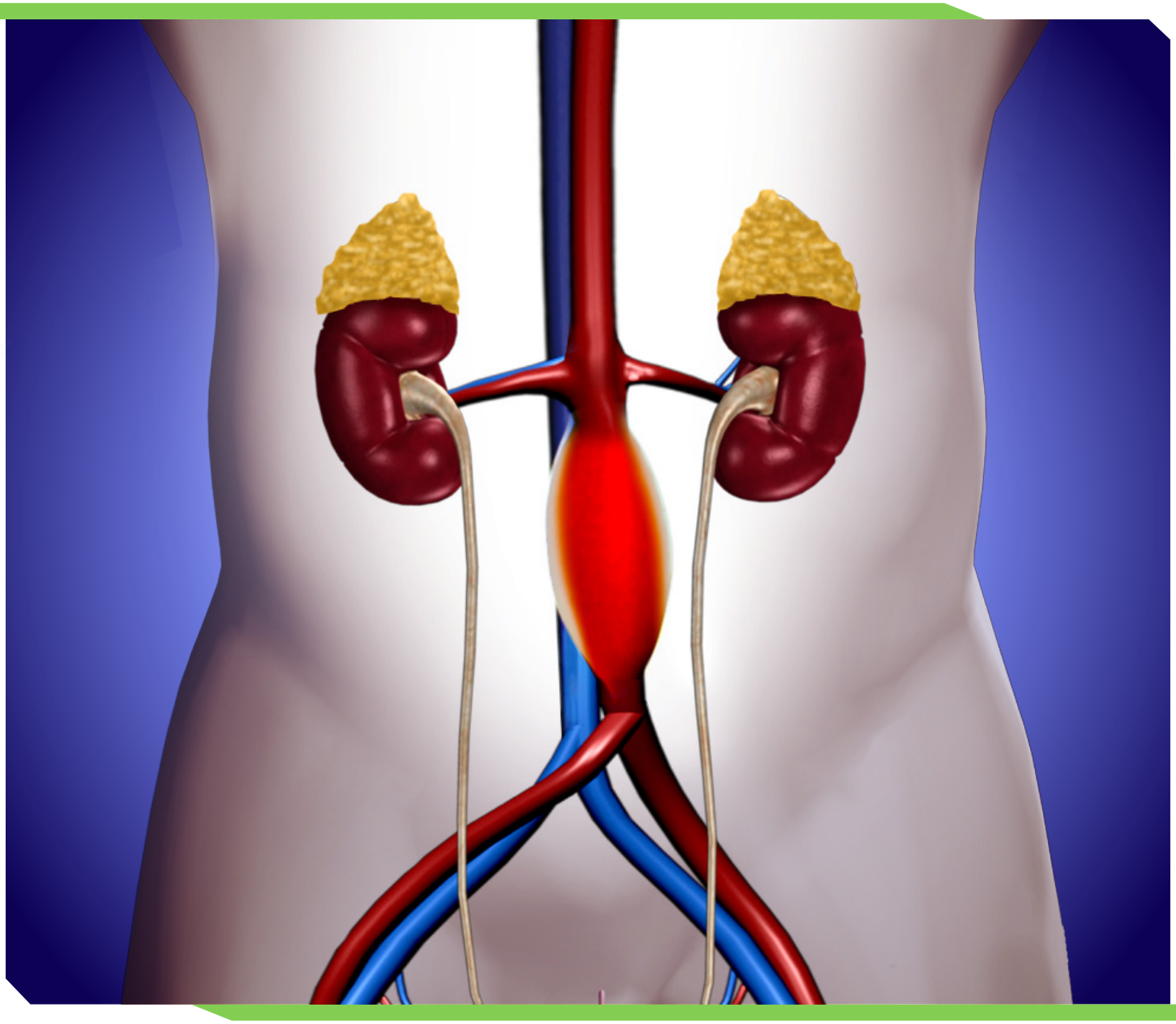
Abdominal Aortic Aneurysm:
A Biomechanical Perspective



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Abdominal Aortic Aneurysm: A Biomechanical Perspective

ANCC Accredited NCPD Hours: 2.3hrs

Target Audience: RN/APRN

Need Assessment

Current management of aortic aneurysms relies exclusively on prophylactic operative repair of larger aneurysms. Great potential exists for successful medical therapy that stops or reduces aneurysm progression and hence alleviates or postpones the need for surgical repair. Preclinical studies and data from pre-operative clinical intervention studies showed that interventions in the pathways of activated inflammatory and proteolytic cascades in enlarging AAA are feasible. Similarly, extensive series of studies in the models of Marfan syndrome-related aortapathy, inherited aortic root aneurysm etc. support the concept of pharmaceutical aorta stabilization.

Objectives

- Discuss the method of biomechanical rupture risk assessment in abdominal aortic aneurysm
- Describe the uncertainty of disease predictions in abdominal aortic aneurysm
- Identify the classification system of abdominal aortic aneurysm
- Describe the causes for abdominal aortic aneurysm
- Discuss the targets for medical therapy for abdominal aortic aneurysm

Goal

The goal of this article is to analyze abdominal aortic aneurysm comprehensively, starting from a biomechanical perspective, exploring etiology and pathophysiology, and concluding with medical management techniques

Introduction

The natural course of an abdominal aortic aneurysm (AAA) is a steady increase of the diameter, and eventually, if left untreated, the aneurysm might rupture. ***In most cases of AAA, this pathophysiological process remains asymptomatic until rupture. Such an event can be prevented by surgical AAA repair.*** The decision to perform surgery is commonly based on 3 characteristics(as shown in fig.1): (1) maximum AAA diameter exceeding 5.0 cm in women and 5.5 cm in men; (2) experience of symptoms; or (3) aneurysm growth rate exceeds 1 cm/year. The first 2 characteristics are relatively easy to identify by imaging or by questioning the patient. However, AAA growth rate can only be considered retrospectively, because a prognostic value for expansion has not yet been acknowledged. In the current AAA management, no marker for aneurysm progression or rupture has been implemented as common practice. This might be explained by little existing evidence and lack of experience with prognostic markers. [1, Rank 4]

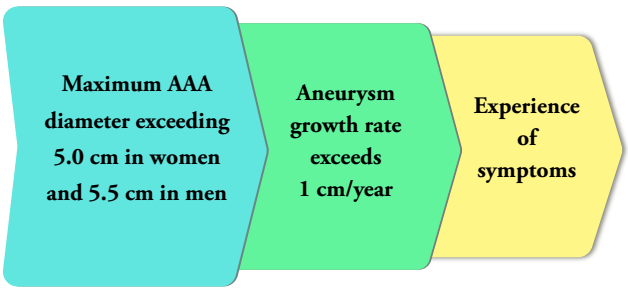

Figure 1: Basic characteristics to perform surgery for Abdominal aortic aneurism

Definition of Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) disease is a serious condition and causes many deaths, especially in males over 65 years. Progressive treatment (i.e., surgical or endovascular AAA repair) cannot be offered to all patients, and according to the best clinical practice, AAA repair is indicated if rupture risk exceeds the interventional risks. While center-specific treatment risks are reasonably predictable, assessing ***AAA rupture risk for individual patients remains the bottleneck in clinical decision making. However, an accurate rupture risk assessment is critical to reduce aneurysm- related mortality without substantially increasing the rate of AAA repair.***

According to the current clinical practice, AAA rupture risk is assessed by the aneurysm's largest transverse diameter and its change over time. Specifically, AAA repair is generally indicated if the largest

> **" The natural course of an abdominal aortic aneurysm (AAA) is a steady increase of the diameter, and eventually, if left untreated, the aneurysm might rupture. "**

diameter exceeds 55 mm or if it grows faster than 10 mm per year. The majority of clinicians follow this advice and use both criteria for clinical decision making. However, this somewhat crude rupture risk assessment is the subject of increasing discussion, and AAAs with a diameters of less than 55 mm can and do rupture (even under surveillance), whereas many aneurysms larger than 55 mm never rupture. Finally, the threshold diameter criterion is already about 20 years old and may no longer adequately reflect current treatment options. [2, Rank 5]

Due to the poor specificity and sensitivity of diameter as an AAA repair indication, the cost-effectiveness of patient treatment for aneurysms is not optimal, and a more individualized AAA repair indication would be of great help. Most important, ***aneurysm rupture is a local failure event in the wall, and global parameters like the largest diameter might not adequately reflect the actual risk for such events. This conclusion also explains why not all ruptures are found at the level of the largest diameter.*** Similarly, monitoring the expansion of the maximum diameter over time lacks sound scientific evidence and also misses spots of fast growth (i.e., areas of potentially compromised wall strength due to incomplete tissue turnover).

The drawbacks of the diameter criterion have stimulated considerable research in the field. Besides the diameter and its change over time, many other clinical risk factors(as shown in fig.2) have been proposed including biomechanical risk indices, AAA shape, female sex, family susceptibility, high mean arterial pressure (MAP), smoking and fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET), a thick intraluminal thrombus (ILT) layer, and rapid increase in ILT volume.

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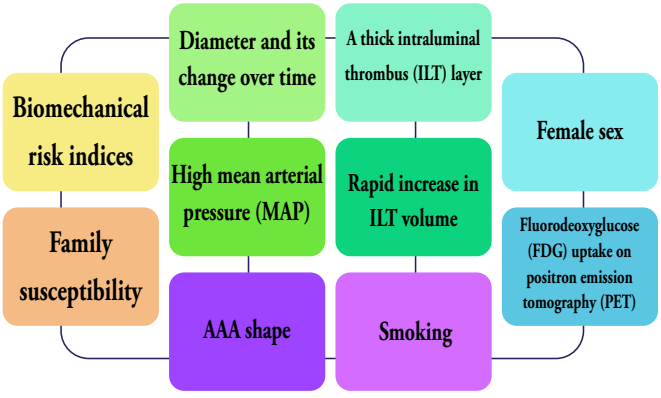

Figure 2: Clinical risk factors of Abdominal aortic aneurysm

In summary, ***an AAA rupture is a complex event, and a better understanding requires a multi-disciplinary approach that is sensitive to local processes in the AAA wall.*** [3, Rank 4]

Abdominal Aortic Aneurysm as an Important Health Problem

AAA is defined as a full thickness dilatation of the abdominal aortic diameter of ≥1.5 times, measured in the anteroposterior plane. In men, this is taken to mean 3 cm or greater. Around 85% of aortic aneurysms occur within the infra-renal segment of the abdominal aorta. The most common risk factors for AAA include smoking, hypertension, hypercholesterolemia, increasing age and family history, in common with other cardiovascular disease. Other risks, such as connective tissue disorders are much less common, and associated with AAA in younger patients.

