RUPTURED ABDOMINAL AORTIC AND ILIAC ARTERY ANEURYSMS

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine at the University of Helsinki, for public examination in lecture room 1, Meilahti Tower Hospital, Helsinki University Hospital, on 9 June 2017, at 12 noon.

Helsinki 2017
In vascular surgery no change for the better has occurred that wise and good men have not opposed

John J. Bergan (1927–2014)
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Ruptured Abdominal Aortic and Iliac Artery Aneurysms
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


The publications are referred to in the text by their roman numerals.
Ruptured Abdominal Aortic and Iliac Artery Aneurysms
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ACE</td>
<td>Anévrysme de l’aorte abdominale, Chirurgie versus Endoprothèse Trial</td>
</tr>
<tr>
<td>ADAM</td>
<td>Aneurysm Detection and Management Trial</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AJAX</td>
<td>Amsterdam Acute Aneurysm Trial</td>
</tr>
<tr>
<td>AP</td>
<td>anteroposterior</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities Study</td>
</tr>
<tr>
<td>ASI</td>
<td>aortic size index</td>
</tr>
<tr>
<td>bEVAR</td>
<td>branched endovascular aneurysm repair</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CAESAR</td>
<td>Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair Trial</td>
</tr>
<tr>
<td>CEA</td>
<td>cost-effectiveness analysis</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIAA</td>
<td>common iliac artery aneurysm</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>cerebrovascular disease</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DREAM</td>
<td>Dutch Randomized Endovascular Aneurysm Management Trial</td>
</tr>
<tr>
<td>ECAR</td>
<td>Endovasculaire ou Chirurgie dans les Anévrysmes aorto-iliaques Rompus Trial</td>
</tr>
<tr>
<td>ESVS</td>
<td>European Society for Vascular Surgery</td>
</tr>
<tr>
<td>EUROSTAR</td>
<td>European collaborators on stent graft techniques for aortic aneurysm repair</td>
</tr>
<tr>
<td>EVAR</td>
<td>endovascular aneurysm repair</td>
</tr>
<tr>
<td>fEVAR</td>
<td>fenestrated endovascular aneurysm repair</td>
</tr>
<tr>
<td>HAART</td>
<td>highly active anti-retroviral therapy</td>
</tr>
<tr>
<td>HILMO</td>
<td>Care Register for Health Care</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HUH</td>
<td>Helsinki University Hospital</td>
</tr>
<tr>
<td>HUS</td>
<td>Helsinki and Uusimaa hospital district</td>
</tr>
<tr>
<td>HUSVASC</td>
<td>HUS vascular registry</td>
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<tr>
<td>IAA</td>
<td>iliac artery aneurysm</td>
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<tr>
<td>IAAA</td>
<td>inflammatory abdominal aortic aneurysm</td>
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ABSTRACT

Aims: Aneurysms of the abdominal aorta (AAA) or the iliac arteries (IAA) are potentially lethal conditions that can be treated with surgical interventions. The emergence of endovascular repair methods in the preceding two decades has changed the way aneurysms are treated today. This shift towards endovascular treatment has resulted in lower immediate mortality from elective AAA surgery, but long-term results are less clear. Because of the high mortality from ruptured AAA (RAAA), screening programmes have been established in Sweden, the United Kingdom and the United States with promising results. In many studies, however, the prevalence of AAA has been shown to be on the decline, possibly undermining the benefit of screening. This study aimed to investigate the population-based mortality from RAAA and the treatment results in Finland. Another aim was to investigate how many of the ruptures could potentially have been prevented by a screening programme. In addition, our goal was to determine what the actual size of an AAA or IAA, specifically an internal iliac artery aneurysm (IIAA), is when it ruptures.

Methods: The study periods varied between sub-studies, ranging from 2000 up until 2014. Data on RAAA patients was obtained from the hospital registries of Helsinki University Hospital and Tampere University Hospital. The Care Register for Health Care of the Finnish Institute for Health and Welfare was used to obtain data regarding the AAA and RAAA treatment for the entire country. Cause-of-death data came from Statistics Finland. Data regarding ruptured IIAA was collected through the Vascunet collaboration from 28 hospitals in seven countries. All data were retrospectively analysed.

Results: The annual RAAA incidence in Finland was 9.5 per 100 000 inhabitants in 2000–2004 and fell to 6.8 per 100 000 in 2010–2014; a similar fall in the incidence was also seen in the HUS area. The results of surgery have improved for both elective and emergency operations. Population-based mortality has also decreased, although over half of the RAAA patients still die outside the hospital. The turn-down rate in Finland, and especially in HUS, is low compared to many international studies. Screening men for AAA at 65 years of age could theoretically prevent a maximum of 79% of AAA ruptures in men – who constitute over 75% of all RAAA patients. The average AAA size at the time of rupture was 77 mm in men and 71 mm in women. The corresponding IIAA size was 68 mm, with no significant sex-related difference.

Conclusions: The treatment of AAA in Finland has evolved in a positive direction. The same general trend of decreasing AAA prevalence seen in many
countries is likely to hold true for Finland as well. Using population-based mortality as an indicator of AAA mortality is important, as this also includes patients who do not reach the hospital in time to be operated on and patients who are turned down for emergency surgery for various reasons. These groups are missed when only operative mortality is examined. Most AAA ruptures occur at well over the 55-mm operative threshold diameter and over the age of 65 years. However, especially among smoking men, rupture at a younger age is not uncommon. IIAA rupture at under 4 cm is rare, and surveillance until this diameter is likely to be safe in most cases.
INTRODUCTION

Globally, there were approximately 168,000 deaths and an estimated 2.9 million years of life lost due to aortic aneurysms (including also aneurysms of the thoracic aorta) in 2015, according to data from the Global Burden of Disease 2015 study. This is 25% more deaths than in 2005, although the age-adjusted mortality rate (per 100,000 inhabitants) has fallen by 7% (Global Burden of Disease 2015 Mortality and Causes of Death Collaborators 2016).

Figure 1  Annual mortality per 100,000 inhabitants due to aortic aneurysms in men aged 50–69 years from 1990 to 2015 in different parts of the world. Data from Global Burden of Disease 2015, Global Health Data Exchange, Institute for Health Metrics and Evaluation. http://ghdx.healthdata.org. (Global Burden of Disease 2015 Mortality and Causes of Death Collaborators 2016).
The most common type of aortic aneurysm is an abdominal aortic aneurysm (AAA). It mostly affects elderly patients, with a clear male predominance. This differs from thoracic aortic aneurysms, which are less common but affect a younger population. The AAA prevalence has decreased in many parts of the world after having increased steadily since World War II. This reduction is mostly credited to the decreasing prevalence of smoking, which is the primary risk factor for AAA. An AAA is most often asymptomatic until the slowly enlarging aneurysm reaches a point where the pressure on the aortic wall exceeds its strength and the aneurysms ruptures. This is a medical emergency with mortality in excess of 80 percent. Immediate surgery is the only treatment for a ruptured aneurysm, although it carries a high perioperative mortality rate.

The insidious natural course of an AAA, often proceeding directly from asymptomatic and unknown to a lethal emergency, has motivated research to develop measures to prevent aneurysm rupture. No pharmacological treatments have been proven to be effective in reducing aneurysm growth or the risk of rupture. Surgical repair is the only therapeutic option to prevent rupture. Elective repair is associated with significantly smaller mortality, but it is not without its risks. Finding the right time for an intervention is paramount so that aneurysms at high risk can be prevented before catastrophic rupture, but patients with aneurysms that are likely to never put the patient at the risk of death are not subjected to unnecessary repair. Because of the tendency of aneurysms to slowly grow, with the risk of rupture incrementally increasing with increasing diameter, surveillance is usually warranted.

An AAA has been seen as ideal for a screening programme, as it can easily and reliably be found with a simple ultrasonographic (US) examination. Based on randomised controlled trials, AAA screening has been implemented in the United Kingdom, Sweden and, to some extent, in the United States. These programmes have been proven effective in reducing AAA-related mortality. Nevertheless, the decline seen in AAA prevalence has diluted the enthusiasm for establishing screening programmes in other countries, even though screening for AAA has consistently been shown to be cost-effective. The up-front costs of screening are, however, considerable, and the benefits come later.

The last couple of decades have seen a huge change in the way in which aneurysms are treated. Endovascular treatment of AAA was pioneered independently from each other by Nikolay Volodos in the Ukraine and Juan Parodi in Argentina. Since the first steps taken by them, endovascular aneurysm repair (EVAR) has become the first-line treatment of AAA in most centres, also in the treatment of ruptured AAA (REVAR). EVAR has evolved into a treatment method with which almost all aortic pathologies can be treated: thoracic aneurysms with TEVAR, and juxtarenal AAAs with branched or fenestrated EVAR (bEVAR and fEVAR). Open repair still has its place, however. Its long-term durability is yet to be matched by EVAR.
A manifestation of the same disease, but less common than AAA and occasionally accompanying it, is iliac artery aneurysm (IAA). Less research has gone into IAA although, in the case of rupture, they can be just as deadly as an AAA. IAAs are generally repaired after they reach a diameter of 30 mm and AAAs after 55 mm. The AAA threshold is based on level I evidence, but the IAA threshold is not.

This study focused on using primarily registry data to evaluate the epidemiology of RAAA and the results of its repair. Finland has long-standing traditions in keeping comprehensive national registries and making these available for researchers. In addition, it is easy to combine data from various registries using personal identity numbers, which are unique for every individual living permanently in Finland.
1 HISTORY OF ANEURYSM SURGERY

1.1 EARLY HISTORY

On Sunday, the 12th ult., Mr. James, one of the surgeons of this institution placed a ligature upon the aorta, in a case of aneurism of the external iliac artery. In one of the Exeter papers, it is stated that the operation was “successfully performed”; but it was that kind of success of which the Irishman boasted when he had killed his hog, for the patient survived the infliction of the knife only two or three hours. It is an appalling operation, and we hope not to hear of its repetition—at least in a case of aneurism of the external iliac artery.

The Lancet: Volume 12, Issue 310, Page 607 (8 August 1829)

The Book of Hearts of the Ebers Papyrus is the first in which aneurysms are described in writing: “If thou examinest a swelling of vessels in any limb of a man, and thou findest that it... grows under thy fingers, at every going... then thou shalt say concerning it: it is a swelling of a vessel... It is vessels that cause it and it arises through injury to a vessel.” This collection of ancient Egyptian medical knowledge dates from ca. 1500 BCE. Fire was stated as the only means of treating an aneurysm, although speaking of these swellings of the vessels, it is also stated that “thou shalt not put thy hand to such a thing” (Ghalioungui 1963). In India, Sushruta (800–600 BCE) described an aneurysm as Sira Granthi or tumour of the blood vessel in the medical text Sushruta Samhita (Verma et al. 2015).

The Greek surgeon Antyllus, who lived in Rome in the 2nd century CE, treated aneurysms with ligation of the arteries entering and leaving the sac and packed the aneurysm sac after opening it. He also described true and false aneurysms. No original writings of Antyllus have been preserved, but his methods were described by Oribasius who lived in the 4th century CE. These are the first recorded attempts to treat aneurysms (Osler 1915). The famous Greek physician Galen (129–216 CE) described aneurysms due to trauma. The treatment of aneurysms by proximal control and opening the sac and ligating the orifices of the entering arteries was also described by the Byzantine Greek physician Aëtius in the 5th century CE (Thompson 1998).
The first descriptions of abdominal and thoracic aortic aneurysm were given by Andreas Vesalius (1514–1564) (Osler 1905). His friend and colleague Ambroise Paré (1510–1590) described a rupture of a thoracic aortic aneurysm: “The aneurismaes which happen in the internall parts are uncurable” (Osler 1909). Paré also noted that syphilis can cause aneurysms through degeneration of the arterial wall (Osler and McCrae 1921). He mentioned that aneurysms can thrombose and also advised against incising inflamed pulsating masses as this can lead to an exsanguinating haemorrhage. He advocated the proximal ligation of aneurysms without opening the sac. Giovanni Battista Morgagni (1682–1771) observed that aneurysm can erode adjacent vertebral bodies (Osler 1905; Thompson 1998). The German surgeon Matthaeus Purmann (1648–1721) operated on an antecubital space aneurysm in 1680 by ligating the artery proximally and distally to the aneurysm. This type of false aneurysm was a common complication of bloodletting by the puncture of the median basilic vein. The Scottish surgeon John Hunter (1728–1793) studied the development of collateral circulation of occluded main arteries. On 12 December 1785 he ligated the superficial femoral artery of a patient with a popliteal aneurysm in the area known today as the Hunter’s canal. The patient and his limb survived, and the aneurysm shrank (Thompson 1998).

Aneurysms of the abdominal aorta were considered very rare. William Osler published the experience at Johns Hopkins Hospital from 1889 to 1904. During that time, there were only 17 cases. The reported incidence at Guy’s hospital in London in the mid-19th century was similar (Osler 1905).

Syphilis was suspected early on as the main culprit of aneurysms (Osler 1909), even though not everyone was convinced. Myers observed that aneurysms were more common in the army than in the navy. Because syphilis was common in both, he suspected that the real cause of the higher incidence in the former must be the mechanical obstruction caused by the tight collar of army uniforms (Myers 1869).

One hypothesis on the origins of syphilis states that the disease was brought to Europe by the crew of Christopher Columbus on their return from the New World in 1493 (Tampa et al. 2014). Arsenamine (Salvarsan or Compound 606), an arsenic compound that was introduced in 1910s, was the first effective treatment. It was supplanted by penicillin in the 1940s. This, along with the increased lifespan, had a significant effect on aortic aneurysms. For example, when Kampmeier published 73 aneurysm cases from the previous 30 years in 1936 in New Orleans, 57% of the patients had syphilis and only “very few” aneurysms were due to atherosclerosis (Kampmeier 1936). A decade later, 102 cases in the Mayo Clinic through to the end of 1947 were reviewed by Estes, and atherosclerotic aneurysms accounted for 96% of all aneurysms (Estes 1950). As atherosclerotic (or degenerative) aneurysms became the most common type, the patients in general also became older, as patients with syphilitic aneurysms tended to be relatively young.
In 1817, the English surgeon Sir Astley Cooper (1768–1841) ligated the aorta of a patient with a leaking iliac aneurysm. He performed the procedure through a small transperitoneal incision and ligated the aorta with a single ligature. The patient’s left leg became ischaemic, and he died 40 hours later (Cooper and Travers 1821). Cooper himself noted later in his lectures that “I know, for my own part, that I would not hesitate to have my own aorta tied, if it would save my life for only forty hours” (Cooper 1830; Thompson 1998).

In the following decades, attempts to ligate the aorta were made but all resulted in the death of the patient. The first successful case of aortic ligation was by American surgeon Rudolph Matas (1860–1957). He ligated the aorta for the treatment of an aneurysm on 9 April 1923 (Matas 1925). The patient developed “a leaking aneurysm of the abdominal aorta at the bifurcation; involving both common iliacs; with progressive retroperitoneal extravasation” as a sequela of syphilitic aortitis. The abdominal aorta was ligated immediately above the sac with two sterilized cotton tape ligatures. According to Matas, “the patient died with her aneurysm clinically cured” a year later due to tuberculosis. Based on a post-mortem examination, the success of this operation, as opposed to previous ligations of the aorta, was attributed to the fact that the cotton ligatures had loosened and allowed a small stream of blood to flow into the aneurysm, creating only a partial occlusion which led to gradual thrombosis of the aneurysm, allowing time for adequate collateral circulation to develop (Matas 1940).

Matas had described his technique of endoaneurysmorrhaphy in a paper entitled “An operation for the radical cure of aneurism based upon arteriorrhaphy” published in 1903, although he had not treated abdominal aortic aneurysms with the technique (Matas 1903). This technique consisted of opening the aneurysm sac after proximal control and removing the thrombus within, suturing the bleeding orifices, and infolding the walls of the sac with several rows of sutures to obliterate the aneurysm cavity. This basic principle, which is the same as was described by Antyllus, is still used in open aneurysm repair combined with the reconstruction of the aorta. As opposed to the complete excision of the aneurysm, it has the advantage of preserving the collateral circulation. In his original article, Matas also suggests that, in certain rare cases of fusiform aneurysms where the walls are not severely diseased, the sac could be folded in a manner that would preserve a lumen the diameter of the native artery (Matas 1903).

The techniques that were used for the treatment of aneurysms before synthetic grafts were varied. They included external compression by medical personnel for even days at a time, treating aneurysm walls with t alc to induce scarring, or wrapping the aneurysms with skin grafts or in cellophane (Fortner and Johansen 1984; Bergqvist 2008). The last-mentioned method was used by Rudolph Nissen to treat Albert Einstein’s abdominal aortic aneurysm in December 1948. Six years later, the aneurysm ruptured and Einstein refused surgical treatment. He died a few days after the rupture on 18 April 1955 (Cohen and Graver 1990).
William Stewart Halsted (1852–1922) tried using silver and aluminium bands to ligate the aorta, but this usually lead to an infection or to a fatal haemorrhage as the bands cut through the aortic wall (Friedman 2005). Alfred Velpeau inserted three pairs of sewing needles into the aorta in order to cause thrombosis in 1831 (Friedman 2005; Bergqvist 2008). Aneurysms were also treated by inserting silver, gold platinum, iron, steel or copper wires to cause thrombosis of the aneurysm. This was first done by Moore, a British surgeon, in 1864. Alfonso Corradi in 1879 applied electricity to the inserted wires (Osler and McCrae 1921). The results were not especially good. Blakemore in New York used progressive constriction of the aorta, with a rubber band wrapped with polythene film proximally to the aneurysm, followed by the insertion of long segments of silver wire into the aneurysm and directing 100 volts of direct current into the wires. This heated the wires to ca 80 degrees Celsius. The goal was to cause controlled, progressive clotting of the aneurysm (Blakemore 1953).

According to Elkin, 25 cases of aortic ligation were published as of 1940, and in only 5 cases the operation was a success (Elkin 1940). In his review published the same year, Bigger concludes as follows: “Up to the present time, all forms of therapy have yielded poor results. Strictly conservative treatment offers little, and wiring, either with or without electrolysis, is at best only palliative. Judging from the literature, only a small number of surgeons have felt that direct surgical attack upon aneurysms of the abdominal aorta was justifiable, and it must be admitted that results obtained by surgical intervention have been discouraging.” (Bigger 1940)

1.2 MODERN TIMES

_The development of safe and controllable anaesthesia as well as the appreciation and understanding of aseptic principles helped transform surgery from an emergency high-risk operation to a more controlled elective procedure, thus also making aortic surgery possible on a whole new level._

On 19 October 1944, Crafoord and Nylin in Sweden performed the first successful end-to-end anastomosis of the thoracic aorta after the resection of an aortic coarctation (Friedman 2005). Freeman reported that, on the 12th of February 1951, his team had repaired an infrarenal aneurysm using the patient’s own iliac vein as a graft. However, this patient died suddenly 6 hours after the operation. After modification of the technique, they used it successfully on subsequent patients (Freeman and Leeds 1951). The first successful resection and reconstruction of an abdominal aortic aneurysm with

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I want to go when I want. It is tasteless to prolong life artificially. I have done my share. It is time to go. I will do it elegantly.

*Albert Einstein (1879–1955) when he was offered repair for a ruptured AAA by Frank Glenn in 1955*
a homograft was performed by Charles Dubost in Paris on 29 March 1951 (Dubost 1954). The graft he used was a thoracic aorta taken from a 20-year old woman 3 weeks previously. It was not long before many reports of successful homograft reconstructions started appearing from several surgical teams.

Dubost’s technique included the resection of the entire aneurysm sac, which could be challenging. In 1966, Oscar Creech combined Matas’ endoaneurysmorrhaphy technique with graft reconstruction without the resection of the aneurysm sac and thus considerably simplified the procedure (Creech 1966). The first successful repair of a ruptured abdominal aortic aneurysm, on 13 March 1953, is credited to Henry Bahnson (Bahnson 1954). Availability was a problem with aortic homografts, and fresh homografts were also prone to degeneration over time and required ABO compatibility. Homograft cryopreservation methods were developed, which led to increased durability and a better storage and availability of grafts (DeBakey and Cooley 1954).

In 1952, Voorhes, Jaretski and Blakemore reported using a tube of Vinyon-N (polyvinyl chloride) cloth, which was used in parachutes, as an artificial substitute of a dog’s aorta and later used the same technique on patients (Voorhees et al. 1952; Blakemore and Voorhees 1954). However, the Vinyon-N did not prove to be a satisfactory material in the long term. Many different materials were also experimented on, including ivory, glass, paraffinned aluminium or silver, gold-plated aluminium and silk (Blakemore and Voorhees 1954; Friedman 2005). Nylon prostheses were attempted but did not prove successful. Teflon (polytetrafluoroethylene, PTFE) and Dacron (polyethylene terephthalate, polyester, PET), developed in the period around World War II, fared better. Michael DeBakey collaborated with textile engineer Thomas Edman to build a knitting machine to make seamless Dacron crafts. Dacron, a DuPont trademark for PET, was synthesised in 1941. The graft was introduced in 1957, and an improved version is still in use. Early knitted grafts were prone to dilatation over time but were still superior to previous synthetic grafts. Szilagyi developed a vascular graft made of elasticised woven Dacron. PTFE was synthesised in 1938 and trademarked as Teflon by DuPont. The grafts in use today are made of expanded PTFE (ePTFE). Their clinical use was first reported in 1976 (Campbell et al. 1976).

As surgeons’ experience with aneurysms increased, more challenging operations, such as thoracoabdominal aneurysm repair became possible. In 1955, Etheredge repaired one by using a temporary shunt from the distal thoracic aorta to the distal abdominal aorta. A homograft was used, and visceral vessels were implanted into it. DeBakey described a similar technique the following year. In 1974, Stanley Crawford reported his experience of repair with a Dacron graft with side-arms used for implanting the visceral vessels (Thompson 1998).
1.3 THE ENDOVASCULAR ERA

There are three stages in the history of every medical discovery. When it is first announced, people say that it is not true. Then, a little later, when its truth has been borne in on them, so that it can no longer be denied, they say it is not important. After that, if its importance becomes sufficiently obvious, they say that anyhow it is not new.

Sir James Mackenzie, 1853 – 1925

The diagnostics and treatment of vascular diseases was revolutionised by arteriography and the development of percutaneous intraluminal procedures. X-rays were discovered by Wilhelm Konrad Röntgen on 8 November 1895. The first arteriograms of a living human were performed by Barney Brooks in 1924 using sodium iodine. In 1929, Reynaldo dos Santos performed the first abdominal aortogram, and in 1963, radiologist Charles T. Dotter (1920 – 1985) inadvertently recanalized an occluded right iliac artery by passing a catheter through the occlusion to perform an abdominal aortogram (Friedman 2005). On 16 January 1964, Dotter and Melvin Judkins performed the first intentional transluminal dilation of a local stenosis of the superficial femoral artery. The first balloon angioplasty was performed by Andreas Grüntzig on 12 February 1974 (Mueller and Sanborn 1995). The development of stents then followed in the 1980s.

Juan Parodi, an Argentinian surgeon, collaborated with radiologist Julio Palmaz, the inventor of the Palmaz stent, in developing the concept of endovascular aneurysm repair. On 7 September 1990, a 70-year-old patient with a 6-cm abdominal aortic aneurysm, deemed unfit for open surgery, became the first patient treated with Parodi’s endovascular aneurysm repair method at the Instituto Cardiovascular de Buenos Aires (Parodi et al. 1991). The procedure was performed under local anaesthesia by Parodi and Palmaz. The stent graft used by Parodi was a knitted Dacron graft that was sutured on to a balloon-expandable stent. The patient lived nine years after the operation, and his cause of death was pancreatic cancer (Yao and Eskandari 2012).

Other research groups were developing similar minimally invasive approaches at the same time as Parodi. Nikolay Volodos of the Kharkov Research Institute of General and Urgent Surgery in Kharkov, Ukraine, created a self-expanding Z stent. The device was patented in the Soviet Union on 22 May 1984. It was first used for treating iliac artery stenosis on 4 May 1985, which marked the first time endovascular stent graft surgery was performed. In March 1987, Volodos implanted a stent graft for the treatment of a traumatic pseudoaneurysm of the descending aorta. In 1989, he attempted to use a stent graft for the repair of an abdominal aortic aneurysm, but because of twisting of the contralateral limb, the procedure had to be converted to an open one. On 12 May 1993, Volodos successfully repaired an abdominal aortic

The first endovascular aneurysm repair (EVAR) in Western Europe was done by Parodi in Nancy, France, in October 1992, and in November 1992 Parodi performed the first EVAR in the United States in New York (Veith et al. 2014). On 21 April 1994, the first ruptured abdominal aortic aneurysm was treated with a stent graft at the Montefiore Medical Center in New York (Marin et al. 1995; Veith et al. 2009). The first published report of emergency repair, however, is of a patient treated in Nottingham in the United Kingdom on 29 October 1994 (Yusuf et al. 1994).

