

Abdominal Aortic Aneurysms: Changing Paradigms in Treatment

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1. Introduction

Abdominal aortic aneurysms (AAA) are a well-recognized cause of morbidity and mortality in older persons. The 20th century has led to many overall advances in surgery and specifically the management of complex and often lethal disease processes. In the early part of last century, advances in anesthesia and critical care allowed for the surgical management of AAA via the open approach, which is to this day still considered by many to remain the gold standard of repair. In the latter part of the last century further advances and innovative thinking led to the minimally invasive endovascular treatment of many AAAs. Endovascular abdominal aortic aneurysm repair (EVAR) has pioneered the treatment of more complex aortic disease and now with greater than 20 years since its début it is in many centers the preferred treatment. There is no longer a feasibility question; these devices have been proven to be safe and efficacious with less perioperative morbidity and mortality than traditional open repair.

In an attempt to improve the world literature and make comparisons more possible amongst the many evolving studies underway globally a need for some commonality in the reporting of results was recognized. The reporting standards for AAA repair, both for endovascular and for open repair have been formulated into guidelines first extended in 1997 and then later updated in 2002. These standards outline the generally measured characteristics touched on by many of the studies reporting on the treatment of aortic aneurismal disease. Included are the common patient characteristics involved in atherosclerotic disease such as tobacco use, hyperlipidemia, hypertension, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, carotid occlusive disease, other associated aneurismal disease and anesthesia risk as outlined by the American Society of Anesthesiology Risk Classification (ASA). These guidelines also address characteristics unique to aneurismal disease known as the anatomical risk factors, such as aortic neck length and angulation as well as access vessels where included with a grading system. Outcome measures of clinical success and the definition of terms such as endotension and endoleak were included. The current devices have gone through several generations of advancement, alteration and modification which has addressed many of the device specific criteria that were offered and for the most part has addressed, and continue to address these limitations as innovation in the field continues.

With further advances and longer length follow up periods many of the earlier unanswered questions are being addressed however in doing so new questions have arisen and the persistent question since the inception of EVAR remains a point of controversy to this day,

namely who should undergo endovascular treatment and who should undergo standard open repair. A significant hindrance has been the lack of ability to compare these studies head to head and gain useful and usable information from them. The reporting standards conceived by the Society for Vascular Surgery (SVS) were an attempt to make such comparisons more uniform for just this reason.

As well as reporting standards in individual studies being a goal of the SVS reporting standards guidelines the drive for successful management of AAA as well as many other diseases has been taken up by the clinical and administrative bodies of large organizations such as the Veterans Healthcare system and the American College of Surgeons based on the VA model. "Soon after introduction of endovascular aneurysm repair (EVAR), with Food and Drug Administration device approval in 1999, robust electronic NSQIP (National Surgical Quality Improvement Program) records immediately began to capture individual facility performances and outcomes for both types of AAA repair. The NSQIP data center provided actual and risk-adjusted analyses for both procedures semiannually. These analyses have been used by its executive board to provide recommendations, often based on site visits, to improve outcomes." ^{1,2} Data bases like these have been adopted and pioneered by other countries as well and continue to add to the knowledge bases with the goal of efficient, high-quality care ².

However, in the face of all of the published standards no one accepted method is used and continued publications of standards and measuring techniques can still be found in both the world literature and in the Journal of vascular surgery such as the recently published Validation of a new standardized method to measure proximal aneurysm neck angulation ³ and the recently reported attempt by the French health agency Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) to determine criteria for the best surgical approach. The high-risk AFSSAPS criteria were however not predictive of postoperative mortality and the authors stated that these should not be used to determine the choice of treatment technique. Other criteria therefore need to be established to determine whether open or EVAR repair should be used. ⁴

In the ever evolving field of AAA treatment there has not been an acceptance of the reporting standards, which makes interpretation difficult to a certain extent, but by the common nature of the studies there does tend to be overlap in the reporting making it possible to draw conclusions all be it in a non-standardized fashion from the recently reported studies.

2. EVAR vs open repair: Basic variables in decision making

There are three basic modalities, which are generally accepted and widely available for the management of abdominal aortic aneurysms. These include observation alone, also known as best medical treatment (BMT), Standard or open repair which is the oldest surgical method and for this reason considered by many to be the gold standard, which can be done either by a transperitoneal, or via the retroperitoneal incision, and the endovascular approach (EVAR). There are other options, which are available at some institutions and represent variations on and combinations of the above approaches, these include laparoscopic abdominal aortic repair and hybrid procedures. Of the 3 commonly available and accepted modalities outlined above, EVAR is the newest and most rapidly progressive in terms of technological innovation and industry driven advancements.