Risk of AAA begins to rise around the age of 50 in men in whom it is significantly more common (ratio of approximately 4:1), and later in women. AAA is usually asymptomatic until it ruptures, although pain in the abdomen or lower back can represent a rapidly enlarging or mycotic aneurysm, which should be considered for emergency repair. Aneurysm-related and all-cause mortality following ruptured AAA remains high (up to 80%),a combination of pre-hospital death and failure to survive to discharge. Recent published analysis calculated a pooled risk of rupture of 3.5% for AAA 5.5–6 cm, 4.1% for 6.1–7 cm and 6.3% for AAA ≥7 cm, with risk accumulating over time. This has decreased over time; previously AAA ≥6 cm carried a rupture risk of 14.1% in men and 22.3% in women, suggesting changes in patient behaviour could contribute to a reduction in AAA-related mortality. The average risk of rupture in women with AAA of between 5–5.9 cm is up to four times as high as in men, hence ongoing debate and suggestions that repair should be considered once diameter reaches 5 cm in women.

Ultrasound imaging can reliably visualise the aorta in 99% of individuals, and has been validated against reconstructed three-dimensional CT imaging of the aorta with the benefits of being non-invasive, non-ionising and not requiring nephrotoxic contrast use. Ultrasound was utilised in all of the major AAA screening trials, and supported the significant body of literature concluding that AAA screening using ultrasound was time-efficient, inexpensive and accurate.

The method at which the aorta is measured is still under considerable debate. The three most widely recognised tech-

niques for measuring the aorta with ultrasound are inner-to-inner (ITI), outer-to-outer (OTO) and leading edge-to-leading edge (LELE). [33, Rank 5]

The Method of Biomechanical Rupture Risk Assessment in Abdominal Aortic Aneurysm

AAA rupture is a local failure event in the wall that occurs when mechanical stress overcomes wall strength and naturally motivates tools of local wall rupture risk assessment. AAA wall pathology is driven by the complex interaction of biochemical and biomechanical events, such that a multidisciplinary approach is needed to better understand and more effectively treat AAA disease. Specifically, ***the Biomechanical Rupture Risk Assessment (BRRA) (usually based on finite element (FE) modeling) supports such a holistic risk assessment and quantitatively integrates many known AAA risk factors. Simply put, biomechanics investigates the stress and strain in biological tissue, and biomechanical indices like peak wall stress (PWS) and the peak wall rupture index (PWRI), have been regularly shown to be higher in ruptured/symptomatic AAAs than in intact/nonsymptomatic AAAs.***

AAA Wall Stress

AAA wall stress is the mechanical response to external forces (like blood pressure) acting on the vessel. Wall stress cannot be measured and is predicted (calculated) by solving the equilibrium equations under certain boundary and initial conditions.

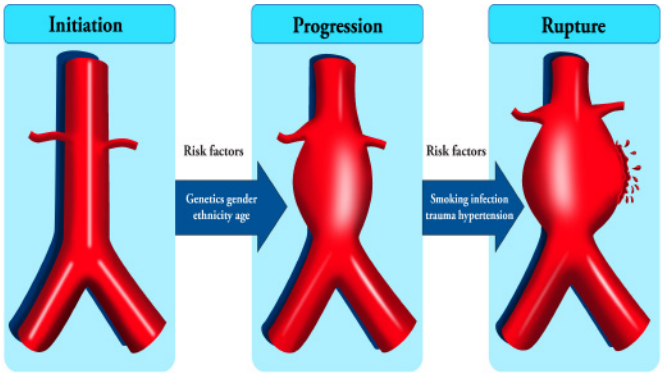

Figure 3: Stages of Abdominal aortic aneurysm and risk factors for each stage

These equations can only be solved analytically (exactly) for a small number of rather simple problems. One of these simple solutions is the well-known ***Laplace equation,*** which gives the wall stress for an inflated thin-walled circular tube. AAA geometry is complex and in most cases cannot be approximated by a thin-walled cylinder, such that wall stress predictions become much more challenging. Specifically, for these biomechanical problems the equilibrium equations can no longer be solved analytically, and wall stress predictions require approximate numerical

approaches like the FE method. ***FE-based wall stress predictions require:***

- Three-dimensional (3D) geometry of the ILT and the vessel wall.
- Mechanical characteristics (constitutive descriptions) of the ILT and wall tissue.
- Assumptions on how the AAA interacts with its surrounding.
- The blood pressure at which wall stress is predicted.

This input information is subjected to uncertainty, and its influence (sensitivity) on wall stress predictions needs to be carefully validated. [3, Rank 5]

Uncertainty of Disease Predictions

Naturally, every model involves making modeling assumptions and reflects the real object only up to a certain degree of completeness. The model should be verified and validated to the degree needed for the model's intended purpose or application. For a BRRA simulation, the required level of modeling details can only be defined in the context of the clinical outcome. Consequently, a good model will include details that improve the clinical outcome and disregard all the other information that reflects current knowledge about the biomechanical problem.

Wall stress computations are not particularly sensitive to constitutive descriptions as long as the wall's low initial stiffness, followed by its strong stiffening at higher strains is respected. Similarly, despite the fact that ITL tissue is highly porous, previous biomechanical studies have demonstrated that a single-phase model predicts AAA wall stress with sufficient accuracy. The FE method solves a discretized biomechanical model (i.e., the wall and ILT are represented by a large number of small regular structural elements, the so-called FEs). [5, Rank 3]

Classification System of AAA

An aneurysm is a localized dilatation of larger blood vessels that is related to regional weakening of the wall structure. Although the large majority of aneurysms presents within arterial tree, venous aneurysms do occur. Aneurysms are generally associated with rupture and a life-threatening haemorrhage, yet ***some aneurysms (in particular popliteal and venous aneurysms) typically manifest through symptoms of acute thrombosis and embolism.***

There are several classification systems for aneurysms. From the perspective of medical therapy the most helpful attribution is that of primary and secondary aneurysms. Primary aneurysms relate to a

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matrix defect in vessel wall (i.e. fibrillin deficiency in Marfan syndrome, Collagen III deficiency in the vascular type Ehlers Danlos syndrome, and unknown defect(s) in aneurysms associated with bicuspid aortic valves). Secondary aneurysms relate to extensive matrix turnover and pathological vessel wall remodelling in response to a primary inflammatory insult (i.e. infection, immune diseases (Kawasaki Syndrome, Giant Cell Arthritis, Behçet syndrome), and the degenerative abdominal aortic aneurysm (AAA)).

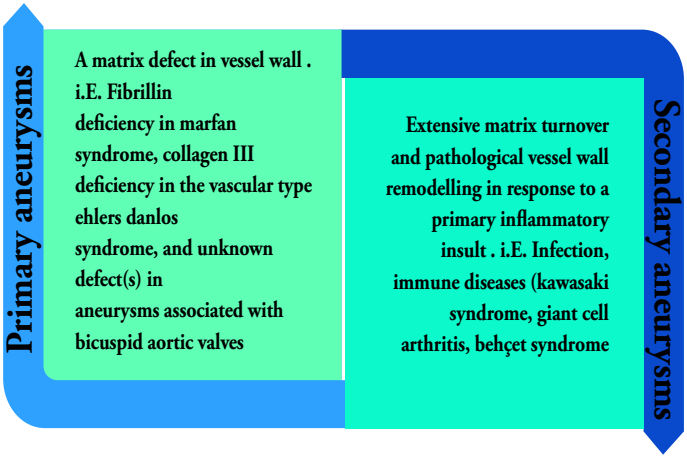

Figure 4: Different types of aneurysm

Although aneurysms occur throughout the vascular tree, there is a remarkable topographic distribution for most aneurysms (i.e. descending thoracic aorta for giant cell arteritis, infrarenal aorta in AAA disease etc.). Although this may be caused by local hemodynamic patterns and associated wall stresses, it likely could reflect ***the different embryologic origins of the vascular tree, which result in a persistent regional diversity in microvascular endothelium, mesenchymal cell characteristics and immunologic make-up.*** The remarkable regional diversity in susceptibility is clearly illustrated by the iliac trajectory. Unlike the adjacent common iliac, internal iliac, and common femoral arteries, the external iliac artery is remarkably resistant to degenerative aneurysms. [4, Rank 4]

What Causes AAA

An AAA is a localized dilatation caused by segmental weakening of the terminal aorta segment. The prevalence of the disease depends on the population studied, with reported prevalence varying between 1.4 and 12.4%.The disease carries a complex genetic predisposition and predominantly affects elderly men with a history of smoking.

AAA's are generally asymptomatic, and are usually diagnosed by screening or as an incidental finding. The natural history of the disease is that of slow progression and ultimate rupture. Ruptured AAA is a dramatic catastrophe, and aortic emergencies constitute one of the leading causes of acute death in elderly males. ***Risk of rupture is minimal in small aneurysms (i.e. less than 50 mm), but progressively increases with enlarging AAA size-- estimated annual rupture risks are less than 1% for AAA with a diameter of 50 mm to over 30% for an AAA exceeding 80 mm diameter.*** [9, Rank 3]

AAA management has been centred for decades on surgical repair of larger aneurysms to mitigate the risks of rupture. Multiple trials have shown no benefit of repair of AAA at sizes below 55 mm diameter, and consequently ***current guidelines advise watchful waiting for aneurysms smaller than 55 mm and preventive repair once the AAA grows over 55 mm,*** possibly with a slightly lower intervention threshold for repair in women.

The two surgical options for repair are: open repair (through a trans-peritoneal or retroperitoneal approach)(as shown in fig.6) or endovascular repair (EVAR) (through a trans-arterial approach)(as shown in fig.7).

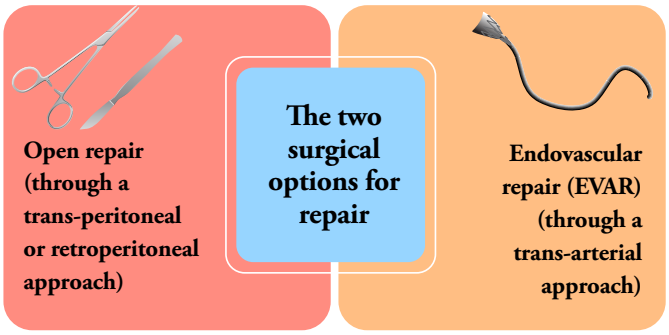

Figure 5: The two surgical options for repair

Decisions for the type of repair are dictated by AAA-specific features such as neck characteristics and proximity to major important branches, as well as by patients' preferences and characteristics such as frailty and obesity.