The first stent grafts were surgeon-made with a Dacron or PTFE graft sutured onto a stent. Some early stent grafts only had a proximal stent and others a stent in the proximal and the distal end of the graft. This meant that a distal endoleak was a common occurrence, and many patients required a second operation in which an aorto-uni-iliac device was placed and the contralateral common iliac was occluded, first by a detachable balloon and later by a covered stent. A femoro-femoral bypass was then carried out. In some cases, instead of a stent, the distal end of the graft was fixated with sutures placed through an arteriotomy at the distal site (Parodi 1996; Veith et al. 2014). Finland’s first EVAR took place on 7 November 1996 at the Surgical Hospital in Helsinki (Aho et al. 2002), the same hospital in which open aneurysm surgery in Finland began almost 40 years previously (Tala 1961).

Commercial versions of stent grafts soon followed the surgeon-made ones. The first one-piece stent graft evolved into modular systems starting with bifurcated devices. On 31 May 1994, the first modular bifurcated stent graft was successfully implanted by Claude Mialhe et al. at Clinique Notre Dame in Draguignan, France (Mialhe et al. 1997). Later, fenestrated and branched devices used for juxta- and suprarenal aneurysms were developed (Park et al. 1996; Browne et al. 1999). The long-term results of the first generation of stent grafts were generally poor (Leurs et al. 2007; Mestres et al. 2010). The technology, however, has evolved and endovascular treatment has become the first-line treatment for AAA in most large centres (Beck et al. 2016). With modern stent grafts, practically every part of the aorta can be treated endovascularly, although some doubt still remains on the durability of these repairs. The treatment of visceral and peripheral aneurysms by endovascular means is also commonplace. At the beginning of the EVAR era, inguinal incisions were made and femoral arteries exposed, but modern EVAR procedures are primarily done percutaneously.

The treatment of aneurysms and the results of treatment were virtually unchanged from ancient Egyptian times until the 1950s when aortic reconstruction could finally be performed. Since then, advancements in surgical techniques, anaesthesia and imaging have reduced the associated morbidity and mortality. The advancements made in endovascular aneurysm repair during the previous three decades have considerably effected how modern aneurysm treatment is performed.
2 ABDOMINAL AORTIC ANEURYSM

2.1 DEFINITION

ANEURYSM (or less commonly aneurism): an abnormal blood-filled bulge of a blood vessel and especially an artery resulting from weakening (as from disease) of the vessel wall

Origin and etymology: Greek aneurysma, from aneurynein to dilate, from ana- + eurynein to stretch, from euryys wide

Merriam-Webster Dictionary

2.1.1 DIAMETER

The Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery defined aneurysm as a focal dilatation of over 50% in diameter compared to the normal diameter of the corresponding artery based on measurements on healthy individuals (Johnston et al. 1991). The values of normal vessel diameters published in the paper, which are derived from several other studies, are shown in Table 1 as well as corresponding threshold values for aneurysmatic dilatation.

Other definitions for aneurysm are an increase in diameter of over 2 standard deviations compared to normal values or a 50% increase compared to the adjacent healthy artery. The former was used in a Swedish study on a 70-year-old population where the normal diameters of different segments of the aorta were defined based on MRI imaging (Wanhainen et al. 2008). These normal values and threshold diameters for aneurysmatic dilatation are shown in Table 1. The definition of a ratio of the suprarenal to infrarenal aortic diameter of over 1.2 is also sometimes used. Normal diameters have not been defined for all arteries, nor are separate values always available for men and women. The normal diameter of the aorta also increases throughout the life of the patient (Dixon et al. 1984; Evans et al. 1992). In general, aneurysm is a focal dilatation of over 50%; a dilatation of under 50% but over normal diameter is called ectasia. Continuous dilatation of over 50% in multiple segments of the arteries is called arteriomegaly (Johnston et al. 1991).

There is no standardised method of defining the maximal diameter of the aorta. It is affected by the plane in which it is measured, the axis used, and from where to where the diameter is measured. The plane used should usually be perpendicular to the centreline of the aorta. The commonly used axes are anteroposterior (AP) or transverse (left-right), but others are used as well. The diameter can be measured from the adventitial layer to the opposite adventitial layer (outer to outer), from the intimal layer to the opposite intimal layer (inner to inner), or from the adventitial layer to the opposite intimal layer.
(leading edge to leading edge or outer to inner). All these methods produce different results, which makes comparisons between studies unreliable (Long et al. 2012). The imaging modality (US, CT, MRI) also affects the results. US is especially prone to inter-observer and even intra-observer error, as it is highly dependent on the experience of the person performing the examination. The acceptable variation between US studies in screening programmes in England and the United States is 5 mm (Beales et al. 2011).

2.1.2 TRUE AND FALSE ANEURYSM
Aneurysms can be classified as true or false aneurysms (pseudoaneurysms) (Cronenwett and Johnston 2014). A true aneurysm is an actual dilatation of the vessel and contains all layers of the vessel wall. A false aneurysm results from a disruption of the vessel wall and a contained haematoma, the wall of which is formed by connective tissue in reaction to the haematoma. False aneurysms are often the result of trauma, in many cases iatrogenic trauma due to arterial puncture. False aneurysms may also form in surgical anastomoses.

Aneurysms can also be classified according to their shape as fusiform or saccular (Cronenwett and Johnston 2014). Saccular aneurysms can be further divided into concentric and eccentric saccular aneurysms. Most degenerative aneurysms are fusiform or concentric saccular. Eccentric saccular aneurysms are often infectious or traumatic in origin. It is also the typical shape of cerebral and intracranial aneurysms. Penetrating aortic ulcers and intramural haematomas caused by a tear in the intima of the vessel, but no further dissection of the vessel wall, may develop into eccentric saccular aneurysms. The rupture risk is not as well-characterised for eccentric saccular as for fusiform or concentric saccular aneurysms.

Aneurysms can be classified according to aetiology. The most common type is a degenerative, or atherosclerotic, aneurysm. Aneurysms arising because of genetic causes can be classified separately, and aneurysms caused by infection are their own group, often called mycotic aneurysms, as are inflammatory aneurysms.

2.1.3 DEGENERATIVE ANEURYSM
Degenerative or atherosclerotic aneurysms are the most common type. Although atherosclerosis and aneurysms are often found in the same patients, the term atherosclerotic aneurysm is somewhat misleading, as according to present knowledge, atherosclerosis is likely not the cause of these aneurysms. The major predisposing factors for AAA are largely same as those for atherosclerosis, but the genes predisposing to atherosclerosis have not been shown to cause AAA formation (Saratzis and Bown 2014). Recently, aneurysm
### Table 1: Diameters of normal arteries and aneurysm thresholds based on two definitions

<table>
<thead>
<tr>
<th>Artery</th>
<th>Mean diameter</th>
<th>SD</th>
<th>Mean aneurysm threshold</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnstone KW et al.</td>
<td>3.3-3.9</td>
<td>0.4</td>
<td>4.0</td>
<td>0.4</td>
</tr>
<tr>
<td>J Vasc Surg 1991-92</td>
<td>2.9-3.0</td>
<td>0.3</td>
<td>3.6-4.5</td>
<td>0.3</td>
</tr>
<tr>
<td>J Vasc Surg 2008-12</td>
<td>2.4-2.7</td>
<td>0.2-0.4</td>
<td>3.6-4.0</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnstone KW et al.</td>
<td>3.3-3.7</td>
<td>0.4</td>
<td>4.2</td>
<td>0.4</td>
</tr>
<tr>
<td>J Vasc Surg 2008-12</td>
<td>2.9-3.0</td>
<td>0.3</td>
<td>3.4-4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>J Vasc Surg 2008-12</td>
<td>2.4-2.7</td>
<td>0.2-0.4</td>
<td>3.4-4.0</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>

**Thoracic aorta**
- Root: 3.5 (0.0)
- Ascending: 3.6 (0.0)
- Descending: 3.5 (0.0)
- Diaphragmatic: 2.3 (0.1)
- Thoracoabdominal: 2.5 (0.8)
- Abdominal aorta: 2.5 (0.8)
- Suprarenal: 2.5 (0.8)
- Infrarenal: 2.5 (0.8)
- Bilateral: 2.5 (0.8)

**Abdominal aorta**
- Celiac: 0.5 (0.0)
- Sup. mesenteric: 0.6 (0.0)
- Common iliac: 1.0 (0.0)
- Internal: 0.5 (0.0)
- Femoral: 0.8 (0.0)
- Common femoral: 0.8 (0.0)
- Posterior tibial: 0.9 (0.0)
- Popliteal: 0.9 (0.0)
- Common carotid: 0.8 (0.0)
- Common carotid: 0.8 (0.0)
- Carotid: 0.8 (0.0)
- Brachial: 0.8 (0.0)
formation as well as atherosclerosis have been begun to be regarded as not just degenerative but an active disease process with inflammation and immunity contributing to it (Libby and Hansson 2015). The pathophysiology of degenerative AAA is discussed in section 2.2.

2.1.4 GENETIC ANEURYSM

Inherited connective tissue diseases, such as Ehlers-Danlos, Marfan, and Loeys-Dietz syndromes, can be a cause of aneurysms. Most often, these types of aneurysms involve the thoracic aorta or are the sequelae of dissection. Sometimes they can, however, be found primarily in the abdominal aorta.

2.1.4.1 Ehlers-Danlos syndrome

Ehlers-Danlos syndrome has several subtypes which have varied clinical presentations and genetic backgrounds. The common link between the subtypes is the alteration of the fibrillary collagen metabolism. The prevalence of Ehlers-Danlos syndrome is estimated to be 1 per 5,000–250,000 births. Characteristic findings include alterations in the skin, ligaments and joints, blood vessels, and organs. Type 4, which has autosomal dominant inheritance, is called vascular Ehlers-Danlos syndrome and contributes to approximately 5% of all cases. The prognosis is the worst of all the Ehlers-Danlos subtypes, the median life-expectancy being 40–50 years. It is caused by deficiency of type III collagen as a result of mutations in the COL3A1 gene. Patients have cutaneous, skeletal and vascular abnormalities. Contrary to the classical manifestation of Ehlers-Danlos syndrome, skin hyperextensibility is not present, but the skin is often transparent and the underlying veins prominent. Easy bruising and rupture of middle-sized arteries as well as of the bowel or the uterus have been described. Obstetric and gynaecologic complications such as premature rupture of membranes, and surgical complications including wound dehiscence and hernia development are typical. Maternal death rates are in excess of 10%. Other Ehlers-Danlos types can also have arterial involvement, but this is less common. There is some evidence of the β-blocker celiprolol being protective against arterial rupture in Ehlers-Danlos patients (Eagleton 2016).

Surgery on Ehlers-Danlos patients is risky because of tissue fragility. A review of all the reported vascular Ehlers-Danlos syndrome cases through to 2010 found 231 patients. Almost half of the patients had an arterial aneurysm, or, in many cases, multiple aneurysms, and one in three presented with a spontaneous rupture of a nonaneurysmatic artery. Of the patients reported after 1996, 44 underwent open surgical procedures, with operative mortality of 30%. Endovascular procedures were performed on 33 patients, with a mortality of 24%. The cause of death in open surgical procedures was most
often intraoperative or postoperative bleeding, while bleeding complications were less frequent after endovascular procedures (Bergqvist et al. 2013).

### 2.1.4.2 Marfan syndrome

Marfan syndrome, an autosomal dominant disease described by French paediatrician Antoine-Bernard Marfan in 1896, has an incidence of approximately 1 per 5000. The syndrome has several phenotypes and is associated with mitral valve disease, thoracic aortic aneurysms (TAA) and dissection, but also with ocular, skeletal and pulmonary manifestations. The cardiovascular manifestations are the primary cause of mortality and morbidity, however. Over 1500 mutations in the FBN1 gene are known to cause the disease. FBN1 encodes fibrillin-1, which is a component of the extracellular matrix and aortic wall. Mutations in FBN1 may affect the extracellular matrix directly or have an effect on the transforming growth factor β (TGFβ) signalling pathways (Saratzis and Bown 2014).

Marfan patients should be under surveillance for aortic root enlargement, and aortic root replacement should be performed when the threshold diameter is reached. After root replacement, roughly 10% of Marfan patients develop a descending aortic dissection. Repair of the descending thoracic aorta is required usually only as a complication of dissection. In 50 patients with Marfan syndrome undergoing thoracoabdominal aortic repair, 82% had a prior dissection (Coselli and LeMaire 1997). AAAs have only been reported in isolated cases in Marfan patients. Of 298 aortic operations for patients with confirmed or suspected Marfan syndrome, only 3 were due to an AAA not caused by dissection (LeMaire et al. 2006). Hagerty et al. published a series of 12 Marfan patients with true AAA. Their literature search revealed only 13 previously reported patients with Marfan syndrome and AAA from 1976 to 2009. The average age of these 13 patients was 37 years (range 16–73), and the average age of their own 12 patients was 44 years (range 18–63). All of the patients also had an aortic root dilation, and all but one had undergone root replacement. Thoracic dissection and branch vessel aneurysms (otherwise uncommon in Marfan syndrome) were also common in these patients. Of the 12 patients, the aneurysm was suprarenal in 5, juxtarenal in 2 and infrarenal in 5 (Hagerty et al. 2017).

Currently, the diagnosis of Marfan syndrome is established by the revised Ghent nosology (Loeys et al. 2010). Some patients that do not fulfil all the required criteria for Marfan syndrome are classified as having MASS (mitral valve prolapse, aortic enlargement, skin and skeletal findings) syndrome, which is characterised by myopia, mitral valve prolapse, mild and nonprogressive aortic dilatation, and nonspecific skin and skeletal marfanoid features (Verstraeten et al. 2016).
2.1.4.3 Loeys-Dietz syndrome

Loeys-Dietz syndrome is a rare autosomal dominant syndrome associated with a mutation in the transforming growth factor β receptor 1 (TGFBR1) or 2 (TGFBR2) genes. Characteristic findings, in addition to aneurysms, include arterial tortuosity, craniofacial involvement such as cleft palate, craniosynostosis or hypertelorism. Aneurysms are most commonly located in the aortic root, but patients may also have thoracic and abdominal aortic dissections. Intracerebral bleeding has also been reported as a common cause of death in Loeys-Dietz patients. The patient phenotypes, however, vary significantly, ranging from mild to severe. In addition to mutations in transforming growth factor β receptors, mutations in genes SMAD3, TGFB2 and TGFB3 have been reported to cause similar disease phenotypes. SMAD3 was primarily classified as aneurysmal osteoarthritis syndrome, although not all patients show osteoarthritis (Morisaki and Morisaki 2016). These can, however, be classified as subtypes of Loeys-Dietz syndrome, with TGFBR1 and TGFBR2 being subtypes 1 and 2, respectively, SMAD3 being subtype 3, and TGFB2 and TGFB3 being subtypes 4 and 5, respectively. SMAD2 mutations have also recently been identified in syndromic aneurysm patients (Verstraeten et al. 2016).

2.1.4.4 Other genetic aneurysms

Aortic aneurysms are also associated with Shprintzen-Goldberg syndrome, which also causes craniosynostosis, skeletal muscle hypotonia, skeletal changes and learning difficulties. The vascular pathology in Shprintzen-Goldberg syndrome is mostly mild, however, and aneurysms and dissections are only found in the aortic root. The disease is caused by mutations in the SKI proto-oncogene gene (Verstraeten et al. 2016).

In addition to syndromic TAA, there are non-syndromic presentations, such as bicuspid aortic valve and TAA and isolated familial TAA (Davis et al. 2014). There are other rare syndromes with high risks of aneurysms formation, such as arterial tortuosity syndrome, which is caused by a mutation in the gene SLC2A10 encoding Glucose Transporter 10, and Menkes disease caused by mutations in gene ATP7A (Morris 2015). Aortic aneurysms and dissection are also more common in patients with autosomal dominant polycystic kidney disease (Morisaki and Morisaki 2016).

2.1.5 INFLAMMATORY ANEURYSM

Inflammatory aneurysms are aneurysms with a strong inflammatory component and a fibrotic reaction around the aneurysm. Inflammation can cause the obstruction of adjacent structures such as the ureters. Inflammatory aneurysms are most commonly located in the infrarenal aorta. According to the consensus statement on surgical pathology of the aorta from the Society
for Cardiovascular Pathology and the Association for European Cardiovascular Pathology, aortic inflammatory diseases can be divided into three categories: (1) atherosclerosis, (2) atherosclerosis with excessive inflammation and (3) aortitis/periaortitis (Stone et al. 2015). In this classification, a typical inflammatory aortic aneurysm is classified as class 2 and the term inflammatory atherosclerotic aneurysm is suggested. Class 3 is reserved for an inflammatory reaction not explained by atherosclerosis, such as those caused by large vessel vasculitides. Periaortitis refers to inflammation restricted to the adventitial layer, and if the inflammation involves the medial and intimal layers, the term aortitis should be used. This category is also divided into infectious and non-infectious (rheumatoid) causes. The typical non-infectious causes of aortitis are large vessel vasculitides – giant cell arteritis and Takayasu arteritis (Ladich et al. 2016).

2.1.5.1 Inflammatory aortic aneurysm

An inflammatory aortic (atherosclerotic) aneurysm (IAAA) is considered a subtype of AAA that comprises 3%–10% of AAA. It is characterised by a diffuse thickening of the aneurysmal wall and extensive fibrous adhesions to adjacent structures. The term inflammatory aneurysm was first used by Walker et al. (Walker et al. 1972). Compared to non-inflammatory AAA, it is associated even more strongly with smoking, the age at presentation is younger (62–68 years), and a family history of aneurysms is more common. There is some evidence that the prevalence is especially high in the northern European population. An IAAA is almost always symptomatic – typically, patients present with back or flank pain, low-grade fever or weight loss. The erythrocyte sedimentation rate is elevated in 40%–88% of IAAA patients. It has been speculated that the rupture risk of an IAAA may be lower than of a non-inflammatory AAA (Tang et al. 2005; Ketha et al. 2014).

IAAA can be grouped together with idiopathic retroperitoneal fibrosis and perianeurysmal retroperitoneal fibrosis into “chronic periaortitis”. Histologically, it lacks the typical medial changes of large vessel vasculitides. The pathogenesis of IAAA is unclear; it has been proposed that inflammation is the cause of aneurysm formation, or that the inflammatory changes develop after the formation of the aneurysm. Inflammation plays a role in all aneurysm formation, and inflammatory cell infiltrates can be demonstrated in all AAAs. IAAA may be one end of a continuous spectrum of AAA disease with varying levels of inflammation rather than a separate disease. Infections by chlamydia pneumoniae, herpes simplex virus or cytomegalovirus have also been proposed as a causative agent in IAAA – and also in AAA development in general. A systemic autoimmune disease has also been proposed as being a culprit for IAAA development, and an association with an increased risk of autoimmune disease has been demonstrated in IAAA patients (Haug et al. 2003).
The indications for surgical treatment are similar to non-inflammatory AAA. Anti-inflammatory therapies have been recommended, mainly with corticosteroids but also with other immunosuppressive drugs such as methotrexate, cyclophosphamide and azathioprine. No guidelines for medical therapy for IAAA exist, however. Steroid therapy may be effective preoperatively to reduce the inflammation and facilitate surgery, but there is also concern that it may weaken the aneurysm wall and increase the risk of rupture. Steroids may also be used if there is a progression of the inflammation or a relapse after surgery. Surgical repair, in many cases, can lead to the resolution of inflammatory changes, but complete regression is seen in only 23\%-53\% of cases. Progression, however, is rare after open surgery. With endovascular treatment, the inflammatory process usually persists, but rarely does it progress significantly. Open surgery can be more challenging than in a normal AAA due to adhesions that frequently involve the duodenum, vena cava, ureters and the left renal vein. The difference in operative mortality between inflammatory and non-inflammatory aneurysms in current practice is small, however, and the long-term mortality is similar (Tang et al. 2005; Ketha et al. 2014).

2.1.5.2 Vasculitides

The main subclasses of large vessel vasculitides are giant cell arteritis and Takayasu arteritis. Giant cell arteritis does not affect patients under 50 years old, whereas Takayasu arteritis is rarely found in patients over 40 years of age. The differentiation between giant cell arteritis and Takayasu arteritis is not possible histologically, and age at presentation is thus the major distinguishing factor between these two vasculitides. It has been postulated that they represent different phenotypes of the same disease. Especially large cell vasculitis may be under-recognised, as it is not uncommon and may not be easily suspected based on clinical manifestation (Chatterjee et al. 2014a).

Giant cell arteritis is a granulomatous inflammatory disease of large- and medium-sized arteries and the most common type of systemic vasculitis in adults in the Western countries. The overall prevalence is approximately 1 in 500 individuals. The mean age of onset is 72 years. The condition most typically involves the medium-sized cranial branches of the arteries originating from the aortic arch. Vision loss can result as a consequence of cranial arteritis. Involvement of the great vessels is rarer, and in these cases, the temporal arteries are often unaffected. Upper extremity claudication can develop due to the involvement of the subclavian and axillary arteries.

The involvement of large vessels in giant cell arteritis may be under-recognised – it tends to occur in roughly one in three patients. It can cause stenoses and occlusions of the subclavian and axillary arteries, carotid and vertebrobasilar arteries, as well as the iliac arteries and their branches. It can also manifest as aortitis leading to aneurysm formation and dissection in the thoracic and, less commonly, the abdominal aorta. The large-vessel giant cell
arteritis presents on average 6 years earlier than cranial disease, and only some 40% of these patients have cranial symptoms, with vision loss being especially uncommon. Aneurysm development, however, tends to be a late complication, occurring 3–5 years after diagnosis, or even later. The symptoms at this point are usually in remission, and the inflammatory markers are normal. This suggests that follow-up of giant cell arteritis patients would be beneficial so that aneurysms are discovered in time. If inflammatory markers are elevated and an enlarging aneurysm is found, glucocorticoid treatment is indicated or, if the patient is already on glucocorticoids, the dose should be increased (Chatterjee et al. 2014a; Ladich et al. 2016).

Giant cell arteritis patients have a 17-fold higher risk of developing a TAA and 2.5-fold higher risk of developing an AAA than the general population. Approximately 12% of the patients developed an aneurysm during a 10-year follow-up. The indications for aneurysm repair are similar to normal aneurysms, although the exact diameter thresholds for these types of inflammatory aneurysms are unknown. In general, the results of surgery in giant cell arteritis patients are less favourable if the disease is active perioperatively (Chatterjee et al. 2014a; Ladich et al. 2016).

Takayasu arteritis is a chronic idiopathic granulomatous large vessel vasculitis. The age of onset is usually 10 to 40 years, and 80%–90% of the patients are women. It is rare in European and North American populations, with an annual incidence of approximately 1–3 per one million inhabitants. The disease is more common in Japan, Southeast Asia, India and Mexico. The incidence in Japan is approximately 150 new cases per year. The condition affects the aorta and its first order branches. It often presents as an occlusive disease of the aorta and large vessels, including the renal arteries. The disease expression is varied, but it most commonly starts from the left subclavian artery and subsequently spreads to the left common carotid artery, the left vertebral artery, as well as the brachiocephalic, right subclavian, right vertebral and right common carotid arteries. The thoracic aorta is commonly affected, and the abdominal aorta and pulmonary arteries are involved in roughly 50% of patients. Involvement of the abdominal aorta and renal arteries is more common in Indian patients (Chatterjee et al. 2014b; Ladich et al. 2016).

The disease can cause varying symptoms resulting from systemic inflammation and vessel involvement, but it can often also progress asymptptomatically. Takayasu arteritis results in circumferential thickening of the vessel and reactive hyperplasia of the intima, which also predisposes patients to secondary atherosclerosis. The proximal aorta may become dilated due to inflammatory injury, but it is generally thought that the severe adventitial thickening seen in Takayasu arteritis prevents aneurysmal dilatation. Hypertension is a common complication of Takayasu arteritis due to renal artery involvement or stiffening of the aorta. As with giant cell arteritis, surgical repair is better performed when the disease is in remission (Chatterjee et al. 2014b; Ladich et al. 2016). There are reports of abdominal
aortic aneurysms due to Takayasu arteritis, but aneurysms are less common than occlusive lesions (Kallappa Parameshvarappa et al. 2013).

