

2014

Management of infrarenal abdominal aortic aneurysm by open repair versus endovascular repair

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Thesis

**MANAGEMENT OF INFRARENAL ABDOMINAL AORTIC ANEURYSM
BY OPEN REPAIR VERSUS ENDOVASCULAR REPAIR**

by

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B.A., Boston University, 2012

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2014

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ABSTRACT

Abdominal aortic aneurysms (AAA) are a pathological dilation of the aorta greater than 2.5cm and affect more than 4% of the male population and 1% of women aged 60 years or older. Screening is recommended among men and women older than age 65, and is covered by Medicare for patients with a family history and men with a history of smoking. Due to its asymptomatic nature, AAA is usually found incidentally during another radiological investigation. Many factors are associated with AAA development, but it is most commonly found in conjunction with atherosclerosis. There is currently no pharmacological intervention specifically for AAA, though statin therapy has shown some promise.

The aneurysm will invariably grow, with an average rate of expansion of less than 0.5cm per year. As the aneurysm grows larger the chance of the rupture increases significantly with this outcome carrying an extremely high rate of mortality. Surgical intervention is recommended once the diameter reaches 5.5cm in men or about 5cm in women. There are two approaches to the repair of the aorta: the open

surgical approach and the endovascular approach. The open surgical procedure replaces the affected portion of the aorta with a graft. The endovascular procedure places an endograft within the intact aneurysm, effectively excluding the affected section of vessel. The endovascular method carries a lower perioperative mortality rate than the open procedure, but over time can require additional surgeries to prevent continued aneurysm expansion due to blood flow in the aneurysm sac. Additionally, lifetime surveillance of the endograft is required to monitor its integrity and effectiveness.

Lifestyle changes and possible pharmacological interventions in patients with AAA should focus on cardiovascular health changes to improve overall health and minimize risk factors for continued development of the aneurysm. In patients who will require repair particular attention should be paid to individual risks and preferences. The open repair procedure may be preferable in patients with better overall health and a longer life expectancy, while endovascular repair may be beneficial for more elderly or frail patients. Research and technology in this area are developing quickly, particularly for endovascular procedures, and the near future may see important changes in the risk-benefit analysis of AAA surgical interventions.

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ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
ACE	Angiotensin Converting Enzyme
CAD	Coronary Artery Disease
CDC	Centers for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
DREAM	Dutch Randomized Endovascular Aneurysm Management
EVAR	Endovascular Aneurysm Repair
EVAR 1/2	UK EndoVascular Aneurysm Management
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IFU	Instructions For Use
MMP	Macrophage Metalloproteinase
SAAAVE	Screening for Abdominal Aortic Aneurysms Very Efficiently
SVS	Society for Vascular Surgery
USPSTF	U.S. Preventive Services Task Force

I. Introduction

1. Historical Perspective

It has been 15 years since the U.S. Food and Drug Administration approved in 1999 the first endovascular device for the repair of abdominal aortic aneurysms (AAA). Since then, support for this approach has grown, as advances are made in the associated technology and its application. This technology represents a far departure from the preferred open surgical treatment of the previous century, and only further from the methods described by the Greek surgeon Antyllus in the 2nd century A.D. With the advancement of new technologies and treatments in medicine and surgery, it is universally prudent to understand the appropriate application thereof and the inherent risks associated with a novel intervention. This is particularly true as the method and technology continue to progress, and as clinical findings influence the way that physicians practice modern medicine.

Aneurysms had been recognized early in human medical history, with accounts dating back to as early as 1000 B.C. in Egypt (Wilton, 2012). During the 2nd century A.D., both Galen and Antyllus set the foundations of the modern definition of the aneurysm. In fact, Antyllus performed the earliest recorded attempts to correct AAA when he ligated both the proximal and distal necks of the aneurysms via laparotomy. Apparently, some small number of his patients was actually able to

survive for a period of time following the procedure – a remarkable occurrence by today’s standards. Variations on Antyllus’ procedure for ligating the aorta continued into the 20th century, with Rudolf Matas performing the first recorded successful aortic ligation, with the patient surviving for a significant time following the operation (Matas, 1940). Matas also fathered the idea of operating upon the aorta with the intent of maintaining blood flow, rather than simply disrupting aneurysm formation. This would go on to become the principal basis for modern treatment techniques including open and endovascular aneurysm repair (EVAR) (Friedman, 2005).

Following work by several surgeons to maintain arterial flow by means of bypass and anastomosis, Arthur Voorhees in the mid-20th century published the results using a synthetic polyvinyl material to bypass the affected portion of an aortic aneurysm (Blakemore & Voorhees, 1954). This work set the stage for the development of the open repair technique in the 1950’s. This became the gold standard of AAA treatment for the latter half of the 20th century, with many advances in surgery making this a safe and effective procedure. However, open repair is a major invasive procedure and poses a serious risk. Therefore the impetus to develop a less invasive technique to resolve the aneurysm bore the endovascular intervention, as an alternative. In 1991, Juan Parodi and colleagues performed the first successful endovascular repair

of an aneurysm by a similar technique to that which is used today (Parodi, Palmaz, & Barone, 1991). This milestone would be the beginning of the new era of AAA intervention.

2. Epidemiology and Risk

AAA affects a significant portion of the population in the U.S., particularly the elderly. It is estimated that 4-8% of men and approximately 1% of women over the age of 60 are affected (Baxter, Terrin, & Dalman, 2008). Several studies published in the latter decades of the 20th century suggested an increasing incidence of AAA (Melton et al., 1984), but some more recent studies are showing a gradual decline (Choke et al., 2012; Norman, Spilsbury, & Semmens, 2011; Sandiford, Mosquera, & Bramley, 2011) - at least in certain regions of the developed world. There is a distinct possibility that this is due to the changing epidemiology of certain major risk factors for AAA.

According to the Centers for Disease Control (CDC) fact sheet, AAA was the “*primary cause of 10,597 deaths and a contributing cause in more than 17,215 deaths*” in 2009. Furthermore, it is reported that about 67% of aortic ruptures – the natural endpoint of the disease – occur in male patients (“Aortic Aneurysm Fact Sheet | Data & Statistics | DHDSP | CDC,” n.d.). Therefore, in 2009, AAA accounted for or contributed to 0.5-0.8%

of the over 2,000,000 deaths in the U.S. This makes AAA the 15th leading cause of death in the United States.

According to most contemporary studies of AAA, the incidence increases with age and the average age of the affected population is approximately 70 years (Wilmink & Quick, 1998). A large multi-centre study of screening protocols was conducted over the course of 13 years to assess the effect on mortality from AAA in the United Kingdom (Ashton et al., 2002; Thompson et al., 2012). In this study, over 70% of AAAs detected on screening were less than 4.5cm in diameter in the study age range of 65-74. This diameter is below that which would typically indicate surgical repair, which immediately suggests a benefit to screening. In fact, the MASS study found a consistent 42% risk reduction across all 13 years of follow-up, including an incidental benefit of 3% reduction in all-cause mortality (Thompson et al., 2012). The US Preventive Services Task Force (USPSTF) recommends a more limited screening program due to the associated economic burden. This includes screening amongst men aged 65-75 who have ever smoked and among men and women with a family history of AAA. In fact, since 2007, Medicare has paid for a single AAA screening ultrasonography among patients fitting the USPSTF guidelines under the Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Act. Underscoring the concerns regarding the costs of screening, however, was an article that

reviewed the effect of the SAAAVE Act on AAA screening, repair, and mortality, which showed that screening within this program has effectively no benefit. (Harris R, Sheridan S, & Kinsinger L, 2012; Shreibati J, Baker LC, Hlatky MA, & Mell MW, 2012).