The majority of patients is currently managed by EVAR. Open repair comes with significant higher perioperative mortality and morbidity; registry-based studies report 30-day mortality rates of approxi-

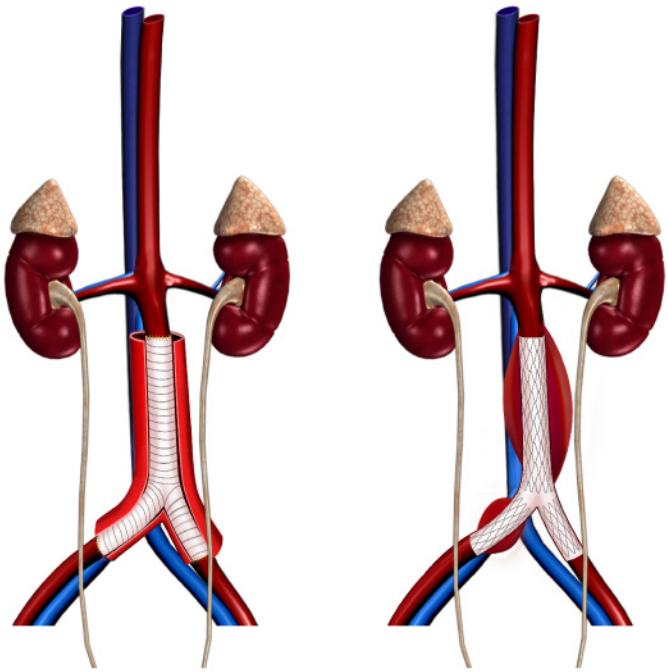

Figure 6: open repair (through a trans-peritoneal or retroperitoneal approach)

mately 4–5% for men and 6–8% for women, and perioperative morbidity of open repair is considerable. However, open repair has an established long-term durability, although incisional hernia remains a common cause of late reintervention. EVAR has superior short-term outcomes, but comes with higher rates of aortic re-intervention, and possibly higher costs. Moreover, there is emerging concern in the published literature about the mid and long-term durability of EVAR with possibly excess late mortality in patients that received EVAR.

Considering the fact that the sole indication for elective AAA repair is rupture prevention, it has been pointed out that medical stabilization of small diameter aneurysms --keep small aneurysms small and thereby prevent or reduce the need for surgical repair--could be advantageous. This has natural appeal to patients and from an economic point of view. Moreover, medical aneurysm stabilization could be beneficial as add-on strategy in patients considered at high risk for endoleak. It is conceivable that in patients who have aneurysm neck prone to dilation, that stabilization of the neck could reduce the incidence of later type. All in all, medical AAA stabilization has been brought forward as an unmet medical need. [6, Rank 5]

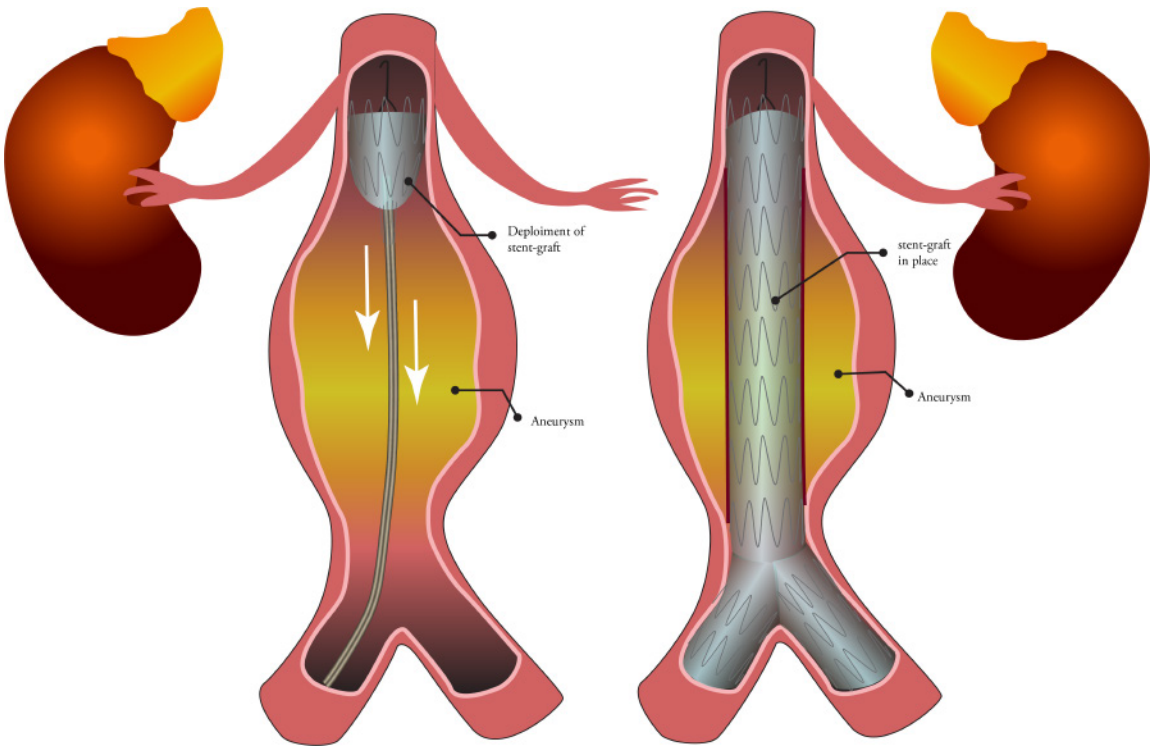

Figure 7: Endovascular repair (EVAR) (through a trans-arterial approach)

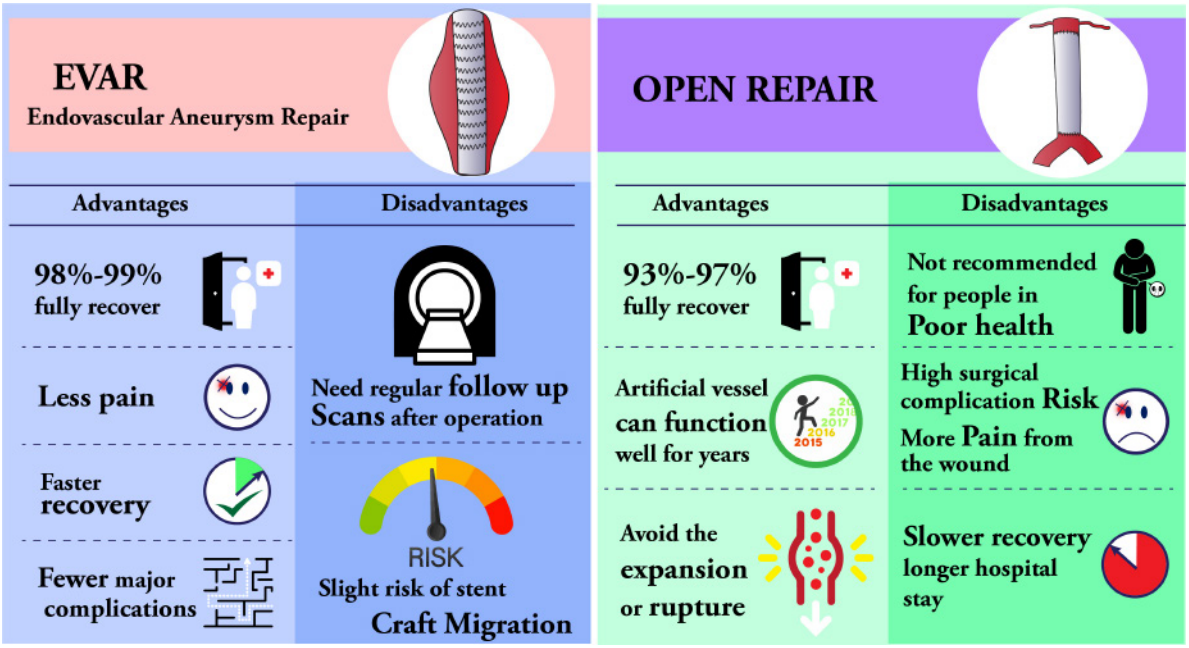

Figure 8: Difference between EVAR and OPEN REPAIR

Targets for Medical Therapy for AAA

Candidate targets for therapy are dictated by the prevailing concepts of the processes driving AAA disease progression. It is generally assumed that AAA progression is driven by a localized inflammatory response and an accompanying proteolytic imbalance. Consequently, proposed interventions directly or indirectly aim at targeting aspects of the inflammatory response, or at rectifying the proteolytic imbalance. The pertinence of these strategies is supported by a wealth of preclinical studies. The vast majority of these are performed in the 'standard' rodent models of AAA disease: the ***'elastase' model.***

The elastase model is based on a transient exposure (generally brief intra-aortic exposure) of an isolated infra-renal aorta segment with porcine pancreatic elastase. The rationale behind the model is the notion that loss of elastin is one of the most notable features of AAA disease. Yet, although the disease is undoubtedly characterized by extensive loss of elastin, it is important to point out that loss of elastin per se is not responsible for the critical wall failure in AAA. First of all, loss of elastin is a very early phenomenon in clinical AAA development, and the elastolysis is virtually complete before the disease reaches the critical 55 mm diameter threshold.