The decision on the specific modality for optimal treatment has long been a matter of controversy, and continues to be so to this day. When planning the optimal treatment for

AAA there are 3 commonly considered variables. The first thing to consider is the size of the aneurysm. There is a well-established correlation between rupture risk and the maximal transverse size of the aorta and rupture⁵. Second is the anatomy or morphology of the aorta. All devices have guidelines for use under the Food and Drug Administration (FDA) which were created to assist the clinician in determining anatomical acceptability of the device to ensure the optimal outcome. In the past there has been a 20-60% reported suitability following the information for use guidelines (IFU)^{6,7} however with advancing technology the delivery systems for these devices have gotten smaller, with hydrophilic coats and the devices themselves have become larger with different configurations which has greatly expanded the anatomic criteria for the use of these devices. Devices used outside of the FDA-IFU guidelines have been associated with increased complication rates and adherence to these guidelines as much as possible is recommended.⁸⁻¹¹

The third variable commonly considered is perhaps the most challenging and can impact the other two variables to varying extents when trying to formulate an appropriate operative strategy. This variable is the patient. Multiple considerations on multiple levels often cloud one's judgment and make this a subjective rather than an objective decision. The elements going into this equation range widely from the patient's co-morbidities and other illnesses are in determining whether they are "fit" for surgery or "high risk", to whether the patient will follow up and be compliant with surveillance imaging, to what the patient's expectations and knowledge are about the purposed intervention to outside influences such as the wishes, knowledge-base and influence family, friends and loved ones have. Putting all of these patient variables together is often a difficult and arduous task that can greatly influence the treatment modality chosen perhaps more than any other variable outlined.

3. Size

The anatomical size, in transverse diameter, has long been established as one of the main indications for treatment vs. observation. The commonly accepted size for the initiation of intervention is 5.5 cm based on several landmark publications and the accepted risk of 1% rupture below this threshold. A threshold diameter of 5.5 cm has been the point of separation commonly used based on the United Kingdom Small Aneurysm trial⁵ and the US Veterans Administration Aneurysm Detection and Management¹² Study. These trials showed no benefit in overall survival to early repair over continued observation for AAAs less than 5.5 cm in diameter, and demonstrated an annual rupture risk for such small AAAs (4.0 cm to 5.4 cm) to be low approximately 1%. These studies were based on open aneurysm intervention. The natural history, despite the treatment threshold, of aneurysms is to continue to grow and then eventually to rupture. In the United Kingdom Small Aneurysm Trial⁵, over 60% of those initially assigned to surveillance had AAA repair by 4 years, and most of those with greater than 5.0 cm AAAs had a repair within 1 year. As a result, many clinicians have dropped the threshold for intervention for AAAs to 5.0 cm in diameter. It is more appropriate to think of size as an indication of when to consider, not whether to consider AAA repair. However when to treat endovascularly remained an open question EVAR has been reported to achieve better outcomes in smaller AAAs¹³ and the importance of size in EVAR outcomes has been recently underscored by an analysis of the European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) database, which showed a statistically significant correlation between size (4.0 to 5.4 cm versus 5.5 to 6.4 cm versus >6.5 cm diameter) and all five outcomes studied (Type

1 endoleak, total mortality, aneurysm-related death, conversion to open repair, and post-EVAR rupture) ^{14 15}. Endovascular repair has been shown to be safer than open surgical repair in patients with large aneurysms, prompting a randomized trial of early endovascular repair vs surveillance in patients with small aneurysms¹⁶. In the PIVOTAL trial the researchers randomly assigned 728 patients with 4 to 5 cm AAAs to early endovascular repair (366 patients) or ultrasound surveillance (362 patients), and Concluded the early treatment with endovascular repair and rigorous surveillance with selective aneurysm treatment as indicated both appear to be safe alternatives for patients with small AAAs, protecting the patient from rupture or aneurysm-related death for at least 3 years ¹⁶. In the Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair (CAESAR) Trial the researchers randomly assigned patients with AAA of 4.1-5.4 cm in a 1:1 ratio, to receive immediate EVAR or surveillance by ultrasound and computed tomography (CT) and repair only after a defined threshold (diameter ≥ 5.5 cm, enlargement >1 cm /year, symptoms) was achieved. Between 2004 and 2008, 360 patients (early EVAR = 182; surveillance = 178) were enrolled. They reported that mortality and rupture rates in AAA <5.5 cm are low and no clear advantage was shown between early or delayed EVAR strategy. However, within 36 months, three out of every five small aneurysms under surveillance might grow to require repair and one out of every six might lose feasibility for EVAR. Concluding that surveillance is safe for small AAA if close supervision is applied.¹⁷ Depending on interpretation and resources this information may help determine when to treat patients with smaller AAA at an earlier stage. Further, it has been suggested that the threshold in women be even lower (e.g., 4.5 cm in diameter) based on women's relatively smaller aortic dimensions, which appear to play a role in their higher risk of rupture and its attendant mortality and in their ¹⁸ lower anatomical suitability for EVAR ^{14,18,19}

