ABDOMINAL AORTIC ANEURYSM

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Thesis mentor: Prof. Dr. Sc. Miljenko Kovačević, dr. med.

The graduation thesis was graded on **June, 25 2024** in **Rijeka**, before the Committee composed of the following members:

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The graduation thesis contains 35 pages, 10 figures, 2 tables, and 192 references.

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Hereby, I want to thank my family from my deepest heart. Realizing this dream would have never been possible without you, I am endlessly grateful for your faith, support, hard work and love.

Sizleri çok seviyorum.

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LIST OF ABBREVIATIONS AND ACRONYMS

AA – Abdominal Aorta
AAA – Abdominal Aortic Aneurysm
ACE-inhibitors – Angiotensin Converting Enzyme-Inhibitors
CAD – Coronary Artery Disease
CHF – Congestive Heart Failure
COPD – Chronic Obstructive Pulmonary Disease
CT – Computed Tomography
CTA – Computed Tomography Angiography
CVD – Cardiovascular Disease
DM – Diabetes Mellitus
ECM – Extracellular Matrix
ESVS – European Association for Vascular Surgery
EVAR – Endovascular Aneurysm Repair
EVAS – Endovascular Aneurysm Sealing
GI – Gastrointestinal
HR – Hazard Ratio
IFN-gamma – Interferon-gamma
IL – Interleukin
ILT – Intraluminal Thrombus
LDL – Low-Density Lipoproteins
MMP – Metalloproteinase
MRI – Magnetic Resonance Imaging
NSAID – Nonsteroidal Anti-inflammatory Drugs
O2- – Superoxide Anion
OSR – Open Surgical Repair
PAD – Peripheral Artery Disease
QALYs – Quality Adjusted Life Years
rAAA – Ruptured Abdominal Aortic Aneurysm
RNA – Ribonucleic Acid
ROS – Reactive Oxygen Species
RR – Relative Risk
SNPs – Single Nucleotide Polymorphisms
Th1 – T-Helper Type 1
Th2 – T-Helper Type 2
TNF-α – Tumor Necrosis Factor Alpha
US – Ultrasonography
VSMC – Vascular Smooth Muscle Cells

1. INTRODUCTION

An Aneurysm is a vascular pathological condition characterized by a localized permanent dilatation of any blood vessel but most commonly affecting the abdominal aorta. In the ancient Greek language, the word ἀνεύρυσμα (aneurysma) translates to “a widening,” or “an opening” (1).

An abdominal aortic aneurysm (AAA) can develop in any part of the aorta located between the diaphragm and where it bifurcates into the iliac arteries. It is characterized by a pathological dilatation of the aorta due to degeneration of the aortic wall. While it loses support, it bulges in the direction of the blood pressure and therefore makes the aorta highly vulnerable to rupture the larger it grows. An aneurysm rupture causes massive internal bleeding with a fatal outcome without successful surgical repair.

Most commonly AAAs occur in the infrarenal segment, accounting for approximately 80% of all cases.

The morphologic character mostly observed in AAA is the concentric or fusiform type of aneurysm where the full circumference of the aorta is pathologically enlarged. Saccular aneurysms are of morphology with only partial involvement of the vessel circumference; in AAA this type is less common.

Further differentiation of aneurysms is the true aneurysm from the false, also known as pseudoaneurysm. A pseudoaneurysm occurs when there is an injury to the vessel wall, causing communication between the artery and surrounding tissue or structures through a small defect, resulting in leakage and collection of blood outside the aorta. In contrast, a true aneurysm is defined by an intact vessel wall, which is weakened and protruding outward, forming a sac that contains all layers of the arterial wall (intima, media, and adventitia).

In accordance with the latest guidelines from the European Society for Vascular Surgery (ESVS) 2019, the prevailing definition of AAA relies on the measurement of the abdominal aortic diameter through ultrasound or CT angiography (CTA). An aneurysm is identified when the diameter of the abdominal aorta (AA) exceeds 3.0 cm, which is significantly larger than the average diameter ranging from 1.5-2.0 cm (2,3). This measurement is particularly reliable for diagnosing AA in men. Alternatively, some researchers suggest an alternative criterion, defining AAA as a maximum infrarenal aortic diameter that exceeds 1.5 times the typical dimensions of the infrarenal or suprarenal aortic diameter. This approach aims to account for personal variations in the width of adjacent aorta and different measurement techniques. Notably, this alternate measurement proves to be more reliable for women and is applicable to cases involving iliac artery aneurysms and other related conditions (3).

2. AIMS AND OBJECTIVES

This thesis aims to provide a thorough exploration of abdominal aortic aneurysms (AAA), encompassing their risk factors, pathogenesis, clinical presentation, diagnostic modalities, ruptures, and management strategies along with their complications.

Globally, AAA poses a significant health threat, with mortality rates among affected individuals surpassing those of the general population, predominantly due to cardiovascular events and ruptures.

Thus, early identification and intervention are essential for the effective therapy of these patients. Primary care physicians, as the frontline healthcare providers, wield the essential tools for diagnosing AAA, leveraging risk factor assessment, comorbidity evaluation, physical examinations, and diagnostic procedures such as ultrasound available in primary care centers. Moreover, this thesis aims to advocate for the engagement of our healthcare system in education and the reduction of modifiable risk factors, particularly smoking, to mitigate mortality rates associated with AAA.

To achieve these aims, this thesis will undertake a thorough literature review, analyzing current evidence, identifying knowledge gaps, and proposing recommendations for future research. Through this comprehensive approach, it is hoped that this thesis will make meaningful contributions to the understanding and management of AAA, ultimately striving towards better patient care and outcomes in this critical area of healthcare.

3. EPIDEMIOLOGY

Abdominal aortic aneurysms (AAA) pose a substantial health concern globally.

The prevalence range for developing AAA is about 4 to 8 percent, predominantly affecting males and maintaining relative stability over the past two decades (4,5).

The ARIC study determined that the risk over the course of a lifetime of developing AAA is around one in 17. Determining the demographics most prone to developing AAA, male gender, smokers, white ethnicity, high stature, and elevated LDL or total cholesterol are linked to a higher risk of both clinical and asymptomatic AAA. This study additionally shows that at the age of 45, the lifetime probability for AAA in women, men, African Americans as well as Caucasians was 3.2%, 8.2%, 3.2%, and 6.5%, in the sequence provided. The risk throughout life for AAA was highest in current smokers (10.5%) and those in the upper two-thirds of pack years (9.0% and 11.1%). Former smokers who quit smoking between the first and fourth visit had a 29% lower AAA likelihood compared to persistent smokers but still had elevated risk than pre-first visit quitters. Women who currently smoke had a similar probability of AAA (8.2%) to male former smokers (8.1%) (6).

Highlighting age as a vital factor influencing occurrence, a particular study found that in males aged 65 to 74 years, the incidence was 55 per 100,000 person-years, which increased to 112 per 100,000 person-years for males aged 75 to 85 years, and further rose to 298 per 100,000 person-years for those surpassing 85 years of age (7). Individuals over 60 years are experiencing a sharp rise in incidence predicting a future increase in prevalence in line with the aging population.

Smoking history continues to be a crucial factor in identifying specific population subsets with a heightened risk of developing AAA (Fig.1). The decrease in the prevalence of tobacco use is strongly associated with decreased AAA-related mortality and a decline in the incidence of AAA diagnosis.

Another screening study, involving 81,150 men, reveals, that the general frequency of screening-detected AAA (diameter >3.0 cm) was 3.4%, marking a decrease from 5.0% in 1991 to 1.3% in 2015 (8). It is crucial to note that these percentages may vary, reflecting the smoking habits within a particular population.

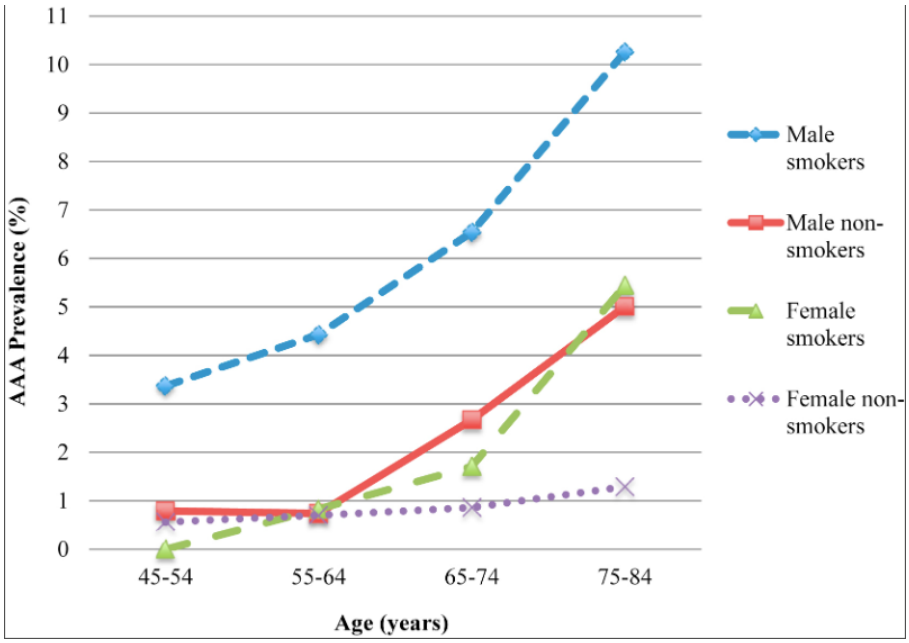

Figure 1: Epidemiology of abdominal aortic aneurysms (9)

4. RISK FACTORS

Understanding both the risk factors and protective factors associated with AAAs is crucial for disease prevention and management. Modifiable risk factors, including hypertension and smoking, contribute significantly to the likelihood of developing AAAs. Meanwhile, nonmodifiable factors like male sex and family history also play significant roles. Through recognizing and mitigating the risk factors, individuals can proactively take measures to lower their chances of developing aortic aneurysms and enhance their overall cardiovascular well-being.

Table 1 provides an overview of relevant risk factors further explained in detail throughout the following segment of this paper.

Table 1: Risk Factors for Abdominal Aortic Aneurysm Diagnosis (10)

Risk factor	Relative risk	95% CIs
Male sex[a]	5.93	4.26, 8.25
Hypertension	1.66	1.49, 1.85
Per 20 mmHg higher systolic blood pressure	1.14	1.06, 1.23
Per 20 mmHg higher diastolic blood pressure	1.28	1.12, 1.46
Current smoking	4.87	3.93, 6.02
Former smoking	2.10	1.76, 2.50
Per 10 pack years	1.78	1.54, 2.06
Family history of aortic aneurysm[a]	3.80	3.66, 3.95
Coronary heart disease[a]	2.29	1.75, 3.01
Peripheral artery disease[a]	2.50	2.12, 2.95
Diabetes	0.58	0.51, 0.66

4.1. Age and Sex

Age stands as a crucial risk factor for AAAs rising as individuals age. Both sexes share advancing age and current smoking as primary risk factors in developing the disease as well as its progression.

After reaching the age of 60 years the likelihood of AAAs significantly rises (Fig.2).

AAA occurrences are significantly higher in men compared to women, with a prevalence four to six times greater (11,12). Moreover, AAAs in women tend to emerge roughly ten years subsequent to men (13). In men, the likelihood of AAA surges nearly 200-fold from the age range of 40–44 to 75–79, with rates increasing from 0.83 to 164 per 100,000 (14).

Notably, women experience a more aggressive disease course, with faster AAA growth rates and a rupture risk four times higher than men (15–17). Despite a lower overall prevalence, roughly 30% of patients with a ruptured AAA are female, often presenting with smaller aneurysm diameters at rupture. In populations under 60 years, the incidence and prevalence are less significant (18).

The true prevalence in females might be underestimated due to the ≥30 mm definition for aneurysms, which may not fully consider body size differences. Altering the threshold to 26–27 mm for women reveals a potential doubling in AAA prevalence among 70-year-olds (19,20).

These findings underscore the critical interplay of age, particularly in conjunction with sex, in the emergence and progression of AAAs.

Risk factor	Aneurysm of the abdominal aorta					
	Men			Women		
	Aneurysm present (*n* = 263)	Aneurysm absent (*n* = 2,699)	*p* value	Aneurysm present (*n* = 74)	Aneurysm absent (*n* = 3,350)	*p* value
Age (years)	66.4 (6.1)	60.8 (10.0)	<0.001	69.4 (5.4)	61.2 (10.2)	<0.001
Height (cm)	175.2 (6.5)	175.1 (6.8)	0.7	162.1 (4.9)	161.5 (6.3)	0.4
Weight (kg)	81.7 (12.8)	79.4 (11.8)	0.003	67.8 (12.9)	67.6 (11.7)	0.9
Body mass index (kg/m^2)	26.6 (3.7)	25.9 (3.3)	0.001	25.8 (4.6)	25.9 (4.4)	0.7

Figure 2: Aneurysms in male compared to female sex (21)

4.2. Smoking

Tobacco use stands out as the key modifiable risk factor contributing to the growth, expansion, and rupture of AAA. Approximately 90 percent of individuals with AAA have a background of nicotine consumption. Among all conditions, lung cancer shows the strongest epidemiological association with smoking tobacco (22). Particular attention should be given to the correlation between male sex and smoking, as males face the highest risk of developing AAA (see Fig. 1). A nested case-control study within a population-based screening program for men aged over 50 reveals that current smokers exhibit a 7-fold increase in the likelihood of developing AAA compared to age-matched nonsmokers. In the same study, it was concluded that nicotine consumption influences AAA growth in a dosage-dependent manner, influenced by both the duration and quantity of smoking (15,23,24). Each year of smoking elevates the relative risk (RR) of AAA by 4%, resulting in a combined RR of 1.87 for every 10 cigarettes smoked daily (25,26). Therefore, both current smokers and ex-smokers have an increased occurrence of aneurysms in contrast to nonsmokers (25). Furthermore, the association between AAA and smoking is even more pronounced than that with coronary artery disease or chronic obstructive pulmonary disease (COPD) (27). COPD has been proposed to have a positive association with AAA irrespective of smoking status (28,29) but yet does not appear to accelerate AAA growth (30). However, it is believed to increase the risk of rupture at smaller diameters (31).

Current smokers face a significantly elevated risk, with a hazard ratio (HR) of 5.55 compared to 1.91 for former smokers (32). It requires roughly a decade for the surplus risk in ex-smokers to diminish by half, and it takes a minimum of 25 years after cessation for it to approximate that of individuals who never smoked (26,33,34). Unfortunately, the risk never returns to that of individuals who never smoked, suggesting that some arterial damage caused by tobacco use may be irreversible (15).