Secondly, clinical experience shows that chemical or surgical (endarterectomy) does not result aneurysm formation. The

validity of this clinical observation is supported by experimental data that show that although elastin critically contributes to the elastic recoil of the aortic wall, it does not contribute to the resilience of the wall. In fact, studies show that the resilience of the wall essentially relies on vascular collagen. This phenomenon is also reflected in the dynamics of the elastase model in which exposure to pure elastin does not immediately induce AAA formation, and in which the initial response following porcine pancreatic elastin preparations is a small increase in aortic diameter, presumably reflecting loss of elastic recoil. The actual aneurysm formation is secondary and reflects a delayed, secondary response, resulting from a secondary inflammatory response. [8, Rank 3]

AAA formation in the elastase models follow a typical pattern with the initial moderate dilatation resulting from loss of elastic recoil, followed by a secondary dilatation, the actual aneurysm formation approximately one week after the elastase induction presumably as result of a secondary inflammatory response. The ultimately dilatation reached varies between 150–200%. [7, Rank 1]

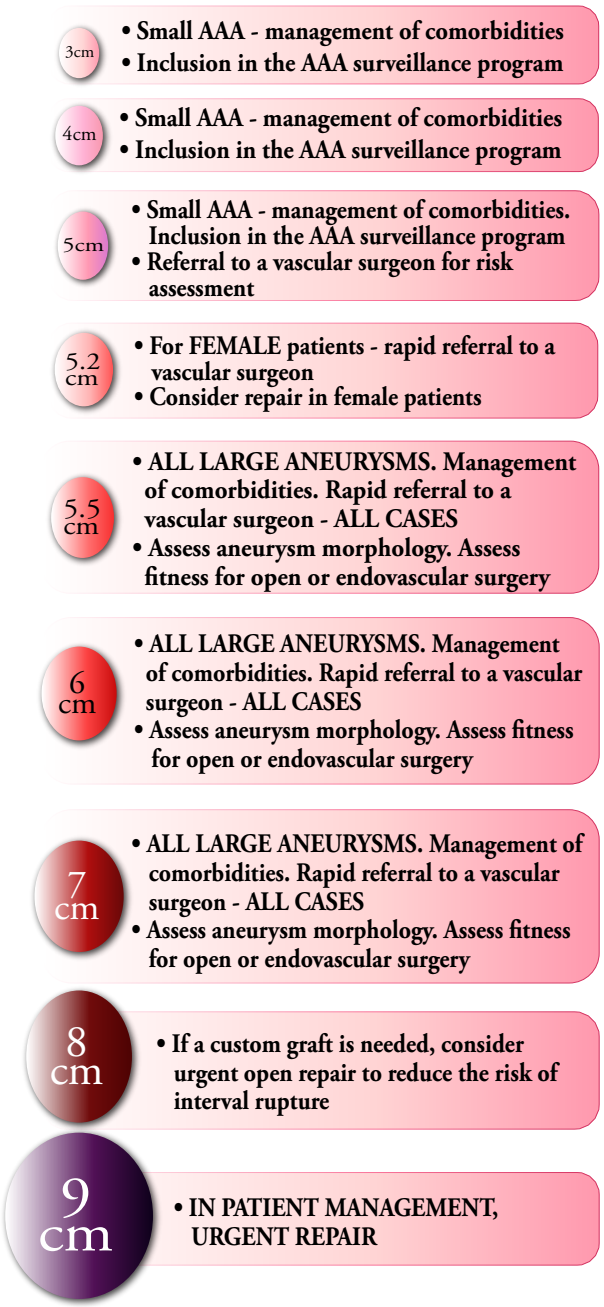

Figure 9: Management and aneurysm size

Medical Therapy for AAA Patients

There are two indications for medical therapy in AAA: cardiovascular risk management and pharmaceutical AAA stabilization.

Epidemiological and cohort studies characterise an AAA as a strong cardiovas-

cular risk factor. In fact, in patients deemed unfit for repair, the risk of dying from non-aneurysm-related (in particular cardiovascular) causes by far exceeds the risk of dying from the AAA. The profound impact of an AAA on overall survival is further illustrated by the relative-survival analysis included in a meta-analysis of patient-survival following open or endovascular repair.

Further evidences suggests that ***cardiovascular risk management is effective in AAA patients,*** hence there is a case for cardiovascular risk management for all AAA patients, irrespective of a possible impact of the risk management on aneurysm progression. Logically, improvement in survival due to reduced cardiovascular risk not only improves the cost-effectiveness of AAA repair, but longer survival will maximize the benefits of an effective pharmaceutical stabilization program. [10, Rank 3]

Preclinical models show the potential of lipid lowering, antihypertensive therapy and platelet aggregation inhibitors in quenching experimental AAA development. Yet, there is little evidence for a beneficial effect of these strategies on clinical AAA progression and stability. The first studies exploring the potential of pharmaceutical therapy for AAA progression were based on observed beneficial associations between β-blocker use and aneurysm progression in two studies. These studies were then followed by a further case control and cohort study, and later by two randomized trials. All these later studies were not confirmative, although the interpretation of the randomized controlled trials is compromised by the poor tolerability of the β-blocker used (propanol) which resulted in a 42% drop out rate in the treatment arm

ACE Inhibitors

The ACE-inhibitors are the second class of anti-hypertensive drugs that received significant attention in the context of AAA stabilization. Enthusiasm was spurred by supportive evidence from experimental studies, and a population-based case-control study that reported an beneficial association between ACE inhibitor use and risk of rupture). This study was followed by a series of non-confirmative studies, one of them suggesting at an adverse association between ACE-inhibitor use and AAA progression.

These controversies were ultimately addressed in another study. This study concluded that, despite more effective blood pressure lowering, the ACE-inhibitor perindopril did not show significant impact on aneurysm growth (compared to both placebo alone and to combined placebo and am-

lodipine). A shortcoming of the study is the lower than anticipated aneurysm growth. As such the trial may lack the sensitivity to detect minor effect sizes. Although the researchers attribute this shortcoming to the high level medical cardiac risk management in the population studied, it is likely that the lower than anticipated growth reflects inclusion of a disproportionate group of patients with relatively small AAAs (approx. 35 mm).

At this point the potential of the type 1 angiotensin-receptor antagonist Telmisartan is under investigation in another study. The rationale for this study is the fact that AT1-receptor antagonists interfere with the negative aspects of angiotensin signalling, but preserve signalling through the ATR1-receptor which is associated with vascular protective activity. Along these lines, beneficial associations have been reported between type 1 AT-receptor antagonist use and AAA progression.

The overall conclusion for antihypertensive therapies is that the available clinical studies refute β-blockers or ACE-inhibitors as pharmaceutical strategies for AAA stabilization. This indirectly confirms absence of a direct association between blood pressure and AAA progression. [11, Rank 4]

> **" According to the best clinical practice, AAA repair is indicated if rupture risk exceeds the interventional risks. "**

Statins

The potential of statins has been evaluated in several studies. Results of these studies are mixed with six studies hinting at a beneficial association between statin use and AAA progression and another six studies failing to show an association between statin use and aneurysm progression. Conclusion from the studies segregates, with the older and smaller studies being confirmative, and the later and larger studies being non-confirmative. On this basis, while the cardiovascular risk benefits of statins are impressive, there is no role for statins as a pharmaceutical strategy stabilizing AAA. [13, Rank 3]

Antiplatelet Therapy

An effect of antiplatelet therapy on aneurysm progression has been explored in six studies. Beneficial effects have been observed in medium sized cohort study of patients under surveillance of a 40–49 mm AAA. Unfortunately, the validity of the study is challenged by the unrealistic high growth rate in the control group (5.2 mm/-

year; anticipated growth rate 2–3 mm/year. A potential effect for combined aspirin-statin treatment has been observed in a sub-analysis of a study evaluating the effect of azithromycin on AAA progression. A benefit for NSAIDs has been reported on the basis of a very small study reportedly patients using NSAID showed reduced AAA progression. [12, Rank 2]

Well-established negative (beneficial) associations exist between diabetic disease and AAA growth rate. Although this has been attributed to diabetes-related factors such as matrix stabilization by enhanced glycation and modulation of inflammation, there are indications that this negative (protective) association relate to off-targets effect of metformin, a biguanide antidiabetic that is first-line medication for type II diabetes.

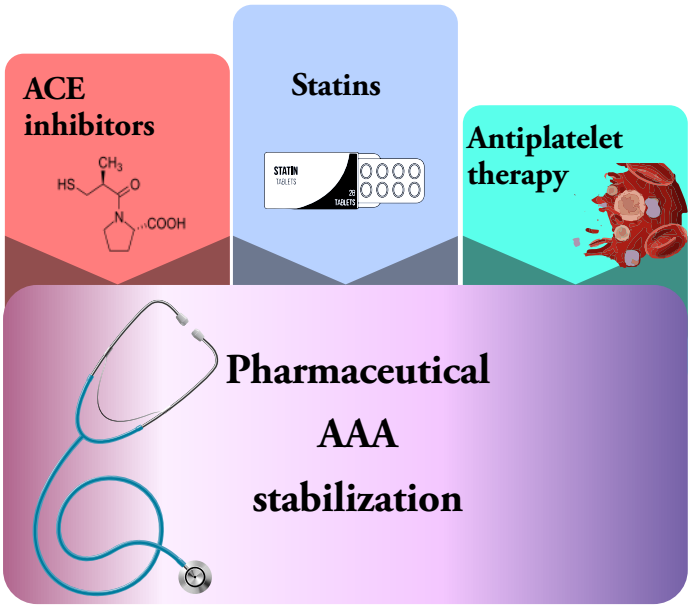

Figure 10: Pharmaceutical AAA stabilization

Generally Accepted Treatment Modalities for Abdominal Aortic Aneurysm

Broadly speaking there are two surgical options for AAA repair. Open surgery requires laparotomy and exposure of the aneurysm, proximal and distal control using arterial clamps, and sewing in a synthetic graft to healthy artery to completely replace the diseased segment. EVAR describes endovascular surgery, in which a fabric covered component stent graft is deployed within the aneurysmal component of the aorta to create an impermeable seal proximally and distally in unaffected areas of the vessel (most commonly a non-diseased infra-renal section of the aorta proximally, and the common iliac arteries distally). Access is obtained via the common femoral arteries in the vast majority of cases.

Diabetes and the Occurrence of Abdominal Aortic Aneurysm

Diabetes mellitus corresponds to a heterogeneous disease characterized by a chronic hyperglycaemia and is generally classified in several categories including mainly type 1 (T1D) and type 2 diabetes (T2D). Although DM represents a major cardiovascular risk factor, the vast majority of epidemiological studies have paradoxi-

cally identified an inverse association between DM and the prevalence and incidence of AAA. Indeed, several reports have shown that diabetic patients develop smaller AAA, as demonstrated by significantly lower aortic diameters compared to non-diabetic subjects. Besides, several studies highlighted lower growth rates of AAA in diabetic patients compared to controls. In practice, the decision to treat AAA takes into consideration the risk of rupture. As large aortic diameter and high growth rate represent major risk factors of rupture, it is not surprising that a negative association between DM and aneurysm rupture was identified.