One large prospective study conducted by Carlos Iribarren and colleagues (2007) investigated a great number of risk factors contributing to the presentation of AAA. The study population was identified between 1965 and 1971 and follow-up continued until 2003. Major factors identified in this study which are associated with AAA included male gender, increasing age, hypertension, and hypercholesterolemia. These are typically considered to be the major risk factors for AAA and are also strongly associated with atherosclerosis; however there was no predictive association between AAA and obesity. In addition, with the rate of AAA amongst smokers being higher to begin with, a dose-dependent relationship was identified. As stated by Iribarren and colleagues, this is consistent with prior studies (Pleumeekers et al., 1995; Strachan, 1991). A more recent study suggested that diabetes might be a negative predictor of aneurysm growth (De Rango et al., 2012).

Smoking is one of the most severe risk factors for AAA formation. Aneurysm related mortality among smokers carries a hazard ratio of up to 6.5 as compared with those who have never smoked (Strachan, 1991). This association between AAA and smoking is more significant than the

association between cigarettes and cerebrovascular disease or Coronary Artery Disease (CAD) (Lederle, Nelson, & Joseph, 2003). These data indicate that smoking could be, as with so many cardiovascular diseases, one of the biggest contributing risk factors to AAA development and progression.

Chronic obstructive pulmonary disease (COPD) may also contribute to aortic dilatation. Macrophage metalloproteinases (MMPs) that function as elastases are upregulated in this disease, and the broad increase in their expression is a possible contributor to the elastin degradation found in the aortic wall of AAA patients (Tetley, 2002). A recent case-control study found an increased prevalence of COPD among patients with AAA (Meijer et al., 2012). The increased prevalence of COPD was noted in both smoking and non-smoking AAA patients, suggesting that the connection between COPD and AAA is independent of cigarette use.

Additionally, infectious agents may contribute to aneurysm development in some patients. Cytomegalovirus, *Herpesviridae*, *Haemophilus influenzae*, and tuberculosis have all been cited as having a possible link to AAA formation (Canaud et al., 2008; Sato & Kobayashi, 2012; Tanaka, Komori, Okadome, Sugimachi, & Mori, 1994). Despite these findings, a direct causal link remains to be seen. *Chlamydiae*

Pneumoniae has also been implicated in AAA development (Karlsson et al., 2000).

3. Pathophysiology of AAA

The normal aorta originates in the left ventricle of the heart and gives rise to the right and left coronary arteries, the brachio-cephalic artery, the left common carotid, and the left subclavian artery before descending. Known as the thoracic aorta, the artery descends on the left side of the spinal column, giving rise to the pericardiac, bronchial, esophageal, mediastinal, and intercostal arteries. The abdominal aorta begins as the vessel penetrating the diaphragm. The first branch to arise from this segment is the celiac axis, followed by the superior mesenteric and renal arteries. The region of the aorta between the renal arteries and the iliac bifurcation gives rise to the inferior mesenteric artery and the lumbar arteries. This region is the most common site in which AAA is found. Finally, the iliac bifurcation gives rise to the common iliac arteries (Gray, 2010).

The most commonly recognized trigger for the development of AAA is an existing atherosclerosis, however there is only a weak link between cause and effect. Weintraub (2009) describes the following: *“Although abdominal aortic aneurysms frequently occur in patients with atherosclerosis and the two disease processes share several common risk*

factors, atherosclerotic lesions are predominantly intimal in location, whereas the media and adventitia are primarily involved in aneurysms. The hallmark pathologic feature of atherosclerosis is foam-cell formation, whereas aneurysms are typified by intense oxidative stress, inflammation, matrix degradation, and apoptosis of smooth-muscle cells.”

The normal aorta has a heavily elastic media that enables the vessel to withstand the demands placed on it by the nature of its location in the arterial tree. The media is delineated from the intima and the adventitia by layers of elastin, the internal and external elastic lamina, respectively. Finally, the adventitial layer of the aorta is heavily populated by collagen that provides a large proportion of the overall resistance to changing hemodynamic factors in the vessel.

Although the abdominal aorta, along with other vessels, stiffen and enlarge with age, the development of a dilatation greater than 2.5cm in the abdominal aorta is considered the beginning of AAA development. The progression of the disease from this point is typically characterized by degradation of elastin in the vessel media and breakdown of collagen, particularly in the adventitia. This breakdown is exacerbated by factors contributing to atherosclerosis, such as inflammation and arterial wall remodeling, promoted in all likelihood by hemodynamic factors affecting the arterial wall stress. The wall tissues of AAA produce great amounts of inflammatory cytokines, chemokines, and prostaglandins. This

inflammatory response leads to the recruitment of immune cells, particularly T-lymphocytes, which stimulate resident macrophages to produce MMPs. MMPs are a group of enzymes, some of which are the primary contributors, along with elastase, to the degradation of elastin. Included amongst MMPs important to AAA are several collagenases and gelatinases, which contribute to the breakdown of Type I and Type IV collagen. This inflammatory degradation of the arterial wall is the primary contributing factor to the mechanical changes which occur to enable aneurysm formation. Finally, the balance of collagen and elastin production with its degradation must be disrupted in order to generate the conditions under which an aneurysm can form. Smooth muscle cells are the principle cells responsible for production of collagen and elastin. Whereas in the case of atherosclerosis smooth muscle cells can proliferate or maintain their normal density, in AAA the density of these cells is often severely reduced. This is the process by which balance is disturbed and AAA progression may continue. (Thompson, Geraghty, & Lee, 2002).

Hemodynamic factors in the aorta are thought to contribute significantly to aneurysm expansion. As the composition of the aortic wall changes, the aorta is allowed to dilate under normal hemodynamic stress. This dilatation has a noticeable effect on the wall stress and tension responses of the tissue to the normal blood flow and pressure.

In a mechanical model of the aorta, this causes the vessel to transition to a morphology that becomes more spherical over time as it expands (Vorp, Raghavan, & Webster, 1998). The infrarenal portion of the aorta is the most common location for AAA formation, probably in relation to these mechanical findings. Dilatation can occur at any place along the vessel, with other common locations being thoracic or juxtarenal aorta. One possible explanation for the common infrarenal localization of AAA is the hemodynamic factors arising from the iliac bifurcation. The division of the aorta at this point, in combination with the typically seen atherosclerotic comorbidities, creates a turbulent environment in the infrarenal portion of the aorta. The pressure and flow within the infrarenal aorta due to these factors could therefore contribute to dilatation and variable aortic morphologies.