Ultimately, smoking does not only influence the AAA development but also accelerates its growth rate by 15-24%, increasing the rupture risk regardless of the aneurysm's diameter, while cessation of smoking ultimately correlates with reduced rates of AAA formation, aneurysm growth, and rupture (8,35–38).

4.3. Family History and Genetic Influences

Having a positive family history indicates double the risk of developing AAA (39–42). Individuals with first-degree relatives who have a history of AAA are particularly susceptible to developing the condition themselves (39,40,43). In cases of familial AAA, affected individuals are prone to develop AAA at an early age, with a faster rate of growth and a higher rupture rate compared to those without a positive history. There are no apparent differences in aneurysm morphology between both patient groups (44,45).

Between 6% to 20% of individuals with AAA have a positive hereditary background (43,46–48), yet apart from rare hereditary disorders like Marfan syndrome or Ehlers-Danlos syndrome (49), specific hereditary patterns explaining familial AAA clusters remain unidentified.

Genetically and epigenetically, microRNAs and long noncoding RNAs are associated with influencing the formation of AAA such as mechanisms sustaining inflammation, apoptosis of smooth muscle cells, and degradation of extracellular matrix (ECM) (50–52).

In terms of single nucleotide polymorphisms (SNPs), genetic variations linked to AAA are diverse and partly overlap with those linked to cardiovascular disease (51,52). Therefore, polygenic effects are highly associated to contribute to AAA development. Presently, the defined genetic predisposition of aneurysmal disease is understood in small portions, but the identified factors offer valuable insights into pathogenetic mechanisms and could potentially function as diagnostic markers and targets in therapy in the years ahead (53,54).

4.4. Ethnicity and Socioeconomic Factors

The AAA prevalence is higher among Caucasian males as opposed to males of African-American, Hispanic, and Asian origin. For instance, among African Americans, AAA incidence is half as frequent as for White Americans (11). Additionally, a study conducted in the United Kingdom revealed that the incidence of AAA in males aged 65 and older shows a tenfold decrease among Asian populations, resulting in a prevalence of 0.45 percent (55).

Despite anatomical or biological differences, disparities in the progression of the disease and its outcomes among different ethnicities may be influenced by factors such as education level, socioeconomic status, and disposable income (23,56). The level of education is of special importance in shaping individuals' perceptions of and approaches to their own health. It is widely recognized that lower levels of education are linked to reduced compliance with prophylactic pharmacotherapy and diminished effectiveness in tobacco cessation (57,58).

4.5. Atherosclerotic Cardiovascular Diseases

AAA patients often exhibit concurrent atherosclerotic cardiovascular diseases (CVDs), such as coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (6,59–61). While CVDs and AAA are typically regarded as distinct entities (62), they frequently coexist owing to the significant overlap in the etiologies and pathogenesis. Hypertension, hyperlipidemia, male gender, and tobacco use are commonly identified contributing factors to the development of both conditions (11,23,55,63). However, a notable difference lies in the influence of diabetes on these conditions (64).

Coronary artery disease affects over 25% of patients with AAA, while peripheral arterial disease affects more than 12% (11,15,45). Prolonged high blood pressure can compromise the strength of the aortic wall over time, and lipid accumulation in atherosclerotic plaques may also contribute to weakening.

Individuals with AAA tend to experience more severe cases of atherothrombotic diseases and face an increased risk to suffer cardiovascular incidents. Consequently, in the presence of a small AAA, affected patients have around 1.5 times greater likelihood of experiencing cardiovascular events compared to those without AAA, with a 3% mortality risk of cardiovascular origin annually (65,66). Despite the heightened risk of AAA ruptures leading to mortality, cardiovascular events remain a primary cause of death in AAA patients (67,68).

4.6. Arterial Hypertension

The onset of growth of AAA is markedly elevated with present hypertension, particularly among women (69). Although high arterial blood pressure doesn't directly impact the growth of AAAs, it does elevate the probability of aneurysm rupture in patients with concomitant hypertension (37). AAA formation and rupture are not only closely linked with the presence of hypertension but are especially considered dose-dependent, with diastolic blood pressure potentially exerting a stronger effect compared to the systolic pressure (35,38,69). As studies suggest, with each increase of 10 mmHg in mean arterial blood pressure, there is an increased risk of rupture by 1.11 times (35).

4.7. Presence of Other Larger Vessel Aneurysms

Pre-existing aneurysms in the arteriae iliaca, femoralis, poplitea, and carotis increase the probability to develop an AAA in patients. Nonetheless, notable distinctions between AAA and other aneurysms of major vessels concerning inflammatory cell infiltration and enzyme activity can be established.

Hence, although other large vessel aneurysms may be present, not all AAAs are associated with them, and vice versa (70). In patients with femoral artery aneurysms, there is an 85 percent chance of also having a concurrent AAA, while individuals with popliteal aneurysms exhibit a 60 percent chance of coexisting AAA (71,72). Additionally, around 25 percent of individuals present with both aneurysms of thoracic and abdominal aorta, with a higher prevalence observed in women compared to men (48 percent versus 28 percent) (73,74). Furthermore, there is evidence of AAA coexisting with intracranial aneurysms. Some advocate for AAA screening in patients diagnosed with intracranial aneurysms (75–77).

4.8. The Protective Role of Diabetes Mellitus

Despite being typically linked with atherosclerosis, most research indicates an inverse relationship between diabetes mellitus (DM) and AAA. Large epidemiological and clinical studies observed consistently that diabetic patients face approximately half the risk of developing AAA compared to non-diabetic individuals (78–80). Additionally, DM patients have a slowed AAA growth rate of about 25 percent and significantly lower rates of rupture (35,37,81). Yet, indicative of their greater cardiovascular burden overall, diabetic patients exhibit heightened mortality following aneurysm repair and experience reduced life expectancy spanning from two to five years (78).

The aortic wall observed in diabetic individuals shows significant thickening accompanied by the hyperglycemic environment, which can exert protective effects both biochemically as well as mechanically for the development of AAAs (82). Interestingly, hyperglycemia might have a potential weakening effect on the formation and progression of AAA, as some research discovered (83).

Additionally, agents used in pharmacotherapy for DM management may inhibit AAA development. Metformin predominantly stands out and is believed to lower the probability of AAA formation and growth (84).

Research suggests that metformin independently reduces inflammatory markers in animal models and slows AAA progression in ongoing studies globally. Present trials seek to elucidate the way metformin modifies the formation of AAA and the expansion or rupture risk (85).

5. PATHOPHYSIOLOGY

The complex aneurysm development in the infrarenal aorta is initially influenced by factors that make the tissue highly susceptible, including its embryonic origin, tissue structure, and specific hemodynamic patterns. Inflammation, particularly when IFN-gamma is inhibited, contributes to the breakdown of key structural components like collagen, elastin, vascular smooth muscle cells (VSMC), and extracellular matrix (ECM) proteins of the aortic wall (86). This ultimately results in a gradual weakening process, leading to the irreversible loss of the artery's elasticity and resilience. Consequently, it contributes to the formation, enlargement, or even rupture of infrarenal aortic aneurysms.

5.1. Anatomy, Embryology and Histology of Infrarenal Aorta

In contrast to other segments of the aorta or iliac arteries, the smooth muscle cells in the infrarenal aorta display a heightened susceptibility to aneurysmal degeneration, stemming from their embryological origin in the paraxial mesodermal somites. Regions originating from somites are notably predisposed to aneurysm development (86).

Throughout the entire length of the aorta, starting from the conus arteriosus and reaching the bifurcation of the iliac arteries, the thickness and amount of elastic lamellae and collagen in the media progressively decrease, and a remarkable tenfold reduction in elastin is observed (87). Additionally, the abdominal aorta has a higher fragility in its vasa vasorum, leading to relatively lower vascularization of the media in contrast to the thoracic aorta (88,89).

5.2. Hemodynamics and Biomechanical Factors

The unique hemodynamic and mechanical properties of the infrarenal aorta make it particularly predisposed to aneurysms (90). As the aorta narrows and branches out, the blood wave amplitude intensifies as it travels towards the lower parts of the aorta (91). The effects of circulatory dynamics at the iliac bifurcation often generate pressure-reflective waves, causing frequent disturbances affecting the hemodynamic patterns within the segment of the aorta. Consequently, there are significant collisions between circulating cells and the wall of the aortic, leading to injuries of endothelium and plaque buildup. Thereby the continuous forces exerted on the aortic wall precipitate continuous injury of endothelium in this specific location (92,93).

5.3. Intraluminal Thrombosis

Various hypotheses have emerged regarding the significance of progressively forming intraluminal thrombus (ILT) in approximately 75% of cases of AAAs, including the tendency of the AAA patients' aortic walls to remodel outwardly to preserve the vessel lumen (94–96).

Within the ILT, the physiologically active material constructed within the arterial lumen significantly contributes to the degeneration and inflammation affecting the medial and adventitial layers of the aortic wall (97,98). The blood flow consistently renews the ILT's inner side with fibrinogen, whereas active fibrinolysis takes place on the outer side (97).

Moreover, circulating cellular elements, including erythrocytes and neutrophils within the luminal region elicit oxidative stress through the release of myeloperoxidase and iron.

The volume of the ILT reduces the availability of oxygen within the aortic wall, possibly heightening the neutrophil response and elastase synthesis. Furthermore, the presence of ILT correlates with reduced arterial wall thickness, increased elastin breakdown, reduced vascular smooth muscle cells (VSMC) in the medial layer, and pronounced inflammation within the adventitial layer, all of which are collectively linked to accelerated AAA growth (99).

5.4. Inflammation

Inflammation primarily drives the formation, enlargement, and rupture of AAA.

As aforementioned, the ILT at the luminal side attracts circulating inflammatory cells, predominantly T-lymphocytes and macrophages, enabling transmural infiltration. The infiltrative process is provided by diapedesis due to neovascular growth in the medial layer, influenced by hemodynamic factors and complement system activation (100). Periadventitial lymph nodes and adventitial vasa vasorum additionally provide an alternative entry route for immune cells to penetrate the aortic wall (90). Moreover, adipocytes located in perivascular tissue promote immune cell activity by releasing proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), IL-6, and IL-8 (101).

CD4+ helper cells are mainly responsible for the inflammatory process by coordinating two separate immunological reactions, including the T-helper type 1 (Th1) and T-helper type 2 (Th2) responses. The Th1 reaction clears intracellular pathogens through the release of cytotoxic cytokines like interferon-gamma (IFN-γ), interleukin-2 (IL-2), and lymphotoxin, leading to macrophage-mediated cellular immunity (86).

In contrast, the Th2 response by CD4+ helper cells secretes IL-4, IL-5, IL-9, IL-10, and IL-13, fostering a robust antibody response, promoting eosinophils, and inhibiting macrophage-mediated immunity (102,103).

The transmural infiltration of inflammatory cells includes the action of polymorphonuclear neutrophils, T-cells, B-cells, macrophages, mast cells, and natural killer cells (104). The prevailing cell types, particularly CD4+ T-cells, B-cells, and macrophages, signify a shift towards a Th2 inflammatory response (102). Additionally, AAA demonstrates an inclination towards Th2 cytokine secretion, primarily IL-4, while inhibiting IFN-γ (103). These Th2 cytokines exert multifaceted effects on smooth muscle cells, the extracellular matrix, and other inflammatory cells involved in AAA growth (103,105).

Furthermore, reactive oxygen species (ROS), notably superoxide anion (O2-), are markedly elevated in diseases of aortic tissue, particularly in tobacco smoking patients (86). ROS, resulting from the abundance of inflammatory cells, contributes to the Th2 inflammatory phenotype (106). They act through nicotinamide adenine dinucleotide phosphate-oxidases, explicitly inducing VSMC apoptosis and amplifying the Th2 inflammatory response driving AAA development (107). Additionally, ROS upregulates enzymes like matrix metalloproteinases (MMPs), further promoting extracellular matrix degradation (108). Additional processes resulting from ROS involve the uncoupling of endothelial nitric oxide synthase, myeloperoxidase, xanthine oxidase, cyclooxygenase, and mitochondrial metabolism (109).

5.5. Oxidative Stress and VSMC Apoptosis

The accumulated content within the ILT contributes to oxidative stress by causing the reaction of nitrogen and oxygen species (ROS). Oxygen- and nitrogen-based free radicals subsequently induce proteolytic enzymes to initiate the degradation pathways along with the apoptosis of vascular smooth muscle cells (VSMCs) and mesenchymal progenitor cells (108,110). Not only does this mechanism weaken the medial wall but also hinders its ability to produce and repair its matrix. Additionally, proinflammatory signals exacerbate VSMC apoptosis (111,112).

Abundant cell death and transformation of contractile VSMCs, known as the 'phenotypic switch', are distinctive features of the weakened wall in aneurysmal aortas (113).

The depletion of smooth muscle cells is accompanied by elastolysis and can clearly be seen in histopathologic examination of aneurysmatic vessel walls (Figure 3).

Emerging neovascularization is observed in the medial layer due to the increased stress on the compromised wall resulting from the loss of VSMCs and the replacement of the endothelial lining by the ILT. However, the emergence of new blood vessels exacerbates the destructive cycle by facilitating the infiltration of circulating inflammatory cells (114).

5.6. Proteolysis

The breakdown of the intricately organized extracellular matrix (ECM) network within the medial layer of the aortic wall is a critical factor in the onset of AAAs. Its deterioration compromises the aorta's capacity to endure blood flow-related strain, and due to disrupted physiological tissue remodeling, the aorta progressively dilates (115). Proteases, enzymes responsible for protein degradation, play an important role by excessively breaking down the structural supporting components of ECM like collagen, elastin, and cell adhesion molecules (100,101) (Figure 4). Additionally, proteases facilitate the detachment and apoptosis of vascular smooth muscle cells (VSMCs) by targeting cell adhesion molecules (112). Inflammatory conditions and oxidative stress exacerbate protease activity, perpetuating a harmful cycle (116). Several protease families, including matrix metalloproteinases (MMPs), cathepsins, and neutrophil elastase, are implicated in AAA development (117,118). Clinical investigations have revealed elevated MMP levels, notably MMP-9 and MMP-2, in both blood and tissue biopsies from AAA patients (119). Furthermore, elevated cathepsin concentrations are related to a heightened vulnerability for AAA development and greater aneurysm sizes (120).