While in the past there was "no disagreement about appropriate treatment for large AAAs in patients with unsuitable anatomic characteristics that preclude EVAR, these patients should have conventional open repair, which has been reported to have low morbidity and mortality rates¹⁴. The advancement of technology has steadily whittled away at these anatomic criteria and continues to push the safe and acceptable anatomical criteria further into what was once considered to be the experimental or anatomically unacceptable range. With this push and the increasing use and availability of the EVAR technology there has been an over all shift in the general clinical practice in many institutions towards the implantation of EVAR, with less and less consideration being given to the surgically fit patient. This has led many clinicians to consider EVAR as the first line treatment for AAA regardless of the patient's characteristics, such as fitness for surgery, or ability to undergo a large abdominal procedure. In many ways this is the trend first set out by the laparoscopic revolution that swept through general surgery some 20-30 years ago. It is rare now to see an open cholecystectomy, and rarer still to see this as a planned first line intervention. The open cholecystectomy is often reserved for the failed laparoscopic approach. So to, it would appear, is the fate of open abdominal reconstruction. While EVAR Has boasted well-documented benefits²⁰⁻²² over open repair including a reduction of aneurysm-related mortality, a decrease in perioperative cardiopulmonary complications as well as of hemorrhage, graft infection and colonic ischemia, as well as reduced patient trauma, reduced hospital stays and faster recovery ²⁰. Even in the face of the EVAR 1 data suggesting that After 12 months there was negligible difference in Health Related Quality of Life (HRQL) between the two groups (EVAR vs Open) ²³. The obvious benefits noted clinically by the patient and surgeons alike have propelled EVAR forward despite all oppositions.

While the above benefits are well documented and the trends outlined it is more apparent that obtaining similar results with less pain and less procedure are the true drivers behind EVAR. The argument against EVAR citing the need for long follow up and the possibility for re-intervention as a downside is far out weighed by the realization of both clinicians and patients alike that a little "check-up" every year or 6 months trumps a week in the hospital and a possible ICU stay for all concerned. Cost is a driving negative force, but if the same results are obtainable with less pain, people, especially Americans will put up with nothing less. Re-interventions often cited as a complication of EVAR are viewed by many patients as simply tune-ups, and despite the extensive reports documenting re-intervention as a negative or down side to EVAR these are often well tolerated and the surgical conversion and explantation of EVAR has become much like the open cholecystectomy.

The shift and trend is now towards EVAR first both in clinicians and patients minds. The drive has been both evidence based and human nature. When looking at an AAA needing repair most surgeons' in this era first check to see if the patient is an EVAR candidate. Almost all other criteria are secondary. If the patient is young and could undergo a big open operation the surgeon and the patients' response is more and more commonly becoming "why" from the sociological point of view. The argument has been posed that a young patient is generally a productive member of society and no matter how well they do with open repair, arguably given EVAR they would rejoin the work force much sooner and even in the face of continued "check-ups" and possible intermittent "tune-ups" they would still be a more productive, over a longer period of time then where they to undergo a open procedure with its associated recovery time and potential risks.

4. The high risk patient

The management of AAA in patients considered to be high-risk remains a challenge. While EVAR was initially studied in this group as an alternative to the open procedure in patients that where considered unfit for the open surgical intervention the pendulum has now swung in the opposite direction. Initially the question of feasibility was addressed using this patient population, now that feasibility is no longer a question and EVAR has been well established as an acceptable method for aneurysm treatment the consideration of appropriateness has come into question.

