ABDOMINAL AORTIC ANEURYSM

Seven, Melissa

UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

UNIVERSITY INTEGRATED UNDERGRADUATE AND GRADUATE STUDY OF MEDICINE IN ENGLISH LANGUAGE

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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.

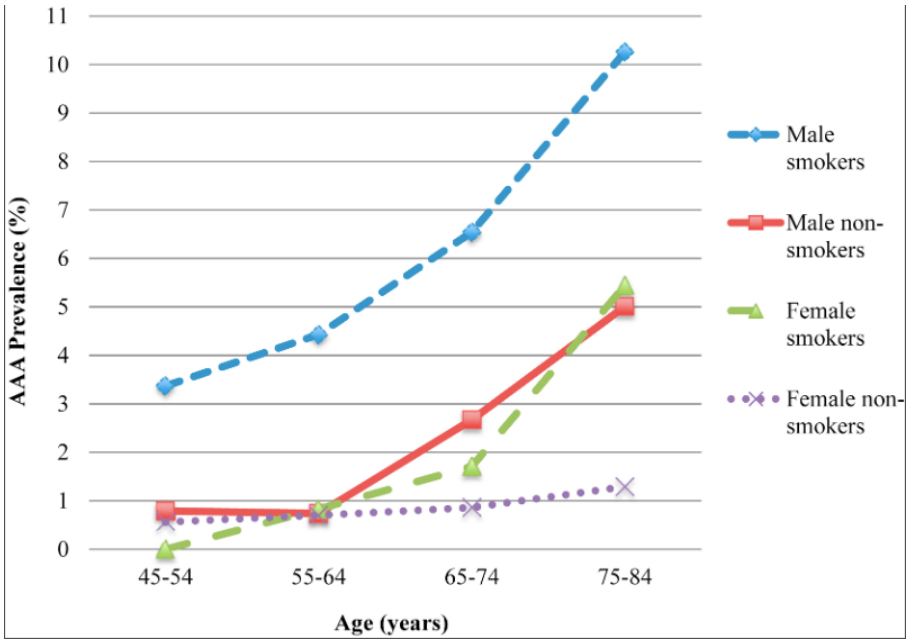

Figure 1: Epidemiology of abdominal aortic aneurysms (9)

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).

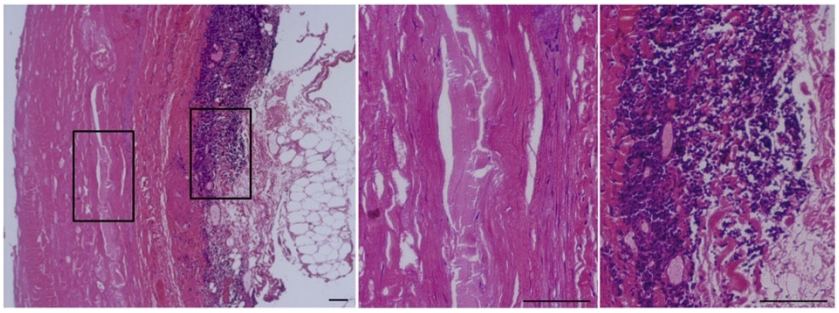

Figure 3: Haematoxylin-eosin stain of the abdominal aorta of a patient with an AAA: absence of VSMC in the middle layer of the vascular wall and immunoinflammatory infiltrate of adventitia (80)

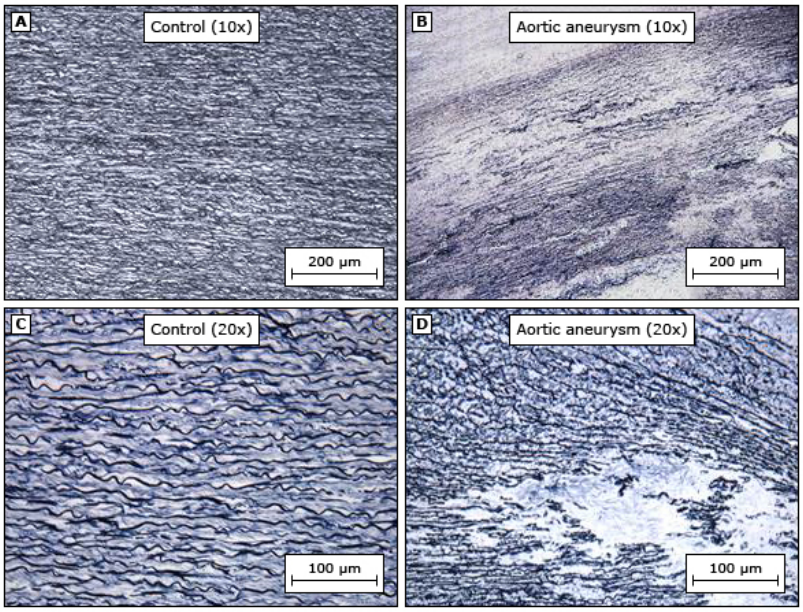

Figure 4: Verhoeff's elastic staining reveals elastic fiber degradation in aortic aneurysm samples at both 10x (B) and 20x (D) magnification, contrasting with control aorta specimens shown at 10x (A) and 20x (C) magnification (86)

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).