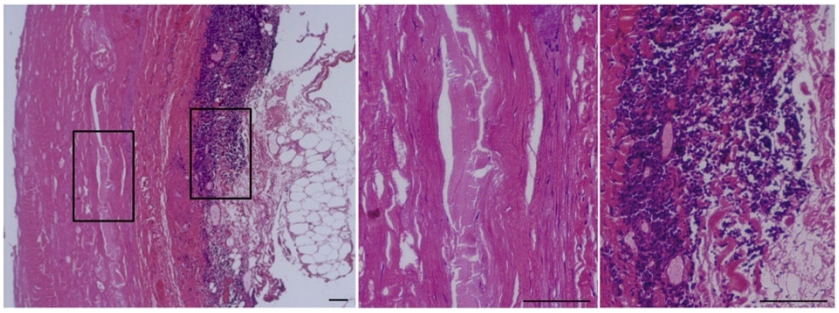

Figure 3: Haematoxylin-eosin stain of the abdominal aorta of a patient with an AAA: absence of VSMC in the middle layer of the vascular wall and immunoinflammatory infiltrate of adventitia (80)

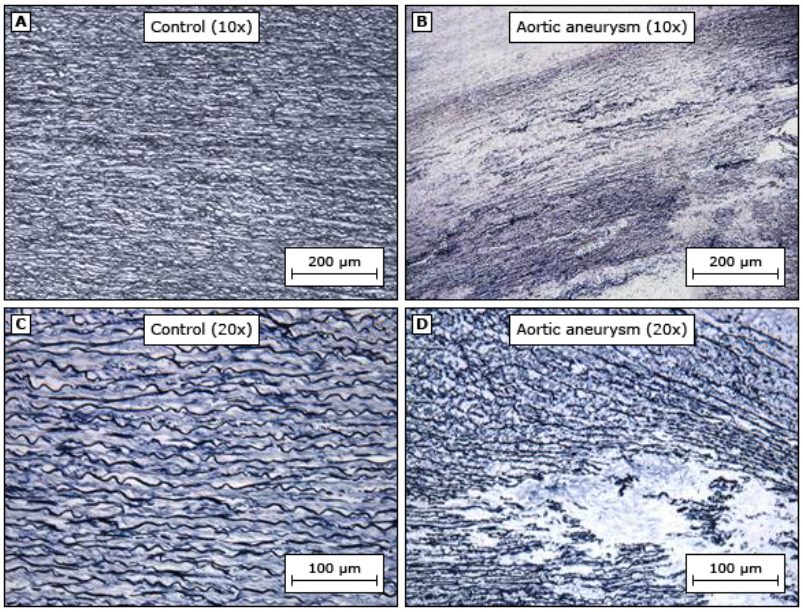

Figure 4: Verhoeff's elastic staining reveals elastic fiber degradation in aortic aneurysm samples at both 10x (B) and 20x (D) magnification, contrasting with control aorta specimens shown at 10x (A) and 20x (C) magnification (86)

6. CLINICAL PICTURE

AAAs typically are silent and are frequently detected unintentionally during diagnostic processes including ultrasound imaging, abdominal computed tomography (CT), or magnetic resonance imaging (MRI) undertaken for unrelated causes (121), or until they enlarge or rupture. Aneurysms that cause symptoms, particularly discomfort and pain upon manual examination, are at a heightened risk of rupture. Prior to rupture, affected individuals might notice mild back, flank, abdominal, or groin discomfort. Of particular concern is isolated groin pain, which can occur due to retroperitoneal expansion pressing on the femoral nerve, sometimes presenting without other associated symptoms, necessitating a heightened awareness for diagnosis. In some cases, AAAs may induce complaints through local compression, potentially causing stomach discomfort, loss of appetite, feeling nauseous, emesis, difficulty urinating, or venous thrombosis. Dorsalgia may arise from deterioration of the AAA extending into nearby vertebrae. Additional complaints may present as abdominal or pelvic discomfort, embolic incidents involving the toes, and fever. Occasionally, small AAAs may cause thromboembolism, resulting in acute claudication. Patients often experience the sensation of a pulsating mass in the abdomen. Progressive symptoms should alert clinicians to the likelihood of impending rupture. Increasing AAA size often triggers abrupt, intense, and persistent lumbar, flank, abdominal, or pelvic pain. Occasionally, loss of consciousness can be the presenting complaint, whereas pain is a less dominant complaint (122).

7. GROWTH AND RUPTURE OF AAA

With a mortality rate of 65–80% overall, the rupture stands as the primary complication of AAAs (123). On a global scale, around 150,000–200,000 fatalities are traced to AAA rupture annually (124). Data from the United States reveal that ruptured AAAs are predicted to be responsible for 4% to 5% of unexpected demises (125). Over recent decades, there has been a decline in the rate of occurrence and fatalities of ruptured AAAs (rAAAs), juxtaposed with an increase in intact AAA diagnoses (126). Half of patients with ruptured AAAs successfully reach the hospital alive, however, among those who do, up to half do not survive the repair procedure (127).

7.1. Growth Factors and Predictive Factors

The pattern of disease progression often follows an inconsistent growth trend with sporadic episodes of aneurysmatic enlargement (90). Typically, most AAAs increase in size over time, with an average growth velocity ranging between 2.2 and 2.8 mm per year (37). However, growth rates can vary significantly among individuals, with roughly half of AAAs never progressing to the point of requiring surgery or risking rupture (128). The risk factors linked to the enlargement and rupture of AAA coincide with those discussed in the "Risk Factors" section pertaining to its development. Among those, studies indicate that smoking as a major modifiable risk factor, significantly influences growth rates, with current smokers experiencing a 20% increase in growth rates (90).

The baseline diameter (Table 2) provides an initial measurement of the aneurysm and serves as a reference point for estimating its growth rate. Subsequent measurements are then utilized to assess the potential for rupture. It is suggested that larger aneurysms generally demonstrate faster growth and higher rupture rates. In conclusive studies, it was determined that for every additional 0.5 cm in diameter, rupture rates double (128). Moreover, there is compelling evidence indicating that rapid aneurysm expansion by more than 2 mm annually substantially predicts clinical events related to AAA (128).

The established association between diameter and the likelihood of rupture forms grounds for establishing adequate monitoring schedules for affected individuals with smaller aneurysms of the aorta (128).

Table 2: Baseline Aortic Diameter Rupture Risk (86)

Baseline aortic diameter rupture risk table

Baseline aortic diameter	12-month rupture risk
3.0-3.9 cm	<1%
4.0-4.9 cm	1%
5.0-5.4 cm*	2.7%
5.0-5.9 cm	1.7-11%
6.0-7.0 cm	5.1-22%
>7.0 cm	19-33%

* Females only.

Adapted from: Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg 2011; 41 Suppl 1:S1.

Additional data from:

1. *Chaikof EL, Dalman RL, Eskandari MK, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg 2018; 67:2.*
2. *Lancaster EM, Gologorsky R, Hull MM, et al. The natural history of large abdominal aortic aneurysms in patients without timely repair. J Vasc Surg 2022; 75:109.*

7.2. Clinical Pictures Of AAA Rupture

When diagnosing a rapidly expanding or ruptured AAA, it is essential to consider abrupt pain of sharp, tearing, or stabbing character in the abdomen or chest, radiating to the back or flank areas. Special attention should be paid to patients over the age of 50 presenting with syncope or accompanying hemorrhagic shock signs, including cold, sweaty, and pale to marbling skin, altered levels of consciousness, tachycardia, and very low blood pressure (122). Nonetheless, the typical triad representing the clinical picture—abdominal or back pain, shock, and a palpable clinical mass—is evident in only roughly half of rAAA cases, often leading to misdiagnoses such as acute coronary syndrome or perforated gastroduodenal ulcer (129). Additionally, diagnosis can be complicated by the unusual clinical presentation of patients experiencing transient bilateral paralysis of the legs along with groin or testicular pain (130).

In cases where rupture occurs into the vena cava, creating large aortocaval fistulae, patients may exhibit symptoms such as tachycardia, leg edema, a sensation of abdominal vibrations, and peripheral ischemia, indicative of subsequent congestive heart failure (CHF) and renal failure (122). Along with primary aortoduodenal fistulae, causing upper gastrointestinal (GI) bleeding, this is less commonly occurring (131).

The rupture's location and extent vary, but without immediate surgical intervention, it invariably culminates in lethal intraabdominal hemorrhage.

The aortic rupture on the retroperitoneal or posterolateral side (Fig.5) is the most commonly observed type, accounting for approximately 80%. For these types, the tamponade phenomenon can limit the bleeding momentarily. Conversely, 20% of ruptures are estimated to arise on the anterior side of the aorta, leading to prompt and extensive intraabdominal hemorrhage with subsequent patient demise (131).

The differential diagnoses to consider are acute gastritis, perforated GI ulcer, appendicitis, pyelonephritis and cystitis in females, nephrolithiasis, diverticulitis, acute pancreatitis, cholelithiasis, bowel ischemia, myocardial infarction, and musculoskeletal pain (122).

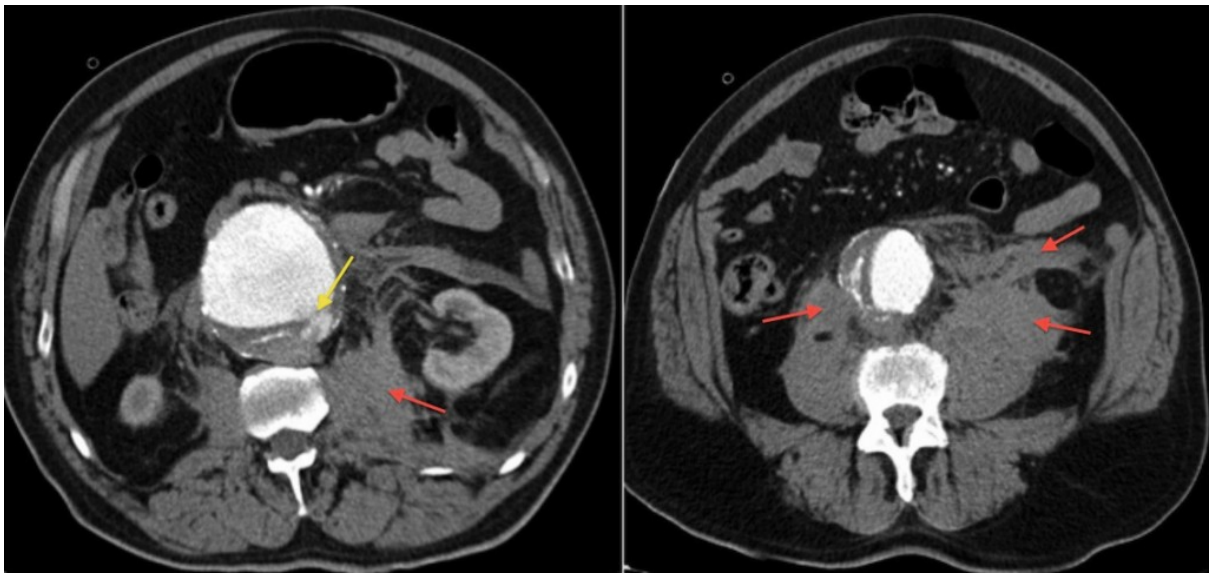

Figure 5: Ruptured AAA: The left image pointing to the leakage of contrast outside the lumen and the right image shows massive retroperitoneal hemorrhage (132)

8. DIAGNOSTIC APPROACH

Over 80% of patients with a ruptured AAA are undiagnosed prior to the event, leading to a misdiagnosis rate of 24-42%. Accurate diagnosis requires a high level of clinical suspicion. While no specific laboratory tests can diagnose AAA, they can help identify related conditions (133).

Conventional radiologic evaluation options include ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) (Fig. 6).

8.1. Imaging Techniques

Ultrasonography (US) is a primary imaging technique for detecting and managing abdominal aortic aneurysms (AAAs). When conducted by trained personnel, US offers nearly 100% sensitivity and about 96% specificity for identifying infrarenal AAAs. It can also detect free peritoneal blood, making it a valuable tool for immediate bedside assessments, especially in elderly patients presenting with abdominal pain. The recommendations from the US Preventative Service Task Force implement screening with ultrasonography for male patients with a smoking history aged 65-75 years, as it reduces mortality associated with rupture and proves cost-effectiveness. Additionally, US achieves useful monitoring of aneurysms that are too small for surgical intervention and for follow-up after endovascular repair. However, US has limitations, including difficulty detecting leaks, ruptures, and branch artery involvement, as well as reduced imaging quality in patients with bowel gas or obesity (133).

CT angiography (CTA) is highly sensitive, nearly 100%, for detecting AAAs and thereby considered the gold standard for diagnosing AAA rupture, making therapeutic decisions, planning treatment, and conducting post-surgical assessments and follow-ups (134). It offers comprehensive anatomical details of the full length of the aorta and the surrounding vasculature, enabling precise evaluation of the aneurysm's dimension and any associated acute or chronic conditions (135). This thorough visualization supports optimized surgical planning. Because of its broad availability, quick imaging capabilities, and minimized exposure to irradiation, CTA has largely replaced traditional interventional angiography for AAA assessment (90).

Preoperative CTA is invaluable for detailing the anatomy of the aneurysm and other intra-abdominal conditions, assessing renal artery location, aortic neck length, iliac artery condition, and identifying anatomical variants such as a retroaortic left renal vein or a horseshoe kidney. In 10-20% of cases, CTA can identify focal outpouchings or blebs that suggest rupture risk, as the aneurysm wall thickens with a thrombus.

CTA is crucial for determining patient eligibility for endovascular aneurysm repair (EVAR), assessing aneurysm neck characteristics, and iliac vessel suitability for device advancement (133).

Offering many of the benefits of CT angiography (CTA) without exposing patients to radiation is the magnetic resonance angiography (MRA). Without requiring iodine-based contrast media, it is an excellent alternative for individuals with severe dye allergies or renal insufficiency (136,137). However, it is important to consider contraindications, namely claustrophobia and certain foreign body implants based on metal. Furthermore, MRA is contraindicated in urgent settings with unstable patients like potential and expected ruptures (138), and it has limitations due to its high cost and limited widespread availability (90).

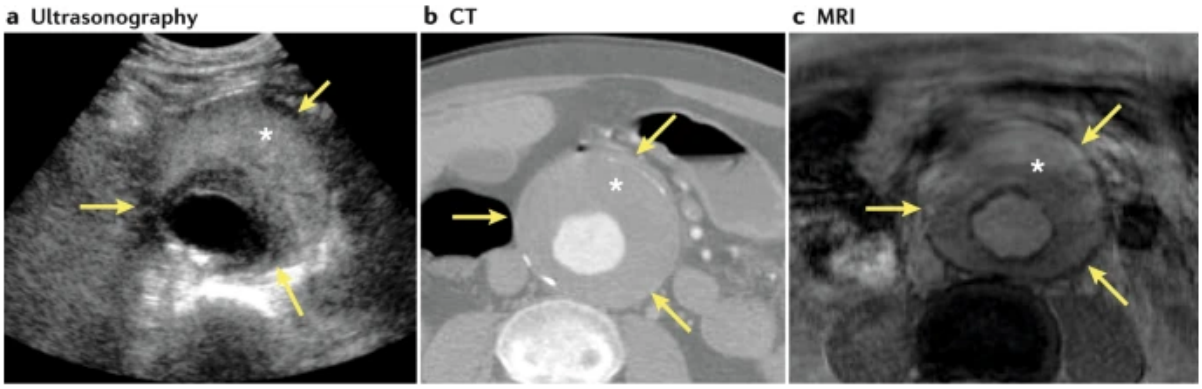

Figure 6: Conventional Imaging Techniques; arrows indicate infrarenal AAA with parietal thrombus (asterisk) in a male patient (139)

8.2. Screening

Research into AAA's natural history has advanced significantly due to extensive screening and surveillance initiatives, notably in the UK and Sweden (8,140). These programs, targeting 65-year-old men for a single ultrasonography scan, have led to a marked reduction in AAA-related fatalities (8,141). Despite generally high participation rates, regional disparities persist, often linked to factors like smoking and ethnicity. Surveillance protocols in vascular departments closely monitor patients based on aortic diameter, typically considering repair around the 55 mm mark (139). Most men identified with AAA through these screenings have smaller AAAs (<45 mm), necessitating ongoing observation with regular ultrasounds. As AAA prevalence declines, there is a need to reevaluate the cost-effectiveness of screening, especially with increasing incidental detection rates.