Behçet’s disease is an inflammatory disease of unknown aetiology. It was first described by Turkish dermatologist Hulusi Behçet in 1937 as a disease with recurrent oral ulcers, genital ulcers and uveitis. Later, it has also been found to have vascular, articular, gastrointestinal, neurologic, urogenital, pulmonary and cardiac involvement. Arterial involvement is seen in less than 5% of cases. The disease often presents in the third or fourth decade of life. It is prevalent in the area from Japan to the Middle East and the Mediterranean countries, but is rarely seen in the Western countries. The highest prevalence has been reported in Turkey, 1 per 250 in the population over 12 years of age. In the United Kingdom, the prevalence is only 0.64 per 100 000. It is equally prevalent in both sexes, but men usually have a more severe form of the disease, which includes vascular involvement. The diagnosis is mainly clinical. The disease is characterised by frequent exacerbations and remissions and usually becomes milder after 5–10 years. Behçet’s disease is unique among vasculitides, because it more often involves the venous than the arterial side of the vasculature and venous thrombosis is typical for the disease. Pulmonary artery involvement is also typical. Arterial involvement is most commonly located in the abdominal aorta but can also affect the carotid, iliac and femoropopliteal arteries. Aneurysms are more common in Behçet’s disease than occlusions with dense fibrotic and lymphatic tissue usually surrounding the aneurysms. Saccular pseudoaneurysms are characteristic findings. Surgical repair is complicated by the high rate of relapse in the perianastomotic site or previously uninvolved sites. This can be reduced by perioperative immunosuppressive therapy (Alpsoy 2016; Seyahi 2016).

There are other non-infectious inflammatory causes that can involve the aorta: rheumatoid arthritis, ankylosing spondylitis, Reiter’s syndrome and, in rare cases, granulomatosis with polyangiitis (Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg Strauss syndrome). A more recently discovered entity is the IgG4-related disease-associated aortitis which may cause inflammatory aortic aneurysms (Ladich et al. 2016).

2.1.6 INFECTED ANEURYSMS

Mycotic aneurysm is often used as a general term for an aneurysm with an infection, although this term more specifically refers to an infected aneurysm due to a cardiogenic septic embolus, first described by William Osler (Osler 1885). Arteries are normally highly resistant to infection. Usually, some kind of pathology of the arterial wall is required, e.g. aneurysm, atherosclerosis, trauma or endothelial dysfunction. Immune deficiency due to steroid use, cancer, malnutrition, diabetes, chronic renal failure, HIV infection or another viral infection such as chronic hepatitis can predispose to arterial infection (Valentine and Chung 2012). Arterial infection often leads to the formation of
an aneurysm or a pseudoaneurysm. Infected aneurysms can be classified as follows (Wilson et al. 1978): (1) Mycotic aneurysm – caused by a septic cardiogenic embolus in an otherwise healthy, nonaneurysmal artery. (2) Infected aneurysm – a pre-existing aneurysm that becomes infected due to bacteraemia. (3) Microbial arteritis – a nonaneurysmal artery becomes infected due to bacteraemia, usually leading to contained rupture and a formation of a pseudoaneurysm. (4) Traumatic infected aneurysm – an infected aneurysm caused by trauma or iatrogenic injury (e.g. drug use, arteriography). (5) Contiguous arterial infection – caused by infection in an adjacent organ spreading into the arterial wall, e.g. vertebral osteomyelitis.

The causative microbes of infected aneurysms have changed significantly during the past century. Whereas aneurysms caused by syphilis were common before the era of antibiotics, these are now exceedingly rare. Mycotic aneurysms due to endocarditis were also common and accounted for more than 80% of arterial infections before antibiotics. Endocarditis has become rare, and so have also true mycotic aneurysms. Arterial trauma due to intravenous drug use and the increase in the number of endoluminal procedures has become the most common cause of arterial infection. Up until 1965, 37% of published cases of infected aneurysms were due to endocarditis, and 10% were caused by arterial trauma. From 1965 to 1984, the situation was reversed, with 51% of cases due to trauma and 10% due to endocarditis (Brown et al. 1984). The aorta is probably the most common location of infected aneurysms, with equal distribution between thoracic, visceral and infrarenal segments (Muller et al. 2001; Oderich et al. 2001). The important difference in the clinical course of an infected aneurysm as opposed to a non-infected one is that it progresses more rapidly, it is more likely to be located in the suprarenal aorta, and rest of the aorta may be otherwise normal (Valentine and Chung 2012). Positive microbial cultures are obtained from approximately 75% of the walls of infectious aneurysms. Interestingly, the thrombus within the aneurysm sac may be culture positive in up to 20% of cases in non-infected aneurysms. This, however, has not been shown to have clinical significance.

The human immunodeficiency virus (HIV) is also associated with cardiovascular complications including aneurysms, occlusive disease, spontaneous arteriovenous fistula and dissections (Pillay et al. 2015). The pathological mechanisms behind these changes are largely unknown, but involve inflammatory responses, changes in vascular smooth muscle and endothelial dysfunction. The inflammatory response to continuing viral infection and viral protein toxicity damage the vascular walls. Although an HIV infection can predispose patients to infected aneurysms caused by opportunistic microbes, it can also cause aneurysms independent of bacterial infection. These aneurysms are often multiple and located at atypical sites, e.g. the carotid and femoral vessels. Aortic and popliteal aneurysms have also been described. HIV-related aneurysms occur in younger patients than degenerative (atherosclerotic) aneurysms and in advanced stages of HIV infection. Aneurysms are typically multiple, saccular or pseudoaneurysmal.
This HIV-associated vasculopathy involves medium-sized and large vessels and thus has some similarities with Takayasu’s arteritis. Chronically HIV-positive patients also show premature atherosclerotic changes, which may not be caused solely by the infection itself but also by its management with highly active anti-retroviral therapy (HAART). Atherosclerotic changes may be accelerated by metabolic changes, e.g. hypercholesterolemia and elevated C-reactive protein increased fibrinogen, which are common in HIV patients on HAART. Cardiovascular disease is a significant cause of mortality and morbidity in HIV-positive patients treated with HAART. HAART drugs are classified as protease inhibitors, nucleoside and non-nucleoside analogues. These cause metabolic complications – hyperlipidaemia, central fat accumulation and insulin resistance result from protein inhibitors. Nucleoside analogues cause lipo-atrophy and mitochondrial damage, while non-nucleoside analogues cause lipid elevation (Pillay et al. 2015). Chronic HIV is an important risk factor for atherosclerosis, and it is important to bear this in mind as more HIV patients survive the infection itself thanks to HAART.

2.1.7 DISSECTION AND ANEURYSM
Arterial dissection is a spontaneous tear in the intima of an artery. Blood flow through the tear and into the arterial wall causes the formation of a channel along an anatomical plane within the media, which is called the false lumen. If the initial tear fails to penetrate further, it causes a penetrating aortic ulcer or an intramural haematoma (Evangelista et al. 2015). The most common site for the entry tear is in the ascending thoracic aorta (Stanford type A) or descending thoracic aorta (Stanford type B). The DeBakey classification is also used: in types I and II, the dissection originates form the ascending aorta and either extends to the descending and abdominal aorta (type I) or is limited to the ascending aorta (type II). Type III dissection originates in the descending aorta and corresponds to Stanford type B dissection (Goldfinger et al. 2014). A dissection can cause acute occlusions of the side branches and aneurysm formation. An aneurysm can develop rapidly after a dissection and rupture, or it may develop gradually over time. In the latter case, the aneurysms are treated primarily following the same principles as with degenerative aneurysms. Roughly 15% of patients with TAA have an underlying dissection (Saratzis and Bown 2014). Late aneurysms that develop after the dissection are often thoracoabdominal aneurysms, and approximately 20% of thoracoabdominal aneurysms are the result of a previous dissection. Uncontrolled hypertension is a risk factor for developing an aneurysm after a dissection. Aneurysm rupture is the most common cause of late death in dissection patients, especially those with a DeBakey type III dissection (Lee et al. 2003; Cronenwett and Johnston 2014).
2.2 PATHOPHYSIOLOGY

The composition of the aortic wall changes considerably from the ascending aorta towards the iliac bifurcation. Elastin is more abundant in the ascending aorta, making it more compliant than the descending aorta, but, overall, the ratio of collagen to elastin decreases along the aorta and the media becomes thinner. The haemodynamic forces also differ along the aorta. The embryological origin of the proximal aorta is different from the distal part. The ascending aorta arises from the neural crest and the abdominal aorta from the mesoderm.

AAA is characterised by destructive extracellular matrix remodelling, vascular smooth muscle cell apoptosis, inflammatory cell infiltration, and medial and adventitial neovascularisation. The tunica media is the layer that is mostly affected. The histopathology of thoracic aneurysms is different, however, characterised by cystic medial necrosis or medial degeneration, and less prominent leucocyte infiltration. Patients with Marfan syndrome typically have a considerable degeneration of medial elastic fibres. A large part of the understanding of the pathological mechanisms behind AAA formation comes from animal studies. There are three commonly used mouse models of AAA: adventitial exposure to calcium chloride, transient perfusion of elastase into the infrarenal aorta, and chronic subcutaneous infusion of angiotensin II. Based on these animal studies, it seems that aneurysm formation results from local inflammatory responses leading to the infiltration of macrophages, neutrophils, mast cells and lymphocytes (primarily T lymphocytes). This, together with various cytokines (e.g. tumour necrosis factor α and transforming growth factor β) and extracellular proteases (e.g. cathepsins and matrix metalloproteinases), leads to vascular smooth muscle cell apoptosis and extracellular matrix degradation. Genetics, and probably also epigenetic modification and DNA methylation, play an important role in AAA formation (Davis et al. 2014; Saratzis and Bown 2014; Davis et al. 2015).

2.3 RISK FACTORS AND COMORBIDITIES

2.3.1 ANEURYSM DEVELOPMENT

Aneurysmal disease in general has a strong hereditary component, especially regarding thoracic or thoracoabdominal aneurysms, which are rarer than AAAs. In the case of TAA it is estimated that 20% of patients have a positive family history. AAAs probably also have a strong genetic component. A family history of AAA is the second strongest risk factor, after smoking, for developing an AAA (Lederle et al. 1997). In a Danish cohort, the AAA prevalence was 3.0% in those with no first-degree relative with an AAA, and 6.7% in those who had a first-degree relative with an AAA (OR 2.2, 95% CI 1.6–3.2). If the first-degree relative was female, the risk was 2.5 times higher than
Review of the literature

if the relative was male (Joergensen et al. 2014). A Finnish study found a family history of AAA to increase the risk more than 4-fold (OR 4.33 (95% CI 1.32–14.23). The AAA prevalence was highest for the proband's male siblings, 22% for those over 65 years of age (Salo et al. 1999).

Monozygotic twins had a higher risk of AAA than heterozygotic twins if the other twin had an AAA, which indicates a genetic effect (Wahlgren et al. 2010; Joergensen et al. 2016). Of the patients with an AAA, 15% had at least one first-degree relative with an AAA and, conversely, those with a first-degree relative had a 12-fold increased risk of developing an AAA. Aneurysms also developed earlier in patients with a positive family history of the disease. The SVS guidelines give a strong recommendation for screening first-degree relatives of patients who present with an AAA (Chaikof et al. 2009).

Despite several gene associations discovered, none of the associations is strong enough to explain the considerable heritability seen with AAA (Jones et al. 2017). The pathology is likely to be multifactorial. Environmental factors such as smoking or obesity can have epigenetic effects by influencing the DNA methylation process and may thus modify the risk conferred by genes (Saratzis and Bown 2014). As well as TAA, intracranial aneurysm also has some common genetic background with AAA, although the populations these diseases affect are quite different (van ’t Hof et al. 2016). Screening patients with intracranial aneurysms for AAA has been proposed (Ball et al. 2016). AAAs are also common in patients with popliteal artery aneurysms, with a reported prevalence as high as over 60% (Henke 2005). Conversely, patients with AAA have a smaller but a clearly increased risk of popliteal artery aneurysms: 19% of AAA patients had a popliteal artery aneurysm over 12 mm in diameter (Tuveson et al. 2016).

Patients with diabetes have a lower prevalence of AAA. In a meta-analysis of large screening studies, the OR was 0.66 (95% CI 0.57–0.74) for diabetes and AAA. AAA growth has also been shown to be slower in diabetic patients. On the other hand, there is evidence that diabetics have higher mortality from AAA repair, as evidenced by the higher 30-day mortality (OR 1.32, 95% CI 1.17–1.49) compared to non-diabetics and the poorer long-term survival during 2–5 years of follow-up (De Rango et al. 2014).

Analysis of the cohort from the Aneurysm Detection and Management (ADAM) trial was the first to show a clear negative correlation between diabetes and AAA which has since been verified in many studies (Lederle et al. 1997). In the same study, smoking was the factor most strongly associated with AAA, the risk increasing with the number of years smoked. The effect of smoking also decreased after quitting. It was estimated to account for 78% of all AAAs of over 4 cm in diameter. The tested risk factors and associated odds ratios are shown in Figure 2.
The strong association between smoking and AAA has been described as early as in 1958 (Hammond and Horn 1958). The association between ever smoking and AAA has been shown to be higher than with occlusive atherosclerotic disease such as coronary artery disease or cerebrovascular disease. The relative risk of death for men was 2.5 (95% CI 2.2–2.8) and 3.5 (95% CI 2.4–5.3), respectively. The association is, however, lower than that seen with COPD or lung cancer, RR 0.56 (0.36–0.86) and 0.38 (0.29–0.50), respectively (Lederle et al. 2003b). Smoking also increases the growth rate of small aneurysms and their risk of rupture (MacSweeney et al. 1994; Brown and Powell 1999).

The Atherosclerosis Risk in Communities (ARIC) study included 15,703 participants that were followed from 1987 to 2011 with a median follow-up of 22.5 years (Tang et al. 2016). Clinical AAA events, i.e. death from rupture or operation due to AAA, or AAA as a hospital discharge diagnosis were recorded. A subgroup of 5,778 also attended an US examination in 2011–2013 to determine the prevalence of asymptomatic AAA. On the condition that the individual survived until 45 years of age, the lifetime risk for clinical AAA was 5.6% (95% CI 4.8–6.1) – men had a higher risk of 8.2% (6.9–9.0), and white individuals had a higher risk than black individuals. Those who had never...
smoked had a significantly smaller risk (2.0%, 1.3–2.5) than those who were former smokers (6.3%, 5.0–7.2). The risk of current smokers was even higher, 10.5% (7.7–11.7). Currently smoking white men had the highest lifetime risk of 17.0% (10.7–20.0). There was a dose-response relationship of lifetime AAA risk and pack-years smoked: from 3.6% (2.2–4.6) for those in the lowest pack-year tertile to 11.1% (8.8–12.4) for those in the highest tertile. Those who had quit smoking 3–8 years earlier had a 29% smaller risk than current smokers, but still an approximately three times higher risk than never smokers. In a multivariate analysis, age, male sex, white ethnicity, smoking status, pack-years of smoking, hypertension, PAD, height, LDL cholesterol, and total cholesterol were all positively associated with clinical AAA. Diabetes and HDL cholesterol were negatively associated. BMI and alcohol consumption showed no association. Age, smoking status and pack-years of smoking yielded the highest risk. An asymptomatic AAA discovered in US screening positively associated with white ethnicity, male sex, smoking status and pack-years of smoking, as well as height and elevated LDL or total cholesterol. The results are similar to an earlier population-based study from Tromsø, Norway, with 7-year follow-up (Forsdahl et al. 2009).

Associations of several risk factors have been analysed in prospective studies using data from the Swedish Mammography cohort and the Cohort of Swedish Men. Women who smoked were found to have a significantly higher incidence of AAA than men who had never smoked. Women were also twice as fast as men in achieving the benefit of smoking cessation. The authors suggested that screening smoking women should be further investigated (Stackelberg et al. 2014b). Large waist circumference conferred a 30% risk of having an AAA requiring treatment in both men and women. BMI, however, was not associated with increased risk, suggesting that it is visceral adiposity, rather than general adiposity, that influences the AAA risk (Stackelberg et al. 2013b). High consumption of fruits, but not vegetables, was found to be associated with a decreased incidence of AAA. The association was stronger with ruptured than with intact AAA (Stackelberg et al. 2013a). Moderate consumption of alcohol was also found to be protective against AAA in men and women. The effect was seen with beer consumption in men, and with wine consumption in women, but not with hard liquor consumption in either sex (Stackelberg et al. 2014a).

### 2.3.2 Expansion Rate and Rupture Risk

The predictor of the AAA rupture risk used in clinical decision-making is the diameter of the aneurysm. An increasing diameter of the aorta is associated with a higher risk of rupture. However, some aneurysms under the operative threshold of 55 mm rupture and many aneurysms over this threshold will not rupture during the lifetime of the patient. This is why better predictors of rupture risk are needed. One suggested marker is the aneurysm volume, which is more sensitive to AAA growth (Kitagawa et al. 2013). Peak wall stress (PWS)
can also be calculated using finite element analysis, which is presently time-consuming and not widely available. The PWS in ruptured and symptomatic aneurysms is higher than in asymptomatic aneurysms (Venkatasubramaniam et al. 2004; Heng et al. 2008).

An aneurysm ruptures when the local wall stress exceeds the tensile strength of the aortic wall. PWS calculations solve only a part of this, as wall strength also varies and this is not addressed by PWS analysis. Aortic outflow obstruction increases PWS but may also signify decreased aortic wall strength. Regardless of the precise mechanism, aortic outflow obstruction, i.e. occlusion in one or more iliac artery, is predictive of an increased AAA rupture risk (Crawford et al. 2016a). Intraluminal thrombus also decreases peak wall stress, even though AAA growth and rupture risk are higher with a large thrombus. The thrombus, which contains proteolytic enzymes and proinflammatory cytokines, may have a weakening influence on the aneurysm wall (Speelman et al. 2010; Crawford et al. 2016b). However, in a comparison of patients with ruptured or intact AAA, thrombus volume did not differ between the groups (Golledge et al. 2014).

Increased expansion rates have been shown to be associated with current smoking and increased diastolic blood pressure. Patients with diabetes show decreased rates of expansion compared to non-diabetics. A larger AAA diameter increases the rate of expansion. The lower expansion rate in diabetics has been proposed to be due to increased glycosylation and the resulting stiffness of the arterial wall (Sweeting et al. 2012; Bhak et al. 2015). The rupture risk has been found to be approximately twice as high in current smokers as in ex/never smokers (HR 2.02, 95% CI 1.33–3.06) and nearly 4 times as high in women than in men (HR 3.76, 95% CI 2.58–5.47); the growth rates between men and women, however, were similar. The rupture risk was higher in people with higher mean arterial pressure or pulse pressure, and in older individuals (Sweeting et al. 2012). The fact that current smokers have a higher expansion rate and rupture risk than ex-smokers underlines the importance of smoking cessation in reducing the AAA growth rate and rupture risk.

COPD has been associated with early, small aneurysm rupture, which has been hypothesised to be due to increased systemic elastolysis leading to decreased aortic wall strength (Crawford et al. 2016a). Peripheral arterial disease (PAD) is also associated with an increased risk of early rupture of small AAA, which may be due to increased peripheral resistance that increases PWS. It is also possible that PAD is a surrogate marker for decreased aortic wall strength (Crawford et al. 2016a).

### 2.3.3 COMMON COMORBIDITIES

Significant, primarily cardiovascular, comorbidities are common in AAA patients and influence their long-term survival more than the AAA itself. In a Danish population-based screening study, 7.8% of men with PAD had an AAA,
and 26% of patients with an AAA had PAD (Grøndal et al. 2015). In an Irish cohort of AAA patients, 30% were found to have a significant internal carotid artery stenosis (of over 50%) and 45% were found to have PAD based on abnormal ankle brachial index or toe brachial index measurements (Gray et al. 2016). In a meta-analysis, the cardiovascular death risk for patients with an AAA smaller than 55 mm in diameter was 3.0% (95% CI 1.7–4.3) per year (Bath et al. 2015). According to the Framingham Risk Score, this corresponds with the cardiovascular risk of a 70-year-old smoking man with diabetes, hyperlipidaemia and hypertension (D'Agostino et al. 2008). The prevalence of ischaemic heart disease (IHD) in patients with small AAA was 44.9%, that of previous myocardial infarction (MI) 26.8%, of heart failure 4.4% and of cerebrovascular disease defined as a previous stroke 14.0% (Bath et al. 2015). A meta-analysis showed the AAA prevalence to be approximately 2.4 times higher in patients with a history of coronary artery disease compared to the general population (Hernesniemi et al. 2015). AAA diameter has been shown to be a marker of non-aneurysm-related cardiovascular mortality before and after aneurysm repair (Brady et al. 2001). Intraluminal thrombus volume is also associated with increased incidence of cardiovascular events as well as AAA growth (Parr et al. 2011).

### 2.4 PREVALENCE

True prevalence of AAA is difficult to ascertain, as most patients with an AAA do not get any symptoms from it during their lifetime. In many cases, AAA mortality or RAAA incidence are used as surrogate markers for prevalence, as these are easier to obtain, but they are also affected by the repair rate of both intact and ruptured AAA as well as mortality from these causes and the reliability of cause-of-death data. Autopsies are uncommon in many countries, which makes cause-of-death data unreliable. Also, the reporting of AAA mortality and prevalence in general has been noted to be inaccurate in many instances (Stather et al. 2014). Data on the actual prevalence of AAA comes from cross-sectional screening studies and from older autopsy studies.

Before the advent of antibiotics, most aneurysms were due to infectious causes, most often syphilis. However, after World War II, the incidence of degenerative AAA rose and syphilitic aneurysms all but disappeared in the Western world. Up until the beginning of the 21st century, the AAA incidence was growing and was estimated to grow still (Heikkinen et al. 2002), which was one of the motivators for initiating large screening programmes. From 1951 to 1968, deaths due to AAA increased by 300% in the United States (Lilienfeld et al. 1987), and a seven-fold rise in prevalence was reported from 1951 to 1980 in Rochester, Minnesota (Melton et al. 1984). However, from 1979 to 1990, the mortality rate remained stable, although hospital discharges and operations because of AAA increased (Gillum 1995). In Western Australia, AAA repair increased until 1992, after which there was a decline in both
elective and emergency repair of AAA. In England and Wales, the mortality and hospital admissions due to AAA rose from 1979 to 1999, the rise being more prominent in women than in men (Filipovic et al. 2005). In Malmö, Sweden, the incidence of RAAA increased significantly from 1971 to 2004, even though the rate of elective repair doubled during the same period (Acosta et al. 2006).

Since the turn of the century, the prevalence has fallen in many studies. In New Zealand, AAA mortality declined by 53.0% for men and by 43.1% for women from 1991 to 2007 (Sandiford et al. 2011). Decreases in AAA mortality and hospital admissions were also observed in Australia from 1999 to 2008 (Norman et al. 2011). The most likely cause of the decline in prevalence has been postulated to be the reduction in smoking. The changes in smoking prevalence seem to take 20–40 years before an effect can be seen in AAA mortality (Lederle 2011; Anjum and Powell 2012). This might also explain why AAA prevalence has not decreased everywhere and has also risen in some countries. An epidemiological study on AAA mortality for several countries from 1994 to 2010 showed that, in most populations included in the study, mortality was declining (Sidloff et al. 2014). The largest mortality drop was seen in the United States, the United Kingdom and Australia, with the age-standardised mortality falling by 6.7%, 6.2% and 6.2% per year, respectively. The drop among the female population was smaller, the largest reductions again seen in the United Kingdom and the United States, with 4% and 3.9% per year, respectively. An increase in male AAA mortality was seen in Hungary (2.7%) and Romania (1.7%); and an increase in female AAA mortality in Hungary (3.5%), Romania (1%), Denmark (2.2%) and Austria (0.5%). In the two last-mentioned countries, the mortality in men was decreasing. Trends in systolic blood pressure, cholesterol and smoking prevalence correlated positively with both male and female AAA mortality. The correlation was highest with smoking prevalence for both sexes.

Estimations of global prevalence have also been attempted: overall, AAA prevalence is higher in the developed countries, where it is generally falling, but it has been estimated to be rising in parts of the developing world (Sampson et al. 2014). The studied populations, however, have mostly been European or American, with little data from elsewhere. AAA has been thought to be less prevalent in Asian populations. One study from Hong Kong shows an overall prevalence of 13.7 per 100 000 inhabitants and 105 per 100 000 for inhabitants for over 65-year-olds. The figures include men and women, with a male to female ratio of 2:1 (Cheng et al. 2003). In a recent study of a Korean population, on the other hand, the AAA prevalence was comparable to contemporary Western figures: 2.0% in men and 0.4% in women (Han et al. 2017).