Typically, a good deal of emphasis has been placed on the diameter of the aorta in relation to risk of sac enlargement and rupture. Despite the fact that aortic diameter has shown itself to be an acceptable surrogate for risk among patients with AAA, it has also been seen that aneurismal morphology plays a role in the progression of AAA (Vorp, Raghavan, & Webster, 1998; Shum et al., 2011). Though the infrarenal aneurysm has a mostly spherical shape with a bias towards bulging anteriorly, there exists a variety of morphologies, and therefore some emphasis has been placed on uncovering how biomechanical analyses

can be used to help predict which patients may see a higher risk of rupture (Kontopodis et al., 2013; Sonesson, Sandgren, & Länne, 1999).

AAA is a multifactorial disease process with many contributing factors. Once a dilatation of the aorta occurs, both molecular and hemodynamic factors affect the disease progression towards rupture, the natural endpoint for AAA. Annually, the rate of rupture in aneurysms measuring less than 5.5cm diameter is approximately 1%. (United Kingdom Small Aneurysm Trial Participants, 2002). Although this risk is low, appropriate management of AAA must be observed at all stages of the disease due to the very high mortality rate in the event of rupture.

II. Management of AAA

1. Screening and Surveillance

All of the risk factors discussed above play a role in AAA development, not only in terms of identifying patients who are at risk but also in determining how physicians will surveil the patient once dilatation has been discovered. Several studies have shown that repair of small aneurysms is not beneficial in terms of survival, particularly the UK Small Aneurysm Trial (Powell, 2007). Therefore surgery is not recommended until the aneurysm reaches the 5.5cm diameter threshold. The recommended follow-up regimen varies with the diameter of the aneurysm (Table 1). For high risk patients, surveillance should be adjusted particularly among those who smoke and those whose aneurysm is growing at an increased rate (Brady, Thompson, Fowkes, Greenhalgh, & Powell, 2004). Given some annual rate of expansion of the aorta in patients with AAA, there is a need for considering medical treatments along with surveillance before the aneurysm reaches a level at which it needs to be repaired.

Table 1: Society for Vascular Surgery Guidelines on Screening and Surveillance. These recommendations are based on collective evidence from large trials of aneurysm growth and screening protocols. Some recommendations contradict the opinion of the United States Preventive Services Task Force. Diameters given are the maximum external diameter of the aorta.

	<u>Men</u>		<u>Women</u>	
	Not High Risk	Family History of AAA or History of Smoking	Not High Risk	Family History of AAA or History of Smoking
Initial Screening	Age ≥ 65 yrs	Age ≥ 55 yrs	None	Age ≥ 65 yrs
Diameter < 2.5cm	Rescreening not recommended	5 year intervals	Not addressed	Rescreening not recommended
Diameter 2.6 - 2.9cm	5+ year intervals			
Diameter 3.0 - 3.4cm	3 year intervals			
Diameter 3.5 - 4.4cm	12 month intervals			
Diameter 4.5 - 5.4cm	6 month intervals			

A study published by the Veteran’s Affairs Cooperative Study Group investigators (Lederle et al., 2002) showed that, across a mean 4.9 years of follow-up, patients with AAA less than 5.5cm showed no difference in mortality between surveillance and elective repair. Similarly, the UKSAT trial (Powell, 2007) showed that at 12 years, there was no statistical difference in mortality between groups of patients

undergoing early operative repair (<5.5cm diameter) or ultrasound surveillance. Interestingly, according to the data from this trial, early surgical repair was more expensive than ultrasound surveillance in the long-term, even when considering that approximately 75% of surveillance patients underwent surgical repair during the 12 years of follow-up. More recently, the PIVOTAL trial (Ouriel, Clair, Kent, Zarins, & Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Investigators, 2010) showed that, for EVAR, repair of aneurysms between 4 and 5 cm diameter does no harm. The reality of this, however, is that EVAR is far more expensive than surveillance and still provides no benefit to repair at diameters less than 5cm. The nature of AAA is that it will continue to expand and therefore patients with a small sac diameter still will require intervention – particular consideration is given to the question of the patient’s life expectancy. The MASS study provided a large-scale estimation of the rate of repair among AAA patients. In the group that received aneurysm screening, the rate of elective repair was about 45%, which agrees with a smaller study investigating screening regimen outcomes (Svensjö, Björck, & Wanhainen, 2013; Thompson et al., 2012).

2. Pharmacotherapeutic Strategies

Due to the close association between AAA and atherosclerosis, HMG-CoA reductase inhibitors have been investigated as a possible avenue by which to arrest AAA growth. Several analyses have shown a lower aneurysm growth rate among patients taking statin drugs (Schlösser et al., 2008; Sukhija, Aronow, Sandhu, Kakar, & Babu, 2006; Takagi et al., 2012), though these findings have seen some disagreement in meta-analysis studies (Twine & Williams, 2011). In spite of the lack of any clear link between cholesterol levels and AAA development, statins demonstrate a wide range of pleiotropic effects. In fact, statins can reduce protease activity among MMPs implicated in aortic wall dilatation (Takagi et al., 2012).

In the same avenue as statins, ACE inhibitors have been investigated as a possible adjunct in AAA surveillance. More so than statin therapy, findings from analyses of ACE inhibitors have been highly variable. One large review of a Canadian database found that the use of ACE inhibitors was correlated with significantly lower rates of aneurysm rupture (Hackam, Thiruchelvam, & Redelmeier, 2006). However, a review of data from the UK Small Aneurysm Trial showed that ACE inhibitors actually seemed to increase aneurysm growth rates (Sweeting, Thompson, Brown, Greenhalgh, & Powell, 2010). These conflicting

findings are enough to call into question the use of ACE inhibitors as appropriate therapy for patients under surveillance.

Due to the proposed significance of the role of MMPs in the development and progression of AAA, and efficacy against the associated *C. pneumoniae*, antibiotics in the tetracycline class have been suggested as a potential intervention for AAA. In a very small pilot study of doxycycline for AAA, researchers found that treatment reduced the expansion rate of aneurysms during the 6-18 month follow-up period (Mosorin et al., 2001). Another small trial that specifically investigated the effect of doxycycline on the proposed inflammatory mechanisms of AAA found that drug therapy significantly decreased levels of several MMPs in the aortic wall tissue, as well as neutrophil elastase and collagenases (Abdul-Hussien et al., 2009). Despite basic scientific evidence and several small scale studies suggesting favorable results of this treatment methodology, Dodd and Spence (2011) note that there is a distinct lack of larger scale trials on this topic, and that further investigation is needed.

Apart from pharmacological therapy, a regimen of cardiovascular health changes is likely to be effective. Smoking cessation, as with atherosclerosis and other diseases, will benefit the patient and slow progression of the aneurysm (Lederle, Nelson, & Joseph, 2003; Mani, Wanhainen, Lundkvist, & Lindström, 2011). Because cardiovascular

factors and overall health may affect the outcomes of surgical intervention, it is of the utmost importance to ensure that all facets of the patient's health are in optimal condition during the surveillance period in the case of the need for surgical repair.