While DM appears as a protective factor of AAA formation and expansion, the prognosis and outcome after AAA treatment also differs between diabetics and non-diabetic patients. Heterogeneous results were found among different studies, some reports revealing increased operative mortality in diabetics, others showing no difference, and some reporting lower mortality. Besides, morbidity following AAA repair was analysed, and DM was identified either as a negative or protective factor of specific post-operative outcomes. Higher rates of complications such as myocardial infarction, infection, or pancreatitis were observed in diabetic patients after AAA open repair, and higher incidence of device-related complications following endovascular AAA repair were found. On the opposite, DM had a protective effect on AAA growth and re-interventions after endovascular repair, but no significant difference in the occurrence of neck dilatation or type 1 endoleaks was identified between diabetics and controls. [22, Rank 5]

Effects of Antidiabetic Treatments

Treatment of DM relies on lifestyle measures associated with blood glucose lowering drugs. Insulin administration is the main therapy for T1D patients. ***Pharmacological treatments mostly used in T2D include insulin sensitizers such as biguanides (metformin) or thiazolidinediones (rosiglitazone, pioglitazone), drugs stimulating insulin secretion such as sulfonylureas or meglitinides, and drugs with incretin effects such as glucagon-like-peptide-1 (GLP-1) receptor agonists (i.e. liraglutide, exenatide, lixisenatide) or dipeptidyl peptidase 4 (DPP-IV) inhibitors (i.e. alogliptin).***

Intriguingly, epidemiological studies have revealed that mechanisms conferring a protective effect of DM on AAA are not only related to the pathophysiology of DM but also to antidiabetic treatments. A study including patients with AAA showed that

the use of antidiabetic drugs was associated with a 56% reduction in AAA growth rate, and this association was independent of confounding factors including other therapeutic agents. In addition, a nested case–control analysis including patients with AAA revealed that metformin, sulfonylurea, and thiazolidinedione use was associated with a lower risk of developing aneurysm. The negative association between metformin use and AAA enlargement and growth was confirmed in other studies. No significant association was found between metformin use and the risk of rupture [24, Rank 3]

Complications Following AAA

Chlamydia Infection

A presumed role for persistent chlamydia infection in the perpetuation of vascular disease including AAA at the millennium époque resulted in three studies with aimed at anti-chlamydia eradication. Two small trials with respectively a single four week course of the antibiotic roxithromycin or repeated (annual) four week courses of roxithromycin reported borderline benefits on aneurysm progression. However, this was not confirmed in a larger study with azithromycin that did not identify an effect of sixteen weeks of macrolide treatment on AAA progression. [14, Rank 2]

> **“ The disease carries a complex genetic predisposition and predominantly affects elderly men with a history of smoking. The natural history of the disease is that of slow progression and ultimate rupture. ”**

Vascular Inflammation

A further series of clinical studies aimed at targeting specific aspects of the vascular inflammation and proteolytic imbalance in AAA. In this respect, there is a longstanding interest in the tetracycline antibiotic doxycycline. Independent of its antibiotic properties doxycycline has been shown to reduce the expression of matrix metalloproteinases (MMP), and to quench their activity. Doxycycline effectively interferes with aneurysm formation in some but not all models of aneurysm formation, and clinical studies showed that doxycycline treatment reduces aortic wall matrix metalloproteinases content and improves the proteolytic imbalance through its effect on aneurysm wall protease inhibitor levels.

Apart from these studies on diameter changes, there is data available for surrogate endpoints (aneurysm wall inflammation). In a randomized study of a few weeks treat-

ment, no effect was observed on the circulating markers osteopontin or kallistatin. Although the authors report an absent effect on AAA growth, it is important to point out that the trial was not adequately powered to detect such an effect.

A highly selective suppression of aneurysm wall inflammation was observed for the selective vitamin D receptor agonist paricalcitol. It was shown that a 2–4 week pre-operative paricalcitol treatment selectively interfered with aspects of medium inflammation, suggesting that the effects of vitamin D are mainly mediated by an effect on calcineurin-mediated inflammation. This notion was confirmed in in-vitro studies. Although plasma lipids do not associate with incident AAA disease, there are weak associations between plasma LDL levels and AAA progression. In this light, the observed superior effects of ezetimide/simvastatin over simvastatin alone on vascular inflammation merit attention, yet it is unclear how these observations relate to the apparent absence of statins on AAA progression. [15, Rank 3]

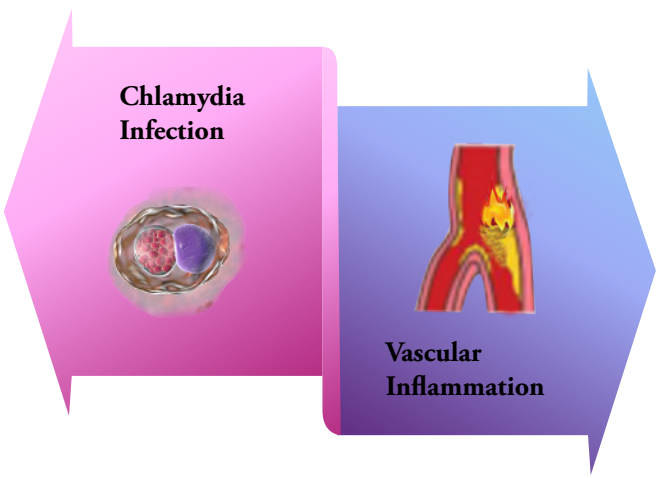

Figure 11: Complications Following Abdominal Aortic Aneurysm

Inflammatory Response Associated with AAA

The apparent translational gap between preclinical and clinical studies challenges the concepts of the processes underlying late stage AAA disease pathophysiology. Undoubtedly, AAA is associated with a sustained and comprehensive inflammatory response, uncontrolled protease activity and excess matrix turn-over. Short-term pre-operative intervention studies in patients undergoing open repair all proved the potential of indomethacin, statins, ACE-inhibitors and doxycycline to effectively quench vascular inflammation and protease activity. Yet, these effects are not followed by reduction of AAA progression. Interestingly, profound immune suppression in the context of solid organ transplantation even results in accelerated AAA progression. Although these aforementioned observations do not exclude a role for inflammation and or protease activity in AAA initiation and progression, they imply involvement of additional, so far unidentified critical factors that are unresponsive to the anti-inflammatory/anti-proteolytic therapies.

Defective Compensatory Repair

One of possible key factors is failing or defective compensatory repair. In fact, interference with compensatory repair mechanisms (stem cell function) may explain the apparent disastrous effects of intense immune suppression, chemotherapy and the unexpected negative effect of doxycycline therapy on aneurysm growth. Moreover, there are clear indications for defective matrix repair in AAA. The disease is associated with complete loss of the normal aortic wall architecture, and the normal aortic matrix is replaced by a collagenous, fibrotic matrix. Although a higher collagen cross-link content in AAA wall samples may imply more stable collagen, this is actually not the case due to defects at the level of collagen fibril organization. In the healthy aortic matrix the collagen fibrils are laid down in supra-molecular, intertwined network structures. As a result, forces are distributed over the wall. Loss of this network behaviour in AAA disease fundamentally impacts the mechanical stability of the wall and may contribute to the aortic wall weakening in the disease. [16, Rank 3]

Fatty Degeneration

Fatty degeneration was recently identified as another potential contributor to the weakening of the aneurysm wall. Fatty degeneration is a known phenomenon in aging and chronically injured muscle, and thought to be a consequence of impaired repair mechanism in the context of chronic injury. Gene-expression studies on AAA wall specimens suggest that progressive adipocyte accumulation associated with rupture.

Unfortunately, perpetual inflammatory cycle and the impaired compensatory repair that are hallmarks of human AAA are not captured in the rodent models of AAA disease. This shortcoming may largely reflect the spontaneous resolution of inflammation in these models and the superior endogenous healing responses of small animal models as well as their inherent resistance to develop chronic fibrosis. In an attempt to create more relevant (viz. rupture prone) AAA models, modified models have been introduced in which interference with the primary healing responses resulted in AAA ruptures. Yet, these models do not recapitulate the chronically impaired and dysregulated healing responses that characterize AAA disease. Absence of fibrotic repair in rodent models of AAA disease also explains the apparent benefit of inducing fibrotic repair in stabilizing growing AAA in rodent models. Since the extensive fibrosis is a hallmark of human AAA disease, and that process of fibrosis results in deposition of a brittle, poor quality matrix, it is ques-

tionable whether a profibrotic strategy will stabilize human AAA. [17, Rank 4]

Considering the wealth of preclinical success and failing clinical attempts to identify molecular strategies for stabilizing AAA disease we must acknowledge that our understanding of AAA disease is far from complete, and that the available small animal models of the disease only partially mimic aspects of the human disease. There appears a recent trend to include (or demand) confirmative studies in a second animal model in preclinical studies. Considering the parallels between the different models, it is dubious whether this increases the likelihood of the findings being more translationally relevant. Future advancement of the field critically relies on an improved mechanistic insight in the processes that sustain the impaired and ultimately failing repair mechanisms in advanced clinical AAA disease. [18, Rank 3]

" Aneurysms occur throughout the vascular tree, there is a remarkable topographic distribution for most aneurysms (i.e. Descending thoracic aorta for giant cell arteritis, infrarenal aorta in AAA disease etc.) "

Formation Process of Abdominal Aortic Aneurysm

The cellular mechanisms responsible for aortic aneurysm formation constitute a complex, orchestrated series of events that result in dramatic pathological changes in the anatomy and function of the arterial wall. Of fundamental importance is the

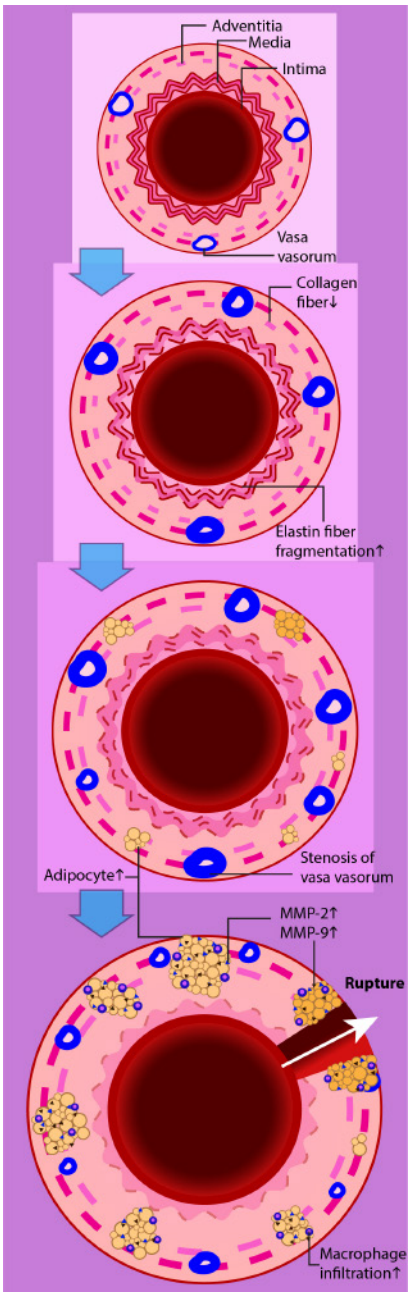

Figure 12: Cell changes during aneurysm rupture

understanding that there are clear and distinct differences between the mechanisms underlying thoracic and abdominal aortic aneurysms. Thus, while ***the physical appearance of thoracic and abdominal aortic aneurysms has striking similarities, the pathophysiological change of these two diseases is quite distinct.*** The epidemiology of AAA formation appears to be distinct from that of atherosclerotic disease.