The large screening studies conducted in the 1990s gave a good indication of true AAA prevalence in the population of men over 65 years of age: 7.9% in Chichester, United Kingdom (Scott et al. 1995); 4.0% in Viborg county, Denmark (Lindholt et al. 2005); 7.2% in Western Australia (Norman et al.
2004); 4.9% in Portsmouth, Southampton, Winchester and Oxford (MASS trial) in the United Kingdom (Ashton et al. 2002). In the American ADAM study of Veterans Affairs (VA) patients (97.3% men), the overall prevalence was 4.2%, but there was a clear difference between the two cohorts screened before or after April 1995. The prevalence in the former cohort was 4.6% and in the latter 3.6% (OR 0.79, 95% CI 0.74–0.83) (Lederle et al. 2000).

The actual prevalence observed in the screening programmes has been considerably lower. A prevalence of 1.7% in 65-year-old men was reported in Middle Sweden in 2006–2010 (Svensjö et al. 2011) and a prevalence of 1.5% for the entire Swedish screening programme from 2006 to 2014. The prevalence in the first 700,000 men screened in the English NAAASP screening programme was 1.34% and seemed to be falling annually (Jacomelli et al. 2016). The latest cohort from NAAASP (01/04/2015-30/03/2016) had a prevalence of 1.12% (https://www.gov.uk/topic/population-screening-programmes/abdominal-aortic-aneurysm).

In countries without screening programmes, AAAs are discovered incidentally, usually while a patient is undergoing imaging studies due to other reasons. In a Canadian study where reports of 79,121 abdominal CT, US and MRI studies from 1996–2008 were reviewed, an incidental AAA was identified in 1.0%. The follow-up of these incidental AAAs was poor. Only 29% had the finding documented in the patient records, and for 15% a follow-up plan was documented (van Walraven et al. 2010).

The AAA prevalence in Finland has not been studied, but there are several reports on the incidence of RAAA (see section 2.6).

### 2.5 NATURAL COURSE

The natural course of an AAA is one of generally slow expansion and eventual rupture. In most cases, aneurysms grow so slowly that the individual will have died before experiencing rupture or any symptoms caused by the aneurysm. Based on data from the Swedish screening programme, roughly 40% of aneurysms detected in 65-year-old men eventually require repair (Wanhainen et al. 2016). If the aneurysm ruptures, the mortality is very high, and nearly 100% of the patients die without emergency surgery. The growth rate increases with increasing diameter, as does the risk of rupture (RESCAN Collaborators et al. 2013).

In historical series, the rupture risk has been considered very high in aneurysms over 55 mm in diameter (Szilagyi et al. 1972). More recent reports, however, show that the rupture risk in patients who have been turned down for surgery due to significant comorbidities or patient preference, for instance, is not as high as previously thought (Parkinson et al. 2015). This might be due to better medical management of risk factors. In approximately half of the patients with large aneurysms that are not treated surgically, the eventual cause of death is rupture of the aneurysm (Parkinson et al. 2015; Scott et al.)
The larger the aneurysm, the more likely it is to cause the patient’s death. Even though the rupture rate of very large aneurysms (over 7 cm) in the meta-analysis by Parkinson et al. (Table 2) is still quite low, much higher rupture risks have also been reported in contemporary series. Scott et al. reported in their single-centre retrospective study a 35% rupture rate per year in these cases. For aneurysms measuring at 5.5–6.9 cm, however, the patients' median survival was over three years (Scott et al. 2016). The rupture risks quoted in the ESVS guidelines include a yearly rupture risk of 10%–22% for AAA 60–69 mm in diameter and 30%–33% for AAA >70 mm (Moll et al. 2011).

Table 2  Annual cumulative rupture rates according to aneurysm size. Modified from Powell et al. 2011b and Parkinson et al. 2015.

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Annual rupture rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–55 mm</td>
<td>0–1.61%</td>
</tr>
<tr>
<td>55–60 mm</td>
<td>3.5%</td>
</tr>
<tr>
<td>61–70 mm</td>
<td>4.1%</td>
</tr>
<tr>
<td>&gt;70 mm</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

Aneurysms under 5.5 cm in diameter have a low rupture risk, generally under 1% per year but increasing with growing diameter (Powell et al. 2011a). The growth rate also increases with growing diameter. For 30-mm aneurysms, the mean time for 10% of them to have reached the repair threshold of 55 mm is approximately 7 years (Table 3) (RESCAN Collaborators et al. 2013).

The growth rates for men and women seemed to be equal, although the rupture risk in women for all AAA sizes was 4-fold greater than in men. The rupture risk of a 45 mm aneurysm in women was comparable to that of a 55 mm aneurysm in men (RESCAN Collaborators et al. 2013). Smokers had a higher and diabetics a lower growth rate, whereas smoking, older age and high blood pressure increased the rupture risk (Sweeting et al. 2012).

The RESCAN collaborators suggested screening intervals of 2–3 years for AAAs of 30–39 mm, 1–2 years for AAAs of 40–44 mm, and 0.5–1 years for AAAs of 45–54 mm, based on the growth and rupture rates of small AAA. Even with the higher limits of these suggestions, the yearly risk of rupture would be maintained at under 1% (RESCAN Collaborators et al. 2013). Aneurysm growth is often not linear but discontinuous and occurs in periods of fast growth followed by no growth or very slow growth. This so-called staccato-growth means that observed fast growth cannot be used to predict the future growth rate (Kurvers et al. 2004).

Even if a patient is considered too frail for elective repair, it does not signify that emergency repair in the case of rupture is futile. In an analysis of RAAA patients treated in HUH, it was noted that 5 out of 12 patients who had been turned down for elective surgery but underwent emergency repair because of rupture survived (Noronen et al. 2013).
Table 3  
Growth rates of different-sized AAA for men and women and the time required for a 10% chance of the aneurysm to have reached 55 mm in diameter. Modified from RESCAN Collaborators et al. 2013.

<table>
<thead>
<tr>
<th>Growth rate in mm/year (95% CI)</th>
<th>Men</th>
<th>30 mm</th>
<th>35 mm</th>
<th>40 mm</th>
<th>45 mm</th>
<th>50 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.28</td>
<td>1.86</td>
<td>2.44</td>
<td>3.02</td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.03–1.53)</td>
<td>(1.64–2.08)</td>
<td>(2.22–2.65)</td>
<td>(2.79–3.25)</td>
<td>(3.34–3.88)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.46</td>
<td>1.98</td>
<td>2.51</td>
<td>3.06</td>
<td>3.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.07–1.85)</td>
<td>(1.65–2.32)</td>
<td>(2.22–2.81)</td>
<td>(2.80–3.33)</td>
<td>(3.36–3.89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to 55 mm (95% CI) in years</th>
<th>Men</th>
<th>7.4</th>
<th>5.0</th>
<th>3.2</th>
<th>1.8</th>
<th>0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(6.7–8.1)</td>
<td>(4.6–5.4)</td>
<td>(3.0–3.4)</td>
<td>(1.7–2.0)</td>
<td>(0.6–0.8)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>6.9</td>
<td>4.8</td>
<td>3.1</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.1–7.8)</td>
<td>(4.3–5.3)</td>
<td>(2.9–3.4)</td>
<td>(1.7–2.0)</td>
<td>(0.6–0.8)</td>
</tr>
</tbody>
</table>

2.6 RUPTURED AND SYMPTOMATIC ANEURYSMS

Rupture is the end point of the natural course of an AAA. It usually presents with sudden abdominal or flank pain that can radiate towards either the groin or back. Haemodynamic instability is often encountered. Rupture can present as bleeding directly into the abdominal cavity or into the retroperitoneum. In the latter case, the surrounding tissues provide tamponade and the haemodynamic collapse may not be as acute. The rupture may also be contained or intramural, if the leak seals spontaneously or the bleeding remains within the aneurysm wall. The population-based incidence of RAAA varies considerably between publications, ranging from 2.86 to 14.13 per 100 000 population (Reimerink et al. 2013b). In Finland, during 1991–1994, an incidence of 6.1 per 100 000 was reported (Kantonen et al. 1999a).

In a Dutch study of RAAA patients who did not undergo treatment, the median survival after arriving at hospital was 2.2 hours (IQR 1–18). The patients who were haemodynamically stable upon arrival, however, had a longer survival, with 96% surviving past 2 hours (van Beek et al. 2015b). The mortality from rupture is very high, 67%–94% (Reimerink et al. 2013b). Without rapid surgical intervention, death is all but unavoidable.

Symptomatic aneurysms are defined as AAAs that have become painful without a breach in the aortic wall (Moll et al. 2011). The onset of symptoms is generally considered a sign of impending rupture. In case of symptomatic aneurysms, haemodynamic instability is absent, but the aneurysm may be tender to palpation. They are often thought to have an intermediate perioperative risk compared to intact and ruptured aneurysms. This is different to symptoms caused by an inflammatory aneurysm where the risk of rupture may actually be less than in a non-inflammatory aneurysm.

A large proportion of RAAA patients die outside a hospital where the rupture could be treated. In a meta-analysis by Reimerink et al., 27%–37% of patients were reported to have died without presenting to a hospital. This estimate is quite unreliable, as the cause of death for patients dying outside
Ruptured Abdominal Aortic and Iliac Artery Aneurysms

the hospital is often unclear. Much larger proportions have also been reported – in the Helsinki and Uusimaa Hospital District (HUS) in Finland during 1996–2004, almost half of patients who died of RAAA never presented to the hospital (Laukontaus et al. 2007). The reported proportion of deaths outside the hospital was smaller in the hospital districts of Pirkanmaa and North Karelia in Finland, with 28% of patients dying outside the hospital (Vänni et al. 2016).

Large variations exist in the number of patients who arrive at hospital with RAAA and are then not operated on. This turn-down rate in many centres is high: 40% in a meta-analysis of 21 studies (Reimerink et al. 2013b), the rate was 52% in Malmö, Sweden, in 2000–2004 (Acosta et al. 2006), 30% in the entire Finland in 1991–1994 (Kantonen et al. 1999a), 27% in Stavanger, Norway, in 2000–2012 (Reite et al. 2015), 17% in Tampere and Joensuu, Finland, in 2001–2011 (Vänni et al. 2016), and 9% in Helsinki, Finland, in 1996–2004 (Laukontaus et al. 2007). In a comparison between the treatment of RAAA patients in England and the United States, differences were observed in the turn-down rate – 42% in England and 20% in the United States – and the turn-down rate was also lower in teaching hospitals compared to non-teaching hospitals in both countries (Karthikesalingam et al. 2014).

Rupture has been suggested to be associated with factors such as atmospheric pressure, phases of the moon and the seasons, but it seems that these factors do not have a noticeable effect on rupture rates (Kozka et al. 2014). Weekends, national holidays and late-night hours, however, do affect mortality.

2.7 TREATMENT

2.7.1 MEDICAL TREATMENT

Aims for medical treatment in abdominal aortic aneurysms can be divided into two categories: Firstly, medical treatment to prevent or inhibit the formation and growth of aneurysms, and secondly, the perioperative medication and the medical treatment for reducing overall mortality in AAA patients.

2.7.1.1 Inhibition of aneurysm growth

Medical treatment for inhibiting aneurysm growth has been the subject of numerous in vitro and animal studies (Davis et al. 2015). However, much of this promising basic research has not translated into practical uses in the clinical management of aneurysms. A Cochrane review on medical treatment of small AAA was published in 2012 and found limited evidence for antibiotic treatment, but, in general, high quality evidence on this subject is scarce (Rughani et al. 2012). Two comprehensive reviews have been recently
Several studies have investigated the effect of statins on aneurysm growth. Increased use of statins has been suggested as being one of the reasons for the decrease in AAA prevalence (Anjum and Powell 2012). No randomised controlled trials (RCTs) exist on this matter, and the evidence from the studies is conflicting. The statin used has not been specified in many of the trials; simvastatin and atorvastatin are those most commonly named, however. The larger and more recent ones of these studies have not been able to show a significant effect from statin use. The RESCAN collaborators analysed the individual patient data of 15 475 patients under surveillance for small aneurysms from 18 studies. The unadjusted analysis showed a significant influence of several cardiovascular drugs, i.e. ACE-inhibitors, β-blockers, calcium channel blockers, and statins, on aneurysms growth. After adjusting for confounding factors (age, year, sex, smoking, body mass index, diabetes, mean arterial pressure, pulse pressure and cardiovascular history), none of the drugs had a statistically significant effect on growth rate (Sweeting et al. 2012). A meta-analysis on the effects of statins on growth rate, combining the RESCAN data with other studies, found a significant reduction in growth rate of 0.63 mm/year (Takagi et al. 2013a). The data was suggestive of publication bias, however, making the results somewhat inconclusive.

A Danish nationwide, population-based, combined case-control and follow-up study investigated the influence of statin use on AAA rupture risk (Wemmelund et al. 2014). The results showed that current statin users had a lower risk of presenting with RAAA than those who had never used statins, adjusted OR 0.73 (95% CI 0.61–0.86). Former statin users had a comparable risk to current users, if they had ceased the use within 2 years. The statin dose did not affect the results. The 30-day mortality of the patient groups was also reported, and mortality was lower in current statin users (46.1% compared to 59.3% in patients never having used statins). The adjusted mortality rate ratio for current statin users was 0.80 (95% CI 0.68–0.95), which corresponds to a 20% reduction in 30-day mortality. Only current statin users seemed to have a survival benefit after RAAA.

The β-blocker propranolol has been studied in three RCTs. It did not have an effect on limiting the growth rate of aneurysms. The compliance with propranolol treatment also proved problematic in the largest of these trials, and 42% of patients were unable to adhere to the treatment dose of 80 mg per day.

In preclinical studies, doxycycline has been one of the most promising drugs for AAA treatment. It affects the remodelling of the extracellular matrix and reduces inflammation by lowering the levels of matrix metalloproteinases (MMP). In a small pilot RCT comprising 32 patients, a promising reduction in AAA growth rate was observed. In another similar RCT of 36 patients, the levels of matrix MMP-9 were reduced, but the growth rate of AAA was unaffected. A large recent RCT (PHAST) had 286 patients, with the treatment published in regard to the clinical use of different medical treatments of AAA (Kokje et al. 2015; Golledge et al. 2017).
group receiving 100 mg doxycycline daily. The study was discontinued at 18 months, as the growth rate in the treatment group was higher than in the control group, although the difference was slight and did not affect the need for interventions (Meijer et al. 2013).

Mast cells have been found to be present in tissue samples of AAA wall. The effect of mast cell inhibitor pemirolast on AAA growth has been studied in one RCT (AORTA). The study had 326 patients divided into a placebo group and treatment groups with three different dosages of pemirolast. There was no difference in the growth rates between the placebo and treatment groups (Sillesen et al. 2015).

The renin-angiotensin system has been suspected to play a role in aneurysm formation and rupture based on data from preclinical studies. Subcutaneous angiotensin II infusion has been used in rodent models to create aneurysms. Several studies have investigated the role of ACE-inhibitors in slowing aneurysm growth. The results, however, have been mixed. One case-control study found a reduction in ruptures in patients on ACE-inhibitors. However, the analysis of the United Kingdom Small Aneurysm Trial patients actually found that the aneurysms in patients on ACE-inhibitors grew faster (Sweeting et al. 2010). Several smaller studies have not found an effect on AAA growth or rupture rate. The AARDVARK trial (Bicknell et al. 2016) investigated the effect of perindopril 10 mg daily, calcium-channel blocker amlodipine 5 mg daily, or placebo on AAA growth rate. Neither drug had a significant effect on AAA growth rate.

The role of antiplatelets on inhibiting AAA growth has been investigated in several studies. Some smaller studies have found an effect on AAA progression, but analyses of patients in larger studies such as the UKSAT or the ADAM trial have not found antiplatelets to have an effect on aneurysm growth (Sweeting et al. 2010; Bhak et al. 2015).

Chlamydia pneumoniae is a widely-spread pathogen causing respiratory infections. Its antigen has been found in many AAA tissue samples. Animal studies have demonstrated that chlamydia pneumoniae can induce atherosclerosis and aortic dilatation. Based on this, antibiotics of the macrolide group have been investigated as a potential drug for reducing AAA growth. Two studies have looked into the effect of roxithromycin on AAA growth and found a small reduction in growth in the treatment group. A larger study with 213 patients (Karlsson et al. 2009), however, did not see any effect on AAA growth rate using azithromycin. The authors did observe a significant reduction in growth rates in those patients that were on statins and ASA, however.

Diuretics and calcium channel blockers have also been studied, but have not been found to have an effect on AAA growth. A small RCT of only 19 patients found that patients on NSAIDs had a lower growth rate than control patients.

The current guidelines for AAA treatment from the Society for Vascular Surgery (SVS) and the European Society for Vascular Surgery (ESVS) are from
2009 and 2011, respectively (Chaikof et al. 2009; Moll et al. 2011). They recommend the cessation of smoking as a first-line measure for reducing AAA growth and rupture risk. Both give a weak recommendation for statin therapy. SVS guidelines also mention doxycycline, roxithromycin, ACE-inhibitors and AT-blockers, but comment that their utility is uncertain. A strong recommendation against the use of β-blockers is also given concerning the indication of reducing AAA growth.

Research on the subject of medical treatment for AAA is active, and many trials are ongoing as of writing of this text (Table 4).

<table>
<thead>
<tr>
<th>Ongoing trial</th>
<th>Treatment(s) studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01904981 (BASE trial)</td>
<td>Atenolol compared to valsartan</td>
</tr>
<tr>
<td>NCT0175833</td>
<td>Doxycycline 100 mg twice daily</td>
</tr>
<tr>
<td>NCT01683084</td>
<td>Telmisartan</td>
</tr>
<tr>
<td>NCT02070653</td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>NCT02225756 (ACA4 trial)</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>NCT02007252</td>
<td>Canakinumab (terminated due to lack of efficiency)</td>
</tr>
<tr>
<td>NCT02846883 (VIVAAA trial)</td>
<td>Allogeneic mesenchymal stem cells</td>
</tr>
<tr>
<td>NCT02345590</td>
<td>Eplerenone</td>
</tr>
</tbody>
</table>

### Table 4: Ongoing trials investigating medical treatment for inhibiting AAA growth and reducing rupture risk. [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov) (January 2017)

#### 2.7.1.2 Reducing mortality

The SVS and ESVS guidelines give few recommendations on medical treatment for reducing mortality, and the ones given primarily focus on perioperative mortality (Chaikof et al. 2009; Moll et al. 2011). Both guidelines recommend β-blockade only in high-risk patients and patients already on β-blockers. The SVS guidelines recommend treatment with bronchodilators for symptomatic chronic obstructive pulmonary disease (COPD) patients and for those with abnormal pulmonary function. The ESVS recommends statin therapy beginning 1 month before surgery and continuing perioperatively and after the perioperative period. Small-dose ASA is recommended perioperatively and postoperatively. Hypertension should also be treated to reduce cardiovascular mortality.

One study showed that perioperative fluvastatin was associated with an improved postoperative cardiac outcome in patients undergoing vascular surgery (Schouten et al. 2009). Statin treatment for patients undergoing vascular surgery is also recommended by the guidelines of the European Society of Cardiology (Schouten et al. 2010).

Patients with an AAA are at a high risk of other, primarily cardiovascular, diseases. Common comorbidities include ischaemic heart disease (IHD), peripheral arterial disease (PAD) and cerebrovascular disease (CVD). Due to the usually long history of smoking, COPD is also common. These are the probable reasons for the increased mortality in the population with AAA. Active secondary prevention for cardiovascular disease in AAA patients would
therefore seem logical. The evidence for this particular patient group, however, is scarce.

A review by the Cochrane Collaboration looked at the influence of medical treatment in reducing mortality and cardiovascular events in patients with AAA. Only one study fulfilled the criteria of being included in the review, leading to the conclusion that there was not adequate evidence to draw any conclusions on the matter (Robertson et al. 2014).

A large study on cardiovascular risk prevention from the United Kingdom found that the 5-year survival of AAA patients on statins, antiplatelets or antihypertensive medications was significantly better than that of those not receiving each treatment. Statins were associated with a 20% lower risk of death, which was similar to the benefit from antiplatelets. Any single antihypertensive drug was associated with a 12% lower risk of death (Bahia et al. 2016).

Secondary cardiovascular prevention is recommended in the United Kingdom by the NICE (the National Institute for Health and Care Excellence) guidelines for individuals with a 10-year cardiovascular risk of over 10%. As the risk of cardiovascular death for a patient with a small AAA is approximately 3% per year, secondary cardiovascular prevention is advisable (Bath et al. 2015). Especially AAA patients with no previous history of symptomatic cardiovascular disease are likely not on adequate secondary prevention, although they would benefit from it.

### 2.7.2 ELECTIVE SURGERY: INTACT ANEURYSMS

In open aneurysm repair (OAR), the surgeon’s experience has been shown to be associated with lower operative mortality (Kantonen et al. 1997). Hospital volume was not associated with mortality in the study by Kantonen et al., although, in another study, it correlated with mortality as well as surgeon volume (Zettervall et al. 2017a). The correlation between mortality and hospital volume was, however, minimal with EVAR, and no correlation was seen between mortality and surgeon volume in EVAR procedures. Another American study found that hospitals that completed fewer than five OARs or eight EVARs per year had significantly higher mortality than those hospitals with a higher number of procedures (Dua et al. 2014a). In the United Kingdom, it was noted that hospital volume effected the long-term outcome of electively treated AAA patients positively (Holt et al. 2012).

Long-term survival after AAA repair is poor, even though short-term survival has improved. Five-year survival in a meta-analysis was only 69%, with no significant improvement from 1969 to 2011. Although after adjustment for patient age, a statistically significant improvement in survival was seen (Bahia et al. 2015). This poor survival is mostly due to high cardiovascular mortality in AAA patients. Survival was poorer in older patients and in those with larger aneurysms. The same finding was mirrored in the 14-year results of the Zenith endograft (Cook, Brisbane, Queensland, Australia),
which showed that survival 14 years after EVAR is 24%, even though AAA-related death was uncommon (Verzini et al. 2017). Decision-making aids have been developed for estimating mortality risk after AAA repair. One model based on data from the British National Vascular Database can be found at http://www.britishaneurysmrepairscore.com (Grant et al. 2013).

2.7.2.1 Indications for repair
The indication for elective repair of AAA is currently based on the maximal diameter of the aorta, although more specific and sensitive methods, e.g. aneurysm volume or PWS and other biomechanical indices, might give a better indication of rupture risk (Kitagawa et al. 2013; Leemans et al. 2017). However, these methods are not readily available in everyday practice, and thresholds for surgical treatment have not been defined.

The diameter threshold for surgical treatment of asymptomatic AAA is 55 mm in both the ESVS and SVS guidelines (Chaikof et al. 2009; Moll et al. 2011). The 55-mm threshold was adopted based on two RCTs, the United Kingdom Small Aneurysm Trial (UKSAT) and the Aneurysm Detection and Management trial (ADAM), that showed no survival benefit in open surgery before a 55-mm diameter (UK Small Aneurysm Trial Participants 1998b; Lederle et al. 2002).

The UKSAT randomised 1090 patients with aneurysms of 40–55 mm in diameter between 1991 and 1995 to open surgical repair or US surveillance. When an aneurysm reached 55 mm, became symptomatic, or other aortoiliac procedures were needed, repair was recommended. Twenty percent of the patients were still alive and under surveillance for an aneurysm of under 55 mm at the end of the study. No difference in survival was seen between the groups (p=0.56). The study showed a possible benefit of surgery for patients who were younger or had larger aneurysms. Older age, larger AAA diameter, lower ABI and lower FEV1 at baseline were indicators for an increased risk of death. The median aneurysm growth rate in the surveillance group was 33 mm per year (IQR 0.20–0.53) (UK Small Aneurysm Trial Participants 1998b). A cost-effectiveness analysis (CEA) also showed that the costs were higher for the early surgery group, although surgically treated patients reported better current health perception in quality-of-life questionnaires (UK Small Aneurysm Trial Participants 1998a). The UKSAT did not show a survival difference between the groups in longer follow-up, although total mortality was lower in early surgery group after eight years (UK Small Aneurysm Trial Participants 2002).

The ADAM trial randomised 1136 patients with 40–54-mm aneurysms to immediate repair or US surveillance. No difference in overall mortality or AAA-related mortality was seen between the two groups, or in subgroups defined by AAA diameter or age (Lederle et al. 2002). A quality-of-life analysis was performed on ADAM trial patients. There was little difference between the surveillance and early repair groups. Impotence was more common in the
early repair group more than 1 year after randomisation, but early repair was associated with improved perception of general health in the first 2 years (Lederle et al. 2003a).