3. Open Surgical Intervention

The typical open operation for an infrarenal AAA is performed under general anesthesia and begins with incision to the peritoneum and retraction of the bowels. The affected portion of the aorta is exposed to the extent of the renal arteries and the common iliac arteries. The aorta is clamped to interrupt blood flow through the vessel, followed by clamping of the iliac arteries. This isolates the aneurysm and allows resection of the affected portion to continue. An incision is made along the length of the aneurysm, exposing the lumen of the vessel in which is typically found a thrombus. After extraction of the thrombotic material, the proximal wall of vessel is divided either partially or completely from the normal aorta in preparation for graft attachment. Subsequently, the graft is measured and fitted to the patient and is anastomosed proximally. With the distal openings of the graft clamped, the anastomosis is checked for leakage by releasing the aortic clamp. Subsequently, the distal branches of the graft are anastomosed with the iliac arteries and again momentary release of the aortic clamp is used to

ensure successful connections. Careful recovery of normal blood flow through the aorta to the limbs is established to complete the grafting procedure. Upon closure, the patient is typically transferred to the ICU for one to two days for careful monitoring (Zollinger, Robert M. & Ellison, E. Christopher, 2010).

Perioperative morbidity among open repair patients has been well determined, as the operation has been in use for about half a century. The mortality rate of the operation has been found as high as 10%, but typically falls in the range of 4-8% (Blankensteijn, Lindenburg, Van der Graaf, & Eikelboom, 1998; Dangas et al., 2012; Huber et al., 2001). Common morbidities of open repair include cardiac events (such as myocardial infarction), pneumonia, renal insufficiency, hemorrhage, and colonic ischemia. The rates of these complications range from 15% for all cardiac complications to 1% for colonic ischemia (Chaikof et al., 2009). Operative morbidity is exacerbated among certain groups of patients. In particular CAD is one of the primary contributors to perioperative, all-cause mortality amongst AAA patients. Diabetes Mellitus has also been suggested as an influential factor in operative outcomes (Leurs, Laheij, Buth, & EUROSTAR Collaborators, 2005). Long-term follow-up of open repair patients is not mandated and therefore is often not well defined in many research studies. For this

reason, the longer term outcomes of open repair are not as clear as for the EVAR procedure.

Common late complications particular to the open procedure include incisional hernias, small bowel obstruction due to adhesion formation, and paranastomotic pseudoaneurysm formation (Chaikof et al., 2009; Edwards, Teefey, Zierler, & Kohler, 1992; Matsumura, Pearce, Cabellon, McCarthy, & Yao, 1999). Graft infection carries a very high mortality rate, though it is a relatively uncommon complication.

4. Endovascular Aneurysm Repair

The endovascular repair procedure for a similar aneurysm is quite dissimilar. Typically, the vascular system is accessed via the femoral artery under general anesthesia; local anesthesia can also be used. A stiff guidewire is advanced, in opposition to blood flow, into the thoracic aorta. The stent graft device is contained in a delivery device which is advanced over the guidewire and positioned in the abdominal aorta under imaging guidance. The device is deployed just below the renal arteries, with the proximal opening of the graft being secured in the wall of the normal aorta. The delivery device continues to be withdrawn to the level of the ipsilateral iliac artery, such that the opening of the graft providing for the contralateral limb is exposed. At this point, the contralateral femoral artery is accessed in order to deploy the

contralateral limb of the graft. The device for delivering this portion is advanced under guidance into the lumen of the main graft. It is deployed in full by securing it within the opening of the main graft at the iliac bifurcation and withdrawing the delivery catheter. Finally, the ipsilateral limb of the graft is deployed in full into the iliac artery (Ashley, Stanley & American College of Surgeons, 2008; Brunicardi, F. Charles et al., 2010).

It is required for the endovascular approach that the endograft be fixed in place within the aorta. This disallows migration of the graft within the vessel and prevents blood from entering the aneurysm sac. To achieve this, the graft must be sealed along the wall of the vessel at the proximal and distal openings, as well as to the wall of the graft itself in the case of the seal between the graft's body and limb. This fixation has been achieved in several ways. In all grafts the proximal end should be sealed to the aortic neck – the region of the normal aorta which extends from the renal arteries to the proximal edge of the aneurismal dilatation. This requirement can be an obstacle, as most graft instructions for use (IFUs) require a neck length of at least 15mm (Schanzer et al., 2011). Fixation of the graft is best achieved by mechanical force at the proximal and distal necks, though only one of these locations needs to serve as an anchor. The graft is typically constructed in such a way that it expands with a radial force sufficient to support the graft and limit migration. To

maximize fixation of the graft, some companies have implemented small hooks or barbs, which are inserted into the vessel wall. The end result is that the endograft hangs from the proximal neck or stands on the distal branches (Benharash et al., 2007).

4a. Endovascular Procedural Morbidities

Perioperative morbidities of the EVAR procedure are fairly limited due to the minimally invasive nature of the procedure. Across many trials comparing open repair and EVAR, the perioperative mortality rate is consistently lower than 2% with a very limited number of trials reporting anything higher. The most common morbidities following EVAR are wound healing complications and ischemia (Adriaensen, Bosch, Halpern, Myriam Hunink, & Gazelle, 2002; Maleux, Koolen, & Heye, 2009). Bowel ischemia occurs in about 1% of patients, while lower limb ischemia from thrombosis or kinking of the endograft occurs in up to 3% of procedures. Less commonly, the endograft can be accidentally placed in such an orientation that it occludes one or both of the renal arteries. On occasion the surgical wound can be found in the crease of the groin - this increases the risk of such complications as infection, which occur in up to 5% of patients. Graft infection, as with open repair, presents a major complication of EVAR. Although the rate of infection is low, it is one of the leading risk factors for conversion to open repair and

a significant contributor to mortality among EVAR patients (Moulakakis et al., 2010; Turney et al., 2013). Finally, arterial injury at the access site can occur in approximately 3% of patients (Mehta et al., 2014).

Finally, a major risk of EVAR is contrast nephropathy (Wald et al., 2006). Due to the need for imaging in the precise placement of the endograft, significant amounts of contrast material are used resulting in a not insignificant risk of acute renal failure. Though only a small proportion of patients will require dialysis, this must be considered during the decision making process. CO₂ angiography has been suggested as an alternative for reducing contrast exposure (Morito et al., 2012; Tessarek, 2013). The tradeoff of this technique, however, is increased procedural time and increased radiation exposure (Chao et al., 2007), and therefore must be used with discretion.