In contrast, screening for AAA in women lacks evidence due to their lower prevalence and later onset of the condition compared to men (20). This raises questions about the effectiveness of widespread screening and suggests a need to focus on targeted approaches for specific risk-prone groups, such as those with a genetic predisposition to AAA or patients having certain aortic diameters or smoking history. Thus, ongoing research aims to determine the most effective screening strategies for both genders, ensuring that resources are optimally utilized to prevent AAA-related complications and fatalities.

9. MANAGEMENT AND TREATMENT

9.1. Indications

Elective AAA repair is recommended under specific conditions to prevent complications. The procedure is recommended in case the AAA overreaches the diameter of 5.5 cm in men or 5.0 cm in women. Additionally, surgery should be performed if the patient experiences symptoms related to the aneurysm or if the AAA is rapidly expanding at a rate of more than 1 cm per year, regardless of its current size (3). Recent guidelines from the European Society for Vascular Surgery (ESVS) recommend repairing an AAA if it is symptomatic and over 4 cm in diameter, or if it grows by more than 10 mm annually, as measured using the inner-to-inner maximum anterior-posterior aortic diameter on an ultrasound (3). Solely surgery is the definitive treatment for AAAs, and it is suggested when the rupture risk outweighs the risks of surgery (90). Presently, around 85% of AAA interventions stem from elective surgery for intact aneurysms, albeit with notable regional differences (142). An aneurysm rupture, however, is an urgent surgical situation requiring prompt intervention, with a notable fatality rate reaching as high as 85% (143).

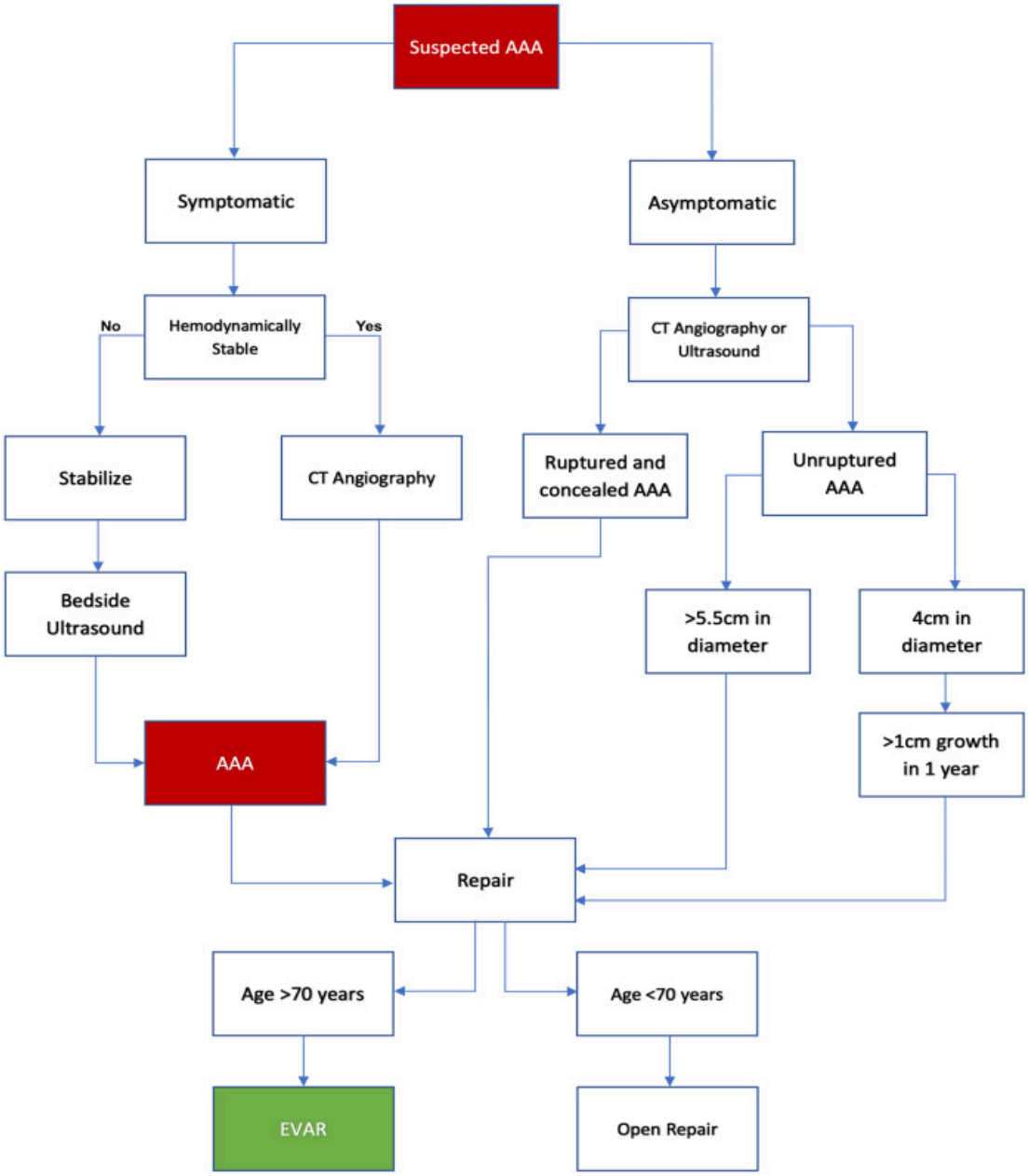

Figure 7: Algorithm of AAA Management (144)

9.2. Open Surgical Repair

Open surgical repair (OSR), is traditionally the gold standard for treating AAAs. The objective is to prevent the rupture of an AAA by substituting the pathological aortic segment with an artificial vascular conduit (Fig.8). The procedure starts with a laparotomy, during which a transperitoneal midline incision is made to visualize the healthy part of the aorta proximal and distal to the aneurysm (145). Alternatively, a left retroperitoneal approach may be utilized. Once the aneurysm is identified and exposed, surgeons confirm the decision of choice for either a cylindrical or Y-shaped dacron prosthesis, depending on whether the aneurysm reaches and involves the iliac arteries or not. Prior to clamping and incising the aorta, the patient receives heparinization to prevent thrombus detachment and distal embolization. Incising the aortic wall, the contents of the aneurysm are resected to allow the placement of the prosthesis. The implanted prosthesis is then connected to the healthy aortic wall using an end-to-end anastomosis technique. Once the prosthesis is implanted, the procedure is concluded by securing the graft through which the aortic wall is used to enclose it to create a safe barrier to the intestines (139).

The procedure for a ruptured aneurysm is almost identical, except that in this situation, it is important to compress the aorta above the aneurysm as soon as possible, either by incising the small omentum and retracting the stomach, after which an assistant stops the blood flow through the aorta by hand or with an auxiliary instrument, or by compressing the aorta above the diaphragm after thoracotomy.

Complications during OSR are primarily cardiac, pulmonary, or renal, including myocardial infarction, pneumonia, and renal insufficiency (146). Postoperatively, this procedure bears risks for complicated wound healing significantly impacting recovery, and midline laparotomy incisions have a higher risk of incisional hernias (147).

Long-term complications may manifest in the form of infected grafts, secondary aorto-enteric fistulas, occlusion of graft limb, and the growth of para-anastomotic aneurysms (148).

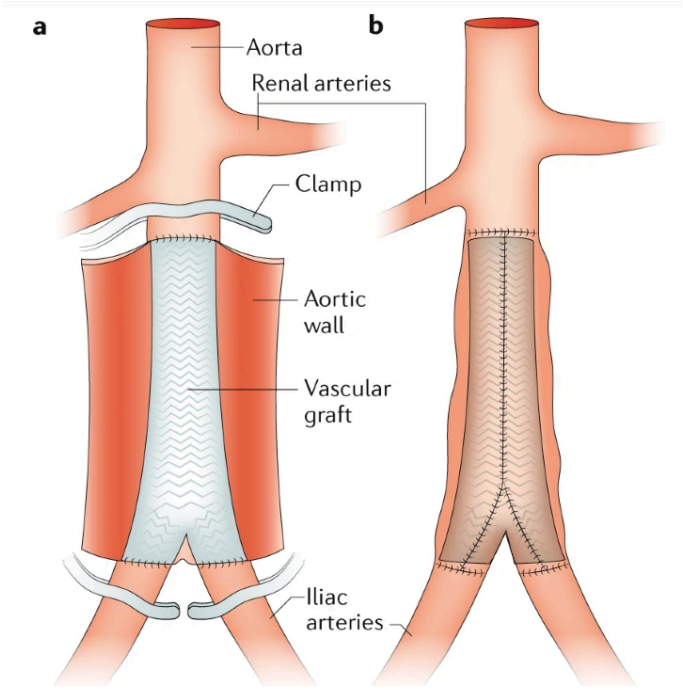

Figure 8: a) A bifurcated vascular graft (Y-shaped) connecting the aorta to both common iliac arteries is utilized to replace the aneurysmal section of the aorta. a) After securing the graft, the aortic wall is wrapped around it to create a barrier to the intestines. (139)

9.3. Endovascular Aneurysm Repair (EVAR)

EVAR is a minimally invasive, fluoroscopic image-guided procedure in which an endograft, or endoprosthesis, is introduced within the abdominal aorta. This endoprosthesis consists of a self-expanding metal mesh framework covered by fabric. The graft is anchored at both the proximal and distal ends of the aneurysm, using radial force to seal it against the aortic wall (Fig.9). This process creates a new pathway for blood flow, effectively bypassing the aneurysm and establishing a new vascular wall. The main objective of EVAR is to prevent the aneurysm from being involved in the main circulation rather than repairing the pathologic segment of the aorta (139).

The procedure involves inserting the stent graft into the AA by accessing through the femoral artery, using the percutaneous route, or via surgical incision (149). Digital subtraction angiography is used to confirm vessel measurements, and the graft is deployed and secured proximally at the aortic neck. Accurate and precise anchoring of the stent graft within the landing zone, necessitates specific structural features, including the aortic neck length, angle, presence of calcifications and thrombus, and its diameter and shape (150). Therefore preoperative assessment of the aortic anatomy, particularly the neck, is one of the most important steps in evaluating the success of endovascular therapy.

Modular, fenestrated, bifurcated, or branched stent graft designs allow customization to specific anatomical structures and accommodate variations like accessory vessels or inadequate landing zones (151).

In cases where the proximal zone for fixation below the renal arteries is inadequate, specialized EVAR approaches, such as fenestrated grafts or the chimney technique, may be employed (152). Fenestrated grafts open access for communicating with the renal arteries and other significant branches, while the chimney technique involves placing additional stents alongside the main graft to maintain blood flow to these arteries.

Careful patient selection is crucial, as performing EVAR on patients lacking the required anatomical features often leads to poorer long-term outcomes; alternative treatments like OSR or advanced EVAR should be considered in such cases (151).

Complications of EVAR include endoleaks, access site issues, and post-implantation syndrome. Endoleaks, which are instances of uncontrolled bleeding within the aneurysmatic pouch, represent a predominant problem that frequently necessitates revision, as further elaborated in the "Postoperative Complications" section. Access site complications are particularly problematic in patients with small, calcified, or tortuous iliac arteries (149).

In 2013, a new endovascular concept, Endovascular Aneurysm Sealing (EVAS), was introduced, which combines stent grafts with polymer-filled endobags that fill the aneurysmal sac to reduce the tendency of endoleak formation, particularly type II endoleaks caused by back bleeding from side branches (139,153). Despite the potential benefits, EVAS has faced challenges, such as instability of the endobags in the presence of intraluminal thrombus (ILT) and issues with graft migration in very large AAAs. These complications have led to revisions in EVAS usage guidelines, and further evidence of full effectiveness is needed.

Initially, EVAR was reserved for patients deemed ineligible for conventional surgical procedures due to frailty. Nonetheless, its indications have since expanded to include lower-risk patients with anatomical suitability, posing a safe alternative to open repair (139).

Most medical centers prefer EVAR as the primary approach (154). However, complex EVAR procedures should be performed at tertiary centers with the necessary expertise. If this is not possible, OSR should be considered to ensure favorable long-term outcomes (139).