Because of the trend towards benefit from early surgery in younger and healthier patients in the UKSAT and ADAM studies, and because the studies were not adequately powered to detect differences in these subgroups, while also considering the increased AAA rupture risk in women, the SVS guidelines give a weak recommendation for considering repair for young, healthy patients, and especially women, with an aneurysm of over 50 mm. According to the ESVS guidelines, repair for women should be considered when the diameter is 52 mm. The ESVS guidelines also include a growth rate of >1 cm per year as an indication for considering repair. This criterion is not in the SVS guidelines. Growth rate is considered unreliable because of variations in measuring AAA diameter and because of the non-continuous growth commonly seen in AAA (Kurvers et al. 2004). The SVS guidelines recommend repairing saccular aneurysms irrespective of diameter (Chaikof et al. 2009).

After the widespread availability of EVAR with lower operative mortality, the rationale for waiting until 55 mm was again questioned. Two RCTs, the Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair (CAESAR) trial (Cao et al. 2011) and the Positive Impact of Endovascular Options for Treating Aneurysms Early (PIVOTAL) trial (Ouriel et al. 2010), investigated EVAR for small aneurysms (41–54 mm and 40–50 mm, respectively) compared to surveillance. Neither study showed a benefit from an early intervention. The Cochrane review on surgery for small asymptomatic aortic aneurysms concluded, based on the four RCTs, that current evidence does not support the repair of aneurysms under 55 mm in diameter (Filardo et al. 2015). There is, however, some evidence suggesting that earlier repair might be beneficial: A comparison of repair thresholds between the United States and England showed that repaired AAAs were a mean (±SE) of 5.3±0.3 mm larger in England than in the United States. The hospitalisation rate due to rupture was twice as high and the aneurysm-related mortality 3.5 times higher in England than in the United States. No causality between these findings could be established by the study, however (Karthikesalingam et al. 2016b).

In cases where the perioperative mortality risk is high, it is often advisable to continue surveillance until a larger diameter is reached. As noted in section 2.5, the rupture risk for an AAA under 7 cm is still relatively low. If the risks are prohibitively high, elective repair can be deferred indefinitely, and repair in the case of rupture may be attempted. The EVAR-2 trial did not show any benefit from treating patients unfit for open surgery with EVAR (EVAR Trial Participants 2005a). In 12-year follow-up there is, however, a fall in AAA-related mortality, but not in overall mortality (unpublished data, presented at the Charing Cross Symposium 2017, April 2017).

In the case of inflammatory abdominal aortic aneurysms (IAAA), the indications for repair are similar to those of asymptomatic AAAs, even though
IAAAs are often symptomatic. The rupture risk of an IAAA is considered to possibly be lower than that of a non-inflammatory AAA. Treatment with anti-inflammatory medication is often warranted (Ketha et al. 2014).

2.7.2.2 Open surgery versus EVAR

In most centres, EVAR is today considered the first-line treatment option for AAA repair (Budtz-Lilly et al. 2017; Powell et al. 2017). This is mostly based on the lower perioperative mortality and shorter hospital stay (Brown et al. 2012). Open repair also requires a longer convalescence time of over 1 month. The benefits of open repair are its high durability and low rate of late complications. The downside of EVAR is the uncertainty about its long-term durability and the requirement of life-long surveillance. Reinterventions are also not uncommon even long after the initial operation. The most common cause for re-intervention is endoleak (Table 5).

Table 5 Classification of endoleaks. Modified from Chaikof et al. 2002 and the ESVS guidelines Moll et al. 2011.

<table>
<thead>
<tr>
<th>Endoleak</th>
<th>Source of perigraft flow</th>
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<tbody>
<tr>
<td>Type Ia</td>
<td>Proximal end of the stent graft</td>
</tr>
<tr>
<td>Type Ib</td>
<td>Distal end of the stent graft</td>
</tr>
<tr>
<td>Type II</td>
<td>Branch leak</td>
</tr>
<tr>
<td>Type III</td>
<td>Stent graft defect (junctional leak or fabric hole)</td>
</tr>
<tr>
<td>Type IV</td>
<td>Fabric porosity</td>
</tr>
<tr>
<td>Type V (endotension)</td>
<td>AAA enlargement without visible endoleak</td>
</tr>
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</table>

The strongest evidence on EVAR compared to OAR comes from four RCTs: the EVAR-1 trial from the United Kingdom (EVAR Trial Participants 2005b), the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial from the Netherlands (Prinssen et al. 2004), the Open Versus Endovascular Repair (OVER) trial from the United States (Lederle 2009), and the Anévrysme de l’aorte abdominale, Chirurgie versus Endoprothèse (ACE) trial from France (Becquemin et al. 2011). Long-term results from three of these studies are also available: DREAM (De Bruin et al. 2010), OVER (Lederle et al. 2012) and EVAR-1 (Patel et al. 2016). Most of the patients included in these studies were men: approximately 90% in EVAR-1 and DREAM and over 99% in OVER and ACE. ACE included only patients with a low or intermediate risk for OAR. A meta-analysis of the four studies showed a significant benefit for EVAR in 30-day mortality (OR 0.32, 95% CI 0.14–0.71), although it is noted that, because of considerable differences in these studies, a traditional meta-analysis is not reliable (Epstein et al. 2014). In all the trials, the re-intervention rate after EVAR was higher than after OAR, although the difference was not statistically significant in the OVER trial. The cost of hospital resource use was also lower in EVAR patients because of the approximately 5 days shorter
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hospital stay. However, this cost was offset by the cost of the endovascular device, except in the United States. In EVAR-1, patients showed a greater loss in the quality of life after OAR for the first 3 months, but there were no significant differences after that. Similar results were seen in DREAM. EVAR-1 and DREAM showed that EVAR patients had a survival benefit up until 2 years, while this time in the OVER trial was 8 years, but in ACE trial there was no difference in survival at any time point.

In a CEA based on the OVER trial, EVAR was found to be cost-effective because of the longer survival benefit. This result was not seen in a CEA based on the three other trials (Epstein et al. 2014). It is notable that the devices used in these trials were of an early generation, the perioperative imaging was less advanced, and hybrid suites were not available. Many procedures were also performed outside the device’s instructions for use (IFU). Some publications have not shown significantly worse results for EVAR performed outside the IFU, but few long-term results have been published (Oliveira-Pinto et al. 2017). Compliance with IFU has been low in many cases, and this has been suspected to be one reason for sac growth during follow-up after EVAR (Schanzer et al. 2011). The long-term results of EVAR-1 also demonstrated a higher late mortality from AAA-related causes. This is something that was observed also in a cohort of Medicare beneficiaries undergoing repair for AAA (Schiermerhorn et al. 2015; Patel et al. 2016). These questions concerning late ruptures after initial repair and the long-term durability of EVAR have caused increased interest in OAR for younger patients with a long life expectancy. A meta-analysis of the RCTs did not show, however, that young and fit patients would benefit from OAR at least during 5 years of follow-up. The same analysis also showed that, although EVAR was generally associated with lower short-term mortality, patients with moderate renal dysfunction and IHD showed no survival benefit (Powell et al. 2017).

Smoking is associated with more additional intraoperative procedures and a higher risk of device migration, but fewer type II endoleaks, which might be because of more atherosclerotic changes in the arteries and increased coagulation in smokers (Koole et al. 2012).

OAR can be performed with either a transabdominal or retroperitoneal approach, with conflicting reports on the merits of these approaches. The retroperitoneal approach is commonly used when the aneurysm extends proximally. One recent report found a lower risk of cardiac and renal complications with the retroperitoneal approach (Teixeira et al. 2016), while another found no significant differences (Buck et al. 2016). A meta-analysis reported that a retroperitoneal approach was associated with fewer cases of postoperative ileus and pneumonia (Twine et al. 2013). In complicated open repair of juxtarenal aneurysms that requires a long period of aortic cross-clamping, temporary perfusion for renal and/or visceral vessels may be required. This can be achieved with, for example, temporary axillorenal bypass (Heinola et al. 2016a).
Laparoscopic aneurysm repair is also practiced, although it has not gained wide popularity because of the steep learning curve (Dion et al. 2001). Some centres have reported good results using this technique (Coscas et al. 2014; Howard et al. 2015a).

The ESVS guidelines recommend follow-up with colour duplex US or CT imaging at 5, 10 and 15 years after OAR to identify perianastomotic aneurysms. After EVAR, the ESVS guidelines suggest CT angiography and plain radiographs at 30 days and 12 months and, thereafter, yearly US surveillance. Increasing diameter or a new endoleak in US surveillance should be followed with CT angiography. If there is any endoleak in the first control examination, CT angiography should also be performed at 6 months. Any type I and type III endoleaks should be repaired (Moll et al. 2011).

There has been some interest in using statins to reduce endoleaks after EVAR, but the data supporting this is quite weak. Some studies have found evidence that statin therapy influences type II endoleak regression and aortic sac stabilisation, but other studies have not found it to have any effect (Pini et al. 2015; Kim et al. 2017).

Long-term results for the Zenith stent graft, which is the oldest graft still in use without major modifications, have been published (Verzini et al. 2017). The risk of reintervention was 12.1% at 5 years, 25% at 10 years and 30% at 14 years. Five-year results for the Endurant stent graft (Medtronic, Minneapolis, MN, USA) showed a reintervention risk of 11% at 5 years (Singh et al. 2016). The reintervention rates of early endografts have been higher, 56.9% at 10 years according to one study (Mestres et al. 2010).

Conversion from EVAR to OAR is sometimes required. This is associated with high perioperative mortality. The risk factors that increased the likelihood of conversion in one study were young age, female sex and non-white ethnicity (Ultee et al. 2016a). Renal complications are not uncommon after OAR or EVAR and are associated with increased mortality. Risk factors for these are elevated baseline glomerular filtration rate, OAR, transfusion and prolonged operation duration (Zettervall et al. 2017b). However, in another publication, there was no difference in renal function 5 years after OAR or EVAR (de Bruin et al. 2013).

### 2.7.3 URGENT SURGERY: SYMPTOMATIC ANEURYSMS

#### 2.7.3.1 Indications and timing of repair

Intact AAAs that require urgent, but usually not emergency, repair are symptomatic aneurysms, infected (mycotic) aneurysms, or infections of a previously repaired AAA (graft infection). Symptomatic aneurysms are considered to have a high rupture risk and are therefore repaired urgently. Inflammatory aneurysms are an exception, as they are often symptomatic but are suspected to have a lower rupture risk than non-inflammatory AAAs.
Mycotic aneurysms can grow fast, but emergency surgery is usually not necessary if the infection can be controlled by antibiotics. Surgery is, however, necessary as a curative treatment, as conservative treatment has a mortality of 100% (Wilson et al. 2016). A definition for aortic graft infection has been proposed by the Management of Aortic Graft Infection Collaboration (MAGIC) (Lyons et al. 2016).

Symptomatic AAA treatment is usually not required immediately. In one study, those repaired within 4 hours of arriving at hospital had a higher mortality rate than those whose operation was delayed so that the patient could be optimised and experienced staff was available (Cambria et al. 1994). In this study, no one died while waiting for the deferred operation. A recent study with an increased use of EVAR, on the other hand, did not indicate that emergency surgery yielded a difference in survival when compared to surgery delayed for at least one day (Soden et al. 2016). However, the authors did see a twofold increased risk of perioperative mortality compared to asymptomatic aneurysms. Another study showed an intermediate long-term survival and major adverse event rate for symptomatic patients compared to asymptomatic or ruptured AAAs (De Martino et al. 2010). Yet another study showed no difference in 30-day survival or major adverse events between symptomatic and asymptomatic patients whose AAAs were treated with EVAR (Stokmans et al. 2012).

A Finnish study demonstrated that emergency repair on haemodynamically stable non-ruptured AAA patients was associated with higher early and late mortality than elective repair. The authors suggested that these patients should undergo urgent cardiac evaluation before surgery to reduce mortality from IHD (Soisalon-Soininen et al. 1999).

### 2.7.3.2 Open surgery versus EVAR

Mycotic aneurysms or graft infections (of prosthetic grafts or EVAR devices) are typically treated with open repair: debridement and either extra-anatomic reconstruction or in situ reconstruction with infection-resistant material, e.g. autogenous veins or cryopreserved allografts (Lyons et al. 2013; Heinola et al. 2016b; Wilson et al. 2016). EVAR can be an option, but it is usually reserved for stabilising the patient for definitive open repair later (Kan et al. 2007). In an analysis of Swedish vascular registry patients treated for mycotic AAA, those treated with EVAR had lower short-term mortality than and a comparable number of infection-related complications or reoperations with those treated with OAR (Sörelius et al. 2016). Most patients in the OAR group were treated with in situ reconstruction, but the material used for reconstruction was not specified. The rates of infection-related complications were 18% for OAR and 24% for EVAR.

There is some evidence that symptomatic AAA patients benefit from an endovascular-first strategy, and this is recommended by the ESVS guidelines (Holt et al. 2010). The suggested time for treatment in the ESVS guidelines is...
the next available elective operating list (Moll et al. 2011). In HUH, symptomatic aneurysms are usually repaired during the same hospital stay.

Large asymptomatic AAAs (over 90 mm) should be considered for urgent repair according to the ESVS guidelines (Moll et al. 2011). A delay in the repair of an AAA can have serious consequences, and rupture while waiting for repair is not uncommon, especially with large AAAs (Noronen et al. 2015).

2.7.4 EMERGENCY SURGERY: RUPTURED ANEURYSMS

In the Netherlands, the centralisation of RAAA treatment to vascular centres with a 24-hour emergency vascular service resulted in better survival (van Beek et al. 2014). In both the United Kingdom and the United States, teaching hospitals had a lower turn-down rate and lower operative mortality than non-teaching hospitals (Karthikesalingam et al. 2014). Transferring RAAA patients to another hospital may seem risky, but in a Dutch study, 96% of patients who were haemodynamically stable upon arrival at the hospital survived for more than 2 hours, which gave time to transfer the patient to a vascular centre (van Beek et al. 2015b). A Finnish study also found no difference in the treatment results of RAAA depending on the transportation distance to the hospital where the patient was operated on (Kantonen et al. 1999b). The quality of life after successful RAAA repair has been shown to be almost the same as that of the age- and sex-adjusted general population (Korhonen et al. 2003).

Based on the IMPROVE trial data, the aneurysm neck length appears to have a significant effect on operative mortality for both OAR and REVAR for RAAA. The reason for the higher mortality in OAR probably results from the need for aortic cross-clamping above the level of the renal arteries (IMPROVE Trial Investigators 2015a). REVAR for RAAA that fall outside the IFU also has higher rates of complications, mortality and graft-related problems than those performed within the IFU (Baderkhan et al. 2016).

2.7.4.1 Open surgery versus EVAR

Current consensus favours first-line REVAR treatment for RAAA, even though neither the IMPROVE (IMPROVE Trial Investigators et al. 2014) nor the smaller Amsterdam Acute Aneurysm (AJAX) trial (Reimerink et al. 2013a) or Endovasculaire ou Chirurgie dans les Anévrysmes aorto-iliaques Rompus (ECAR) trial (Desgranges et al. 2015) showed any immediate survival or cost-effectiveness benefit from REVAR. Similar findings were seen in a Swedish study with no difference in perioperative or midterm survival between centres with an REVAR-first or an OAR-first strategy (Gunnarsson et al. 2016).

However, there were several other benefits from an REVAR-first approach: the patients were likelier to be discharged faster and directly to their home, and the early quality-of-life indicators were better (IMPROVE Trial Investigators
The 3-year results of the IMPROVE trial strongly support the endovascular first therapy with a clear mortality and cost-effectiveness benefit for REVAR (unpublished data, presented at the Charing Cross Symposium 2017, April 2017).

Re-interventions after REVAR were not more common than after OAR in IMPROVE, although in the AJAX trial, the patients who survived their initial hospital stay had a higher re-intervention rate if they had been primarily treated with REVAR (van Beek et al. 2015a). IMPROVE also found REVAR to be cost-effective, with a >0.90 probability at all realistic willingness-to-pay thresholds. Both of these findings contradict those seen with elective EVAR. In contrast to IMPROVE, the AJAX trial found REVAR prohibitively expensive and not cost-effective. Much of this finding was suspected to be because of the high conversion rate (Kapma et al. 2014). A retrospective CEA from Cambridge, United Kingdom, found that REVAR was as cost-effective as OAR for RAAA at least up to three years. The OAR costs were higher perioperatively, but REVAR generated costs later from re-interventions and surveillance. These costs did not exceed the perioperative OAR costs, but with longer follow-up, REVAR might become less cost-effective (Rollins et al. 2014). Some centres have also reported better long-term survival after the adoption of a REVAR-first strategy (Ullery et al. 2015).

2.8 SCREENING

As an AAA is commonly asymptomatic and often goes undiscovered until rupture, which in turn has a very high mortality rate, the disease has been considered ideal for screening. Aneurysms can be easily found and followed with a non-invasive US examination, which also fits in well with the ideology of screening. US has a high sensitivity and a specificity of close to 100% (Lindholt et al. 1999). There have been four RCTs that have explored the utility of screening in reducing mortality from AAA. Based on these studies, three countries have implemented national screening programmes.

2.8.1 STUDIES ON SCREENING

The first population-based AAA screening trial was conducted in Oxford, United Kingdom, in 1988. It included 825 men aged 65–74 years, only little over half of whom attended. The prevalence of AAA was 5.4% (Collin et al. 1988). After this small non-randomised study, four RCTs followed: The Chichester trial (Chichester, United Kingdom) in 1989–1994 (Scott et al. 1995), the Viborg trial (Viborg county, Denmark) in 1994–1999 (Lindholt et al. 2005), the Western Australian trial 1996–1999 (Norman et al. 2004), and the Multicentre Aneurysm Screening Study (MASS; Portsmouth, Southampton, Winchester, and Oxford, United Kingdom) in 1997–1999 (Ashton et al. 2002).
The Chichester study, which was a pilot study for the much larger MASS trial, was the only one that included women as well as men. It included 15,775 patients (6,433 men) aged 65–80 years. The Viborg trial and the MASS trial were larger and included only men and younger age groups – 12,639 men aged 64–73 years and 67,800 men aged 65–75 years. The Western Australian trial included 38,480 men aged 65–83 years, with 33.4% being 75–83 years of age. This age group was included in order for the study to have adequate power. The AAA prevalence in men in these studies ranged from 4.4% in Viborg and 4.9% in MASS to 7.2% in Western Australia and 7.6% in Chichester. Twelve per cent of the discovered AAAs were over 55 mm in diameter upon initial scans in Viborg and MASS, but only 7% in Western Australia.

The number of elective AAA repairs was approximately 2–4 times higher in the invited groups compared to controls. Emergency procedures fell to roughly half the number seen in the control group, however. The Chichester, Viborg and MASS trials all showed a reduction in AAA-related mortality in the group that was invited to screening when compared to the control group. The relative risk reduction was 42% in Chichester and MASS, and 67% in the Viborg trial. In the Western Australian trial, AAA-related mortality was not significantly reduced, mostly because of the high number of deaths in those that were invited but did not attend. The conclusion of the authors was that “the success of screening will depend on choosing the best target age group (probably men aged 65–74 years), excluding ineligible men, and minimising delay between becoming eligible for screening and actual screening”. In the MASS trial, the reduction in non-fatal RAAA was similar to the reduction in AAA mortality.

Long-term results are also available for the four RCT studies: 15-year follow-up for Chichester (Ashton et al. 2007), 14-year follow-up for the Viborg trial (Lindholt et al. 2010), 13-year follow-up for the MASS trial (Thompson et al. 2012), and 12.8-year follow-up for the Western Australian trial (McCaul et al. 2016). The benefit from screening could still be seen in the Chichester population after 15 years, although the reduction at 15 years in AAA-specific mortality had dropped from the 42% at 5 years to only 11% and was not statistically significant. The risk of AAA rupture increased after 10 years from the initial scan. Of the patients with a detected AAA who had died during the follow-up in the MASS trial, 58.2% had not had a RAAA or undergone AAA repair. The number of operations in the invited group was about twice as high as in the control group, and the number of emergency operations was half of the number in the control group. Thirty-day surgical mortality was 4.2%. Repair was done with EVAR in 12.8%, with a mortality rate of 1.8%. The mortality in this later report compares favourably to the rate of 6% in the initial MASS report. The relative risk reduction for AAA-related deaths was 42% in the invited patients and 52% in those who actually attended.

Because AAA deaths are still uncommon, the absolute risk reduction was only 0.46% during the follow-up. The number of men needed to be invited to screening to prevent one death during 13 years was 216. This compares favourably to, for instance, breast cancer screening, in which the number of
individuals needed for screening is approximately 400. All-cause mortality was reduced by 3% in the invited group (HR 0.97, 95% CI 0.95–0.99). Eight years after the initial scans, the number of RAAs increased in the invited group, but was still lower than in the control group. Rescreening those with an aortic diameter of 25–29 mm 5 years after the initial scan was suggested (Thompson et al. 2012).

In the Viborg trial, the patients with an aortic diameter of 25–29 mm upon the initial scan were rescreened 3–5 years later, and 28% had developed an AAA, although the largest was only 48 mm in diameter. The conclusions of the Western Australian trial did not change after longer follow-up. The reduction in AAA-related mortality was only 8% even in the subgroup of 65–74 year-olds and not statistically significant. The deaths from AAA in those patients who actually attended the screening, however, were halved. The authors attributed the lack of benefit from screening to the low rate of rupture and death from AAA, the high rate of elective surgery in the control group, and the low attendance to screening (68% compared to 76.6% in Viborg and 80.3% in MASS).

During the surveillance in the Viborg study, 36% of those with an AAA of under 5 cm in the initial scan were operated on. The AAA-related risk reduction remained high at 66% after long-term follow-up. The decrease in all-cause mortality compared to the control group was 2% but not statistically significant. The same trend of roughly double the number of elective procedures and half the number of emergency procedures was also seen in the long term.

Several meta-analyses have been published on the combined data of these four RCTs. With the inclusion of the 15-year results of the Chichester trial, the 13-year results of the MASS trial, the 14-year results of the Viborg trial and the 11-year results of the Western Australian trial, the 2.7% reduction in all-cause mortality reached statistical significance (Takagi et al. 2013b). The estimated number of individuals needed to be invited to screening to save one life was 156. As AAA accounted for only 2% of the deaths in this population, it is likely that there are also other causes for the reduction in all-cause mortality besides the reduced AAA-specific mortality. It is possible that addressing cardiovascular risk factors during the screening process has a beneficial effect on mortality.

The thorough review of the RCTs and other related studies by the United States Preventive Services Task Force (USPSTF) concluded that one-time screening for 65-year-old men, especially those who have ever smoked, is effective in reducing AAA-related mortality. The original review and screening recommendation was published in 2005 and updated in 2014 (Fleming et al. 2005; Guirguis-Blake et al. 2014a; Guirguis-Blake et al. 2014b). This review, however, concluded that the effect on all-cause mortality was not statistically significant, although it was later pointed out that their rounding was incorrect and the reduction in all-cause mortality would actually reach statistical significance (Lederle 2016a). The all-cause mortality reduction remained
statistically significant even after including the most recent negative long-term data from the Western Australian trial (Lederle 2016b).

There are several on-going trials on AAA screening listed on ClinicalTrials.gov (January 2017). Some of these focus on screening in suspected high-incidence groups such as patients with peripheral arterial disease or carotid stenosis (NCT01248533). There is also a study looking into US in AAA screening in smoking Israeli Arab Men (NCT02306304). The population-based screening studies listed are from Norway (screening for abdominal aortic aneurysm in 65-year-old males in Oslo, NCT01248533), and Denmark (randomised preventive vascular screening trial of 65–74-year-old men in the Central region of Denmark, NCT00662490).

2.8.2 RESULTS OF SCREENING PROGRAMMES

Currently, there are three national AAA screening programmes: one in the United Kingdom, one in Sweden and one in the United States. The actual AAA prevalence has been much lower in these screening programmes than in the RCTs. This affects the cost-effectiveness of screening, and some doubt over the benefit of AAA screening has been expressed. The initial results from the screening programmes have recently been published and are reviewed below.

The United Kingdom National Screening Committee concluded in November 2005 that, based on evidence from existing studies, US screening should be offered to men in their 65th year. The National Health Service (NHS) Abdominal Aortic Aneurysm Screening Programme (NAAASP) was implemented beginning from July 2009, covering the entire England by April 2013 (Davis et al. 2013). Screening has since also been implemented in Scotland, Wales and Northern Ireland. The NAAASP also includes advice from a vascular nurse specialist concerning a healthy lifestyle, smoking cessation and diet, and a recommendation to take antiplatelet and statin therapy, unless contraindicated. The men aged over 65 years – who will not receive an invitation to screening – can, nevertheless, self-refer to their local screening programme.