4b. Endoleaks and Endoleak Management

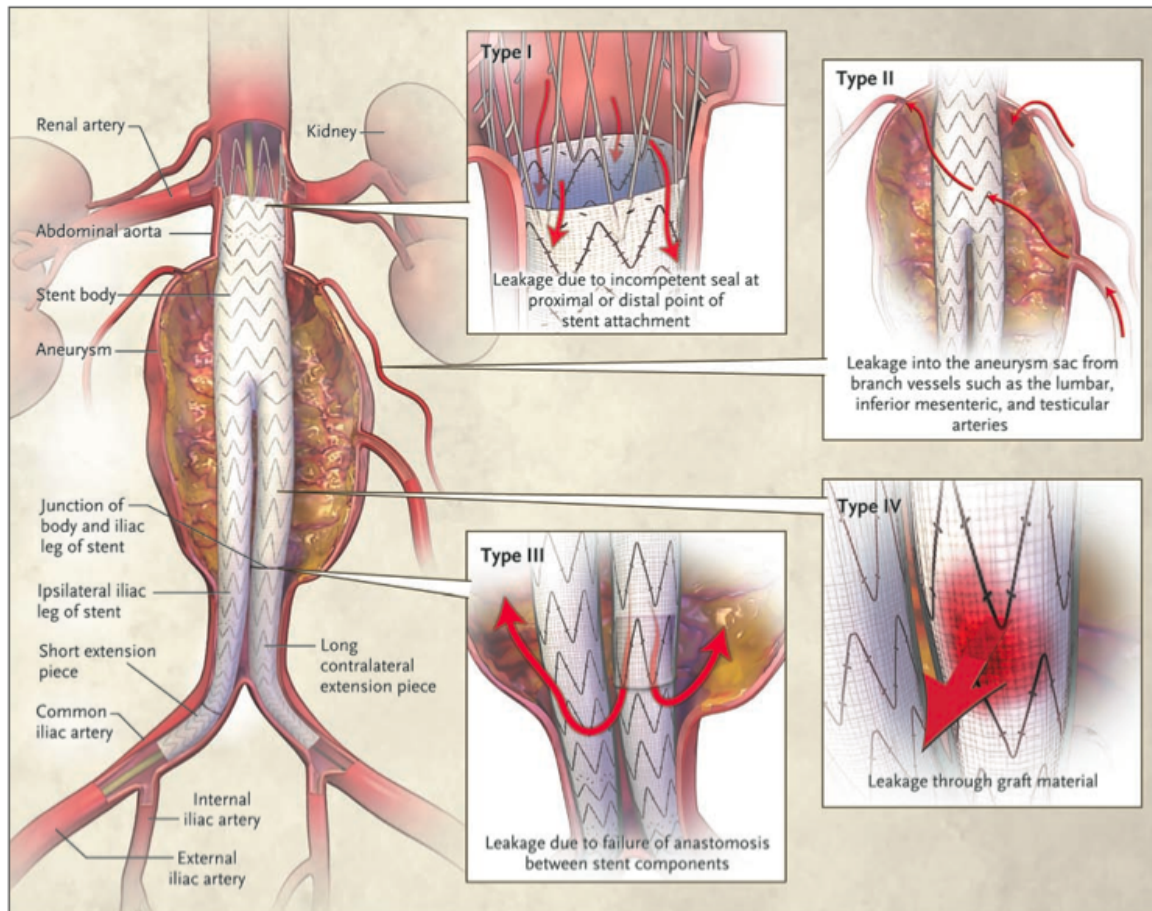


Figure 1: Endoleaks Type I-IV. Type I endoleak evolves from an inappropriate seal of the endograft to the arterial wall. Type II endoleak is caused by retrograde flow through the aneurysm sac. The Type III endoleak shown here is the result of failure to seal two sections of the endograft. Type IV endoleak arises from fluid diffusion through a porous graft pressurizing the aneurysm sac. This figure was taken from Greenhalgh, et al. (2008) *New England Journal of Medicine*.

The goal of the endograft is to completely exclude the affected segment of the aorta, with blood flowing freely through the lumen of the graft. The discovery of blood flow into the aneurysm sac is known as an endoleak. The flow of blood within the sac can lead to pressurization of the aneurysm and cause continued expansion. This is the primary complication arising from EVAR and it has been estimated that this leads to a necessary secondary intervention in 20% of patients (Lederle et al. 2012; Mehta et al., 2010).

Endoleaks are divided into five categories. Type I endoleaks are caused by inadequate fixation of the graft material to the wall of the aorta due to a loss of mechanical force or migration of the graft. This constitutes a major failure of the graft as no exclusion of the aneurysm has been achieved. A common useful fix for this type of endoleak is to use a balloon to reestablish fixation with the aortic wall (Faries et al., 2003). If discovered during the initial graft placement, this can be fixed intraoperatively, but if this arises during postoperative follow-up, a secondary procedure is required. There is a further subdivision of Type I endoleaks, with Type Ia occurring in the proximal segment of the graft and Type Ib occurring distally. While Type Ia can usually be fixed by balloon as described, Type Ib endoleaks are often remedied by extending the distal limb of the graft and establishing fixation more distally in the vessel.

Type III endoleaks occur when the material of the endograft fails to create a competent channel along the aneurysm length. This is most often due to a failure of the seal between the body of the graft and the distal limbs of the iliac branches. Rarely, this type of endoleak can occur due to breakdown of the graft material (Abouliatim, Gouicem, Kobeiter, Majeski, & Becquemin, 2010; Faccenna, Bresadola, Alunno, & Gattuso, 2012). The typical procedure for repairing Type III endoleaks is to place a small stent at the location of the graft failure, enabling full exclusion of the aneurysm.

The direct leakage of blood at physiological pressures into the aneurysm sac causes immediate pressurization and essentially negates the effect of the intervention. This leads to an increasing diameter and an increasing risk of rupture in these patients (Buth & Laheij, 2000). One database review found that among patients with late rupture following EVAR, more than 40% were linked with Type I and III endoleaks (Schlösser et al., 2009). Both Type I and III endoleaks are serious in nature and must be treated in order to maintain the integrity of the repair.

Type II endoleaks are one of the most common causes of endograft complications, observed in up to 30% of patients following elective EVAR (Ozdemir et al., 2013; Turney et al., 2013). They arise from retrograde blood flow through small branches of the aorta which remain patent after

the endograft implantation. Common sources of this retrograde flow are the lumbar arteries and the inferior mesenteric artery. It is worth noting that there is a requirement for at least two vessels to remain patent as the flow of blood within the sac requires both an ingress and an egress.

There is a variable prevalence of Type II endoleaks and a meaningful rate of spontaneous resolution. Combined with a low rate of secondary interventions for this indication, the management of these endoleaks has been less clear (Sheehan et al., 2006). Type II endoleaks are often detected later in the follow-up period and these patients present with a significantly increased chance of aneurysm expansion at the five year mark (Zhou et al., 2013; Cieri et al., 2013). However, studies show that this aneurysm expansion is equally likely to continue among patients who have undergone reintervention and those who have not (Cieri et al., 2013; Jouhannet et al., 2014). The source of the endoleak may play a role in the success of secondary interventions. A retrospective review by Gallagher and colleagues (2012) found that the source of the Type II endoleak affects the success of reintervention. Patients with an inferior mesenteric artery source achieved a 72% success rate when undergoing an additional procedure, while patients with a lumbar artery source only achieved a 40% success rate.

Type IV endoleaks arise from leakage of blood through the graft material. This can be due to increased porosity of the graft, but it is

considered to be self-limiting and no treatment is necessary. Type V endoleaks are also known as endotension. The pressurization of the aneurysm in this case is caused by transmission of pressure from the lumen of the graft to the wall of the aorta. The causes of this type of endoleak are not well defined, but include leakage of fluids across the graft walls, and transmission of pressure through thrombotic material within the aneurysm. Treatments for this type of endoleak must be individualized.

4c. Patient Follow-up

In the case of endovascular repair, the common standard of follow-up care is CT surveillance of the aneurysm at post-operative months 1, 3, 6, 12 and annually thereafter (Chaikof et al., 2009). This is a significant burden to the patient and the health care system in terms of both radiation exposure and cost efficiency. In comparison, for open repair, the recommendation by the Society for Vascular Surgery is follow-up CT at five year intervals. The follow-up regimen, particularly among EVAR patients, has raised the question of radiation exposure. The lifetime estimated risk of cancer death arising from CT among patients in the typical AAA repair age group (50-85 years) is less than 0.2% (Brenner & Hall, 2007), however the sheer number of patients undergoing EVAR each year means this could affect a significant population.