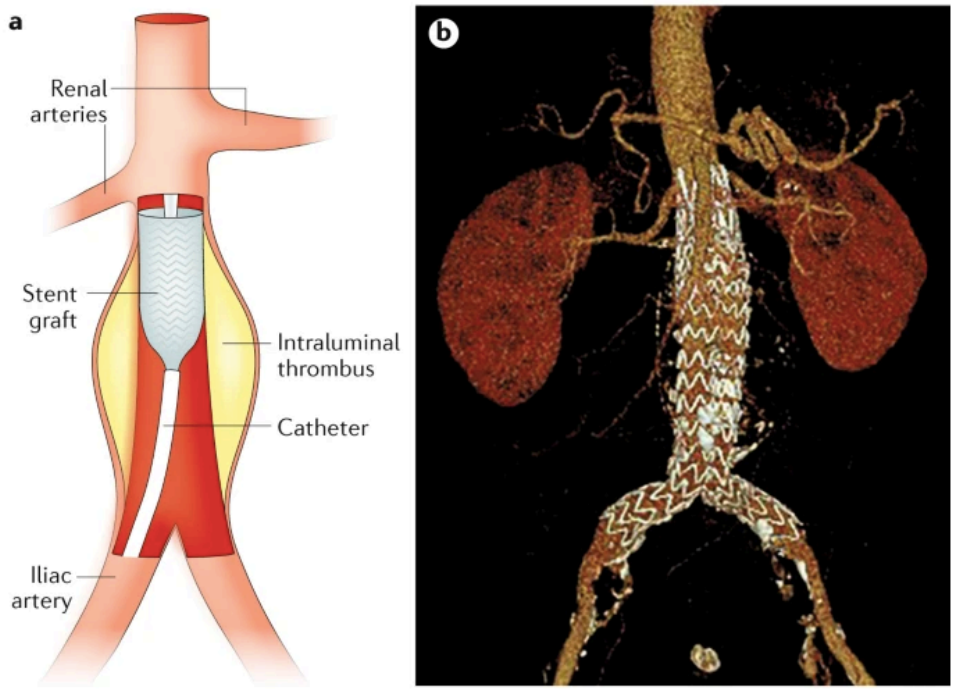

Figure 9: a) Deployment of graft. The top section of the stent graft is deployed, revealing the proximal part of the stent graft within the aorta beneath the renal arteries, effectively sealing the neck proximally to the aneurysm. b) CT image of the EVAR stent graft showing two extended grafts continuing into the common iliac arteries. (139)

9.4. Comparison of Open Surgery to EVAR

Multiple randomized and observational studies have compared the results of endovascular and open approach to aneurysm repair for AAAs. The DREAM (Dutch Randomized Endovascular Aneurysm Management) trial, for instance, proved that EVAR had significant temporary benefits over OSR. Specifically, EVAR showed lower 30-day mortality rates (1.2% compared to 4.6% for OSR), reduced complication rates (11.7% versus 26.4%), and a shorter average hospital stay (6 days versus 13 days) (155). However, these early advantages did not translate into long-term survival benefits. Over a six-year period, EVAR patients experienced higher reintervention rates (29.6% compared to 18.1% for OSR) (156,157). The UK EVAR 1 trial also noted an initial survival benefit for EVAR, which did not persist at the check-up after four years (158). After 15 years, the overall survival rate was reduced among EVAR patients compared to the ones openly repaired, largely due to increased instances of secondary aneurysmal sac rupture and higher cancer mortality among EVAR patients (159).

Recent advancements in stent graft technology, including more flexible designs and improved materials, are expected to enhance the long-term durability of EVAR (160,161).

Nonetheless, it may also be necessary to address EVAR-associated adverse events, namely continuous endoleaks or growth of the aneurysm sac, as well as infected grafts (90).

Initially devised for patients deemed unsuitable for open surgery, EVAR has emerged as the preferred technique for elective AAA repairs when technically feasible (3). Currently, over three-fourths of these procedures are conducted via endovascular means (22). However, a center needs to perform at least 30 cases annually of both techniques to maintain proficiency (3,22). EVAR is particularly suitable for those affected by cardiac or pulmonary disease, offering the advantage of being performed under local, epidural, or general anesthesia (162). Yet, the endovascular method does not yield extended survival advantages for patients deemed too weakened for OSR, and for those currently unfit for elective surgery, it is crucial to optimize their physical abilities and cardiovascular well-being before reviewing their suitability for surgery (163).

As aforementioned, the choice of surgical technique should be tailored to the aneurysm's morphology and patient history, with a special focus on their chronic illnesses and physical status (164). For instance, OSR is indicated for patients whose anatomical conditions are not suitable for EVAR, such as short landing zones or significant thrombus formation (165). Additionally, patient adherence to follow-up surveillance is crucial for EVAR, as it requires lifelong monitoring to detect late-onset complications like endoleaks or stent graft migration (166). Regarding rAAA, current comparisons indicate that EVAR shows improved results and cost-effectiveness in up to three years of follow-up (167).

The sustained elevated fatality rates but greater longevity of open repair surgery must be carefully counterweighted by the reduced initial death rate but lesser long-term longevity of EVAR (168).

Overall, both therapeutic methods have their distinct advantages and limitations, and the decision should be based on individual patient factors and anatomical suitability.

9.5. Conservative Management and the Role of Pharmacotherapy

Currently, no pharmacological treatments prove to reduce the rate of growth or potential to rupture of AAAs (3). Thus, operative treatment remains exclusively the choice for true cure. Managing small AAAs involves carefully weighing the risks of surgery against the likelihood of aneurysm rupture. Conservative management, or "watchful waiting," is recommended when the risk of surgery outweighs the rupture risk (169). This approach involves regular monitoring and adherence to guidelines for managing cardiovascular disease through optimal lifestyle modifications and medical care, aiming to ensure safety and cost-effectiveness (170). Studies underline that this proves superiority to early elective repair, which does not provide significant advantages for patients with small AAAs (171).

Effectively managing factors precipitating CVD is essential to enhance results and involves lifestyle modifications combined with medications to manage conditions like hypertension and dyslipidemia (172). Smoking cessation is particularly important, significantly reducing postoperative complications when achieved well before elective AAA repair (173). A balanced diet and physical activity also play vital roles in reducing obesity, consequently lowering cardiovascular disease (CVD) risks and improving surgical outcomes (174).

Pharmaceutical management for limiting cardiovascular risks includes the use of statins to lower LDL cholesterol levels, which should be reduced to below 2.8 mmol/L for low-risk patients, below 1.8 mmol/L for intermediate-risk patients, and below 1.4 mmol/L for high-risk patients (175).

Antihypertensive drugs should be administered using an individualized approach, considering each patient's comorbidities and contraindications, to maintain systolic blood pressure below 140 mmHg (68). Antiplatelet agents are also recommended to avoid cardiovascular incidents. Studies have shown that patients on statins, antiplatelet therapy, or antihypertensive medication have significantly improved five-year survival rates (68).

Despite extensive research into various drug classes, no pharmacological treatment has yet been proven to efficiently diminish AAA expansion or averting rupture (3). Early investigations into beta-blockers, ACE inhibitors, and antibiotics like doxycycline and macrolides yielded insufficient results (176–180).

Statins' impact on AAA progression remains controversial (181) and other drug classes, such as NSAIDs, mast cell inhibitors, calcium channel blockers, diuretics, and angiotensin II receptor blockers, also display less to no success (182–184). Antiplatelet therapy with acetylsalicylic acid or ticagrelor only shows an effect on growth rates among minor studies (185).

Recent research has focused on the antidiabetic drug metformin, which has consistently been linked to diminished AAA expansion in clinical trials (186). Present clinical trials continue to investigate its potential benefits in nondiabetic patients, raising hopes for a new effective treatment.

Future pharmacological strategies to limit AAA growth involve drugs targeting mRNA, so-called microRNAs. With the goal to disrupt key molecules involved in the pathogenesis of AAA, these emerging therapies hold promise for effective AAA management in the future (187).

9.6. Management of Ruptured AAA

rAAA is a critical emergency due to sudden and extensive bleeding into the intra- or retroperitoneal cavity. Immediate action is crucial to secure the diagnosis and plan the appropriate surgical option for the patient. Based on their hemodynamic stability, a computed tomography angiography (CTA) or intraoperative angiography is performed to assess anatomical suitability for EVAR (188). Both open surgical repair (OSR) and EVAR are viable options for repairing rAAA. EVAR is generally preferred if the aneurysm's anatomy allows for it. Studies have shown that EVAR and OSR portrayed similar frequencies of fatality, with no significant variance in the incidence of cardiac or respiratory failure (143). Additionally, revision rates of interventions are equally frequent between the two methods (167). However, EVAR often results in faster patient discharge and an increase in QALYs, making it a cost-effective option. The utilization of EVAR for emergencies, including ruptures, has notably surged over the last twenty years, indicative of enhanced outcomes for both EVAR and OSR (143). Nonetheless, the high fatality associated with unfavorable outcomes from EVAR in cases of rAAA demonstrates that the choice of surgical method should be primarily based on anatomical suitability rather than hemodynamic condition (143). This approach ensures the most effective and safest treatment for patients with rAAA.

9.7. Postoperative Complications

Postoperative complications following surgery for AAAs vary between OSR and EVAR.

Despite its minimal invasiveness, EVAR bears various complications including surgical exposure issues, systemic and ischemic adverse effects due to clot embolization or covering of side branches, stent-graft limb stenosis or occlusion, and infection complications (189). Local complications of the incision sites involve groin hematoma, infection, or lymphocele, and may require imaging for assessment. Arterial thrombosis, dissection, or pseudoaneurysm formation can additionally occur, requiring preoperative evaluation of access vessels. Contrast-induced nephropathy is a concern, with carbon dioxide as an alternative contrast agent. Ischemic complications post-EVAR include bowel and spinal cord ischemia, renal artery occlusion, and limb thrombosis due to thrombotic deposits dislodged during EVAR.

Both EVAR and OSR are associated with complications such as spinal cord ischemia and postoperative erectile dysfunction with similar incidence (190).

Aortic stent-graft infection, while rare, can lead to septicemia and mortality, with contamination during EVAR or secondary infection sources being possible causes. Diagnosis involves clinical signs and radiological findings, with treatment typically involving removal of the endograft and excision of the aneurysmal sac with subsequent bypass procedures.

Immediately post-procedure, there is a risk of aneurysm rupture, necessitating conversion to open surgery, stent misplacement, and myocardial infarction.

Special emphasis should be placed on one of the most characteristic and unique complications of EVARs, which is the occurrence of endoleaks, manifesting as either early or late complications (191). Endoleaks, where blood continues to flow into the aneurysm sac, are further categorized into distinct types (Fig.10). Type I endoleaks take place at the proximal (Ia) or distal (Ib) fixation points of the graft, resulting from improper sealing at the graft attachment sites. Type II is due to retrograde blood flow from collateral vessels like the lumbar or inferior mesenteric arteries, Type III occur due to separation of stent-graft components, Type IV are caused by blood flow through the pores of the stent-graft, and Type V is identified by continued aneurysm sac growth with no detectable leak.

Another characteristic late EVAR complication includes stent migration, which refers to the displacement of the graft from its original position due to loss of fixation (192).

The incidence of complications following open surgical repair (OSR) of AAAs varies across different studies (192). Common post-operative complications include pulmonary issues (42%), cardiac complications (18%), renal complications (17%), ischemic colitis (9%), and disturbed wound healing (7%).

While postoperative end-organ ischemia, such as colonic ischemia, acute lower limb ischemia, or spinal ischemia, occur less commonly, they are severe and require close monitoring. Therefore, patients undergoing OSR should be closely monitored for the development of these conditions. Late complications of OSR typically involve the development of incisional hernias.

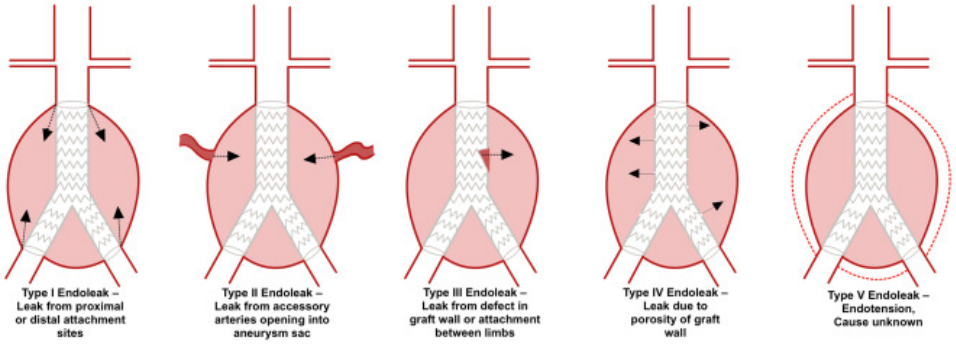

Figure 10: Endoleak types (191)

10. CONCLUSION

The persistence of AAA as a significant health concern is underscored by the prevalence of smoking in developing countries and the increasing geriatric demographic within industrialized areas. This trend correlates with an aging population, where AAA is often diagnosed at older ages, further compounded by the expanded eligibility for elective AAA repair facilitated by the introduction of EVAR. Despite advancements in AAA management, challenges persist, including controversies in operative management, disparities in morbidity and mortality among demographic groups, and the need for lifelong surveillance for AAA patients.

The efficacy of minimally invasive EVAR has revolutionized both elective and emergency AAA cases. However, challenges such as long-term durability, the requirement for continuous monitoring, and limitations among patients not meeting the anatomical criteria persist, requiring ongoing research and development efforts. Controversies surrounding the operative management of complex AAA cases, especially those extending close to or above the renal arteries, remain unresolved, highlighting the need for adapted endovascular techniques. The importance of interdisciplinary collaboration among vascular surgeons, angiologists, and interventional radiologists plays a pivotal role in continually optimizing and advancing AAA management, both scientifically and clinically. Continuous surveillance, often utilizing ultrasonography, is essential for AAA patients to determine the timing of elective repair. Despite the prevalence of small AAAs detectable through non-invasive screening, the quest for therapeutic agents to prevent further AAA growth remains a primary objective. Genetic and molecular studies have identified potential targets, yet effective drug development remains limited by the absence of properly conducted randomized trials. Looking ahead, advancements in translational biology and pharmacological research offer promising avenues for novel therapeutic approaches in AAA management.

Comprehensive knowledge of AAA epidemiology, genetic mechanisms, and underlying pathways holds the key to improving outcomes and developing effective prophylactic therapies. In summary, addressing the complexities of AAA requires a multifaceted approach, encompassing advancements in medical science, epidemiological insights, and innovative therapeutic strategies. By continuing to expand our understanding and refine our interventions, we can strive towards better management and improved outcomes for individuals diagnosed with abdominal aortic aneurysms.

11. SUMMARY

Abdominal aortic aneurysm (AAA) arises from aortic wall degeneration, resulting in irreversible dilation, exceeding normal diameter by over 50%. Predominantly affecting males, its occurrence ranges from 4 to 8 percent, with smoking as a key factor. AAA has multifactorial in origin, with genetic predisposition, advancing age, gender, smoking, and ethnicity. The pathogenesis of infrarenal aortic aneurysms involves factors such as tissue susceptibility, inflammation, and irreversible breakdown of ECM via proteolysis and apoptosis of VSCM in the aorta. Clinical presentation varies from asymptomatic to symptomatic, guiding treatment pathways. The gold standard diagnostic tools include ultrasound and CTA. Treatments encompass conservative measures, pharmacological intervention, and invasive options like endovascular repair (EVAR) or open surgery. Post-EVAR complications are characteristically endoleaks and stent migration, while groin hematoma, infection, dissection, pseudoaneurysm formation, bowel and spinal cord ischemia along with renal artery occlusion and limb thrombosis are additional possibilities. Specific complications of open surgery include wound complications, incisional hernia, and end-organ ischemia. In the case of ruptured AAA (rAAA), prompt assessment of hemodynamic stability and anatomical suitability is crucial for determining the optimal surgical approach. An emphasis on anatomical suitability guides the choice of surgical method. Overall, understanding the complexities of AAA management and promptly preventing the rupture of the aneurysm is critical for optimal patient outcomes.