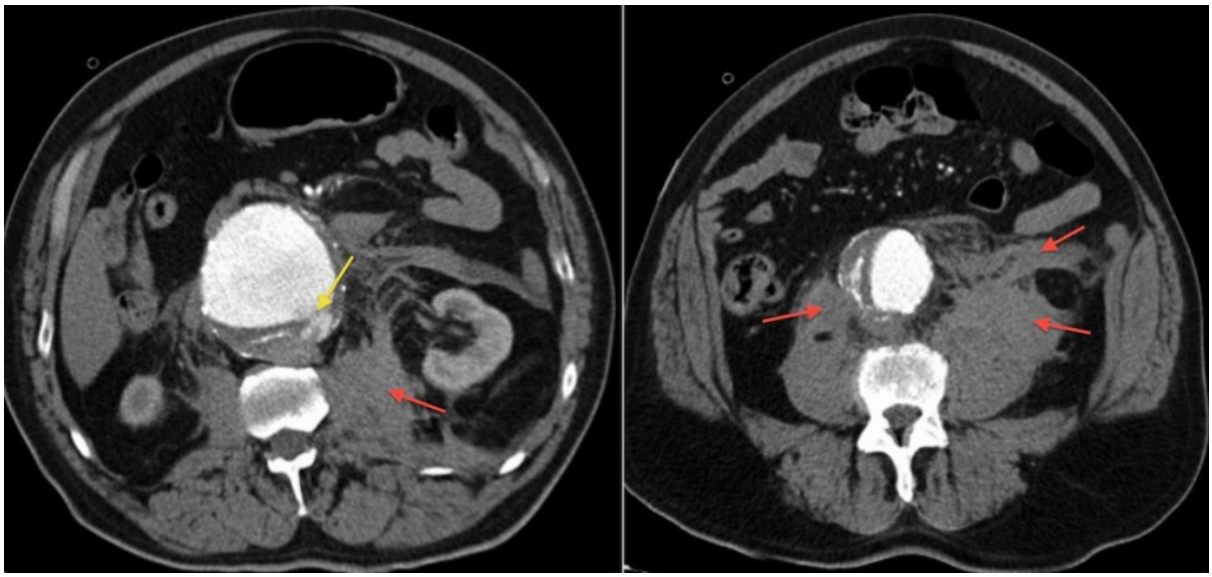

Figure 5: Ruptured AAA: The left image pointing to the leakage of contrast outside the lumen and the right image shows massive retroperitoneal hemorrhage (132)

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).

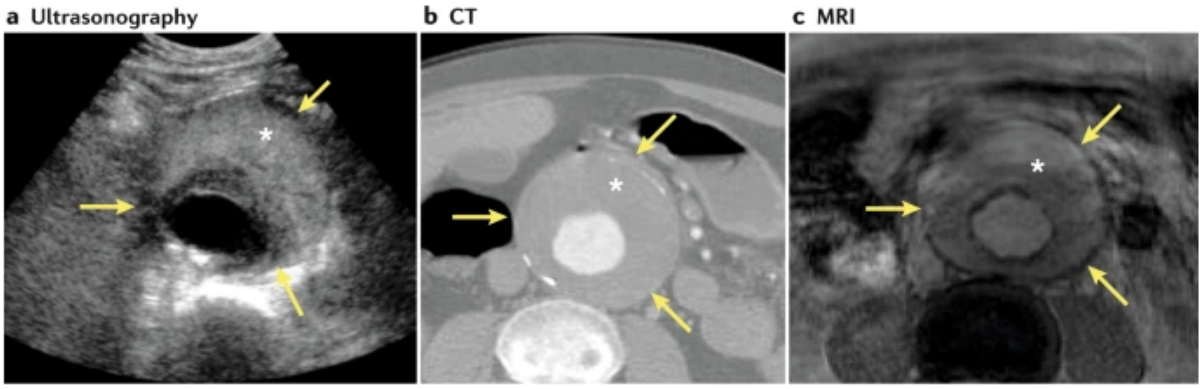

Figure 6: Conventional Imaging Techniques; arrows indicate infrarenal AAA with parietal thrombus (asterisk) in a male patient (139)

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).