One approach to the problem of cost and exposure has been to limit the follow-up of EVAR patients (Kirkpatrick, Wilson, Williams, & Gordon, 2013). In a single-center review of patient records, it was found that among patients with a normal one month CT evaluation, 7.1% of patients developed an endoleak. Of these patients, about 3% required reintervention, and these endoleaks were discovered after the 3rd year annual CT follow-up. Furthermore, between groups with a normal and abnormal 1 month CT, the group with normal results showed significantly less aneurysm expansion. It may therefore be possible, on a case-by-case basis, to safely provide less frequent follow-up to these patients (Tomlinson et al., 2007).

Another approach that has been heralded as a safe alternative to CT has been the use of ultrasound. It has been shown that color Doppler ultrasound shows a strong correlation with CT imaging, but that it may be less sensitive and therefore less useful in detecting endoleaks (AbuRahma, Welch, Mullins, & Dyer, 2005). One systematic review found that ultrasound sensitivity was as low as 69%, but with a specificity that exceeded 90% (Ashoke et al., 2005). It was also found that ultrasound was effective at identifying Type I and III endoleaks as opposed to Type II, but this finding was non-significant. Several more recent studies have contradicted these conclusions, showing a great efficacy of ultrasound surveillance with contrast material to enhance

imaging, including its ability to detect some endoleaks which were unavailable on CT imaging (Collins, Boros, & Combs, 2007; Henao et al., 2006). Under a paradigm in which ultrasound was used as the primary method of follow-up, it was found that ultrasound was safe and effective in practice and when modeled against a case series (Chaer et al., 2009). Several studies have shown that contrast enhanced ultrasound may be an appropriate alternative to CT follow-up, particularly following a normal one month CT, and tailored follow-up is appropriate in stable patients (Go, Barbato, Rhee, & Makaroun, 2008; Sternbergh III, Greenberg, Chuter, & Tonnessen, 2008).

Ultrasound follow-up to reduce the cost and radiation exposure of CT imaging could be an effective management strategy for EVAR patients. This decision should be made on an individualized basis and CT is still the gold standard as there is conflicting evidence about the sensitivity of ultrasound to detect endoleaks. In addition to general monitoring for graft infection and cardiovascular corollary events, close follow-up including imaging is vital to patient safety.

5. *Open Repair vs. Endovascular Repair*

With the evolving face of AAA surgical interventions, EVAR has shown great promise as an intervention as studies have found a reduction of perioperative morbidity and mortality. Furthermore, the relative ease of the procedure on the patient's behalf makes this approach appealing and can be appealing to patients for the immediate quality of life. However, while many trials have seen short-term benefits to EVAR, follow-up results over time have brought the long-term efficacy of EVAR into question. A relatively high rate of necessary reintervention, need for lifetime follow-up, and high costs have made the choice between EVAR and open repair a substantial tradeoff. Moreover, the post-operative and long-term management of AAA patients is evolving and requires further study. It is important for both patient and provider to understand this balance of variables when choosing between these procedures.

Over the past decade, several major studies have been undertaken comparing patient outcomes following open and endovascular repair for AAA. It is widely accepted that perioperative mortality is significantly reduced amongst appropriate patients undergoing EVAR as opposed to open repair. As time passes, however, the patient outcomes become less definite. Questions remain regarding how to most appropriately manage EVAR patients and what kind of follow-up and reintervention is

necessary to maintain the effectiveness of the repair. Long-term outcomes and follow-up data from many of the large clinical trials continue to be published, shedding light on how EVAR patients fare over time and what problems are common and need to be monitored.

5a. *The DREAM Trial*

In 1999, the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial was undertaken to broadly investigate the outcomes of elective AAA surgical management. Follow-up publications from this trial continue to provide important data on patient outcomes following elective surgery. The trial was a smaller one, including 345 patients in treatment groups. These participants had aortic dilatations of at least 5cm and were appropriate candidates for surgical intervention, including a requirement of at least two years life expectancy – in other words, participants were low risk patients. Patients were randomized to undergo EVAR by an experienced team (more than five procedures) using FDA approved and IDE devices, or conventional open repair (Prinssen, Buskens, & Blankensteijn, 2002).

The DREAM trial participants first reported data in the year after enrollment ended (Prinssen et al., 2004). Immediate benefits to EVAR repair included a lower rate of general anesthesia usage, a shorter operative time, lower amount of blood loss, and shorter ICU stays. The

operative data, however, did show a significantly higher rate of iliac artery sacrifice in the endovascular repair group. Post-operatively at 30 days, patients in the EVAR group showed a lower rate of mortality and a lower rate of systemic complications. The open repair group, expectedly, had a significantly lower risk of graft related complications.

These results have been supplemented by additional follow-up at several times over the years. Most importantly, the DREAM trial participants released two-year outcomes data showing changes in the relationship between open and endovascular repair advantages. At two years post-operatively, the mortality rates between both groups had been equalized (Blankensteijn et al., 2005). Furthermore, the complication-free survival rate was similar between the two groups. These data indicate a decrease in the benefit to EVAR as time passes, though it has been noted that the rates of aneurysm-related mortality remained lower in the endovascular treatment group. In other words, a significantly greater number of patients who underwent EVAR died during post-operative follow-up as compared to the open repair group. In addition, open repair proved to be significantly more permanent during the first two years of follow-up as the reintervention rate for the EVAR group was nearly three times greater than the open repair group (hazard ratio 2.9). These data were the first long-term set to be provided during this time period and raised questions about the viability of the endovascular

approach over time (Bush, Mureebe, Bohannon, & Rutherford, 2008). Recently, data from this study revealed that over the long-term there is no difference in renal function between the two groups (de Bruin et al., 2013). The estimated glomerular filtration rate in both groups declined over time, but neither group fared better than the other. Considering the need for lifelong follow-up, particularly for patients undergoing EVAR, it is important that renal function is preserved. While renal function declined in both groups, the decline was within ranges found in the normal population. This finding shows that the choice of EVAR as an intervention will not affect the quality of follow-up care that is provided.

Some additional data were produced by this trial with regards to quality of life – a factor which is very important considering the population being studied. The DREAM investigators administered a set of questionnaires to patients about their quality of life at intervals of 3 and 6 weeks, 3, 6, and 12 months post-operatively, as well as preoperatively. An analysis showed that both interventions negatively impacted quality of life inside the 3 immediate post-operative weeks, but with EVAR patients faring significantly better. On all measures EVAR patients returned to baseline level by 6 weeks, yet open repair patients remained significantly below baseline in some, but not all, measures (Prinssen, Buskens, Blankensteijn, & On behalf of the DREAM trial participants, 2004). Overall, this and other studies have shown that it

can take up to 6 months for open repair patients to recover their quality of life to preoperative levels (Aquino, Jones, Zullo, Missig-Carroll, & Makaroun, 2001; Lloyd, Boyle, Bell, & Thompson, 2000). On a more specific measure of quality of life, sexual dysfunction, it was found that AAA intervention increased rates of sexual dysfunction significantly, but that patients undergoing EVAR were able to recover within 6 weeks while open repair patients took about 3 months to recover fully (Prinssen et al., 2004).