Contributions of Different Cell Types

Apoptosis of smooth muscle cells and degeneration of the aortic media have long been identified as hallmark of AAA pathology. Inflammation, production of reactive oxygen species, and stress have all been associated with smooth muscle cell apoptosis in AAA. This loss of structural integrity is key to aortic dilation and rupture. Of interest is that the vast majority of AAA occur below the level of the renal arteries which may reflect the differing embryologic origins of vascular smooth muscle cells. In the distal abdominal aorta, the mesoderm gives rise to aortic vascular smooth muscle cells whereas the thoracic aorta smooth muscle cells arise from the neural crest.

While it is obvious that changes in vascular smooth muscle cells of the media are pivotal to the development of AAA, many other cell types are involved in addition to smooth muscle cells including endothelial cells, neutrophils, monocyte/macrophages, lymphocytes, adipocytes, mast cells and platelets. The functional contributions of these cell types is sometimes obvious as in the case of vascular smooth muscle cells. In other cases, studies have utilized depletion strategies in order to define their relative contributions.

The precise role of the endothelium has not yet been fully explored but, it is clear that these cells do play a critical role in that endothelial Nitric Oxide Synthase uncoupling and endothelial biomechanical signal transduction have roles in AAA formation. In the case of platelets, while von Willebrand factor (VWF) may not be essential for AAA formation, the presence of thrombus in AAA portends a worse outcome and suggests that there are yet to be determined functional contributions of platelets to AAA development and rupture. [20, Rank 2]

The Renin Angiotensin System

The demonstration of induction of AAA by angiotensin II (Ang II) infusion in apoE and LDL receptor knockout mice is certainly the most direct data in terms of documenting a causal relationship between the renin-angiotensin system and AAA formation. Earlier reports in mice overexpressing angiotensinogen and renin on a high

salt diet first suggested this relationship as these animals developed AAA. These data are consistent with additional studies showing that angiotensin converting enzyme inhibition limited AAA formation in the elastase model. Thus, it appears that angiotensin II may induce AAA but, it may not be sufficient as in most cases, additional factors (e.g., elevated cholesterol) appear to be required to induce AAA. The source of Ang II generation is complex and several studies raise the possibility that, in addition to angiotensin converting enzyme, chymase expressed in mast cells may contribute to local generation of angiotensin II. The absolute magnitude of the contribution is less clear due to the additional role of chymase in matrix metalloproteinases activation and apoptosis.

Angiotensin II effects on the cellular components of the aorta have been extensively studied and include many of the cellular mechanisms described below including production of reactive oxygen species, induction and activation of matrix metalloproteinases , and infiltration of inflammatory cells. Rather disappointingly, clinical trials have failed to demonstrate a benefit of angiotensin converting enzyme inhibition on AAA growth rate and in at least one study, may have had an adverse effect. The reason for this discrepancy is unclear and may reflect deficiencies in the available models, effects on disease initiation vs. progression, or the endpoint of aortic diameter [19, Rank 4]

Cell Inflammation and Pathways

A hallmark of AAA formation is an intense inflammatory response involving essentially all of the classic cellular constituents of inflammation as well as local inflammatory responses in the arterial wall. Neutrophil infiltration occurs very early on in AAA, but is transient. Observations in the elastase model showed that treatment with neutrophil neutralizing antibodies slowed AAA expansion suggesting a functionally relevant role for neutrophils. However, more recent data suggests that neutrophil extracellular traps may be an important component of the continued inflammation in AAA. Finally, neutrophils are a source of reactive oxygen species that can be generated by several enzymatic sources.

Macrophage infiltration of AAA is one of the most consistent pathological findings and certainly not surprising given the biological function of these cells and their production of matrix metalloproteinases , cytokines, and chemokines as well as their ability to remove cellular debris. Interestingly, owing to their ability to express different phenotypes encompassing both inflammatory and reparative functions,

macrophages participate in both the pathogenesis of AAA as well as the repair response. This can occur through classical cytokine pathway or through more novel mechanisms. [22, rank 5]

Cytokine production by both immune cells and cells native to the vessel wall ultimately drive the inflammatory responses leading to AAA formation. As reviewed in detail elsewhere, numerous studies have identified the involvement of multiple cytokines in AAA formation. These encompass both inflammatory and anti-inflammatory cytokines. While extremely complex and incompletely understood, suffice it to say that cytokine production by both inflammatory cells and the resident cells of the vascular wall contribute to a pathological feedback loop further enhancing inflammation.

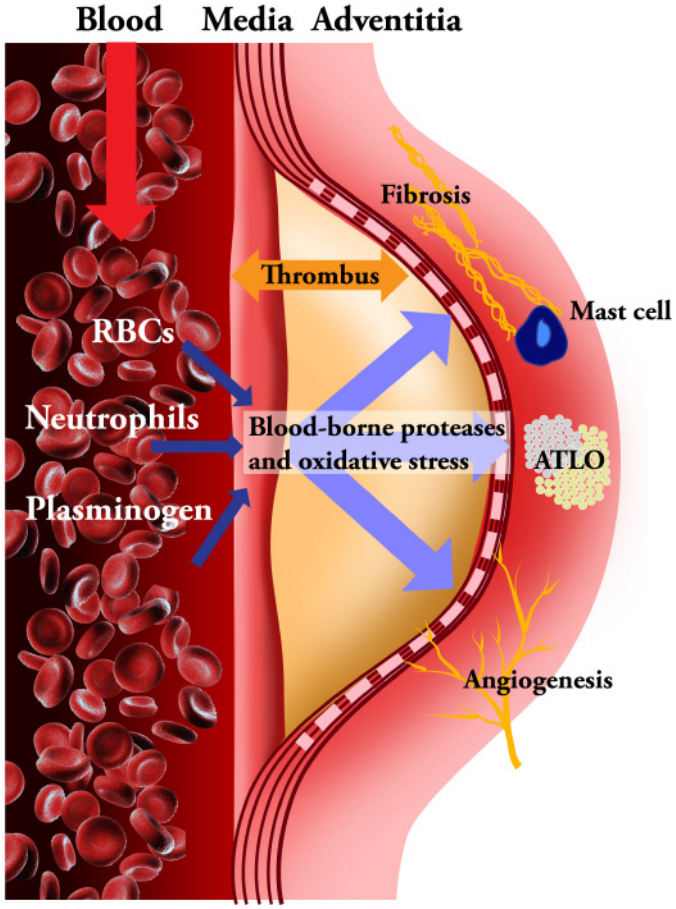

Figure 12: changes in blood vessel during aneurysm development

Reactive Oxygen Species

Reactive Oxygen Species (ROS) play a central role in the development of AAA. Some of the earlier observations in human tissues showed that superoxide levels were elevated in the smooth muscle and inflammatory cells of AAA specimens. Many of the known pathological effects of excess ROS including activation of matrix metalloproteinases s, induction of pro-inflammatory genes, and apoptosis, are key pathological features of AAA. Animal studies have shown that administration of vitamin E as an antioxidant led to decreases in AAA size and rupture. Several studies have shown that smooth muscle-specific overexpression of catalase prevented early mechanical changes in the aortic wall after Ang II infusion as well as inhibition of AAA formation [22, Rank 2]

Uncoupled endothelial nitric oxide synthase (eNOS) has been proposed to be a contributor to ROS production in a variety of vascular diseases processes in general and specifically in AAA. Importantly, folic acid administration was shown to prevent AAA formation. Data suggest that ROS derived

from uncoupled endothelial Nitric Oxide Synthase also contribute to AAA formation.

Risk Factors of Abdominal Aortic Aneurysm

The strongest risk factors for AAA are male sex, family history, and cigarette smoking. How these risk factors impact the known cellular mechanisms of AAA is key to understanding of the disease(as shown in fig.14). The overall rate at which AAA affects men is higher than women at ratio of 5:1. In both the elastase and the angiotensin II models, males exhibit a higher incidence and larger AAAs when compared to females. A very striking gender-based difference in the disease is its progression over time. A population based study examining the incidence of AAA in men and women as a function of age showed that in the 40–60 year age group (pre- and early post-menopausal women), the rate of AAA was eleven times higher in men than women. In the 60–90 year group this difference falls to three times, and by age 90 men and women have AAA at an equivalent rate.

There is not a single, causal mechanism responsible for the sex-dependent differences in the incidence of AAA. There are many clinical and pre-clinical studies examining the role of sex hormones on AAA demonstrating complex and sometimes paradoxical effects. While endogenous estradiol is likely protective, exogenous estrogen replacement has shown conflicting results in human studies with both increases and decreases in AAA events in women receiving hormone replacement therapy.