The 5-year results of the NAAASP have been published for the first 700 000 screened men and the first 1000 men referred to treatment for an AAA >5.4 cm (Jacomelli et al. 2016). The annual cohort was approximately 300 000 men. For 700 000 men to attend, 896 287 had to be invited, yielding an acceptance rate of 78.1%. The acceptance of screening varied from 61.7% to 85.8%, depending on the area; social deprivation also affected attendance. The mean aortic diameter was 1.8 cm (range 0.7–11.1). The prevalence of any AAA was 1.34%, and 8% of these aneurysms were >5.4 cm in diameter. There was also evidence that the prevalence was falling annually. Of the self-referred over 65-year-old men from the same period, 27 421 were scanned, and their AAA prevalence was 2.80%, with 5.5% of the aneurysms being over 5.4 cm.

Of the 1000 men referred to a vascular centre due to an AAA of over 5.4 cm, 51% were 65-year-olds with a large AAA detected in the first screening, 43%
were patients whose aneurysm grew during surveillance to a diameter of over 5.4 cm, and 6.2% were self-referred patients found to have a large AAA on the initial or subsequent scans. The initial scan revealing a large AAA was found to be false in 3.2% of cases. AAA repair was performed for 870 patients. The median time from referral to surgery was 10 weeks. The national goal in the United Kingdom is for surgery to take place within 8 weeks of the referral, and this was accomplished for 40.5% of patients. Six patients died after referral but before surgery, two due to a ruptured AAA. Open repair was chosen for 52% of patients and EVAR for 46% (the type of procedure was unknown for the rest). Perioperative mortality was 0.8%–0.9% for open and 0.7% for endovascular repair – which is lower than the 2015 National Vascular Registry rate of 1.5%.

In 2005, based on the published RCTs on AAA screening, the United States Preventive Services Task Force (USPSTF) recommended the screening of all men aged 65–75 years who have ever smoked 100 cigarettes or more. Medicare, which covers over 65-year-old Americans, does not include preventive services; these have to be added through legislation. In 2007, the Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Act came into effect, and the screening US was covered by Medicare, if the examination was performed during the first six months (later changed to 12 months) of enrolment in Medicare as part of the “Welcome to Medicare” package (Lederle 2008; Shreibati et al. 2012). As of January 2014, this restriction has been removed, and otherwise eligible Medicare beneficiaries can also receive their referrals to US from other sources besides the “Welcome to Medicare” visit and without a time limit (www.cms.gov). The SAAAVE Act, contrary to the USPSTF guidelines (LeFevre and U.S. Preventive Services Task Force 2014), includes not only men 65–75 years of age, but also men and women who have a family history of AAA. The SVS guidelines, on the other hand, recommend screening to all men at or older than 65 years, and screening at 55 years for those men with a family history of AAA. Screening is also recommended for women aged 65 or older who have ever smoked or have a family history of AAA (Chaikof et al. 2009).

The Department of Veterans Affairs (VA) adopted a less strict policy than Medicare from the start by not excluding those already in the system (Lee et al. 2009). There are also other smaller screening programmes for AAA in the United States, many of which have screened primarily women and younger age groups than suggested by guidelines (Lederle 2008). The complicated eligibility for Medicare-covered screening has resulted in a situation in which only 1% of the eligible 1 000 000 beneficiaries were screened in 2007 (Chun et al. 2013). The implementation of the SAAAVE Act also did not seem to have an effect on the AAA repair rate, the AAA rupture rate or all-cause mortality (Shreibati et al. 2012).

Because of the way screening is organised in the United States, data on the results of the programmes is difficult to obtain. There are, however, some reports from large screening centres. The VA Northern California Health Care
System has published a retrospective analysis of its screening results for 9,751 patients from 2007 to 2011 (Chun et al. 2013). However, 28.2% of the patients were inappropriately screened, i.e. they did not fulfil the screening criteria. The mean age was 71.5 years and declined during the study period, and 99.6% were men. AAA prevalence was 7.2%, and only 6.6% of these were over 5.5 cm in diameter. Only 67.4% of the large aneurysms were repaired. Of the patients with a large AAA, 26.1% died during the 5-year follow-up, but only one RAAA fatality was reported. Operative mortality is not reported.

In Sweden, a general AAA screening programme for 65-year-old men was first introduced in the county of Uppsala, with other counties since adopting a similar system (Wanhainen and Björek 2011). The system reached nationwide coverage in 2015 and recently changed from being independently organised by the 21 counties to being a national programme (Wanhainen et al. 2016). Contrary to the NAAASP, patients with a known AAA are not excluded from the screening programme. This has a small effect of approximately 0.5%-points (the prevalence of known AAAs in Sweden in men aged 65 years) when comparing the prevalence numbers from these two screening programmes (Svensjö et al. 2011). The annual cohort is approximately 60,000 men aged 65 years.

From 2006 to 2014, a total of 312,784 men aged 65 years were invited to the Swedish screening programme (Wanhainen et al. 2016). The attendance rate was 84%. AAA prevalence was 1.5%, with approximately 650 AAAs detected annually. The proportion of AAAs of ≥5.5 cm was 7%. Detected aneurysms were operated on in 18% of patients during the study period, 58% with open repair and 42% with EVAR. The operative mortality at 30 days was 0.9%–1.3% after open repair and 0.3% after EVAR. The general perioperative mortality for AAA surgery was 1.5% in Sweden. AAA-specific mortality declined by 39% from 74/100,000 in 2000 to 45/100,000 in 2014. There was a clear correlation between the length of the screening programme and AAA-specific mortality, with counties that had screened for ≥6 years having lower mortality than counties having screened for <4 years. A linear regression analysis showed a mean reduction of 4% in AAA mortality for each year of screening. In a stepped-wedge cluster randomised trial design, AAA mortality was 25% lower in the screening group than in the control group. Using a Markov model, the estimated long-term relative risk reduction of AAA-related death was 40%. The number needed to screen was 667 and the number of screening-detected aneurysms needed to operate was 1.5 to prevent 1 death. The prediction is that 40% of screening-detected AAAs will eventually be repaired, meaning 106% more elective repairs than with no screening, but a 59% reduction in repairs due to RAAA. The low surgical mortality figures mean that the number of extra patients dying from elective repair, if compared to no screening, is 1 to 2 per year (0.1%–0.3% of men with screening-detected AAA) (Wanhainen et al. 2016). No difference in complication rates between repair for screening-detected and non-screening-detected AAAs has been observed in Sweden (Linné et al. 2014). The repair rate for intact AAA in Sweden
increased until 2010 after which it has stabilised at around 27/100 000 inhabitants over 50 years of age. The incidence of RAAA and the 30-day mortality rate for both intact and ruptured AAA repair has decreased (Lilja et al. 2017).

Operative mortality for screening-detected aneurysms seems to be lower than for incidentally discovered aneurysms (Lindholt and Norman 2011), which seems to hold true with the results from the NAAASP and the Swedish programme.

These recent reports from Sweden and the United Kingdom seem to confirm the findings of the RCTs in that screening is an effective preventive health measure and cost-effective even with a lower-than-anticipated prevalence of AAA.

### 2.8.3 COST-EFFECTIVENESS OF SCREENING

CEA is a commonly used method to estimate the costs of health benefits that can be achieved by adopting new interventions. The result is usually expressed as an incremental cost-effectiveness ratio (ICER), which states the additional cost of one intervention compared to another (or to no intervention) in relation to the achieved health benefit, often expressed in quality-adjusted life-years (QALYs). QALY is calculated by multiplying the health-related quality of life associated with a health state (expressed as 0.00 for dead and 1.00 for perfect health) with its duration (Neumann et al. 2017). Health-related quality of life can be described as “the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy” (Patrick and Erickson 1993). First and foremost, CEA is meant to be used as one decision-making tool in allocating limited health care resources (Neumann et al. 2017).

The willingness-to-pay threshold varies from country to country, and using a single fixed ICER threshold is not appropriate for all cases. Some general guidelines exist, however – e.g. the one used by NICE specifies an ICER of under £20 000–30 000 (€23 700–35 600 or $25 300–38 000 as of April 2017) per QALY as effective use of health care resources (NICE 2013). Factors that affect the results of CEA include defining the effects of intervention, the method of calculating QALYs (no gold standard for defining health-related quality of life exists), defining costs (whether to include only health-care related costs or a wider range of societal costs), the time horizon used for analysis (should be long enough to show the differences, both positive and negative, in the consequences of the intervention), and the discount rate (effects and cost experienced later rather than sooner are given less weight). Because of the uncertainties in CEA modelling it is important that sensitivity analysis, in which a wide range of possible variables are used, is performed (Neumann et al. 2017).

There have been several CEAs of AAA screening, which overwhelmingly show that screening is likely to be cost-efficient. Some criticism of
methodological problems in some of these analyses, however, has been expressed (Campbell et al. 2007).

Based on data from the MASS trial, one-time screening in 65-year-old men had an ICER of £2 320 per life-year gained (95% uncertainty interval £1 600-£4 240) over a 30-year time horizon. This was quite similar after adjusting for quality of life, £2 970 (£2 050-£5 430) per quality-adjusted life-year (QALY) gained. The ICER calculated with the same model is considerably higher, when a shorter time horizon is used – at 4 years, it was £72 670, and at 10 years £7 970 per life-year gained (Kim et al. 2007).

The MASS trial-based CEA was updated in 2014 with current costs and parameters observed in NAAASP in order to evaluate the cost-effectiveness of the English screening programme. It was noted that the cost of screening and surgical procedures had risen faster than the general health service inflation. The model used for the previous study was also calibrated according to the 10-year results from MASS as well as the rupture and expansion rates from other recent trials. The analysis used a 30-year time horizon. The ICER was £5 758 (£5 467-£9 443) per life-year gained and £7 370 (£5 467-£9 443) per QALY gained. This is more than the £2 970 per QALY predicted by the original model. Nevertheless, even when using a low willingness-to-pay threshold of £10 000 per QALY, the programme would be cost-effective with 99% probability. According to the model, the ICER would rise above the NICE threshold of £20 000 per QALY if the prevalence were to fall as low as 0.35% compared to the observed 1.5% AAA prevalence among 65-year-old men (Glover et al. 2014).

Cost-effectiveness was also analysed in the final report of the Viborg trial after a 14-year follow-up. The report showed a considerably lower ICER of €157 (-€3 292-€4 011) per life year gained and €179 (-€4 083-€4 682) per QALY gained. The authors noted that the 50% reduction in acute AAA surgery, as was seen in the Viborg trial, almost outweighed the cost of screening and extra elective operations resulting from it. This is because the most expensive burden came from emergency surgery, which was more common in the control arm of the study (Lindholt et al. 2010).

A CEA by Wanhainen et al. showed that cost-effectiveness was rather insensitive to variations in the cost of screening and surgery, but the risk of rupture and long-term survival had a significant effect on the cost-effectiveness. They used a Markov model with the patient’s life time or the age of 100 years as the time horizon. In this study, the cost per life year gained was $10 474 with one screening of 65-year-old men or $13 900 per QALY gained; screening 60-year old men was as effective ($11 100 per life-year gained) but gained more life years. Rescreening those with a negative initial scan after 5 years did not significantly affect the cost per life-year gained ($11 946). Although populations with a high prevalence of AAA, such as smokers and cardiovascular patients, seem good candidates for more specific screening programmes, their lower life expectancy countered the increased prevalence: ICER was $10 695 per QALY gained in smokers and $10 392 per QALY gained.
in cardiovascular patients. If a screening-detected aneurysm was assumed to cause a hypothetical 5% reduction in QALY because of worrying about the aneurysm, the cost rose to $75 100 per QALY gained (Wanhainen et al. 2005).

A CEA of screening in Norway and the Netherlands, that used a lifetime analysis with a Markov Model, was published in 2011. In the Netherlands, the ICER was €4 340 per life-years gained and, in Norway, €9 860 per life-years gained. The report noted that a prevalence of less than 1% combined with an incidental AAA detection rate of above 15% would tip the scales towards no cost-effectiveness (Spronk et al. 2011).

An analysis using a Markov model based on MASS trial data as well as data from a Swedish prevalence study and the Swedvasc registry resulted in an ICER of €14 706 per QALY in 13-year follow-up and €7 570 per QALY gained in a lifetime analysis. The model was based on an AAA prevalence of 1.7% and management with EVAR in 50% of cases. Screening was predicted to be cost-effective down to a prevalence of 0.5%. (Svensjö et al. 2014b).

There are several other studies that have come to the conclusion of positive cost-effectiveness of AAA screening, with one exception from Denmark. That study used a decision tree and Markov model hybrid. Lifetime ICER was £43 485 per QALY (Ehlers et al. 2009). The model from this negative study was later found to be erroneous. The same model, after corrections, was used for the basis of the Finnish CEA which was published in 2011 by the National Institute for Health and Welfare. It concluded that the ICER for screening 65-year-old men was €6 237 per life-years gained (Mäklin et al. 2011) and that the screening would likely be more cost-effective than the current practice of no screening. No screening was, however, subsequently initiated.

The latest CEA based on the Swedish screening data shows a high probability of cost-effectiveness at a contemporary setting with a cost of €4 832 per life-year gained and €6 325 per QALY gained (Hager et al. 2016). Another Swedish CEA, however, showed a somewhat higher ICER of €15 710 for a 35-year time horizon. This would still be considered cost-effective by the commonly used thresholds (Zarrouk et al. 2016).

### 2.9 SEX-RELATED DIFFERENCES IN AAA

Differences in prevalence of AAA and outcome of the disease between the sexes are well known, but results from studies and experiences in different centres are conflicting, and their implications on the best treatment strategy for women are uncertain (Lo and Schermerhorn 2016). Explanations for the lower prevalence in women have been searched for in the pathophysiological mechanisms of aneurysm formation, in which sex hormones may play a part. Oestrogen has been shown to have a protective effect against aneurysm formation at least in animal and in vitro studies (Makrygiannis et al. 2014).

The only screening RCT that included women was the Chichester trial (Scott et al. 1995). The prevalence in women was six times lower than in men.
for all age groups. The overall prevalence was 1.3% compared to the 7.6% in men. Women presented with an AAA approximately 10 years later than men, and the average rupture age was 6 years higher than in men, with the majority of women with a RAAA being over 80 years of age (Scott et al. 2002). The study arrived at the conclusion that screening women would not be a viable option.

The prevalence of AAA in a Swedish cohort of 70-year-old women was 0.5% (95% CI 0.4–0.7), but 2.1% (1.0–3.7) among women who were current smokers (Svensjö et al. 2013). A review of screening studies that included women (the previous study by Svensjö et al. included) found a prevalence ranging from 0.37% to 1.53%. Smoking and older age increased the prevalence, with current smokers having the highest values (Ulug et al. 2016).

Smoking may also confer a larger risk of AAA on women than on men, and female smokers are likely to have a higher prevalence of AAA than men who have never smoked (Stackelberg et al. 2014b). Current screening programmes have been estimated to be cost-effective up until the prevalence falls under 0.35% in the United Kingdom (Glover et al. 2014) and 0.5% in Sweden (Svensjö et al. 2014a), which suggests that screening smoking women may be cost-effective with the caveat that the patients discovered in screening would be approximately 10 years older. In a CEA, screening 65-year-old women was found cost-effective with an ICER of $5 911 per life-year gained, but the decrease in AAA-specific mortality was only 32%, which is lower than in men (Wanhainen et al. 2006). The cost-effectiveness seen in the model was the result of the higher rupture risk in women. In the model, AAA prevalence in women was estimated to be 1.1%, which seems higher than the actual prevalence but still lower than the prevalence among female smokers.

The rupture risk for an AAA of any size in women is higher than in men, although the growth rate is probably not significantly different (Thompson et al. 2013). The size of vessels is generally smaller in women and the same-sized aneurysm might thus mean a more advanced stage of disease than in men.

Rupture patients, in comparison to electively treated patients, are more likely to be women and older (Dua et al. 2014b). After rupture, the outcome in women is also worse. However, a report from the Vascular Study Group of New England found no difference in the proportion of women with RAAA compared to men, nor was sex predictive of 30-day or 1-year mortality (Lo et al. 2013).

A higher turn-down rate has been reported for female RAAA patients (Dueck et al. 2004). An American study showed a 7.7% higher 30-day mortality rate in female patients who underwent RAAA repair; the difference was seen in both OAR and REVAR but was larger with OAR. Women were also less likely to be discharged directly home after repair (Mureebe et al. 2010). In a more recent study, perioperative or long-term mortality did not differ between men and women regardless of treatment method (De Rango et al. 2017). There was, however, a trend towards women possibly benefiting more from an endovascular-first strategy. The same was also seen in an individual
patient data analysis of the three RCTs comparing OAR to REVAR in RAAA (Sweeting et al. 2015).

A lower diameter threshold for women has been suggested due to the higher rupture risk, but because of reports of higher mortality from elective repair, no definite consensus has been reached (Bown and Powell 2014; Vavra and Kibbe 2014). Both the ESVS and SVS guidelines, however, suggest repair for women at a lower diameter (Chaikof et al. 2009; Moll et al. 2011). The UKSAT, ADAM, or the two smaller RCTs comparing repair of small AAA to surveillance included few women and were likely underpowered to be able to show benefit for earlier repair in women.

The results of elective repair are also somewhat inconclusive. Women are known to be less likely to meet the IFU criteria for EVAR (Sweet et al. 2011). The Vascular Study Group of New England found that women were less likely to undergo EVAR, probably due to this reason. Complication rates, at least partly due to access problems related to smaller vessels, were higher for women, as was morbidity after EVAR but also after OAR. No difference was seen in 30-day or 1-year mortality between the sexes, however (Lo et al. 2013). The EUROSTAR study group found that women had higher complication rates and a higher number of re-interventions after EVAR than men. A Kaplan-Meier analysis showed worse long-term survival for women. In an adjusted Cox regression model, the effect of sex was no longer statistically significant for survival, but remained significant for event-free survival (Grootenboer et al. 2013).

In an English study of NHS hospital patients, women, in addition to being older, had a higher incidence of COPD and rheumatological disease, but fewer cardiovascular risk factors (Desai et al. 2016). Short- and long-term mortality was significantly higher, and post-operative complications more common. In an American study using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) data, women were found to be at a higher risk of 30-day mortality and major complications after intact AAA repair even after adjusting for AAA diameter, but if adjustment was made based on the aortic size index (ASI), the differences were less significant. The authors concluded that this might be a better indicator for a repair threshold (Deery et al. 2017). ASI is calculated by dividing the AAA diameter with the body surface area (BSA). This can be calculated by the following formula: 

\[
\text{BSA} = 0.20247 \times \text{weight}^{0.425} \times \text{height}^{0.725}
\]

(Du Bois and Du Bois 1989).

During long-term surveillance after repair, however, women do not seem to have a higher number of endoleaks, re-interventions, limb occlusions or other post-repair complications than men (Lo and Schermerhorn 2016).

There is some evidence that medical management of cardiovascular risk factors is inferior in women, which may contribute to higher perioperative mortality. IHD is more commonly underdiagnosed and undertreated, and women are less likely to be on statins (Mikhail 2005).
3 ILIAC ARTERY ANEURYSMS

3.1 DEFINITION

In 1817, Sir Astley Cooper ligated the aorta of a man with a traumatic external iliac artery aneurysm. This was the first reported operation performed for an iliac artery aneurysm (IAA) (Cooper 1830). The first reported repair of a common iliac artery was by Valentine Mott, who in 1827 reported a successful ligation of the common iliac artery (Mott 1827). Since then, only sporadic reports of individual cases or small patient series have been published. No RCTs or prospective reports on the subject have been published. IAAs are rare, even though they are the most common intra-abdominal aneurysms after AAAs.

Based on the Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery criteria, the threshold for common iliac artery aneurysm would be 1.8 cm in men and 1.5 cm in women, and for internal iliac aneurysm 0.8 cm in both sexes (Johnston et al. 1991). The definitions used in the literature are varied, ranging range from 1.5 to 2.5 cm, and do not usually differ between the common and internal iliac arteries.

3.2 NATURAL COURSE

In a report from 1988, IAAs constituted 3% of all atherosclerotic, noncranial aneurysms and 2.2% of all intra-abdominal aneurysms (Richardson and Greenfield 1988). These figures are derived from clinical practice before the widespread use of imaging studies. In an autopsy study of 26 251 patients, 0.03% were found to have an isolated IAA (7 in total, 5 common, 1 external and 1 internal) and 0.6% an aortoiliac aneurysm, whereas 3.2% had an AAA (Brunkwall et al. 1989). Thus, in this study, IAA constituted almost 20% of all intra-abdominal aneurysms. The common iliac artery is most often the location of an IAA, and aortic aneurysms often extend into this vessel. The internal iliac artery, which is also known as the hypogastric artery, is the second most common location. Isolated aneurysms of the iliac arteries, however, are most often found in this vessel. The external iliac artery is rarely aneurysmatic, likely due to embryological reasons, as it develops from a different cell population than the common and internal iliac arteries. In a report from the Mayo Clinic, out of 438 patients with a common iliac artery aneurysm (CIAA), 86% had a concomitant AAA, 65% also had a contralateral CIAA, 29% had an internal iliac artery aneurysm (IIAA), and only 3% had an aneurysm of the external iliac artery (Huang et al. 2008).

Reports on the expansion rates of IAA are varying. Santilli et al. reported expansion rates of 0.5–1.5 mm/year for aneurysms of <30 mm and 2.5–2.8
mm/year for those >30 mm in diameter. Although 37.5% of the aneurysms did not show any growth during a mean follow-up of 31.4 months, all aneurysms between 40 and 49 mm expanded. Those that were over 50 mm were emergently repaired (Santilli et al. 2000). Huang et al. reported a median expansion rate of 2.9 mm/year, with higher rates in patients with hypertension (Huang et al. 2008).

The reported diameter of ruptured IAA has been quite large: a mean diameter of 78 mm was reported by McCready et al. and 75 mm by Lowry and Kraft; Richardson and Greenfield reported diameters ranging from 35 to 18 mm (Lowry and Kraft 1978; McCready et al. 1983; Richardson and Greenfield 1988). The aneurysms in these studies were mostly those located in the common iliac artery. Huang reported the median diameter of ruptured CIAA to be 60 mm (Huang et al. 2008). In a review of isolated IIAA, the mean diameter of ruptured aneurysms was 83 mm; for symptomatic aneurysms it was 76 mm (Wilhelm et al. 2014).

Several reports from the early 20th century mention a subgroup of young women with an IIAA attributed to pregnancy and delivery (Maclaren 1913), but these types of aneurysms are not found in contemporary publications. IAA caused by infection and iatrogenic trauma, e.g. after hip or lumbar surgery or gynaecologic operations, have been described (Dix et al. 2005).

### 3.3 TREATMENT

#### 3.3.1 INDICATIONS

In 1983, McCready et al. proposed 30 mm as the threshold diameter for IAA repair (McCready et al. 1983). This is the most commonly referenced indication for repair. Santilli et al. proposed in 2000 that CIAAs larger than 3.5–4.0 cm should be repaired (Santilli et al. 2000).

In the case of symptomatic aneurysms, repair should be performed at a smaller diameter. Symptoms can be caused by the expansion of the aneurysms or compression of pelvic organs by the aneurysm. Krupski et al. reported on 21 patients, with symptoms in 57%, most commonly abdominal pain, but also neurologic symptoms, claudication and urinary symptoms (Krupski et al. 1998). Huang et al. reported 29% of patients being symptomatic, most commonly experiencing abdominal pain. They also reported two patients with acute deep venous thrombosis and three arteriovenous fistulas out of the total 438 patients (Huang et al. 2008). According to Santilli et al., only patients with aneurysms larger than >40 mm in diameter reported symptoms (Santilli et al. 2000). Out of 55 patients, Richardson and Greenfield reported 45% as asymptomatic, 33% with acute pain suggesting rupture or expansion and 9% with chronic pain attributed to compression of nerve roots or abdominal viscera. They also reported two patients with arteriovenous fistula – these
patients had dyspnoea and fatigue. Urologic symptoms such as flank pain, urgency or frequency was reported in 7% (Richardson and Greenfield 1988).

3.3.2 OPEN SURGERY AND ENDOVASCULAR REPAIR
The historical choice for treating an IAA was ligation, but since the development of vascular prostheses, endoaneurysmorrhaphy and reconstruction became the first-line options. In the case of the internal iliac artery, ligation has still often been the only option. Similarly to what has occurred in AAA repair, EVAR has become the primary treatment method for IAA.