These data suggest that EVAR has a distinct benefit to the patient in terms of quality of life; however, this is not a sustained and long-term benefit. Furthermore, the surgeon should be aware of this benefit when making recommendations to the patient as it could certainly have an effect on how the patient approaches the decision to undergo surgical intervention.

5b. EVAR 1 and 2

With enrollment beginning in 1999, the UK EndoVascular Aneurysm Repair Trials (EVAR 1 and EVAR 2) enrolled participants in the UK until 2004. EVAR 1 was a comparison of endovascular versus open repair in patients eligible for either, with aortic dilatations greater than 5.5cm. EVAR 2 included only patients who were deemed unfit for open repair, and so compared endovascular repair with surveillance.

Both trials followed patients for a primary endpoint of mortality, and secondary endpoints which included reintervention rates and graft failures. The initial results of the EVAR 1 trial – the 30-day mortality results – indicated similar findings to the DREAM trial with a much larger number of patients (1,082), which helped to validate the findings of the former study. Operative mortality was significantly reduced among patients receiving endovascular treatment in comparison to open repair, but it was found that there was a significantly higher rate of secondary intervention among this group (Greenhalgh, 2004). Through four years of follow-up in the EVAR 1 trial, there was a sustained benefit for patients undergoing EVAR in terms of aneurysm related mortality, but the all-cause mortality rate was equivalent in both groups (EVAR trial participants, 2005).

Long-term results of the EVAR 1 trial were given over eight years of follow-up (The United Kingdom EVAR Trial Investigators, 2010). It was found that across time, the benefit to EVAR in aneurysm related deaths was not sustained, and that mortality was equivalent between groups. Reintervention rates in the EVAR groups were significantly higher than the open repair group, with only about half of patients receiving endovascular intervention being free of complications at eight years.

In contrast, the EVAR 2 trial, for patients who were ineligible for open repair, found that there was a significant benefit to EVAR over eight

years of follow-up in terms of aneurysm related mortality (The United Kingdom EVAR Trial Investigators, 2010). However, this benefit did not translate to increased overall survival, with the all cause mortality converging at eight years. Comparing results from EVAR 1 and 2, the graft complication rates and reintervention rate were similar. This suggests that EVAR is no more of a risk in patients who are unfit for open repair than patients who are eligible (Brown et al., 2012).

An interesting result from the EVAR trials was that within the first five years of follow-up there was no statistical difference between groups on measures of cardiac events. EVAR 1 showed a non-significant decrease in cardiovascular events among EVAR patients as opposed to open repair, but this did not reach significance (Brown, Thompson, Greenhalgh, Powell, & Participants, 2011). This suggests that, while there is a possibility that EVAR could spare some morbidity and mortality compared to open repair, this should only be considered in patients who are perhaps at higher risk. In EVAR 2, there was no difference between patient groups on measures of cardiovascular outcomes (Brown, Greenhalgh, Thompson, Powell, & EVAR Trial Participants, 2010). In this case, these findings suggest that EVAR should be safe in the case of a patient who is unfit for open repair, in terms of cardiovascular corollaries.

5c. OVER Trial

The Open Versus Endovascular Repair Veteran's Affairs Cooperative Study Group trial (OVER) was a prospective randomized trial conducted within the Veteran's Affairs system comparing open and endovascular repair for AAA. This was similar to the DREAM and EVAR 1 trials, however patient criteria were modified (Lederle et al., 2009). Selection criteria included aneurysms greater than 5cm in diameter, as well as aneurysms greater than 4.5cm in diameter with a recent history of rapid enlargement. In agreement with previous studies, the first report from the OVER trial found a significantly reduced mortality in the short-term, but the primary outcome of this study was the long-term mortality. Operative and aneurysm related morbidity was similar between both groups, however the endovascular repair group did show a significantly increased rate of claudication.

At the two-year mark of the study, data supported the assertion that EVAR resulted in a sustained benefit in operative mortality. Of note, the data produced by the OVER trial differed from both the EVAR 1 and DREAM trials. Thirty-day mortality was lower among patients in the OVER trial than either of the others in both EVAR and open repair groups (Lederle et al., 2009). When the long-term results of this trial were released it was seen that the initial sustained benefit to EVAR was eliminated over the eight years of study follow-up (Lederle et al., 2012).

Subgroup analyses of patients showed several significant differences. Of primary note amongst these was the effect of age. The presumption of the authors was that results would corroborate the supposition that EVAR would result in better outcomes for the elderly who would be at greater surgical risk when undergoing the major open repair procedure. However, the long-term results of this study showed a significant difference between hazard ratios for those on either side of 70 years old, with greater EVAR survival amongst younger patients. Additionally, the date of patient randomization apparently played a role, with a later enrollment showing a hazard preference for EVAR. This might suggest that as EVAR became more widely used and as skill and technology improved, the endovascular procedures became more safe and successful. Finally, within the OVER trial, there was a trend towards more frequent secondary interventions among EVAR patients, but this difference was statistically insignificant. This differs from what was found in both the DREAM and EVAR 1 trials (Blankensteijn et al., 2005; The United Kingdom EVAR Trial Investigators, 2010), which showed endovascular repairs to more often require a secondary intervention. Logically, this is acceptable, but the authors of the OVER trial note that neither of the previous trials involved close follow-up of open repair patients for operative morbidity whereas their trial did (Lederle et al., 2012).

Prior to the publication of these more recent trials, some of the published evidence had shown that EVAR might have been unfavorable in comparison to traditional open repair, and this had prompted some experts to decry the use of endovascular technologies (Collin & Murie, 2001). But EVAR is again gaining favor as an elective approach (Rutherford, 2006), and results of the OVER trial “*suggest that endovascular repair continues to improve and is now an acceptable alternative to open repair*” (Lederle et al., 2012). Still, these major trials and others have demonstrated and validated certain issues with endovascular repair – namely the need for subsequent interventions and lifelong follow-up.

5d. Epidemiological Considerations

Several factors have been identified as possible contributors to failure of both open and endovascular aneurysm surgeries. Comorbidities such as metabolic syndrome and CAD have been shown to be associated with increased risk following endovascular repair, while extensive atherosclerosis and renal insufficiency have been associated with failures of open aneurysm repair (Coscas et al., 2010; Hall et al., 2013). Aside from pathophysiological factors such as these, epidemiological factors have also been shown to have an important association with elective repair.