Keywords: abdominal aortic aneurysm, clinical presentation, ruptured AAA, EVAR, open surgical repair

12. LITERATURE CITED

1. Antoniou GA, Antoniou AI, Antoniou SA, Lazarides MK. A historical perspective of medical terminology of aortic aneurysm. J Vasc Surg. 2011 Nov;54(5):1527–8.

2. Silaghi H, Branchereau A, Malikov S, Andercou A. Management of small asymptomatic abdominal aortic aneurysms - a review. Int J Angiol. 2007 Sep;16(04):121–7.

3. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019 Jan;57(1):8–93.

4. Scott R. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. The Lancet. 2002 Nov;360(9345):1531–9.

5. Lederle FA. The Rise and Fall of Abdominal Aortic Aneurysm. Circulation. 2011 Sep 6;124(10):1097–9.

6. Tang W, Yao L, Roetker NS, Alonso A, Lutsey PL, Steenson CC, et al. Lifetime Risk and Risk Factors for Abdominal Aortic Aneurysm in a 24-Year Prospective Study: The ARIC Study (Atherosclerosis Risk in Communities). Arterioscler Thromb Vasc Biol. 2016 Dec;36(12):2468–77.

7. Howard DPJ, Banerjee A, Fairhead JF, Handa A, Silver LE, Rothwell PM, et al. Population-Based Study of Incidence of Acute Abdominal Aortic Aneurysms With Projected Impact of Screening Strategy. J Am Heart Assoc. 2015 Aug 25;4(8):e001926.

8. Oliver-Williams C, Sweeting MJ, Turton G, Parkin D, Cooper D, Rodd C, et al. Lessons learned about prevalence and growth rates of abdominal aortic aneurysms from a 25-year ultrasound population screening programme. Br J Surg. 2017 Dec 19;105(1):68–74.

9. Marcaccio CL, Schermerhorn ML. Epidemiology of abdominal aortic aneurysms. Semin Vasc Surg. 2021 Mar;34(1):29–37.

10. Golledge J, Thanigaimani S, Powell JT, Tsao PS. Pathogenesis and management of abdominal aortic aneurysm. Eur Heart J. 2023 Aug 1;44(29):2682–97.

11. Lederle FA, Johnson GR, Wilson SE. Abdominal aortic aneurysm in women. J Vasc Surg. 2001 Jul;34(1):122–6.

12. Scott RAP, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. Br J Surg. 2005 Dec 8;82(8):1066–70.

13. McFarlane MJ. The epidemiologic necropsy for abdominal aortic aneurysm. JAMA. 1991 Apr 24;265(16):2085–8.

14. Sampson UKA, Norman PE, Fowkes FGR, Aboyans V, Song Y, Harrell Jr. FE, et al. Estimation of Global and Regional Incidence and Prevalence of Abdominal Aortic Aneurysms 1990 to 2010. Glob Heart. 2014 Mar 1;9(1):159.

15. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, et al. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. J Vasc Surg. 2010 Sep;52(3):539–48.

16. Chabok M, Nicolaides A, Aslam M, Farahmandfar M, Humphries K, Kermani NZ, et al. Risk factors associated with increased prevalence of abdominal aortic aneurysm in women. Br J Surg. 2016 Jul 18;103(9):1132–8.

17. Boese AC, Chang L, Yin KJ, Chen YE, Lee JP, Hamblin MH. Sex differences in abdominal aortic aneurysms. Am J Physiol-Heart Circ Physiol. 2018 Jun 1;314(6):H1137–52.

18. Ulug P, Sweeting MJ, Von Allmen RS, Thompson SG, Powell JT, Ulug P, et al. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. The Lancet. 2017 Jun;389(10088):2482–91.

19. Wanhainen A, Themudo R, Ahlström H, Lind L, Johansson L. Thoracic and abdominal aortic dimension in 70-year-old men and women – A population-based whole-body magnetic resonance imaging (MRI) study. J Vasc Surg. 2008 Mar;47(3):504–12.

20. Svensjö S, Björck M, Wanhainen A. Current prevalence of abdominal aortic aneurysm in 70-year-old women. Br J Surg. 2013 Jan 8;100(3):367–72.

21. Singh K. Prevalence of and Risk Factors for Abdominal Aortic Aneurysms in a Population-based Study : The Tromso Study. Am J Epidemiol. 2001 Aug 1;154(3):236–44.

22. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018 Jan;67(1):2-77.e2.

23. Iribarren C, Darbinian JA, Go AS, Fireman BH, Lee CD, Grey DP. Traditional and Novel Risk Factors for Clinically Diagnosed Abdominal Aortic Aneurysm: The Kaiser Multiphasic Health Checkup Cohort Study. Ann Epidemiol. 2007 Sep;17(9):669–78.

24. Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk Factors for Abdominal Aortic Aneurysms: A 7-Year Prospective Study: The Tromsø Study, 1994–2001. Circulation. 2009 Apr 28;119(16):2202–8.

25. Wilmink TBM, Quick CRG, Day NE. The association between cigarette smoking and abdominal aortic aneurysms. J Vasc Surg. 1999 Dec;30(6):1099–105.

26. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of abdominal aortic aneurysm: a systematic review and meta-analysis of prospective studies. Sci Rep. 2018 Oct 3;8(1):14786.

27. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. J Vasc Surg. 2003 Aug;38(2):329–34.

28. Flessenkaemper I, Loddenkemper R, Roll S, Enke-Melzer K, Wurps H, Bauer T. Screening of COPD patients for abdominal aortic aneurysm. Int J Chron Obstruct Pulmon Dis. 2015 Jun;1085.

29. Meijer CA, Kokje VBC, Van Tongeren RBM, Hamming JF, Van Bockel JH, Möller GM, et al. An Association between Chronic Obstructive Pulmonary Disease and Abdominal Aortic Aneurysm beyond Smoking. Eur J Vasc Endovasc Surg. 2012 Aug;44(2):153–7.

30. Takagi H, Umemoto T. No association of chronic obstructive pulmonary disease with abdominal aortic aneurysm growth. Heart Vessels. 2016 Nov;31(11):1806–16.

31. on behalf of ALICE (All-Literature Investigation of Cardiovascular Evidence) Group, Takagi H, Umemoto T. Association of chronic obstructive pulmonary, coronary artery, or peripheral artery disease with abdominal aortic aneurysm rupture. Int Angiol [Internet]. 2017 Jun [cited 2024 May 11];36(4). Available from: https://www.minervamedica.it/index2.php?show=R34Y2017N04A0322

32. Jahangir E, Lipworth L, Edwards TL, Kabagambe EK, Mumma MT, Mensah GA, et al. Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. J Epidemiol Community Health. 2015 May;69(5):481–8.

33. Stackelberg O, Björck M, Larsson SC, Orsini N, Wolk A. Sex differences in the association between smoking and abdominal aortic aneurysm. Br J Surg. 2014 Aug 11;101(10):1230–7.

34. Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, et al. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1 937 360 people in England: lifetime risks and implications for risk prediction. Int J Epidemiol. 2015 Feb;44(1):129–41.

35. Sweeting MJ, Thompson SG, Brown LC, Powell JT. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. Br J Surg. 2012 Apr 4;99(5):655–65.

36. Norman PE, Curci JA. Understanding the Effects of Tobacco Smoke on the Pathogenesis of Aortic Aneurysm. Arterioscler Thromb Vasc Biol. 2013 Jul;33(7):1473–7.

37. Thompson S, Brown L, Sweeting M, Bown M, Kim L, Glover M, et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health Technol Assess [Internet]. 2013 Sep [cited 2024 May 7];17(41). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta17410/

38. Bhak RH, Wininger M, Johnson GR, Lederle FA, Messina LM, Ballard DJ, et al. Factors Associated With Small Abdominal Aortic Aneurysm Expansion Rate. JAMA Surg. 2015 Jan 1;150(1):44.

39. Larsson E, Granath F, Swedenborg J, Hultgren R. A population-based case-control study of the familial risk of abdominal aortic aneurysm. J Vasc Surg. 2009 Jan;49(1):47–51.

40. Joergensen TMM, Houlind K, Green A, Lindholt JS. Abdominal Aortic Diameter Is Increased in Males with a Family History of Abdominal Aortic Aneurysms: Results from the Danish VIVA-trial. Eur J Vasc Endovasc Surg. 2014 Dec;48(6):669–75.

41. Van De Luijtgaarden KM, Rouwet EV, Hoeks SE, Stolker RJ, Verhagen HJ, Majoor-Krakauer D. Risk of abdominal aortic aneurysm (AAA) among male and female relatives of AAA patients. Vasc Med. 2017 Apr;22(2):112–8.

42. Salo JA. Familial Occurrence of Abdominal Aortic Aneurysm. Ann Intern Med. 1999 Apr 20;130(8):637.

43. Ogata T, MacKean GL, Cole CW, Arthur C, Andreou P, Tromp G, et al. The lifetime prevalence of abdominal aortic aneurysms among siblings of aneurysm patients is eightfold higher than among siblings of spouses: An analysis of 187 aneurysm families in Nova Scotia, Canada. J Vasc Surg. 2005 Nov;42(5):891–7.

44. Akai A, Watanabe Y, Hoshina K, Obitsu Y, Deguchi J, Sato O, et al. Family history of aortic aneurysm is an independent risk factor for more rapid growth of small abdominal aortic aneurysms in Japan. J Vasc Surg. 2015 Feb;61(2):287–90.

45. Van De Luijtgaarden KM, Bastos Gonçalves F, Hoeks SE, Majoor-Krakauer D, Rouwet EV, Stolker RJ, et al. Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair. J Vasc Surg. 2014 Feb;59(2):275–82.

46. Wanhainen A, Bergqvist D, Boman K, Nilsson TK, Rutegård J, Björck M. Risk factors associated with abdominal aortic aneurysm: A population-based study with historical and current data. J Vasc Surg. 2005 Mar;41(3):390–6.

47. Sakalihasan N, Defraigne JO, Kerstenne MA, Cheramy-Bien JP, Smelser DT, Tromp G, et al. Family Members of Patients with Abdominal Aortic Aneurysms Are at Increased Risk for Aneurysms: Analysis of 618 Probands and Their Families from the Liège AAA Family Study. Ann Vasc Surg. 2014 May;28(4):787–97.

48. Kuivaniemi H, Shibamura H, Arthur C, Berguer R, Cole CW, Juvonen T, et al. Familial abdominal aortic aneurysms: Collection of 233 multiplex families. J Vasc Surg. 2003 Feb;37(2):340–5.

49. Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac Surg. 2017 Nov;6(6):582–94.

50. Mangum KD, Farber MA. Genetic and epigenetic regulation of abdominal aortic aneurysms. Clin Genet. 2020 Jun;97(6):815–26.

51. Jones GT, Tromp G, Kuivaniemi H, Gretarsdottir S, Baas AF, Giusti B, et al. Meta-Analysis of Genome-Wide Association Studies for Abdominal Aortic Aneurysm Identifies Four New Disease-Specific Risk Loci. Circ Res. 2017 Jan 20;120(2):341–53.

52. Bradley DT, Badger SA, McFarland M, Hughes AE. Abdominal Aortic Aneurysm Genetic Associations: Mostly False? A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2016 Jan;51(1):64–75.

53. Wu Z yuan, Trenner M, Boon RA, Spin JM, Maegdefessel L. Long noncoding RNAs in key cellular processes involved in aortic aneurysms. Atherosclerosis. 2020 Jan;292:112–8.

54. Zalewski DP, Ruszel KP, Stępniewski A, Gałkowski D, Bogucki J, Komsta Ł, et al. Dysregulation of microRNA Modulatory Network in Abdominal Aortic Aneurysm. J Clin Med. 2020 Jun 24;9(6):1974.

55. Salem MK, Rayt HS, Hussey G, Rafelt S, Nelson CP, Sayers RD, et al. Should Asian Men be Included in Abdominal Aortic Aneurysm Screening Programmes? Eur J Vasc Endovasc Surg. 2009 Dec;38(6):748–9.

56. Zommorodi S, Leander K, Roy J, Steuer J, Hultgren R. Understanding abdominal aortic aneurysm epidemiology: socioeconomic position affects outcome. J Epidemiol Community Health. 2018 Oct;72(10):904–10.

57. Wallach-Kildemoes H, Andersen M, Diderichsen F, Lange T. Adherence to preventive statin therapy according to socioeconomic position. Eur J Clin Pharmacol. 2013 Aug;69(8):1553–63.

58. Cavelaars AEJM. Educational differences in smoking: international comparison. BMJ. 2000 Apr 22;320(7242):1102–7.

59. Elkalioubie A, Haulon S, Duhamel A, Rosa M, Rauch A, Staels B, et al. Meta-Analysis of Abdominal Aortic Aneurysm in Patients With Coronary Artery Disease. Am J Cardiol. 2015 Nov;116(9):1451–6.

60. Grøndal N, Søgaard R, Lindholt JS. Baseline prevalence of abdominal aortic aneurysm, peripheral arterial disease and hypertension in men aged 65–74 years from a population screening study (VIVA trial). Br J Surg. 2015 Jun 10;102(8):902–6.

61. Yao L, Folsom AR, Alonso A, Lutsey PL, Pankow JS, Guan W, et al. Association of carotid atherosclerosis and stiffness with abdominal aortic aneurysm: The atherosclerosis risk in communities (ARIC) study. Atherosclerosis. 2018 Mar;270:110–6.

62. Toghill BJ, Saratzis A, Bown MJ. Abdominal aortic aneurysm—an independent disease to atherosclerosis? Cardiovasc Pathol. 2017 Mar;27:71–5.

63. Alcorn HG, Wolfson SK, Sutton-Tyrrell K, Kuller LH, O'Leary D. Risk Factors for Abdominal Aortic Aneurysms in Older Adults Enrolled in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 1996 Aug;16(8):963–70.

64. Palazzuoli A. Prevalence of risk factors, coronary and systemic atherosclerosis in abdominal aortic aneurysm: Comparison with high cardiovascular risk population. Vasc Health Risk Manag. 2008 Aug;Volume 4:877–83.

65. Bath MF, Gokani VJ, Sidloff DA, Jones LR, Choke E, Sayers RD, et al. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015 Jun 10;102(8):866–72.

66. Freiberg MS, Arnold AM, Newman AB, Edwards MS, Kraemer KL, Kuller LH. Abdominal Aortic Aneurysms, Increasing Infrarenal Aortic Diameter, and Risk of Total

Mortality and Incident Cardiovascular Disease Events: 10-Year Follow-Up Data From the Cardiovascular Health Study. Circulation. 2008 Feb 26;117(8):1010–7.

67. Goodney PP, Tavris D, Lucas FL, Gross T, Fisher ES, Finlayson SRG. Causes of late mortality after endovascular and open surgical repair of infrarenal abdominal aortic aneurysms. J Vasc Surg. 2010 Jun;51(6):1340-1347.e1.