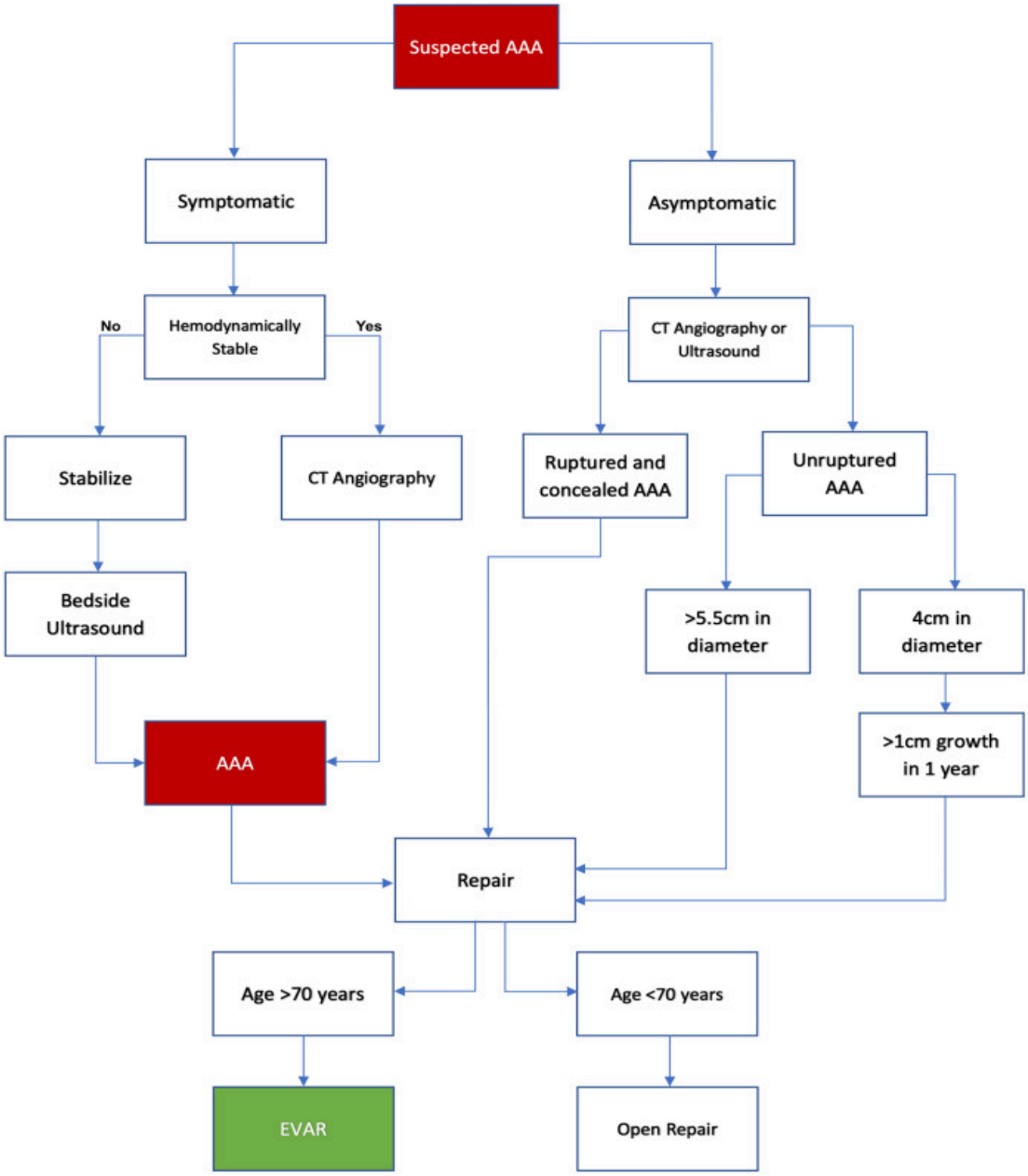

Figure 7: Algorithm of AAA Management (144)

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).