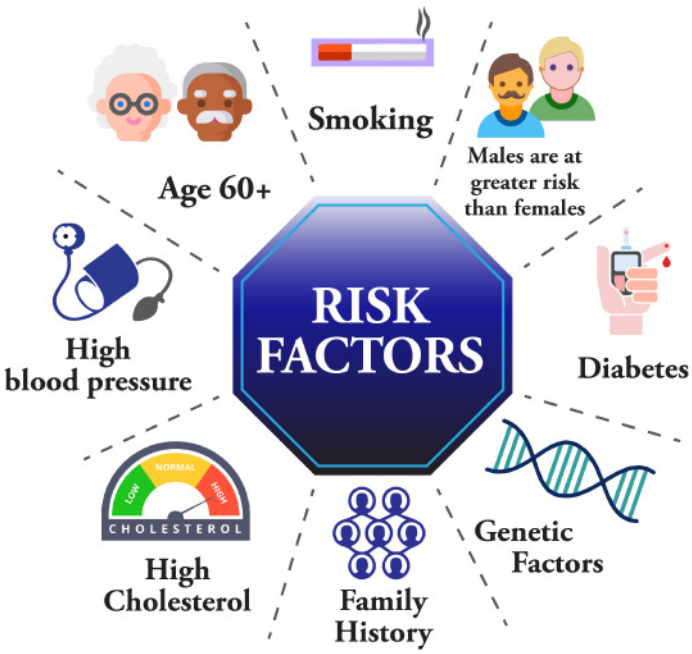

Figure 13: Risk factors of Abdominal Aortic Aneurysm

Conversely, androgen signaling increases production of reactive oxygen species, expression of angiotensin II receptors, inflammation in the arterial wall and counteracts the effects of exogenous estrogen. Very interestingly, specific loci on the Y chromosome have been linked to activation of the renin angiotensin system and subsequent AAA formation. These data suggest that androgen-mediated events are the primary drivers of sex differences in AAA. However, in human studies, low testosterone levels were shown to be independently

associated with the presence of AAA. Whether this discrepancy is due to differences in disease state or is related to lack of translation of models to the human disease state is unclear. [26, Rank 4]

The local difference in vascular hemodynamics may also contribute to the sex differences in AAA in that local shear stress patterns differ between males and females as a result of differences in abdominal blood flow patterns to the reproductive organs. In addition, mechanical properties of the aorta exhibit sex-dependent differences that are also age-dependent. This may be due to altered extracellular matrix content and cross linking of the extracellular matrix which ultimately reflect androgen-mediated physiology as described above. The downstream effectors of differential androgen and estrogen signaling involve essentially all of the same cellular mechanisms of AAA as described above with reported differences in production of ROS, inflammatory mediators, extracellular matrix composition and inflammatory cells.

The mechanisms of other risk factors are less clear. Genetic factors are discussed in a separate section of this compendium. Cigarette smoking is a complex stimulus and there are likely multiple components in cigarette smoke that promote vascular disease. It has been shown that cigarette smoke extract induces expression of matrix metalloproteinases -2 as well as matrix metalloproteinases -9 and that nicotine, through increased expression of matrix metalloproteinases -2 induces AAA. The mechanisms of other, protective risk factors including diabetes and race remain unknown. [25, Rank 5]

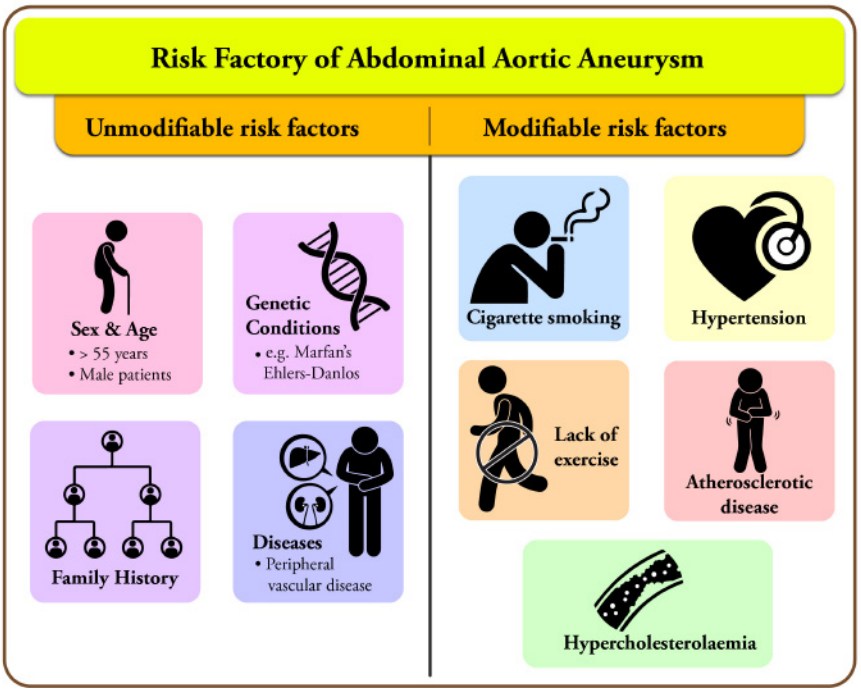

Figure 14: Non modifiable and Modifiable risk factors

Role of Extracellular Matrix in AAA

As is the case for AAA, TAA is characterized in part by abnormalities in the extracellular matrix that compromise the structural integrity of the aorta. Studies have implicated several genetic variants in proteins that directly impact the mechanical characteristics of the aorta leading to TAA. Among these is lysl oxidase, which is responsible for cross linking collagen and elastin. Genetic data are supported by experimental studies in which administration of beta-aminopropionitrile (a lysl oxidase inhibitor) to mice in the setting of angiotensin infusion leads to aneurysmal dilation of the aorta at multiple locations. Interestingly, beta-aminopropionitrile is naturally occurring in sweet peas and either feeding experimental sweet peas or those eating sweet peas results in aortic aneurysms among other manifestations related to loss of collagen and elastin structure. It is important to note that the effects of beta-aminopropionitrile are not specific to the thoracic aorta suggesting that other factors are likely involved. In addition, it is unknown if genetic variants in other members of the lysl oxidase family contribute to TAA formation. [27, Rank 4]

Some forms of Ehlers-Danlos Syndrome are associated with TAA and aortic dissection. Ehlers-Danlos Syndrome encompasses a group of diseases due to mutations in collagen genes. The vascular phenotype variant of Ehlers-Danlos (type IV) is due to one of several mutations in the type III pro-collagen gene and is associated with TAA and other vascular abnormalities. The formation of aneurysm and dissection in affected individuals is presumably due to the compromise of the mechanical integrity of the wall.

One of the initial, major contributions to our understanding of TAA came from observations related to Marfan Syndrome with the finding there was a mutation in the fibrillin 1 gene. Subsequently, additional mutations in fibrillin 1 have been identified. Several works have also implicated variants in the large latent TGF binding protein. [27, Rank 5]

Role of Smooth Muscle Cells in AAA

Smooth muscle cells are the major cellular constituent of the aorta and their loss through apoptosis or necroptosis is a major defining feature of both AAA and

> **“ There are two indications for medical therapy in AAA: cardiovascular risk management and pharmaceutical AAA stabilization. ”**

TAA. Genetic studies have shown that ***several mutations in the contractile proteins of smooth muscle cells predispose individuals to TAA.*** This suggests that smooth muscle contractile function plays an important role in TAA though the mechanism is unclear. Possibilities include both a structural, load bearing function or a signal mechanical signal transduction function as proposed in the section of this compendium devoted to the genetic basis of aortic aneurysms.

Inflammation

Inflammation is a cardinal feature of AAA but the data supporting a role for inflammation in TAA are less extensive. There are intriguing data suggesting that there is some commonality between AAA and TAA and that the structural changes described above may lead to increased production of reactive oxygen species and inflammatory responses. Both T cells and macrophages are present in the media of TAA a finding that is supported by genomic analysis of human TAA samples which revealed upregulation of multiple inflammatory pathways. While there is evidence of inflammation in TAA and plausible mechanisms for the induction of inflammation in TAA, the data set currently available is somewhat limited. [28, Rank 4]

> **" AAA wall pathology is driven by the complex interaction of biochemical and biomechanical events. AAA geometry is complex and in most cases cannot be approximated by a thin-walled cylinder "**

Similarities in Cellular and Molecular Mechanisms of AAA

The major conclusion to be derived from the evolving literature defining the cellular and molecular mechanisms of thoracic and abdominal aortic aneurysms is that while thoracic and abdominal aortic aneurysms have striking similarities at the gross anatomical level, the underlying pathophysiology has quite distinct differences. AAA and TAA are best considered as different disease processes with inflammation as hallmark of AAA formation and distinct alterations in extracellular matrix formation perhaps being a common feature of TAA. However, we must be cautious about such sweeping generalizations as they may be driven by the experimental approaches used to study these diseases and in essence, be self-fulfilling prophesies because of these approaches.

The vast majority of the studies of AAA have been fuelled by the emergence of several relatively simple models. While informative that angiotensin II can induce AAA in the

appropriate settings, the extensive use of this model raises the question; Does the fact that angiotensin II is a potent pro-inflammatory stimulus inform us about the fundamental pathophysiology of AAA or does it constrain us to an exclusive focus on inflammatory mechanisms? Similarly, in the case of TAA, much of the mechanistic work has been driven by genetic models that are often derived from human disease where unique genetic mutations have been identified. While extraordinarily informative, this approach is also somewhat limited in terms of the generalizability to the greater population of individuals with sporadic TAA. Indeed, the relatively limited number of more "generic" models of TAA (i.e., those that are not based on a specific genetic mutation) may be a limiting factor in the study of TAA disease mechanisms. Several clinical trials in humans using pharmacological approaches sometimes fail to produce the predicted effects which is likely a consequence of the limitations of available models. [30, Rank 3]

Modifiable Risk Factors in AAA

Smoking

The principal modifiable risk factor for AAA is smoking. Many reports have showed the extremely strong correlation between smoking and AAA. Moreover, ***a linear association between number of cigarette smoked or years of smoking and prevalence of AAA has been shown.*** In another study, an association shown between a decline in the prevalence of AAA and the years of widespread smoking cessation was evident. Intriguingly, smoking seems to be a substantially greater risk factor for AAA than for occlusive atherosclerotic disease. Smoking is also an important factor in the progression of AAA. In a recent meta-analysis using data from 15,475 patients with small (3–5.5 cm) AAAs, current smoking was associated with an increased rate of expansion (compared with nonsmokers) of 3.5 mm/year. Smoking was also associated with an increased risk of rupture regardless the AAA diameter.

This strong association between smoking and AAA has led many to investigate the molecular mechanism that can explain this deleterious effect. In a AAA model treated with benzopyrene (an important constituent of cigarette smoke), increased gene expression of matrix metalloproteinases was evident. Exposure to tobacco smoke in model of AAA showed increased progression of AAA even in mice deficient for matrix metalloproteinases and elastase. This progression was explained by altered activity of the immune system. Moreover, nicotine (a major component of cigarette smoke) can promote the developing of AAA in an animal model through activation of adenosine monophosphate-activated kinase. Finally, it has been demonstrated in vitro that extract of ciga-

rette smoke can inhibit expression of prolyl hydroxylase, thus decreasing collagen synthesis. [33, Rank 4]

Hypertension

While a strong association between smoking and AAA is evident, the association between hypertension and AAA is weak. In a retrospective study with a cohort more than 3 million people, hypertension was associated with AAA and in a prospective study with 7-year follow-up, the probability for AAA in patients with hypertension was slightly but significantly higher. Finally, in a population-based study with both historical and current data, the association between hypertension and AAA failed to reach the statistical significance. Where hypertension does matter is in the fact that high blood pressure seems to be a more important risk factor for growth and rupture of AAA.