68. Bahia SS, Vidal-Diez A, Seshasai SRK, Shpitser I, Brownrigg JR, Patterson BO, et al. Cardiovascular risk prevention and all-cause mortality in primary care patients with an abdominal aortic aneurysm. Br J Surg. 2016 Nov 1;103(12):1626–33.

69. Kobeissi E, Hibino M, Pan H, Aune D. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2019 Jun;34(6):547–55.

70. Ramella M, Bernardi P, Fusaro L, Manfredi M, Casella F, Porta CM, et al. Relevance of inflammation and matrix remodeling in abdominal aortic aneurysm (AAA) and popliteal artery aneurysm (PAA) progression. Am J Transl Res. 2018;10(10):3265–75.

71. Whitehouse WM, Wakefield TW, Graham LM, Kazmers A, Zelenock GB, Cronenwett JL, et al. Limb-threatening potential of arteriosclerotic popliteal artery aneurysms. Surgery. 1983 May;93(5):694–9.

72. Graham LM. Clinical Significance of Arteriosclerotic Femoral Artery Aneurysms. Arch Surg. 1980 Apr 1;115(4):502.

73. Larsson E, Vishnevskaya L, Kalin B, Granath F, Swedenborg J, Hultgren R. High Frequency of Thoracic Aneurysms in Patients with Abdominal Aortic Aneurysms. Ann Surg. 2011 Jan;253(1):180–4.

74. Chaer RA, Vasoncelos R, Marone LK, Al-Khoury G, Rhee RY, Cho JS, et al. Synchronous and metachronous thoracic aneurysms in patients with abdominal aortic aneurysms. J Vasc Surg. 2012 Nov;56(5):1261–5.

75. Ball BZ, Jiang B, Mehndiratta P, Stukenborg GJ, Upchurch GR, Meschia JF, et al. Screening individuals with intracranial aneurysms for abdominal aortic aneurysms is cost-effective based on estimated coprevalence. J Vasc Surg. 2016 Sep;64(3):811-818.e3.

76. Kim DH, Van Ginhoven G, Milewicz DM. Familial Aggregation of Both Aortic and Cerebral Aneurysms: Evidence for a Common Genetic Basis in a Subset of Families. Neurosurgery. 2005 Apr 1;56(4):655–61.

77. Norrgård Ö, Ängqvist KA, Fodstad H, Forssell Å, Lindberg M. Co-existence of abdominal aortic aneurysms and intracranial aneurysms. Acta Neurochir (Wien). 1987 Aug;87(1–2):34–9.

78. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and Abdominal Aortic Aneurysms. Eur J Vasc Endovasc Surg. 2014 Mar;47(3):243–61.

79. Xiong J, Wu Z, Chen C, Wei Y, Guo W. Association between diabetes and prevalence and growth rate of abdominal aortic aneurysms: A meta-analysis. Int J Cardiol. 2016 Oct;221:484–95.

80. Shantikumar S, Ajjan R, Porter KE, Scott DJA. Diabetes and the Abdominal Aortic Aneurysm. Eur J Vasc Endovasc Surg. 2010 Feb;39(2):200–7.

81. Takagi H, Umemoto T, for the ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Negative association of diabetes with rupture of abdominal aortic aneurysm. Diab Vasc Dis Res. 2016 Sep;13(5):341–7.

82. Climent E, Benaiges D, Chillarón JJ, Flores-Le Roux JA, Pedro-Botet J. Diabetes mellitus as a protective factor of abdominal aortic aneurysm: Possible mechanisms. Clínica E Investig En Arterioscler Engl Ed. 2018 Jul;30(4):181–7.

83. Miyama N, Dua MM, Yeung JJ, Schultz GM, Asagami T, Sho E, et al. Hyperglycemia limits experimental aortic aneurysm progression. J Vasc Surg. 2010 Oct;52(4):975–83.

84. Pafili K, Gouni-Berthold I, Papanas N, Mikhailidis DP. Abdominal aortic aneurysms and diabetes mellitus. J Diabetes Complications. 2015 Nov;29(8):1330–6.

85. Raffort J, Hassen-Khodja R, Jean-Baptiste E, Lareyre F. Relationship between metformin and abdominal aortic aneurysm. J Vasc Surg. 2020 Mar;71(3):1056–62.

86. Chung J. Epidemiology, risk factors, pathogenesis, and natural history of abdominal aortic aneurysm.

87. Davidson JM, Hill KE, Mason ML, Giro MG. Longitudinal gradients of collagen and elastin gene expression in the porcine aorta. J Biol Chem. 1985 Feb 10;260(3):1901–8.

88. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. Understanding the pathogenesis of abdominal aortic aneurysms. Expert Rev Cardiovasc Ther. 2015 Sep 2;13(9):975–87.

89. Wolinsky H, Glagov S. Nature of Species Differences in the Medial Distribution of Aortic Vasa Vasorum in Mammals. Circ Res. 1967 Apr;20(4):409–21.

90. Kessler V, Klopf J, Eilenberg W, Neumayer C, Brostjan C. AAA Revisited: A Comprehensive Review of Risk Factors, Management, and Hallmarks of Pathogenesis. Biomedicines. 2022 Jan 2;10(1):94.

91. McDonald DA. Regional pulse-wave velocity in the arterial tree. J Appl Physiol. 1968 Jan;24(1):73–8.

92. Morbiducci U, Kok AM, Kwak BR, Stone PH, Steinman DA, Wentzel JJ. Atherosclerosis at arterial bifurcations: evidence for the role of haemodynamics and geometry. Thromb Haemost. 2016;115(03):484–92.

93. Chistiakov DA, Orekhov AN, Bobryshev YV. Effects of shear stress on endothelial cells: go with the flow. Acta Physiol. 2017 Feb;219(2):382–408.

94. Golledge J. Abdominal aortic aneurysm: update on pathogenesis and medical treatments. Nat Rev Cardiol. 2019 Apr;16(4):225–42.

95. Golledge J, Norman PE. Atherosclerosis and Abdominal Aortic Aneurysm: Cause, Response, or Common Risk Factors? Arterioscler Thromb Vasc Biol. 2010 Jun;30(6):1075–7.

96. Johnsen SH, Forsdahl SH, Singh K, Jacobsen BK. Atherosclerosis in Abdominal Aortic Aneurysms: A Causal Event or a Process Running in Parallel? The Tromsø Study. Arterioscler Thromb Vasc Biol. 2010 Jun;30(6):1263–8.

97. Tong J, Holzapfel GA. Structure, Mechanics, and Histology of Intraluminal Thrombi in Abdominal Aortic Aneurysms. Ann Biomed Eng. 2015 Jul;43(7):1488–501.

98. Koole D, Zandvoort HJA, Schoneveld A, Vink A, Vos JA, Van Den Hoogen LL, et al. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. J Vasc Surg. 2013 Jan;57(1):77–83.

99. Torres-Fonseca M, Galan M, Martinez-Lopez D, Cañes L, Roldan-Montero R, Alonso J, et al. Fisiopatología del aneurisma de aorta abdominal: biomarcadores y nuevas dianas terapéuticas. Clínica E Investig En Arterioscler. 2019 Jul;31(4):166–77.

100. Pagano MB, Zhou H fang, Ennis TL, Wu X, Lambris JD, Atkinson JP, et al. Complement-Dependent Neutrophil Recruitment Is Critical for the Development of Elastase-Induced Abdominal Aortic Aneurysm. Circulation. 2009 Apr 7;119(13):1805–13.

101. Kugo H, Moriyama T, Zaima N. Adipocytes and Abdominal Aortic Aneurysm: Putative Potential Role of Adipocytes in the Process of AAA Development. Curr Drug Targets. 2018 Aug 10;19(11):1228–32.

102. Koch AE, Haines GK, Rizzo RJ, Radosevich JA, Pope RM, Robinson PG, et al. Human abdominal aortic aneurysms. Immunophenotypic analysis suggesting an immune-mediated response. Am J Pathol. 1990 Nov;137(5):1199–213.

103. Schönbeck U, Sukhova GK, Gerdes N, Libby P. T(H)2 predominant immune responses prevail in human abdominal aortic aneurysm. Am J Pathol. 2002 Aug;161(2):499–506.

104. Vanderlaan PA, Reardon CA. Thematic review series: the immune system and atherogenesis. The unusual suspects:an overview of the minor leukocyte populations in atherosclerosis. J Lipid Res. 2005 May;46(5):829–38.

105. Yoshimoto T, Paul WE. CD4pos, NK1.1pos T cells promptly produce interleukin 4 in response to in vivo challenge with anti-CD3. J Exp Med. 1994 Apr 1;179(4):1285–95.

106. Miller FJ, Sharp WJ, Fang X, Oberley LW, Oberley TD, Weintraub NL. Oxidative stress in human abdominal aortic aneurysms: a potential mediator of aneurysmal remodeling. Arterioscler Thromb Vasc Biol. 2002 Apr 1;22(4):560–5.

107. Thomas M, Gavrila D, McCormick ML, Miller FJ, Daugherty A, Cassis LA, et al. Deletion of p47phox attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein E-deficient mice. Circulation. 2006 Aug 1;114(5):404–13.

108. Wiernicki I, Parafiniuk M, Kolasa-Wołosiuk A, Gutowska I, Kazimierczak A, Clark J, et al. Relationship between aortic wall oxidative stress/proteolytic enzyme expression and intraluminal thrombus thickness indicates a novel pathomechanism in the progression of human abdominal aortic aneurysm. FASEB J. 2019 Jan;33(1):885–95.

109. Quintana RA, Taylor WR. Cellular Mechanisms of Aortic Aneurysm Formation. Circ Res. 2019 Feb 15;124(4):607–18.

110. Cafueri G, Parodi F, Pistorio A, Bertolotto M, Ventura F, Gambini C, et al. Endothelial and Smooth Muscle Cells from Abdominal Aortic Aneurysm Have Increased Oxidative Stress and Telomere Attrition. Schmidt HHHW, editor. PLoS ONE. 2012 Apr 13;7(4):e35312.

111. Emeto TI, Moxon JV, Au M, Golledge J. Oxidative stress and abdominal aortic aneurysm: potential treatment targets. Clin Sci. 2016 Mar 1;130(5):301–15.

112. Morgan S, Yamanouchi D, Harberg C, Wang Q, Keller M, Si Y, et al. Elevated Protein Kinase C-δ Contributes to Aneurysm Pathogenesis Through Stimulation of Apoptosis and Inflammatory Signaling. Arterioscler Thromb Vasc Biol. 2012 Oct;32(10):2493–502.

113. Rowe VL, Stevens SL, Reddick TT, Freeman MB, Donnell R, Carroll RC, et al. Vascular smooth muscle cell apoptosis in aneurysmal, occlusive, and normal human aortas. J Vasc Surg. 2000 Mar;31(3):567–76.

114. Blassova T, Tonar Z, Tomasek P, Hosek P, Hollan I, Treska V, et al. Inflammatory cell infiltrates, hypoxia, vascularization, pentraxin 3 and osteoprotegerin in abdominal aortic aneurysms – A quantitative histological study. Kuivaniemi H, editor. PLOS ONE. 2019 Nov 8;14(11):e0224818.

115. Jones B, Tonniges JR, Debski A, Albert B, Yeung DA, Gadde N, et al. Collagen fibril abnormalities in human and mice abdominal aortic aneurysm. Acta Biomater. 2020 Jul;110:129–40.

116. Erdozain OJ, Pegrum S, Winrow VR, Horrocks M, Stevens CR. Hypoxia in Abdominal Aortic Aneurysm Supports a Role for HIF-1α and Ets-1 as Drivers of Matrix Metalloproteinase Upregulation in Human Aortic Smooth Muscle Cells. J Vasc Res. 2011;48(2):163–70.

117. Tchougounova E, Lundequist A, Fajardo I, Winberg JO, Åbrink M, Pejler G. A Key Role for Mast Cell Chymase in the Activation of Pro-matrix Metalloprotease-9 and Pro-matrix Metalloprotease-2. J Biol Chem. 2005 Mar;280(10):9291–6.

118. Geraghty P, Rogan MP, Greene CM, Boxio RMM, Poiriert T, O'Mahony M, et al. Neutrophil Elastase Up-Regulates Cathepsin B and Matrix Metalloprotease-2 Expression. J Immunol. 2007 May 1;178(9):5871–8.

119. Stather PW, Sidloff DA, Dattani N, Gokani VJ, Choke E, Sayers RD, et al. Meta-analysis and meta-regression analysis of biomarkers for abdominal aortic aneurysm. Br J Surg. 2014 Sep 8;101(11):1358–72.

120. Lv BJ, Lindholt JS, Wang J, Cheng X, Shi GP. Plasma levels of cathepsins L, K, and V and risks of abdominal aortic aneurysms: A randomized population-based study. Atherosclerosis. 2013 Sep;230(1):100–5.

121. Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: A comprehensive review. Exp Clin Cardiol. 2011;16(1):11–5.

122. Saum A Rahimi. Medscape; 2023. Abdominal aortic aneurysm clinical presentation. Available from: https://emedicine.medscape.com/article/1979501-clinical

123. Li X, Zhao G, Zhang J, Duan Z, Xin S. Prevalence and Trends of the Abdominal Aortic Aneurysms Epidemic in General Population - A Meta-Analysis. Folli F, editor. PLoS ONE. 2013 Dec 2;8(12):e81260.

124. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020 Oct;396(10258):1204–22.

125. Schermerhorn M. A 66-Year-Old Man With an Abdominal Aortic Aneurysm: Review of Screening and Treatment. JAMA. 2009 Nov 11;302(18):2015.

126. Schermerhorn ML, Bensley RP, Giles KA, Hurks R, O'Malley AJ, Cotterill P, et al. Changes in Abdominal Aortic Aneurysm Rupture and Short-Term Mortality, 1995–2008: A Retrospective Observational Study. Ann Surg. 2012 Oct;256(4):651–8.

127. Harris LM, Faggioli GL, Fiedler R, Curl GR, Ricotta JJ. Ruptured abdominal aortic aneurysms: Factors affecting mortality rates. J Vasc Surg. 1991 Dec;14(6):812–20.

128. Thompson AR, Cooper JA, Ashton HA, Hafez H. Growth rates of small abdominal aortic aneurysms correlate with clinical events. Br J Surg. 2009 Dec 10;97(1):37–44.

129. Azhar B, Patel SR, Holt PJE, Hinchliffe RJ, Thompson MM, Karthikesalingam A. Misdiagnosis of Ruptured Abdominal Aortic Aneurysm: Systematic Review and Meta-Analysis. J Endovasc Ther. 2014 Aug;21(4):568–75.