There are particular challenges to treating IAAs and aortoiliac aneurysms. Occluding the internal iliac artery is often necessary when there is an aneurysmatic common iliac artery in order to get a good landing zone in the external iliac artery. When there is a slightly aneurysmatic common iliac artery and a concomitant AAA, a large-diameter limb can be used to achieve an adequate sealing zone. This “bell-bottom” technique, however, has the downside of leaving the IAA untreated, leading to continuing dilatation of the common iliac artery and a high risk of the development of distal type I endoleak as well as rupture of the IAA. Techniques using parallel grafts, chimneys and snorkels have also been described to achieve the preservation of internal iliac artery flow (Lobato and Camacho-Lobato 2013).

Currently, there are dedicated stent grafts for preserving flow to the internal iliac artery. These iliac branched stent grafts are available from three manufacturers: Zenith (Cook, Brisbane, Queensland, Australia), Excluder (W.L. Gore & Associates, Flagstaff, Arizona, USA) and E-iliac (Jotec GmbH, Hechingen, Germany). Endovascular aneurysm sealing with the Nellix (Endologix, Irvine, California, USA) device has also been used in treating IAA.

3.3.3 COMPLICATIONS
The preservation of at least one internal iliac artery is preferable, as its occlusion can lead to complications ranging from buttock claudication to ischaemia of the bowel or the spinal cord. The incidence of fatal ischaemic complications after the occlusion of the internal iliac artery has been reported to be 2.8% at 30 days. Buttock claudication was seen in 25.3% of patients 30 days after discharge. Those patients whose internal iliac artery was occluded distally as well, most commonly due to an aneurysm of the vessel, had a higher incidence of buttock claudication, 43.0%. Persisting claudication was present in 85% at 18 months (Jean-Baptiste et al. 2014). Chitragari et al. reported buttock claudication in 21.2%, buttock necrosis in 5%, erectile dysfunction in 2.7%, colonic ischaemia in 7.0%, and spinal cord ischaemia in 9.0% of vascular surgery patients with ligation or embolization of the internal iliac artery. Embolization, especially distal embolization, of the internal iliac artery was associated with more complications than proximal ligation (Chitragari et al. 2014).
2015). When treating aortoiliac aneurysms, internal iliac artery occlusion carried a 29.2% (95% CI 24.2-34.7) risk of buttock claudication. Higher incidence was seen in those with a bilateral interruption of internal iliac artery flow than those with a unilateral interruption (36.5% versus 27.2%, OR 1.7). The morbidity associated with internal iliac artery preservation techniques, on the other hand, was minimal and results were good (Kouvelos et al. 2016). It also appears that simple coverage of the internal iliac artery results in fewer complications than pre-emptive embolisation with no clear difference in endoleak and re-intervention rates (Kontopodis et al. 2017).

3.3.4 RESULTS OF REPAIR

In a review of patients that included mostly cases treated before the advent of modern endovascular techniques, the mortality was 52.9% after the repair of a ruptured internal iliac artery, 10.3% after the repair of a symptomatic aneurysm, and 0% after the repair of an asymptomatic aneurysm (Wilhelm et al. 2014). Richardson and Greenfield reported operative mortality of 20% in a group with ruptured and intact IAA (Richardson and Greenfield 1988) and Huang et al. a 30-day mortality of 3%. The mortality after elective repair was only 1%, but mortality after emergency repair was 27%. EVAR was used in 10% of the cases. Clinically significant ischaemic colitis was noted in 4 and spinal cord ischaemia in 2 patients out of all 438 patients. Primary and secondary patency were 99.4% and 100%, respectively, with no difference between open and endovascular repair. The length of hospital stay was significantly shorter for EVAR patients. An endoleak was seen in 31% of the stent graft patients at discharge and in 20% at the last available imaging study after a median follow-up of 1.6 years. The incidence of buttock claudication was 5% after open repair and 34% after EVAR, although in open cases where the internal iliac artery was ligated the incidence was 27%. Most patients reported improvement of symptoms during follow-up (Huang et al. 2008).

A 9.3% occlusion rate for the internal iliac branch of the Zenith IBS device during a 26.6-month follow-up has been reported. Six of the 13 patients with branch occlusion developed buttock claudication. Out of all the patients included in the study, 12.1% required secondary interventions. Mortality was 1.4%, and major complications were seen in 4.3% (Jongsma et al. 2017). The 6-month primary patency of the internal iliac component of the Gore Excluder device has been reported to be 94%. Reinterventions were required in 7.1% of patients (van Sterkenburg et al. 2016). The Jotec E-iliac device results have also been reported. At 1 year, the survival rate was 98.5% with all internal iliac limbs open, although two common iliac and one external iliac occlusions occurred (Mylonas et al. 2016).

The Nellix system has been used in treating common iliac artery aneurysms. The proposed advantage of the system is that it does not need a healthy landing zone in the common iliac artery. The internal iliac artery remained patent in 98% during the 5-year follow-up. It had to be occluded in
three patients in order to extend the sealing zone into the external iliac artery. In cases where the common iliac artery could only partially be excluded, the authors of the report found that the annual growth rate of the aneurysm was actually higher (0.56 mm/y) than when the common iliac artery aneurysm was left untreated (0.16 mm/y). The completely excluded aneurysm, on the other hand, did not expand (Krievins et al. 2016).
Ruptured Abdominal Aortic and Iliac Artery Aneurysms
AIMS OF THE STUDY

The purpose of this study was to evaluate the incidence of RAAA and the results of RAAA repair in Finland in general and in the Helsinki and Uusimaa Hospital District in particular. The study also included IAAs, focusing especially on IIAAs, as these aneurysms often co-exist with an AAA and may also rupture causing similar symptoms.

The specific aims were:

1. To evaluate the changes in incidence and treatment results of RAAA during a 15-year period in Finland. (I)
2. To evaluate the proportion of RAAA patients who die outside the hospital or are turned down for emergency repair. (II)
3. To determine the number of AAA patients whose aneurysm ruptured under the screening age or the elective repair threshold diameter. (III)
4. To evaluate the size of IIAA at the time of rupture and its implications on the threshold diameter for elective treatment. (IV)
Ruptured Abdominal Aortic and Iliac Artery Aneurysms
METHODS

All the sub-studies were approved by the Institutional Review Board of Helsinki University Hospital. Study I was approved by the Institute of Health and Welfare (THL) and the Office of the Data Protection Ombudsman. The use of cause-of-death data in studies I and II was approved by Statistics Finland.

1 PATIENTS

Patients for all the studies were collected and the data analysed retrospectively. Data was acquired from hospital records, the HUSVASC register and from the registers of THL and Statistics Finland as well as from the registers and records of Tampere University Hospital for study III and from hospitals in Sweden, Norway, Australia, New Zealand, Germany and Hungary for study IV.

Table 6  Key patient characteristics for all four studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>% women</th>
<th>Mean age (SD)</th>
<th>Area</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>RAAA</td>
<td>4949</td>
<td>21.4</td>
<td>75.8 (9.3)</td>
<td>Finland</td>
</tr>
<tr>
<td></td>
<td>Intact AAA</td>
<td>4956</td>
<td>12.8</td>
<td>71.5 (8.3)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>RAAA</td>
<td>712</td>
<td>23.3</td>
<td>76.5 (9.6)</td>
<td>HUH</td>
</tr>
<tr>
<td>III</td>
<td>RAAA</td>
<td>587</td>
<td>16.9</td>
<td>73.6 (9.5)</td>
<td>HUH and TAUH</td>
</tr>
<tr>
<td>IV</td>
<td>RIIAA*</td>
<td>63</td>
<td>12.7</td>
<td>76.6 (9.0)</td>
<td>VASCUNET</td>
</tr>
</tbody>
</table>

I

All major vascular surgery in Finland is performed in the 15 central and 5 university hospitals. The catchment areas of these hospitals make up the 20 hospital districts. The university hospitals function as central hospitals for their own districts but also act as referral centres for central hospitals. Referrals are usually addressed to predetermined university hospitals. Data covering the entire country for all patients treated for intact or ruptured AAA during 2000–2014 came from the Care Register for Health Care (HILMO) of THL. The selection of data was based on ICD-10 codes I71.3 (RAAA) and I71.4 (intact AAA). The register includes all contacts to specialised health care and
entails data on the surgical procedures performed. The codes for the procedures were used to differentiate between EVAR and open surgery. Mortality data came from the Finnish cause-of-death register at Statistics Finland. These data were combined using the personal identity numbers specific to each permanent resident of Finland. In total, 4949 RAAA patients and 5068 patients who had undergone elective AAA repair were identified. Reoperations and foreign citizens were excluded from the analysis.

II
All RAAA patients treated in HUH during 2003–2013 were recovered from the HUSVASC register, and patients turned down for operative treatment were identified from the hospital records. Death certificate data was obtained from Statistics Finland for all patients with RAAA as their cause of death (ICD-10 code I71.3). This data was linked with hospital records using personal identity numbers. The identified RAAA patients in the HUS area numbered 712. Reoperations and patients referred from outside HUS were excluded.

III
Patients treated for RAAA in HUH and TAUH were identified from the hospital records of the respective hospitals, and their comorbidities were also retrieved from vascular registers and hospital records. All patients who had undergone a CT examination where the rupture of the aneurysm was confirmed were identified from this cohort. The CT images were reviewed and the maximal AP diameter was measured. Patients admitted to HUH and TAUH during the study period numbered 587, and CT images were available for 327 patients.

IV
Data on ruptured IIAAs were requested from the international VASCUNET group with a standardised data collection form. Aneurysm location and size as well as concomitant aneurysms in other aortoiliac arteries were recorded, as were the patients’ age, sex, treatment method and survival. The maximal diameter of the aneurysm was measured from CT images, if available, or taken from the original radiologist’s report. Patient data was obtained from a total of 28 hospitals in Hungary (15 patients), Australia (14 patients), Sweden (12 patients), New Zealand (7 patients), Norway (6 patients), Finland (6 patients) and Germany (3 patients). The data from individual countries was combined. Sixty-three patients with a ruptured IIAA were identified from 2002 to 2015.
2 DATA ANALYSIS

I
The age-adjusted RAAA incidence per 100 000 inhabitants was calculated for the entire Finland and for each hospital district separately. Time trends were analysed for incidence and mortality.

Survival was analysed according to treatment method and sex. Data was adjusted for age according to the overall Finnish age distribution in 2014. Data was split geographically based on the patients’ home community, regardless of where the actual repair was performed, and analysed according to hospital district to see whether major geographical differences in EVAR activity (as opposed to open repair) or in population-based repair rate could be found. Time trends in mortality were also investigated and causes of death analysed for OAR and EVAR patients. The turn down rate was estimated based on patients who arrived at the hospital because of RAAA but did not undergo repair.

II
The place of death for RAAA patients was identified from the cause-of-death register. Patients were divided into those who died outside the hospital, those who arrived at the hospital but were turned down for repair, those who died within 30 days of repair, and those who survived at least 30 days after repair. These groups were compared. Surgical mortality, population-based age-adjusted mortality and the incidence of RAAA were calculated.

III
The age of RAAA patients was analysed in relation to comorbidities and smoking status. The proportion of patients who were under the age used for screening programmes in Sweden and the United Kingdom (65 years) was calculated. These proportions were also calculated separately for smoking and non-smoking men and women to see whether smoking or sex had an effect on rupture age. Risk factors were analysed against the patient’s age in a univariate analysis and in a multivariate model with cut-off at 65 years to see which risk factors would predict early rupture at an earlier age or, conversely, be protective against it.

For those patients with a CT scan where the diameter of the aneurysm at the time of rupture could be measured, a similar analysis was performed using the AP diameter. This was evaluated for associations with comorbidities, sex and smoking status. A multivariate model was constructed with a 55-mm maximum AP diameter as cut-off.

IV
The mean diameter of the ruptured IIAAs was calculated, and concomitant aneurysms were noted. The proportion of IIAAs that ruptured under the diameter of 3 or 4 cm was compared with the proportion of AAA ruptures at under 5.5 cm in study III. This was done to get a rough estimate of the rupture risk of small IIAA compared to small AAA. Surgical mortality at 30 days was calculated for EVAR and OAR. Patient survival after ruptured IIAA repair was analysed.

3 STATISTICAL METHODS

For all the studies, SPSS versions 22–24 (IBM, Armonk, NY, USA) were used for statistical analysis. Student’s t-test was applied for comparisons of continuous variables, e.g. aneurysm diameter and patient age. Comparisons between proportions were performed using the \( \chi^2 \) test. Survival was analysed with the Kaplan-Meier method (IV) or Cox regression (I). Comparison between groups in Kaplan-Meier analysis was performed with log rank (Mantel-Cox) test. Binary logistic regression was used for multivariate analysis of the risk factors of AAA rupture at under 55 mm or 65 years (III). Only factors with \( p < 0.2 \) in Student’s t-test or \( \chi^2 \) test were included in the multivariate analysis. Linear regression was used for analysing time trends in RAAA incidence and mortality (II). In all studies, \( p \)-values under 0.05 were considered statistically significant.
RESULTS

1 RAAA INCIDENCE IN FINLAND (I)

The incidence of RAAA has decreased from 2000 to 2014. If divided into three 5-year periods (2000–2004, 2005–2009 and 2010–2014), there is a decline in the number of patients between the second and the third period: 1656 patients in the first period, 1743 in the second and 1550 in the third. During the same time, however, the population of Finland has increased and grown older. This means that the population at risk has become considerably larger: there were 777 198 inhabitants over 65 years of age in 2000 but 1 091 388 in 2014. Therefore, the incidence per 10 000 inhabitants has seen a more dramatic change: 9.5 (95% confidence interval 9.1–9.9) during the first period, 8.8 (8.5–9.2) during the second, and 6.8 (6.5–7.1) during the third. The trends were similar for both men and women, but the overall the incidence in women was much lower than in men – 2.4 (2.3–2.6) and 14.5 (14.2–14.9), respectively – for the whole study period.

Table 7 Incidence of and mortality from RAAA, and the elective AAA repair rate in Finland per 100 000 inhabitants for both sexes together and separately with 95% confidence intervals.

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<tr>
<td><strong>RAAA</strong></td>
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<tr>
<td>Incidence</td>
<td></td>
<td></td>
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<tr>
<td>All</td>
<td>9.5 (9.1–9.9)</td>
<td>8.8 (8.5–9.2)</td>
<td>6.8 (6.5–7.1)</td>
<td>8.4 (8.2–8.6)</td>
</tr>
<tr>
<td>Men</td>
<td>16.5 (15.8–17.2)</td>
<td>15.3 (14.6–16.0)</td>
<td>11.9 (11.3–12.5)</td>
<td>14.5 (14.2–14.9)</td>
</tr>
<tr>
<td>Women</td>
<td>2.8 (2.5–3.0)</td>
<td>2.6 (2.3–2.9)</td>
<td>1.9 (1.7–2.1)</td>
<td>2.4 (2.3–2.6)</td>
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<tr>
<td><strong>RAAA</strong></td>
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<tr>
<td>Mortality</td>
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<tr>
<td>All</td>
<td>6.4 (6.1–6.7)</td>
<td>6.1 (5.9–6.3)</td>
<td>4.7 (4.5–5.0)</td>
<td>5.7 (5.6–5.9)</td>
</tr>
<tr>
<td>Men</td>
<td>13.1 (12.5–13.7)</td>
<td>12.0 (11.7–12.4)</td>
<td>9.4 (8.9–9.9)</td>
<td>11.5 (11.1–11.8)</td>
</tr>
<tr>
<td>Women</td>
<td>2.5 (2.3–2.8)</td>
<td>2.3 (2.2–2.5)</td>
<td>1.7 (1.4–1.9)</td>
<td>2.2 (2.0–2.3)</td>
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<tr>
<td><strong>AAA</strong></td>
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<tr>
<td>Repair rate</td>
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<tr>
<td>All</td>
<td>6.7 (6.4–7.1)</td>
<td>7.4 (7.0–7.7)</td>
<td>7.0 (6.6–7.3)</td>
<td>7.0 (6.8–7.2)</td>
</tr>
<tr>
<td>Women</td>
<td>1.3 (1.2–1.5)</td>
<td>1.7 (1.5–1.9)</td>
<td>1.5 (1.3–1.7)</td>
<td>1.5 (1.4–1.7)</td>
</tr>
</tbody>
</table>

A significant fall in mortality per 100 000 inhabitants can also be observed between the third and the preceding two periods, but not between the first two periods: 6.4 (6.1–6.7) during the first period, 6.1 (5.9–6.3) during the second, and 4.7 (4.5–5.0) during the third (Table 7). Once again, the trends are similar for both sexes. Operative mortality for RAAA decreased significantly: 30-day
mortality was 43.8% (39.7–47.9) during the first period and 36.3% (32.2–40.4) during the last (p=0.012). REVAR was rarely used, but its use still increased from 0.8% to 8.6% from first period to the last. There were clear regional variations in RAAA incidence between the 20 Finnish hospital districts (Figure 3).

The absolute number of elective procedures increased: 1447 during the first period, 1739 during the second and 1882 during the third. Because of the increase in population, the repair rate per 100 000 inhabitants did not show a significant rising trend: 6.8 (6.5–7.1) during the first period, 7.5 (7.2–7.8) during the second and 7.2 (6.9–7.6) during the last. EVAR procedures increased from 18.6% (16.6–20.6) to 50.2% (47.9–52.4) between the first and third period. During the last period, it also seemed that women were significantly more often treated with EVAR than men: 57.3% (55.1–59.6) and 49.1% (46.9–51.4), respectively. Large variations could be seen between hospital districts in how active they were in referring patients for EVAR, with some referring a clear majority and some almost none even during the last period.

Figure 3  Annual RAAA incidence per 100 000 inhabitants in the 20 Finnish hospital districts during 2000–2014. The incidence is shown according to the patient’s local hospital district, regardless of where the actual operation was performed.
2 PREHOSPITAL RAAA MORTALITY (I,II)

Of the 712 patients who suffered a RAAA in the HUS area during 2003–2013, 76.7% were men. Three hundred and thirty patients with RAAA arrived at HUH, 81.2% of whom were men. Thus, 382 patients, 53.7% of all RAAA patients, died before reaching a hospital where the ruptured aneurysm could be treated. This is similar to the corresponding percentage of 52.5% in study I for the entire Finland. The patients who died outside the hospital were more likely to be women and older than those who arrived at HUH. Only 37.3% of the women who suffered a RAAA arrived at the hospital as opposed to the 49.1% of the men (p=0.008). Given that female patients in general were significantly older (mean age 82.6 years, SD 7.4 compared to 74.7 years, SD 9.4), the difference is, however, not statistically significant in study II after age adjustment (p=0.070). In study I, however, comprising all Finnish patients, it remained statistically significant even after age adjustment. The mean age of the patients arriving at HUH was 74.3 years compared to the 78.4 years for those who died prehospital (p<0.001) (Table 8). The most common location for death outside HUH was another health care facility (46.6%) or the home (42.4%).

Table 8  RAAA patients from studies I and II. The number of patients, and percentage out of all RAAA patients (4949 in study I and 712 in study II) in parentheses, who died outside the hospital, were turned down for repair, died within 30 days of repair, or survived at least 30 days after repair. The numbers for both sexes are shown separately with the proportion out of all female or male patients (1058 women and 3891 men in study I, 166 women and 546 men in study II) in parentheses. Mean age in years and standard deviation is also shown. Numbers are not standardised for age.

<table>
<thead>
<tr>
<th>Study</th>
<th>Died prehospital</th>
<th>Turned down</th>
<th>Operated on</th>
<th>Died after operation</th>
<th>Survived &gt;30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of RAAA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2599 (52.5%)</td>
<td>663 (13.4%)</td>
<td>1687 (34.1%)</td>
<td>652 (13.2%)</td>
<td>1035 (20.9%)</td>
</tr>
<tr>
<td>II</td>
<td>382 (53.7%)</td>
<td>34 (4.8%)</td>
<td>296 (41.6%)</td>
<td>97 (13.6%)</td>
<td>199 (27.9%)</td>
</tr>
<tr>
<td>Women (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>653 (61.7%)</td>
<td>194 (18.3%)</td>
<td>211 (19.9%)</td>
<td>105 (9.9%)</td>
<td>106 (10.0%)</td>
</tr>
<tr>
<td>II</td>
<td>104 (62.7%)</td>
<td>16 (9.6%)</td>
<td>46 (27.7%)</td>
<td>18 (10.8%)</td>
<td>28 (16.9%)</td>
</tr>
<tr>
<td>Men (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1946 (50.0%)</td>
<td>469 (12.1%)</td>
<td>1476 (37.9%)</td>
<td>547 (14.1%)</td>
<td>929 (23.9%)</td>
</tr>
<tr>
<td>II</td>
<td>278 (50.9%)</td>
<td>18 (3.2%)</td>
<td>250 (45.8%)</td>
<td>79 (14.5%)</td>
<td>171 (31.3%)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>77.0 (9.1)</td>
<td>79.5 (9.0)</td>
<td>72.6 (8.9)</td>
<td>75.6 (7.9)</td>
<td>70.6 (8.9)</td>
</tr>
<tr>
<td>II</td>
<td>78.4 (9.2)</td>
<td>84.4 (6.8)</td>
<td>73.2 (9.2)</td>
<td>76.9 (8.3)</td>
<td>71.3 (9.1)</td>
</tr>
</tbody>
</table>
3 TURN-DOWN RATE FOR RAAA (I,II)

![Graph showing age distribution of RAAA patients](image)

**Figure 4** Age distribution of all RAAA patients according to whether they were alive or dead 30 days after rupture. The sexes are shown separately. Data from Study I.

The turn-down rate for surgical treatment at HUH was low, 10.3% during 2003–2013. One year, all the patients who arrived were operated on (turn-down rate 0%) and in another 27% were denied repair. This still compares favourably to the turn-down rate of 35% for the entire Finland seen in study I. The patients turned down for repair were considerably older than those operated on (84.4 years [SD 6.9] compared to 73.2 years [SD 9.2], p<0.001). Women were more likely to be turned down for repair, but this is mainly explained by advanced age, and the difference is not statistically significant after age adjustment. The patients not operated on died mostly on the same day they arrived at HUH: the median day of death was 0 (IQR 0–1 days).

In study II the average age of the patients who survived at least 30 days after surgery was 71.3 years (SD 9.1). The overall, in-hospital and operative mortality was highly dependent on age: 50% of those under 70 years survived after RAAA as opposed to only 20% of those over 70 years, while the operative mortality was 17% for the younger patients and 42% for the older patients. Overall, only 28% of all patients who suffered RAAA were alive after 30 days.
Results of study I were similar: patients who died of RAAA were older than those who survived, female patients, in general, being older than men (Figure 4). However, if a RAAA patient survived the 90-day postoperative period, his survival was similar to that of a patient undergoing surgery for an intact AAA (Figure 5).

Figure 5  Kaplan-Meier survival estimates of patients undergoing intact AAA repair and repair for RAAA. a.) Overall 10-year survival. b.) 10-year survival if the patient survived the first 90 days after repair. Data from study I.

4  AAA RUPTURE AT UNDER SCREENING AGE (III)

The mean age of RAAA patients at HUH and TAUH during 2002–2013 was 73.6 years (SD 9.5). Out of all patients, 18.3% were under 65 years of age. Only 3.0% of women, who were on average 8 years older than male patients, were under this age, as opposed to the 21.4% of men (Figure 6). In logistic regression analysis, the odds ratio (OR) for rupture at under 65 years was 15.4 (95% CI 2.1–115.1) when comparing men to women. Smoking also carried a higher risk for early rupture, with an OR of 2.1 (1.2–3.7). Only 13.0% of those who had never smoked or had quit over 5 years previously were under 65 years of age, whereas 28.4% those who currently smoked or had quit less than 5 years previously were under 65 years of age. In the cohort of male smokers, the proportion of early ruptures was the highest, with 31.7% of patients being under 65 years, compared to the 15.8% among male non-smokers. In the logistic regression model, in addition to male sex and smoking, IHD was also
associated with early rupture: patients with diagnosed IHD were less likely to have an early rupture (OR 0.37, 95% CI 0.19–0.71). This would seem counterintuitive but may be because these patients were more likely to be on adequate medication for cardiovascular secondary prevention and maybe also more likely to have had their AAA diagnosed and repaired before the rupture.

Figure 6 The age-distribution of RAAA patients according to sex, and men according to smoking status. The percentages denote the proportion of patients aged under 65 years. Data from study III.

