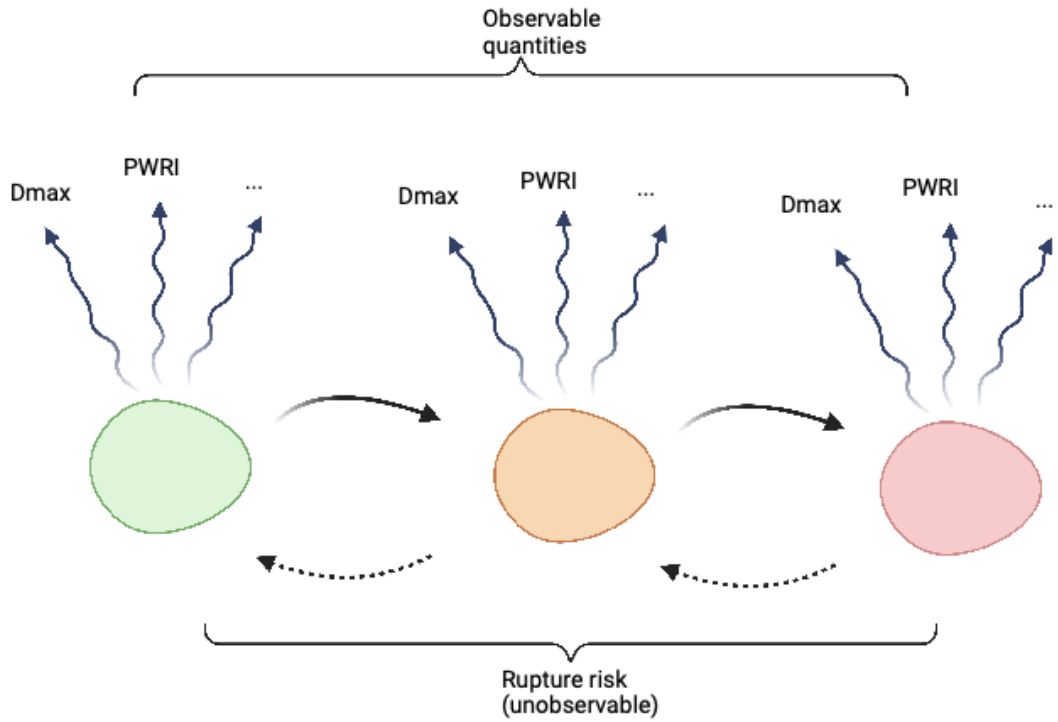

Figure 7–1. Model of AAA rupture risk as a latent process, and observable quantities at different states that represent surrogate markers.

Previously, for instance, high density lipoprotein was considered a surrogate marker for cardiovascular disease, but its pharmacological modulation did not affect cardiovascular outcomes, or showed instead increased mortality [309,310]. Anti-arrhythmogenic therapies, that decreased the number of arrhythmogenic events also paradoxically led to an increased mortality in the patients that were prescribed active therapy [311].

In the case of AAAs, growth inhibition has been the primary endpoint. Care must, however, be taken to evaluate the potential and implementation of therapies solely focusing on growth prevention. If the growth rate of AAAs is slowed, prior to an intervention limit, without affecting the rupture risk, a larger number of AAAs may rupture under surveillance instead of being surgically treated. Further, the postponement of therapy by a slower growth rate may for many lead to a delayed surgery, where operative risks associated with age and comorbidities may have increased. Abolition of the ILT of AAAs may contribute to slower growth, but as results in this thesis suggest, it may instead paradoxically increase rupture risk.

Table 7-1. Pharmacological AAA studies, and their outcome measures.

Study	Medication	Primary outcome	Measurement technique
AARDVARK (2016)	Perindopril	Aneurysm diameter growth rate over 2 years	Ultrasonography, outer-to-outer antero-posterior ultrasound measurements in the longitudinal plane
TEDY (2020)	Telmisartan	Difference in AAA diameter growth over 2 years	Ultrasonography, Maximum anterior-posterior outer-to-outer orthogonal AAA diameter
TicAAA (2020)	Ticagrelor	AAA volume measured with magnetic resonance imaging (8 mm slices).	Magnetic resonance imaging (8 mm slices), manual delineation in axial slices.
Propranolol (2002)	Propanolol	Diameter growth rate of the aneurysm	Ultrasonography, outer border of the anteroposterior diameter.
Azithro-mycin (2009)	Azithromycin	Diameter expansion rate of the AAA after 18 months	Ultrasonography, widest anterior-posterior diameter (measured in both axial and transverse angles).
NTA3CT (2020)	Doxycycline	Change in abdominal aortic aneurysm maximum transverse diameter	CT, Maximum transverse diameter was measured perpendicularly to the centre line
AORTA (2015)	Pemirolast	Change in aortic diameter	Ultrasonography, leading edge to leading edge, perpendicular to centreline antero-posterior.

Outcome measures from selected studies conducted in AAA growth are shown in **Table 7-1**. Most studies have used US, which has, as discussed in the background section, large reported interobserver variability, and surveillance curves with US do not always muster

confidence in the reliability of these measurements to detect small changes in AAA growth. One study used MRI, but with thick slices to survey AAAs, which may also limit exactness of measurements [121], but included a secondary endpoints of thrombus volume change [121]. Recently in the trial of telmisartan, a blood pressure medication, PWS and PWRI [312] have been evaluated in a post-hoc analysis. The treatment had a positive impact on these parameters, despite no effect on AAA growth. The effect in this study was mediated by change in blood pressure.

As the clinical care of patients with AAAs is based on maximal diameter measurements, this still stands as a reasonable primary endpoint. Care must, however, be taken to for appropriate and precise measures. To fully elucidate the effect of the treatment, the evaluation of morphological and biomechanical change in patients receiving the treatment may be helpful.

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