130. Jones J, Skandhan A. Abdominal aortic aneurysm rupture. In: Radiopaedia.org [Internet]. Radiopaedia.org; 2013 [cited 2024 May 21]. Available from: http://radiopaedia.org/articles/25600

131. Assar AN, Zarins CK. Ruptured abdominal aortic aneurysm: a surgical emergency with many clinical presentations. Postgrad Med J. 2009 May 1;85(1003):268–73.

132. St.Vincent's University Hospital Radiology Department [Internet]. Available from: http://www.svuhradiology.ie/case-study/ruptured-aortic-aneurysm/

133. Saum A Rahimi. Medscape; 2023. Abdominal Aortic Aneurysm Workup: Approach Considerations, Laboratory Studies, Ultrasonography. Available from: https://emedicine.medscape.com/article/1979501-workup#showall

134. Hallett RL, Ullery BW, Fleischmann D. Abdominal aortic aneurysms: pre- and post-procedural imaging. Abdom Radiol. 2018 May;43(5):1044–66.

135. Kumar Y, Hooda K, Li S, Goyal P, Gupta N, Adeb M. Abdominal aortic aneurysm: pictorial review of common appearances and complications. Ann Transl Med. 2017 Jul;5(12):256–256.

136. Long A, Rouet L, Lindholt JS, Allaire E. Measuring the Maximum Diameter of Native Abdominal Aortic Aneurysms: Review and Critical Analysis. Eur J Vasc Endovasc Surg. 2012 May;43(5):515–24.

137. Brambilla M, Cerini P, Lizio D, Vigna L, Carriero A, Fossaceca R. Cumulative radiation dose and radiation risk from medical imaging in patients subjected to endovascular aortic aneurysm repair. Radiol Med (Torino). 2015 Jun;120(6):563–70.

138. Ayache JB, Collins JD. MR Angiography of the Abdomen and Pelvis. Radiol Clin North Am. 2014 Jul;52(4):839–59.

139. Sakalihasan N, Michel JB, Katsargyris A, Kuivaniemi H, Defraigne JO, Nchimi A, et al. Abdominal aortic aneurysms. Nat Rev Dis Primer. 2018 Oct 18;4(1):34.

140. Ashton HA, Gao L, Kim LG, Druce PS, Thompson SG, Scott RAP. Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms. Br J Surg. 2007 May 18;94(6):696–701.

141. Wanhainen A, Hultgren R, Linné A, Holst J, Gottsäter A, Langenskiöld M, et al. Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. Circulation. 2016 Oct 18;134(16):1141–8.

142. Beck AW, Sedrakyan A, Mao J, Venermo M, Faizer R, Debus S, et al. Variations in Abdominal Aortic Aneurysm Care: A Report From the International Consortium of Vascular Registries. Circulation. 2016 Dec 13;134(24):1948–58.

143. Acher C, Acher CW, Castello Ramirez MC, Wynn M. Operative Mortality and Morbidity in Ruptured Abdominal Aortic Aneurysms in the Endovascular Age. Ann Vasc Surg. 2020 Jul;66:70–6.

144. Abdominal aortic aneurysm: diagnosis and management [Internet]. London: National Institute for Health and Care Excellence (NICE); 2020 [cited 2024 May 18]. (National Institute for Health and Care Excellence: Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK556921/

145. Ma B, Wang Y nan, Chen K yang, Zhang Y, Pan H, Yang K. Transperitoneal versus retroperitoneal approach for elective open abdominal aortic aneurysm repair. Cochrane Vascular Group, editor. Cochrane Database Syst Rev [Internet]. 2016 Feb 5 [cited 2024 May 17]; Available from: https://doi.wiley.com/10.1002/14651858.CD010373.pub2

146. Salata K, Hussain MA, De Mestral C, Greco E, Aljabri BA, Mamdani M, et al. Comparison of Outcomes in Elective Endovascular Aortic Repair vs Open Surgical Repair of Abdominal Aortic Aneurysms. JAMA Netw Open. 2019 Jul 10;2(7):e196578.

147. Nicolajsen CW, Eldrup N. Abdominal Closure and the Risk of Incisional Hernia in Aneurysm Surgery – A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2020 Feb;59(2):227–36.

148. Biancari F, Ylonen K, Anttila V, Juvonen J, Romsi P, Satta J, et al. Durability of open repair of infrarenal abdominal aortic aneurysm: A 15-year follow-up study. J Vasc Surg. 2002 Jan;35(1):87–93.

149. Antoniou GA, Antoniou SA. Editor's Choice – Percutaneous Access Does Not Confer Superior Clinical Outcomes Over Cutdown Access for Endovascular Aneurysm Repair: Meta-Analysis and Trial Sequential Analysis of Randomised Controlled Trials. Eur J Vasc Endovasc Surg. 2021 Mar;61(3):383–94.

150. Belvroy VM, Houben IB, Trimarchi S, Patel HJ, Moll FL, Van Herwaarden JA. Identifying and addressing the limitations of EVAR technology. Expert Rev Med Devices. 2018 Aug 3;15(8):541–54.

151. Kontopodis N, Galanakis N, Tzartzalou I, Tavlas E, Georgakarakos E, Dimopoulos I, et al. An update on the improvement of patient eligibility with the use of new generation endografts for the treatment of abdominal aortic aneurysms. Expert Rev Med Devices. 2020 Nov 1;17(11):1231–8.

152. Williamson AJ, Babrowski T. Current endovascular management of complex pararenal aneurysms. J Cardiovasc Surg (Torino) [Internet]. 2018 Apr [cited 2024 May 19];59(3). Available from: https://www.minervamedica.it/index2.php?show=R37Y2018N03A0336

153. Böckler D, Holden A, Thompson M, Hayes P, Krievins D, De Vries JPPM, et al. Multicenter Nellix EndoVascular Aneurysm Sealing system experience in aneurysm sac sealing. J Vasc Surg. 2015 Aug;62(2):290–8.

154. Buck DB, Van Herwaarden JA, Schermerhorn ML, Moll FL. Endovascular treatment of abdominal aortic aneurysms. Nat Rev Cardiol. 2014 Feb;11(2):112–23.

155. Prinssen M, Verhoeven ELG, Buth J, Cuypers PWM, Van Sambeek MRHM, Balm R, et al. A Randomized Trial Comparing Conventional and Endovascular Repair of Abdominal Aortic Aneurysms. N Engl J Med. 2004 Oct 14;351(16):1607–18.

156. Blankensteijn JD, De Jong SECA, Prinssen M, Van Der Ham AC, Buth J, Van Sterkenburg SMM, et al. Two-Year Outcomes after Conventional or Endovascular Repair of Abdominal Aortic Aneurysms. N Engl J Med. 2005 Jun 9;352(23):2398–405.

157. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven ELG, Cuypers PWM, et al. Long-Term Outcome of Open or Endovascular Repair of Abdominal Aortic Aneurysm. N Engl J Med. 2010 May 20;362(20):1881–9.

158. Greenhalgh R. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. The Lancet. 2004 Sep;364(9437):843–8.

159. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. The Lancet. 2016 Nov;388(10058):2366–74.

160. Endovascular Repair of Aortic Aneurysm in Patients Physically Ineligible for Open Repair. N Engl J Med. 2010 May 20;362(20):1872–80.

161. Lederle FA. Outcomes Following Endovascular vs Open Repair of Abdominal Aortic AneurysmA Randomized Trial. JAMA. 2009 Oct 14;302(14):1535.

162. Kalko Y, Ugurlucan M, Basaran M, Aydin U, Kafa U, Kosker T, et al. Epidural Anaesthesia and Mini-Laparotomy for the Treatment of Abdominal Aortic Aneurysms in Patients with Severe Chronic Obstructive Pulmonary Disease. Acta Chir Belg. 2007 Jan;107(3):307–12.

163. Sweeting MJ, Patel R, Powell JT, Greenhalgh RM. Endovascular Repair of Abdominal Aortic Aneurysm in Patients Physically Ineligible for Open Repair: Very Long-term Follow-up in the EVAR-2 Randomized Controlled Trial. Ann Surg. 2017 Nov;266(5):713–9.

164. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014 Sep 14;35(35):2383–431.

165. Katsargyris A, Lenhardt. Michael Florian C, Marques De Marino P, Botos B, Verhoeven EL. Reasons for and Outcomes of Open Abdominal Aortic Repair in the Endovascular Era. Ann Vasc Surg. 2021 May;73:417–22.

166. Spanos K, Karathanos C, Athanasoulas A, Sapeltsis V, Giannoukas AD. Systematic review of follow-up compliance after endovascular abdominal aortic aneurysm repair. J Cardiovasc Surg (Torino) [Internet]. 2018 Jun [cited 2024 May 19];59(4). Available from: https://www.minervamedica.it/index2.php?show=R37Y2018N04A0611

167. IMPROVE Trial Investigators. Comparative clinical effectiveness and cost effectiveness of endovascular strategy *v* open repair for ruptured abdominal aortic aneurysm: three year results of the IMPROVE randomised trial. BMJ. 2017 Nov 14;j4859.

168. Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, et al. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017 Feb 3;104(3):166–78.

169. Bown MJ, Sweeting MJ, Brown LC. Surveillance Intervals for Small Abdominal Aortic Aneurysms: A Meta-analysis. J Vasc Surg. 2013 Jun;57(6):1720–1.

170. Filardo G, Powell JT, Martinez MAM, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Vascular Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Feb 8 [cited 2024 May 19]; Available from: https://doi.wiley.com/10.1002/14651858.CD001835.pub4

171. UK Small Aneurysm Trial participants, Powell JT. Final 12-year follow-up of Surgery *versus* Surveillance in the UK Small Aneurysm Trial. Br J Surg. 2007 May 18;94(6):702–8.

172. Galiñanes EL, Reynolds S, Dombrovskiy VY, Vogel TR. The impact of preoperative statin therapy on open and endovascular abdominal aortic aneurysm repair outcomes. Vascular. 2015 Aug;23(4):344–9.

173. Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. Eur Heart J. 2013 Nov 2;34(42):3259–67.

174. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health: A Critical Review. Circ Res. 2019 Mar;124(5):779–98.

175. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in

collaboration with the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018 Mar 1;39(9):763–816.

176. The Propranolol Aneurysm Trial Investigators. Propranolol for small abdominal aortic aneurysms: Results of a randomized trial. J Vasc Surg. 2002 Jan;35(1):72–9.

177. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. The Lancet. 2006 Aug;368(9536):659–65.

178. Sweeting MJ, Thompson SG, Brown LC, Greenhalgh RM, Powell JT. Use of angiotensin converting enzyme inhibitors is associated with increased growth rate of abdominal aortic aneurysms. J Vasc Surg. 2010 Jul;52(1):1–4.

179. Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: A randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 2001 Oct;34(4):606–10.

180. Vammen S, Lindholt JS, Østergaard L, Fasting H, Henneberg EW. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. Br J Surg. 2002 Nov 29;88(8):1066–72.

181. Takagi H, Yamamoto H, Iwata K, Goto S, Umemoto T. Effects of Statin Therapy on Abdominal Aortic Aneurysm Growth: A Meta-analysis and Meta-regression of Observational Comparative Studies. Eur J Vasc Endovasc Surg. 2012 Sep;44(3):287–92.

182. Franklin IJ, Walton LJ, Brown L, Greenhalgh RN, Powell JT. Non-steroidal anti-inflammatory drugs to treat abdominal aortic aneurysm. Br J Surg. 2002 Dec 24;86(5):707–707.

183. Sillesen H, Eldrup N, Hultgren R, Lindeman J, Bredahl K, Thompson M, et al. Randomized clinical trial of mast cell inhibition in patients with a medium-sized abdominal aortic aneurysm. Br J Surg. 2015 Jun 10;102(8):894–901.

184. Wilmink A. Are antihypertensive drugs associated with abdominal aortic aneurysms? J Vasc Surg. 2002 Oct;36(4):751–7.

185. Karlsson L, Gnarpe J, Bergqvist D, Lindbäck J, Pärsson H. The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms - A prospective randomized double-blind trial. J Vasc Surg. 2009 Jul;50(1):23–9.

186. Fujimura N, Xiong J, Kettler EB, Xuan H, Glover KJ, Mell MW, et al. Metformin treatment status and abdominal aortic aneurysm disease progression. J Vasc Surg. 2016 Jul;64(1):46-54.e8.

187. Miyake T, Miyake T, Kurashiki T, Morishita R. Molecular Pharmacological Approaches for Treating Abdominal Aortic Aneurysm. Ann Vasc Dis. 2019 Jun 25;12(2):137–46.

188. Lloyd GM, Bown MJ, Norwood MGA, Deb R, Fishwick G, Bell PRF, et al. Feasibility of preoperative computer tomography in patients with ruptured abdominal aortic aneurysm: a time-to-death study in patients without operation. J Vasc Surg. 2004 Apr;39(4):788–91.

189. Maleux G, Koolen M, Heye S. Complications after endovascular aneurysm repair. Semin Interv Radiol. 2009 Mar;26(1):3–9.

190. Berg P, Kaufmann D, Van Marrewijk CJ, Buth J. Spinal Cord Ischaemia After Stent-graft Treatment for Infra-renal Abdominal Aortic Aneurysms. Analysis of the Eurostar Database. Eur J Vasc Endovasc Surg. 2001 Oct;22(4):342–7.

191. Yanamaladoddi VR, Sarvepalli SS, Vemula SL, Aramadaka S, Mannam R, Sankara Narayanan R, et al. The Challenge of Endoleaks in Endovascular Aneurysm Repair (EVAR): A Review of Their Types and Management. Cureus. 2023 May;15(5):e39775.

192. Avishay DM, Reimon JD. Abdominal Aortic Repair [Internet]. StatPearls [Internet]; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554573/

13. CURRICULUM VITAE

Melissa Seven was born on November 24, 1998, in Dortmund, Germany. There she attended the schools Petri-Grundschule from 2005 to 2009 for her elementary education and continued at Stadtgymnasium from 2009 to 2017 for her secondary and high school education, completing her A levels in 2017. Pursuing her lifelong dream of becoming a doctor, she moved to Rijeka, Croatia, to study medicine. Studying abroad provided invaluable experience and strengths. During university, Melissa used her semester breaks to gain insights into various medical fields, including internal medicine, visceral surgery, gynecology and obstetrics, cardiothoracic surgery, vascular surgery, and ophthalmology. This hands-on experience deepened her knowledge and skills. In the summer of 2023, Melissa completed an Erasmus+ Traineeship in Vienna at the Allgemeines Krankenhaus in the Vascular Surgery department. Her primary focus throughout her studies has been on surgery, which is also the subject of her thesis. She presented her research on the cost-effectiveness of rivaroxaban with or without aspirin in stable cardiovascular disease at the 12th Adriatic and 8th Croatian Congress of Pharmacoeconomics and Outcomes Research in April 2024, in Lovran, Croatia.

Melissa Seven is set to obtain her medical degree in July 2024, becoming the first doctor in her family.