5 AAA RUPTURE AT UNDER THE OPERATIVE THRESHOLD DIAMETER (III)

The mean AP diameter for RAAA patients at HUH and TAUH during 2002–2013 was 75.6 mm (SD 15.8). Only female sex was significantly associated with rupture at a smaller diameter, with an OR of 3.2 (95% CI 1.4–7.5) for rupture under the diameter of 5.5 cm compared to men. The mean diameter was 70.5 mm (15.5) in women and 76.8 (15.7) in men (p=0.005). The size of the aneurysm did not differ between smokers and non-smokers – 74.2 mm (14.6) and 76.6 (17.1), respectively, p=0.250. When compared to the operative limits
suggested by the ESVS guidelines, 11.5% (95% CI 3.5–19.9) of women were under the 52-mm threshold and 5.6% (2.9–8.4) of men under the 55-mm threshold. The difference between the proportions was not statistically significant, p=0.099. The number of women, however, was low, and the confidence intervals are thus wide. Overall, 94.4% of all ruptured aneurysms were over the operative limits suggested in the guidelines.

6 RUPTURE OF IIAA (IV)

The mean age and sex distribution of ruptured IIAA patients were quite similar to those of RAAA patients - 87% were men and the mean age was 76.6 years (SD 9.0). With only 8 female patients, no significant age difference between the sexes could be seen: 76.2 years (SD 8.9) for men compared to 79.8 years (SD 9.0) for women, p=0.296. Most of the patients (70%) had at least one concomitant aneurysm in the common iliac artery or the abdominal aorta. In 44% of the cases, the IIAA was bilateral. Rupture was as common for the right as for the left IIAA (Figure 7).

The mean diameter of the ruptured IIAAs was 68.4 mm (SD 20.5), with no clear difference between the sexes - 69.2 mm (SD 20.9) for men and 62.3 mm (16.8) for women, p=0.406. Only 1 patient (2% of all patients) had a rupture of an IIAA of less than 30 mm in diameter, while 4 patients (6%) had a rupture at under 40 mm. If this is compared to the data on AAA ruptures from study III, the risk of rupture at under 40 mm is roughly equal to that of AAA rupture.
at under 55 mm. In study III, 8% of the ruptures occurred in patients with an aneurysm measuring under 55 mm in diameter.

All the IIAA patients in this cohort were treated surgically, the majority (73%) with open repair and the rest with endovascular repair. Mortality at 30-days was 12.7%, with no difference between the open and endovascular groups, even though the endovascularly treated were older, with a mean age of 80.9 years (SD 5.5) compared to the 75.1 years (SD 9.0) among the patients in the open repair group. \( p=0.021 \). The Kaplan-Meier survival estimate was 74.5% (SE 5.7%) at 1 year and 50.6% (SE 7.8%) at 5 years. The median follow-up was 18.3 months (IQR 2.0–48.3).
DISCUSSION

1 RAAA INCIDENCE

The results on incidence of RAAA from this study seem to fit in with other contemporary data. AAA prevalence has been shown to be on the decline, which is likely true for Finland as well. No contemporary data on AAA prevalence in Finland exists. The RAAA incidence has been studied before, and our results show that the incidence has started to decline, as has been seen in many studies from various countries. Part of the falling incidence may be explained by the increase in elective repair. The age-adjusted repair rate on population level has not increased, but the absolute number of operations has. This is due to the increase in the elderly population most at risk of AAA. The repair rate has remained the same, even though emergency repair rates have fallen, which means that more of the total number of aneurysms are repaired as planned procedures and not as emergencies. The increase in elective repair may be explained by an increased use of EVAR, which has enabled treating patients previously considered to fall outside the treatment due to comorbidities. The age of patients whose aneurysms were repaired rose only slightly during the 15 years, median age rose from 71 to 73 years, indicating that the subgroup of elder and frail patient, that underwent repair, was unlikely to be considerably larger in the later years of the study than at the beginning. A more likely explanation for the growing number of elective repairs is an increase in detection of asymptomatic AAA, most likely because of the more liberal use of imaging in health care overall.

The benefit of treating AAA patients unfit for OAR with EVAR has not been demonstrated, and long-term survival does not seem to be better, because a large portion of the mortality comes from exactly those comorbidities which prevent OAR rather than the aneurysm itself (EVAR Trial Participants 2005a). The fact that the rise in the age of patients undergoing repair was quite small suggests that sufficient control is exercised and patients who will likely not benefit from EVAR are not operated on.

The results of elective repair have also improved, and mortality from both OAR and EVAR has a falling trend, even though the 30-day mortality for either method has not decreased in a statistically significant manner. However, the overall 30-day mortality for elective repair fell significantly from 6.2% (5.0–7.4) to 2.8% (2.1–3.6), because the majority of the repairs during the last part of the study were done with EVAR rather than OAR. Also, OAR results for
women do show a significant change if we look at the 90-day mortality instead of 30-day mortality: it has fallen from 11.5% (95% CI 6.3–16.8) in 2000–2004 to 3.6% (0.0–7.2), p=0.03. Improvements in the mortality rate of elective AAA repair have been observed internationally even though the patients undergoing repair are older. This fall in mortality rate is mostly due to increased use of EVAR. There are, however, some worrying signs that mortality from open repair might be on the rise (Budtz-Lilly et al. 2017). No increase in mortality after open repair could be seen in study I, however. The mortality for both treatment methods showed a falling trend from 2000-2004 to 2010-2014.

The previously reported RAAA incidence figures from Finland are shown in Table 9. In the HUS area, the incidence in 1996–2004 was reported as 5.4 per 100 000 inhabitants, which is somewhat lower than the Finnish average (Laukontaus et al. 2007). This seems to correlate well with the results of the present study and with what is known about the changes in the prevalence of AAA seen elsewhere in the world. The incidence showed an increase up until 2000–2004, after which point it started to decrease.

The incidence in the HUS area seems to be lower than that of Finland in general, 4.3 per 100 000 in study II 2003-2013. The age-adjusted incidence in study I for the entire Finland from 2000 to 2014 was 8.4 (95% CI 8.2–8.6) per 100 000, while in 2010–2014 it was 6.8 (6.5–7.1) per 100 000. The incidence variations in RAAA that were seen in study I across Finland are compatible with the known increase in cardiovascular morbidity from southern and western Finland towards the northern and eastern parts of the country (Saarela and Finnäs 2010). Some of the variations between different studies might also be due to age adjustment; e.g. study I was standardised according to the age distribution in the entire Finland in 2014 to make different regions and time periods comparable. However, the incidences in study II or in the previously published studies are not standardised for age.

Table 9  RAAA incidence per 100 000 inhabitants in Finland according to previous studies and studies I and II. Study I is divided in three 5-year periods. Incidences are not adjusted.

<table>
<thead>
<tr>
<th>Study</th>
<th>Area</th>
<th>Population</th>
<th>Years</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rantakoko et al. 1983</td>
<td>Turku</td>
<td>140 000</td>
<td>1959–1979</td>
<td>4.8</td>
</tr>
<tr>
<td>Kantonen et al. 1999a</td>
<td>Finland</td>
<td>5 100 000</td>
<td>1991–1994</td>
<td>6.1</td>
</tr>
<tr>
<td>Heikkinen et al. 2002</td>
<td>Pirkanmaa</td>
<td>430 000</td>
<td>1990–1997</td>
<td>6.3</td>
</tr>
<tr>
<td>Laukontaus et al. 2007</td>
<td>Helsinki and Uusimaa</td>
<td>1 340 000</td>
<td>1996–2004</td>
<td>5.4</td>
</tr>
<tr>
<td>Study I (unadjusted)</td>
<td>Finland</td>
<td>5 200 000</td>
<td>2000–2004</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 290 000</td>
<td>2005–2009</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 410 000</td>
<td>2010–2014</td>
<td>5.7</td>
</tr>
<tr>
<td>Study II</td>
<td>Helsinki and Uusimaa</td>
<td>1 510 000</td>
<td>2003–2013</td>
<td>4.3</td>
</tr>
</tbody>
</table>
There is some variation in the corresponding figures reported from other countries. In Oxfordshire, United Kingdom, the 2002–2014 incidence of acute AAA was 9 per 100 000 inhabitants and the mortality 5 per 100 000 (Howard et al. 2015b). In Sweden, the RAAA incidence before the adoption of a national screening programme was 11 per 100 000 inhabitants in Malmö in 2000–2004 (Acosta et al. 2006). There was a significant increase compared to the period from 1971 to 1986, when the incidence was 5.6 per 100 000 (Bengtsson and Bergqvist 1993). Since the screening began, emergency repairs in Sweden have been reported to have decreased by half (Wanhainen et al. 2016). The incidence in the catchment area of Stavanger University Hospital in Norway was 11 per 100 000 inhabitants over 30 years and the mortality 7.5 per 100 000 (Reite et al. 2015). In a review of population-based RAAA incidence, it ranged from 2.86 to 14.13 per 100 000 inhabitants (Reimerink et al. 2013b). The included studies were from 1977 to 2012. The incidence was the lowest in 1972–1977 in north Hertfordshire, England (Armour 1977) and the highest in 1981–1986 (Thomas and Stewart 1988) in Waltham Forest, England.

The apparent fall in AAA prevalence, which is mirrored in the decrease in RAAA incidence, is likely primarily due to the decrease in smoking prevalence that is seen in many Western countries as shown in Figure 8 (Sidloff et al. 2014). In 1979, 27% of the Finnish population aged over 15 years were daily...
smokers, but in 2014 only 16%. In men, the change is even more pronounced, from 36% to 17% (Varis and Virtanen 2015).

2 MORTALITY AND TURNDOWN

Mortality from emergency repair after RAAA also shows a decreasing trend which is statistically significant: the 30-day mortality was 43.8% (39.7–47.9) in 2000–2004 and 36.3% (32.2–40.4) in 2010–2014 (p=0.012). The clear decrease in population-based RAAA mortality, however, cannot be caused by these relatively small advances in the results of repair. This is something that is not specific to Finland but is seen also in England and Wales, for example (Anjum et al. 2012).

The age-adjusted mortality from rupture in England and Wales was reported to have fallen from 40.4 to 25.7 per 100 000 inhabitants aged over 50 years from 1997 to 2009. This is still higher than the mortality in HUS during 2003–2013 in the population aged over 65 years in study II, which was 20.9 (13.2–28.7). Emergency hospital admissions in all age groups for RAAA also decreased from 18.6 to 13.5 per 100 000 English and Welsh inhabitants (Anjum et al. 2012).

The 30-day mortality after RAAA was 40.1% in England and 29.3% in Sweden in 2003–2012, and the 90-day mortality was 44.0% and 33.4%, respectively (Karthikesalingam et al. 2016a). The corresponding numbers in Finland were 32.8% and 35.5%, respectively, in HUS for 2003–2013 (study II) and 36.3% and 40.3%, respectively, in all of Finland in 2010–2014 (study I). The five-year Kaplan-Meier survival estimate after RAAA was 46.3% in Sweden and 38.6% in England. The corresponding unadjusted survival rate from study I is 42.1%.

The turn-down rate in Finland is generally very low and is significantly lower in HUH (10%) than the mean turn-down rate for the entire country (28%). Internationally, turn-down rates of well over 50% have been commonly reported (Reimerink et al. 2013b). In our studies, the reasons for declining surgical treatment for RAAA patients were not investigated. The likeliest reasons are that the patient was deemed moribund and would have died with or without surgery, and the patient’s own wishes. It has been argued, however, that in the modern era no patients with RAAA should be turned down, as they will certainly die without treatment (De Rango et al. 2016). Advanced age does not seem to mean that repair is futile, either. In study II, even though mortality was the higher the older the patient was, there were still over 90-year-old patients who survived the repair, even though the mortality was very high.

The prehospital mortality of RAAA is difficult to ascertain, as the cause of death, in many cases, is impossible to verify if no post-mortem is carried out. The number of autopsies has decreased in many countries in recent decades.
Finland has traditionally had a high percentage of post-mortem examinations, but this has decreased as well. The autopsy rate (including medicolegal and medical autopsies) was over 30% during most of the 2000s, but has fallen after 2009. It was still over 20% in 2015 (Data from Statistics Finland). Compared to the autopsy rate of the study by Reite et al. in Stavanger, Norway, where the autopsy rate was less than 1%, the rate in Finland is still high.

AAA deaths, in general, are very likely to be listed as cardiac deaths in patients with an unknown AAA that ruptures and the patient dies suddenly. This is because IHD is very common among patients with AAA. On the other hand, patients with a known AAA who die suddenly may be listed as having died from the AAA, even though the cause of death may actually have been a cardiac death. This latter group is, however, likely to be quite small.

3 IMPLICATIONS FOR AAA SCREENING

A surprisingly large percentage of smoking men who suffered a RAAA were under 65 years of age (III). The proportion of smoking men aged 20–64 years in the HUS area in 2013 was 18.1% (Data from Institute of Health and Welfare, 2016). A man’s 65th year is when he is invited to screening in the United Kingdom and Sweden; in the United States, screening is suggested for men aged 65–75 years who have ever smoked. In the United Kingdom and Sweden, there is no prerequisite of smoking history to be eligible for screening.

If there had been a screening programme in effect in the HUS area during 2002–2013 and every 65-year-old man would have attended, and all ruptures in the attended population could have been prevented, 79.6% of ruptures in male population would have been prevented. The true number would have been much smaller and likely close to the 50% reduction in emergency procedures seen in Sweden (Wanhainen et al. 2016). This is because the attendance is never 100%, and the risk of AAA mortality is often higher in the population that does not attend screening (Norman et al. 2004; Lindholt et al. 2005). Also, the mortality from elective repair is not 0%, even though it is very low in England and Sweden – 0.8% and 0.9%, respectively (Jacomelli et al. 2016; Wanhainen et al. 2016), which is lower than what is found in elective repair outside screening and lower than the mortality in Finland. The number of elective repairs also increases with screening – in Sweden it has doubled (Wanhainen et al. 2016) – which means that more patients are subject to operative risks, not just mortality but morbidity as well.

To reach the patients who suffer rupture at under 65 years of age would require screening at an earlier age. This, however, would not be as cost-effective, as the incidence in younger age groups is low. The strategy of screening at 60 years and rescreening 5 years later has also been found to be cost-effective. It resulted in a larger number of life years gained than a single
scan at 65 years in a CEA using a Markov model (Wanhainen et al. 2005). Screening smokers at an earlier age would be one choice, although earlier screening would increase the need of rescreening patients at a later time. This is something that has already been suggested with the screening age of 65 years because of ruptures that are seen starting from 8 to 10 years after the initial screening (Thompson et al. 2012). A second round of screening would increase costs, even if it just included those who had a subaneurysmal aorta in the first screening. Rescreening these aortas 5 years after the initial screening has been estimated to have only a small effect on costs, and programmes should still be well within the limits that are considered cost-effective (Wanhainen et al. 2005).

Limiting the screening at 65-years to smoking men and screening all 75-year-old men and potentially women as well has been suggested (Howard et al. 2015b). The logic behind this is that, in the Oxfordshire population, it was noted that two thirds of ruptures occurred when the patient was over 75 years of age. However, this does not seem to apply to the population of the HUS district. In study III, over half of the rupture patients were aged under 75 years, even in the group of non-smoking men (Figure 9).

A screening programme for AAA has been advocated in Finland. The consensus from the United Kingdom and Sweden would suggest that the programmes are cost-effective, even if not as cost-effective as the RCTs had led us to expect, due to the falling prevalence. Mortality from RAAA has been
shown to be on the decrease, and the results of elective treatment have improved. One alternative to screening all men would be a more targeted programme focusing on risk groups. Screening PAD and IHD patients has been suggested because of the high prevalence of AAA in these populations (Barba et al. 2005; Giugliano et al. 2012; Vänni et al. 2015). The problem with this approach is that the patients in these groups are often those with a short life expectancy unrelated to AAA, and high surgical risks because of significant comorbidities. There have also been attempts to devise a scoring system, that could be used for focused screening, to identify patients with a high risk of AAA (Kent et al. 2010).

Screening programmes are not without their critics. It has been questioned whether the ethical issues and the psychological harm caused by screening have been adequately evaluated (Johansson et al. 2015). The result of turning previously asymptomatic and subjectively healthy people into patients with a potentially lethal disease can cause emotional distress and a reduction in the quality of life.

The MASS trial did investigate the effect of screening on patients’ mental well-being through several questionnaires. The detection of an aneurysm had a short-term effect on some of the scores used, but the effect disappeared after 12 months (Ashton et al. 2002). The validity of these general, non-disease-specific questionnaires is, however, uncertain.

Although clearly preventing AAA-related deaths, screening also results in deaths – albeit very few. The mortality from elective procedures is still significant, even with EVAR, and some of the patients who die because of elective surgery might not have otherwise died due to the AAA. The estimated risk of death from elective repair of a screening-detected aneurysm is approximately 1 per 10 000 invited men, and elective mortality for screening-detected AAA is lower than of incidentally detected AAA (Svensjö et al. 2014a). However, the risk of actually causing more deaths than preventing exists, especially if patients are operated on with unclear indications.

Operating on asymptomatic patients with aneurysms smaller than 55 mm in diameter is alarmingly common in some countries and might tip the balance towards harm (Beck et al. 2016; Lederle 2016b). From an ethical point of view, it is imperative that patients are well and truly informed of the risks and benefits of screening (Brownsword and Earnshaw 2010). In practice, it is difficult to say, however, what amount of information is enough for the patient to give his informed consent. In the case of choosing whether to attend screening, the relevant information is mainly given through a letter mailed to the patient. The more information this letter includes, the less likely it is to be read and understood. Patients’ understanding of their disease has been scarcely studied, but in a recent American study that used a new AAA-specific questionnaire, it was demonstrated that their understanding was poor, regardless of whether they were under AAA surveillance or their AAA had been repaired (Suckow et al. 2016).
Another problem encountered with screening programmes is that a person can be under surveillance for several years only to be turned down for operative treatment because of high operative risks when the threshold diameter is finally reached (Lim et al. 2015). This can understandably be a frustrating and traumatic experience for the patient and, were this common, also considered a waste of resources.

4 AAA IN WOMEN

Study III demonstrated that the number of aneurysm ruptures at under 55 mm was low. Women were more likely to suffer a rupture at a smaller diameter. This finding fits with the previously observed 4-times higher rupture risk in women compared to men for all aneurysm sizes (RESCAN Collaborators et al. 2013). This implies that a lower repair threshold for women is warranted. The guidelines of the ESVS suggest repair at 52 mm for women, and the American SVS guidelines suggest that repair after 50 mm should be considered (Chaikof et al. 2009; Moll et al. 2011). The reported worse prognosis for women after elective repair (Desai et al. 2016), however, might counter the benefit of earlier surgery. The results from study I show no difference in age-adjusted 30- or 90-day mortality between the sexes after elective treatment. No difference in long-term mortality was seen, either. However, women were less likely to reach the hospital alive, as 57.4% (95% CI 54.4–60.4) died outside the hospital as opposed to the 51.3% (49.7–52.9) of men, even after adjusting for age. Palliative treatment after RAAA was also more likely for women who reached the hospital – 37.9% (33.2–42.6) compared to 26.2% (24.3–28.2) in men. In study II, similar trends were seen in the HUS area, but they were not statistically significant after age adjustment.

The operative mortality after RAAA in study I was also higher for women, 48.1% (41.3–54.8) compared to the 39.0% (36.5–41.5) for men after 30 days, and 52.0% (45.3–58.8) compared to 42.0% (39.5–44.5) after 90 days. The long-term mortality after repair, however, was not significantly different between the sexes. If, indeed, the results of elective repair are similar for women but results after rupture are significantly worse than for men, it would seem beneficial to treat women at a smaller diameter than men. Women are known to more often be outside the IFU for EVAR and more likely to be offered conservative treatment for a non-ruptured AAA, and they also have a higher complication rate than men (Lo and Schermerhorn 2016). Women with AAA are also likely to have more significant comorbidities than men (Skibba et al. 2015). This might be why women only constitute 12.8% of all elective AAA patients but 21.4% of all RAAA patients in study I. The proportion of women out of RAAA patients that undergo surgery is 12.5%, which is explained by
their overrepresentation in deaths outside the hospital and among patients turned down for repair.

5 RUPTURED IIAA

Study IV showed that IIAAs are generally large at the time of rupture, with a mean diameter of 65 mm. The repair threshold of 30 mm is commonly quoted in the literature. It is based on a study that included only seven ruptures, none of which were of an aneurysm of the internal iliac artery (McCready et al. 1983). Aggressive treatment has been advocated, as largely historical data has shown high mortality (Wilhelm et al. 2014). However, more recent reports suggest that the mortality may not be as high as previous reports suggest. For CIAAs, surveillance until a diameter of 35–40 mm has been suggested (Santilli et al. 2000). Data from study IV shows that this higher limit would likely be safe for IIAAs as well. Comparison with data from study III suggests that the number of patients whose aneurysm would rupture before this threshold is roughly equal for AAAs of under 55 mm and IIAAs of under 40 mm. We also showed that the results of ruptured IIAA repair are at least as good as those of RAAA repair. The short-term mortality was slightly lower, but long-term results were similar. This is likely to result from the lower life-expectancy due to cardiovascular comorbidities seen in patients with aortoiliac aneurysms.

Using the 30-mm threshold would obviously prevent more ruptures, although likely not many. Mortality from elective IIAA repair, which these days is mostly performed with EVAR, likely has similar mortality to AAA repair. However, the morbidity is possibly higher. A large portion of the morbidity related to AAA repair comes from occluding the internal iliac arteries. This is something that invariably has to be done when repairing an IIAA, subjecting the patient to a not insignificant risk of ischaemic complications (Jean-Baptiste et al. 2014; Chitragari et al. 2015). The most catastrophic of these are ischaemia of the spinal cord, which can result in temporary or permanent paralysis, and ischaemia of the colon, which is associated with high mortality (Ultee et al. 2016b). More common complications are buttock claudication and impotence, both of which can have a significant impact on patients’ quality of life.
6 LIMITATIONS OF THE STUDY

The study is limited by its retrospective and register-based nature. Registers have missing data and erroneously entered data, which may affect results. The main register used in study I, the HILMO, is not a vascular register but is used primarily for administrative purposes, and thus not all information is readily available and assumptions have to be made in interpreting the data. The sheer volume of data and number of patients is so large that small errors are unlikely to affect this kind of analysis of mostly national-level data and trends. A limitation of the HILMO registry that may affect data from some hospitals during the early period of study I is that procedures performed using the radiology departments' coding system may not have been registered in HILMO. This may result in the omission of some early EVAR procedures. The problems of using cause-of-death data have been discussed previously in this chapter.

Data in the HUSVASC register is entered prospectively by vascular surgeons performing the operations, which means the information it contains is more reliable and pertinent for vascular surgery research. The data on comorbidities is, however, often missing and, in the case of study III, the data missing from the register was searched from patient records. Information on smoking was quite often not noted at all in patient records. Also, quantifying smoking, e.g. by using pack-years, could have been more informative, as smoking is known to have a dose-response to AAA risk (Tang et al. 2016). However, this was not possible with the data available.

Study IV included data that was retrospectively collected from 28 hospitals in 7 countries. Harmonising data from so many sources is problematic, as different centres might measure and report aneurysm diameters, for example, differently. Steps were taken to achieve uniform data by re-measuring aneurysms from original CT images, but this was not possible in all cases and measurements had to be taken from radiologist’s reports.
CONCLUSIONS

1. RAAA incidence has fallen during the studied 15-year period and at the same time treatment results have also improved (I).
2. The proportion of patients who died outside the hospital is large, over 50%. This is more than in many previous publications. The proportion seems to be similar in the HUS district (II) as in Finland in general (I), with no observable change during the past 15 years (I). The turn-down rate in HUS is low, only 10%, which is lower than in Finland in general. This does not, however, seem to result in higher operative mortality, as has been reported elsewhere (II).
3. Aneurysm rupture under the age of 65 is rare in women, but not very uncommon in men, especially among current smokers or those who have quit during the past 5 years. In this population, nearly a third of all ruptures occurred before the patient’s 65th year. The diameter of the aneurysm at the time of rupture did not seem to be affected by smoking, but women were at a higher risk of rupture at under 55 mm in diameter than men.
4. IIAAs were, on average, almost 70 mm in diameter at the time of rupture. The most commonly referenced threshold for operative treatment is 30 mm. Only 1 ruptured aneurysm in the series was under this size. As mortality was similar or better than after RAAA, raising the threshold to 40 mm should be safe and associated with an acceptable rupture risk comparable to that of AAA.
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