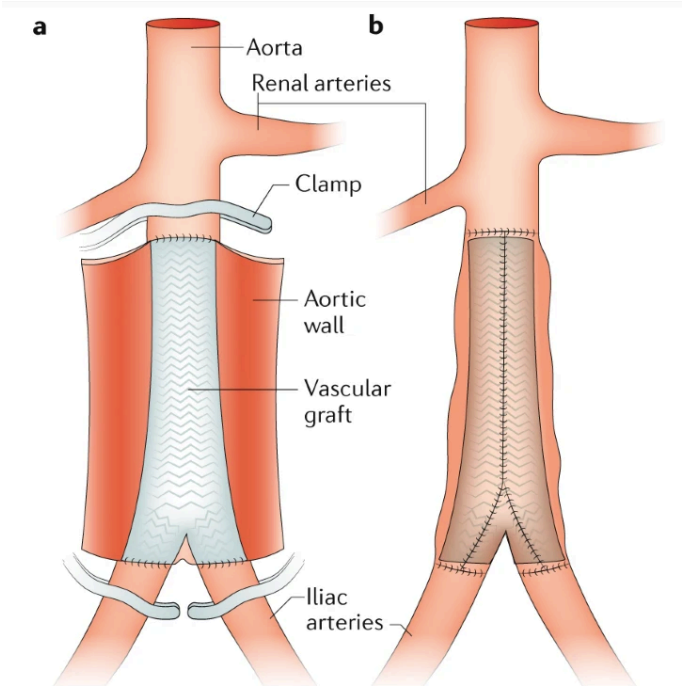

Figure 8: a) A bifurcated vascular graft (Y-shaped) connecting the aorta to both common iliac arteries is utilized to replace the aneurysmal section of the aorta. a) After securing the graft, the aortic wall is wrapped around it to create a barrier to the intestines. (139)

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).

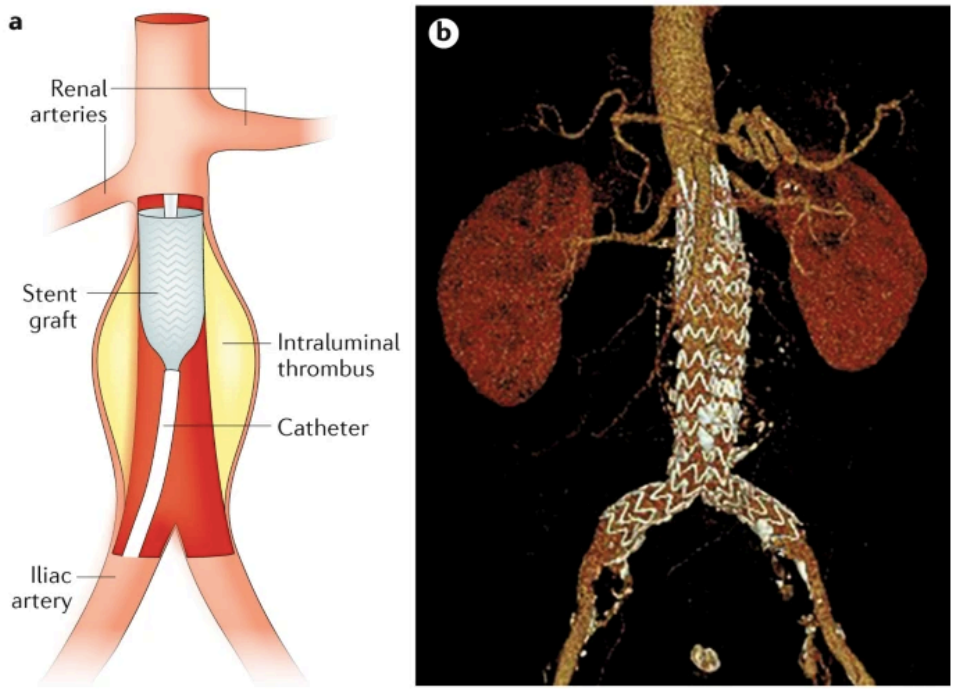

Figure 9: a) Deployment of graft. The top section of the stent graft is deployed, revealing the proximal part of the stent graft within the aorta beneath the renal arteries, effectively sealing the neck proximally to the aneurysm. b) CT image of the EVAR stent graft showing two extended grafts continuing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

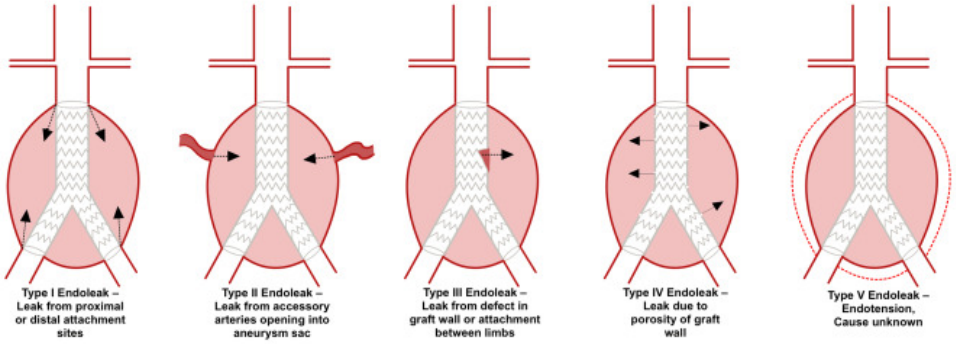

Figure 10: Endoleak types (191)

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

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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.