Surgery is a major undertaking at any point in life, and the magnitude only increases with age. With an annual risk of rupture for aneurysms of 5 cm being approximately 5%, repair may be unnecessary for very elderly or infirm patients (Mohler, Emile R., 2014). Members of the Vascular Study Group of New England retrospectively analyzed over 2,000 elective repairs of infrarenal AAA with an eye to life expectancy. They point out that the 5.5cm threshold for intervention “*assumes that the annual risk of rupture exceeds the operative mortality risk and that the patient will otherwise survive long enough to overcome the up-front risk of surgical treatment*” (De Martino et al., 2013). Patients were included in the analysis if they underwent elective AAA repair for aneurysms between 5.5 and 6.5cm diameter located in the infrarenal region of the aorta. Compared with patients treated by EVAR, the proportion (30%) of patients undergoing open repair were younger and had less cardiovascular risk factors for surgery – with the exception of smoking history, which was more prevalent among patients who underwent an open repair procedure. Overall mortality data was consistent with findings from the previous major trials comparing open and endovascular repair. For analysis, patients were stratified by risk based on long term mortality profile. It was found that there is a significantly different five year survival among patients in each of these risk groups, with major contributions to increased mortality coming from recent myocardial

infarction, increasing age, COPD, and renal insufficiency. The authors suggest that survival among patients with several comorbidities may be less than 50% at the five year interval. This should be taken into strong consideration when deciding whether it is appropriate to treat AAA patients by surgical means, especially given that the patient's age may be an independent factor in determining the long term outcome of the procedure (Cadili, Turnbull, Hervas-Malo, Ghosh, & Chyczij, 2012).

In the long-term, open repair and EVAR have been seen to be equivalent in terms of mortality. Therefore open repair in patients with extended life expectancies can reduce the cost and burden of follow-up associated with EVAR and reduce the risk of secondary intervention – including eliminating the potential need for conversion to open repair, which is approximately 1%. In contrast, patients with reduced life expectancies may enjoy some benefit from EVAR while avoiding the risk of open surgery and the burden of reinterventions and follow-up in the extended term.

As much as there is a gender difference in AAA presentation, it remains unclear if there is a gender difference in repair. Several studies have presented conflicting information about mortality with respect to gender. Egorova and colleagues (2011) found that women experienced a higher mortality rate from elective repair despite lower rates of comorbidities. In contrast, Lo and colleagues (2013) found that while

women experience a higher mortality rate following open repair, there is no difference in EVAR mortality. This finding is disputed by another study showing a significant increased EVAR mortality among women (Mehta et al., 2012). Though mortality outcomes are conflicting and unclear, studies of gender differences in elective repair agree that there is a significantly higher rate of complication among women as compared to men, especially among women undergoing EVAR (Egorova et al., 2011; Grootenboer, Myriam Hunink, Hendriks, van Sambeek, & Buth, 2013; Lo et al., 2013; Mehta et al., 2012). These differences have been primarily attributed to anatomical differences in women, which could be a source of bias in evaluating the literature on gender differences in AAA repair, including conflicting findings (Dubois, Novick, Harris, DeRose, & Forbes, 2013).

5e. Economic Impact

The cost burden of aneurysm surgery is significant, as can be seen from data in the several major randomized clinical trials comparing open and endovascular repair. In the DREAM trial, investigators found that the average cost of the open repair procedure was about \$18,000 while the cost of EVAR averaged over \$25,000 (Prinssen et al., 2007). In their analysis of cost-effectiveness, investigators concluded that open repair is most likely the preferred method of treatment in terms of the economic

impact of one additional quality-of-life-year gained due to the excessive cost of EVAR. The OVER trial also analyzed the cost of intervention. Their data on operational cost was similar to that in the DREAM trial, but investigators went a step further to look at the total incurred costs of the operations. It was found that the mean cost of open repair was non-significantly higher than EVAR, and the median cost was equivalent (Stroupe et al., 2012). Costs limited to the operation itself remained significantly higher in the EVAR group opposed to the open repair group. A possible explanation for the disagreement between these trials cited by the authors is the timing of the studies (Lederle & Stroupe, 2012). Hospital costs increased significantly between the beginning of DREAM trial enrollment and the end of OVER trial enrollment, with associated hospital costs accounting for the majority of increased costs in the open repair group.

The EVAR 2 trial provides another perspective on the issue of costs in endovascular repair due to the exclusion of open repair due to ineligibility. Although EVAR provided a significant benefit to these patients in terms of aneurysm-related survival, there was no translation of this benefit to an overall increased survival (The United Kingdom EVAR Trial Investigators, 2010). The associated costs in the treatment group exceeded \$22,000 while cost in the non-treatment group was less than \$7,000 with a net result of equivalent mortality. Interestingly, the

cost of endovascular repair does not appear to have significantly affected the choice to perform this procedure among either patients or hospitals, with EVAR rates rising over the past decade. As cost-effectiveness continues to be an important factor in healthcare decision-making, understanding the costs of EVAR from a provider's perspective is important. Stone et al., (2014) studied the financial implications of EVAR in a single-center experience. Because the vast majority of AAA patients are enrolled in the Medicare program, researchers used the Centers for Medicare and Medicaid Services remuneration levels as a benchmark, and found that the net hospital cost exceeded revenues by over \$4,000 per EVAR procedure. On average, 52% of the operative costs were accounted for by the endograft. Most notably, as reported by the group, the data places this institution in the lowest quartile of costs as compared to other comparable academic medical centers.

The high cost of EVAR devices puts the practice of endovascular repair at high risk in the future. As political focus in the United States continues to shift towards fiscal restraint, the likelihood that hospitals will continue to perform this procedure at a loss is declining. With the endograft market growing to almost \$2,000,000,000 in revenue in 2012, the need for lower cost devices may drive future development on the technology and manufacturing side (Research and Markets, 2013).

Discussion and Conclusion

For much of the 20th century, open repair was the only option for patients with AAA. The advent of endovascular repair provided a novel approach to aneurysm repair and expanded patient options. In comparison to open repair, EVAR has a perioperative benefit in terms of mortality. Recent evidence even suggests a benefit to extending this method to patients who are not eligible to undergo open repair. However, EVAR also carries risk in the form of a high reintervention rate and a lifelong need for rigorous follow-up, dampening the enthusiasm generated by the availability of a novel alternative.

Despite any concerns, EVAR has proven to be a significant advance in the care of patients with infrarenal AAA. Future developments will focus on reductions in the need for reintervention, and the consequent reduction in follow-up costs. New devices are already being developed as technology advances rapidly. For example, the Nellix system from Endologix (ELGX: Irvine, CA) aims to eliminate Type II endoleaks by filling the aneurysm sac, and is currently enrolling patients in its first clinical trial. In the short term, the development of safer and more sensitive imaging technologies may become applicable to AAA surveillance and follow-up. Modalities such as CO₂ angiography, contrast enhanced ultrasound, low cost MRI, and low power CT will likely impact the way endovascular patients are monitored.

Over the extended term, open repair and EVAR are equivalent in efficacy. The conundrum arises in the cost of care and the accumulation of risk. Current changes in the healthcare system of the United States could dictate how these surgeries are approached in the future. Open repair is significantly less costly in comparison to EVAR and the EVAR procedure requires a shorter hospital stay. If EVAR is rebranded as an outpatient procedure, and reimbursement rates for the surgery decline, the endovascular approach could be all but obviated with the exception of patients who can pay out of pocket or who are ineligible for open repair.

Management of AAA is complex and expensive, and no definitive stratification exists to guide physicians on how to treat such patients. With the advent of EVAR, a novel approach is now available. In spite of doubts about the efficacy of this method, endovascular management of AAA patients has opened a new avenue of intervention for patients and broadened the population to whom treatment is available. Therefore patient preferences and physician's judgement will, for now, remain the guiding principles of AAA management.

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