Obesity

Discordant data exist about the association of AAA with obesity: in a large retrospective analysis involving more than 3 million people, body mass index (BMI) > 25 was associated with an increased risk of AAA. In analysis of ultrasonography in 12,203 men aged 65 to 83 years, a correlation between obesity and AAA was shown, with a stronger correlation in obese patients with a high waist circumference. However, in other prospective studies, high BMI was not associated with risk of AAA. In a recent population-based cohort study, waist circumference was associated with increased risk of AAA, while high BMI was not. While BMI reflects total adiposity, waist circumference is more reflective of visceral adiposity. Therefore, it may be that visceral adiposity, rather than total adiposity, is important in the development of AAA [35, Rank 4]

Diabetes

Further confirming the difference between classic occlusive cardiovascular diseases (CAD and peripheral artery disease, where diabetes is one of the most important risk factors), in AAA, diabetes appears to have a protective effect. A similar result was found in a study with a different design, convincing of the protective role of diabetes against developing an AAA. Since then, many other reports have confirmed the protective role of diabetes. Another study summarized the results of seven different meta-analyses and confirmed the protective role of diabetes for AAA. The protective role of diabetes is evident not only for the development of AAA but also in decreasing the growth rate of the aneurysm. A recent meta-analysis estimated an annual mean effect of diabetes on grow rate of –0.6 mm/year.

The physio pathological explanation

for the protective effect of diabetes remains elusive. Both mechanics and molecular mechanisms have been postulated. In diabetic patients, a thickening of the aortic wall is evident—a factor well known to aortic surgeons. According to Laplace's law, a thicker aortic wall decreases wall stress. Wall stress is considered pivotal for progression of AAA. From a molecular point of view, different mechanisms have been proposed. The advanced glycation end products typical of diabetes cause cross-linking of collagen fibers. In vitro, this cross-linking inhibits the proteolysis and secretion of matrix metalloproteinases that are involved in AAA formation. Moreover, the presence of the end products advanced glycation promotes proliferation of the SMCs in the media. Hyperglycemia also suppresses plasmin, itself an activator of matrix metalloproteinases s leading to a further decrease in overall matrix metalloproteinases activity. [34, Rank 2]

Atherosclerosis

Although atherosclerotic changes are often seen in AAA, the relationship is not a casual one. Both epidemiological data and molecular studies provide evidence that AAA is a different disease from classical atherosclerotic occlusive disease. Interestingly, almost every factor associated with AAA is also associated with DNA methylation, and analysis could be conducted to elucidate this link.

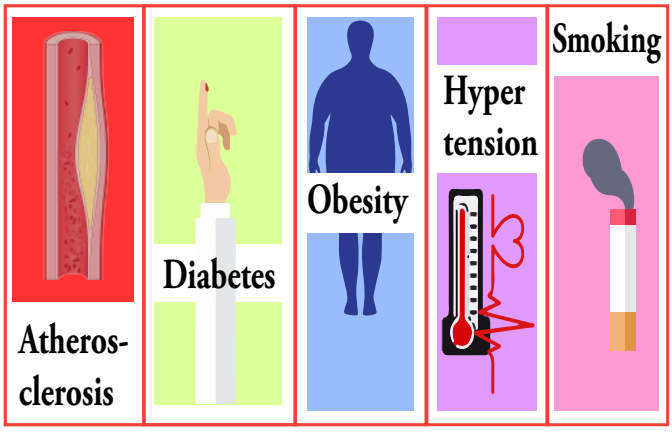

Figure 15: Modifiable risk factors of Abdominal Aortic Aneurysm

Influence of Genetics on AAA

After smoking the second most important risk factor for AAA is the family history, with a positive history raising the possibility of AAA development. Interestingly, patients with a female relative with AAA are even more strongly affected, manifesting a 2- and 0.5-fold higher risk than patients with a male relative with AAA. The strong association of positive family history and AAA in wide epidemiological studies, together with the growing evidence number of specific gene association strongly supports genetic influence on the AAA development.

Since those pioneering observations, the genetic influence on AAA has been confirmed from many different perspectives. The higher prevalence of AAA in white men compared with other races suggests a genetic predisposition. Based on interviews of

patients with AAA, the percentage of positive family ranges from 6.1 to 19.2 to 35.7%, with a mean around 15% . The observed prevalence of AAA in first-degree family members after ultrasonography screening ranges between 9 and 19 and 29%. [37, Rank 1]

This high level of concurrence of AAA between first-degree relatives confirms a genetic influence in the development of AAA. From a clinical perspective, it was noted that familial AAA (FAAA) tends to present and to rupture at a younger age compared with sporadic AAA (SAAA). Moreover, FAAA manifests a greater incidence of rupture when compared with SAAA. The different clinical behavior of FAAA compared with SAAA corroborates the importance of genetic predisposition. Finally, the twin registry revealed that the twin of a monozygotic twin with AAA suffered a risk of AAA that was 71 times that of the monozygotic twin of a person without AAA.

Many studies have attempted to characterize the specific pattern of genetic inheritance. In a study, researchers performed segregation analysis of patients who underwent emergency repair for rAAA and suggested a recessive model of inheritance. In another study, researchers examined 233 families with at least two members with AAA, reporting that ~75% of their data fitted an autosomal recessive inheritance pattern, while in the remaining 25%, an autosomal dominant pattern better explained their results. They conclude that the lack of consistency in the mode of inheritance may be indicative of multifactorial disease with multiple genetic and environmental risk factors. [33, Rank 3]

Indications for AAA Surgery

The decision about whether an AAA requires repair depends on an accurate balance between the risk of mortality from AAA rupture and the risk of surgery. Considerations regarding patient general life expectancy also enter into the equation. ***AAA diameter is the strongest predictor of aneurysm rupture, and the rupture risk increases exponentially with increase in aneurysm diameter.***

Although diameter is undoubtedly the key factor, it cannot be the unique criterion for the decision. The overall characteristics of every single patient and the specific characteristics of the AAA (e.g., familial vs. sporadic) must be considered as well. International (both European and North American) guidelines recommend surgery when the AAA diameter exceeds 55 mm in men and 50 mm in women.

Beyond the loss of late survival benefit, other most worrisome aspect of endo-

vascular repair is the continued risk of AAA rupture after the repair. This is related to the mechanism of the endovascular repair itself. To remain in situ, the stent graft needs to exert a radial force against the "neck" of the aneurysm (really, against the proximal and distal stent landing zones). This force can cause dilatation of the proximal neck, permitting device migration and development of endoleak termed type Ia proximal and type Ib distal. [38, Rank 4]

Conclusion

Abdominal aortic aneurysms remain one of the leading causes of morbidity and mortality in patients over the age of 65. Despite increased evidence supporting the utility of screening for AAAs in high risk patient populations, the most common way that these are detected is incidentally while undergoing an ultrasound, radiography of the back or abdomen, CT scan, or MRI for the evaluation of another problem. While CTA with 3D reconstruction remains the standard modality for pre-operative imaging, case planning, and postoperative surveillance, ultrasound is being increasingly used for post-operative surveillance in patients with stable aneurysm sac sizes and good anatomy. Endovascular repair has become the preferred therapy for the management of infrarenal AAAs and accounts for up to 80% of repairs in some institutions due to decreased perioperative morbidity and mortality as well as faster initial recovery times. However, concerns about the long-term durability of EVAR and the need for repeat intervention even after 8–10 years mandates lifelong surveillance in these patients. This fact also reiterates the importance of considering open repair in younger patients with low cardiac,pulmonary, and renal risk factors. [40, Rank 5]

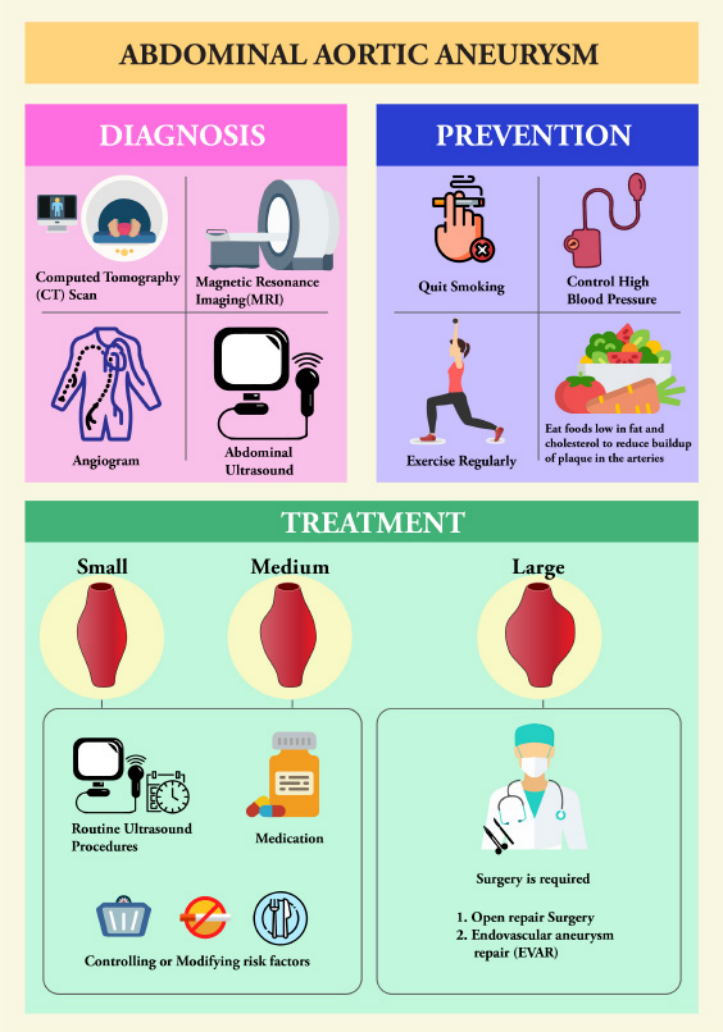

Figure 16: Diagnosis, prevention, and treatment of Abdominal Aortic Aneurysm

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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