The EVAR-2 Trial which used the cohort of patients that where excluded for the EVAR-1 trial as mentioned earlier concluded after a mean 4 years of follow up that EVAR had a considerable 30-day operative mortality in patients already unfit for open repair of their aneurysm. EVAR did not improve survival over no intervention and was associated with a need for continued surveillance and reinterventions, at substantially increased cost. Ongoing follow-up and improved fitness of these patients is a priority²⁴ published in 2005.

Endovascular aneurysm repair (EVAR) is associated with superior short-term mortality rates but unclear long-term results and has not been shown to improve survival in patients unfit for open repair (OR)²⁵. A group using the Swedish vascular registry conducted population-based study with the aim evaluating the outcome after elective EVAR compared with OR in a high-risk patient cohort. They reported that elective OR of aortic aneurysms seems to have a better outcome compared with EVAR in this specific, population-based, high-risk patient cohort after adjusting for covariates, and that they cannot confirm the benefit of EVAR from previous registry studies concluding that in clinical practice, OR may be at least as good as EVAR in high-risk patients fit for surgery.²⁵(Swedish study)

This prompted a Department of Veteran Affairs analysis citing that “recent results after endovascular abdominal aortic aneurysm repair (EVAR) have brought into question its value in patients deemed at high-risk for surgical intervention.”²⁶ The Department of Veteran Affairs (VA) National Surgical Quality Improvement Program (NSQIP) is the largest prospectively collected and validated United States surgical database representing current clinical practice. Utilizing this database a study was designed to evaluate outcomes after elective EVAR performed in high-risk veterans. This retrospective review analyzed 2296 pts (EVAR, n = 788; open, n = 1580) who underwent elective aneurysm repair from May 2001 to December 2004 and met the high risk criteria. High-risk criteria analyzed included age > or =60 years, American Society of Anesthesiology (ASA) classification 3 or 4, and the comorbidity variables of history of cardiac, respiratory, or hepatic disease, cardiac revascularization, renal insufficiency, and low serum albumin level. The primary end points were 30-day and 1-year all-cause mortality.²⁶ The investigators concluded that veterans deemed high-risk for surgical therapy, outcomes after elective EVAR are excellent, and the procedure is relatively safe in this special patient population. Our retrospective data demonstrate that patients with considerable medical comorbidities and infrarenal abdominal aortic aneurysms benefit from and should be considered for primary²⁶ EVAR.

Another American group conducted an interesting study in response to the EVAR-2 publication to determine the outcome in the United States after endovascular repair (EVAR) of infrarenal abdominal aortic aneurysms (AAAs) in patients at high-risk for open surgery. They independently audited, high-compliance, chart-verified data sets, and compared those results with open surgery. Interestingly in an attempt for head to head comparability they defined High-risk to match the EVAR-2 trial and included age of > or =60 years with aneurysm size of > or =5.5 cm, plus at least one cardiac, pulmonary, or renal comorbidity. They then analyzed data from five multicenter investigational device exemption clinical trials leading to Food and Drug Administration (FDA) approval finding 565 EVAR patients that met the high-risk criteria, and 61 OPEN patients that met high-risk criteria. Primary outcome comparisons included AAA-related death, all-cause death, and aneurysm rupture. Secondary measures were endoleak, AAA sac enlargement, and migration.

After analysis they concluded that endovascular repair of large infrarenal AAAs in anatomically suited high-surgical-risk patients using FDA-approved devices in the United States is safe and provides lasting protection from AAA-related mortality. EVAR mortality remained comparable with OPEN up to 4 years.²⁷

An Italian group analyzed their data to determine the best treatment for high-risk patients with abdominal aortic aneurysms (AAA) using the ASA classification guidelines and found a total 375 patients who underwent AAA repair, 168 (45%) belonged in ASA classes III and IV (85 OPEN and 83 EVAR). After analysis they concluded that except patients with small aneurysms (< 6 cm), in whom the risk of death at 1-year due to comorbidities exceeds the risk of a ruptured aneurysm, all patients at high surgical risk (ASA class IV) benefit from AAA repair. Patients with small aneurysms must undergo strict surveillance to assess growth and aneurysmal wall changes to prevent unexpected rupture.²⁸

Another American investigation looked at The 2001-2004 Nationwide Inpatient Sample in a direct response to EVAR-2 hypothesizing that The nationwide in-hospital mortality for patients with the highest risk undergoing EVAR in the United States is lower than that reported in EVAR trial 2. They found that 65 502 EVARs were performed with an in-hospital mortality of 2.2%. Risk-adjusted in-hospital mortality rates ranged from 1.2% to 3.7% compared to the substantial in-hospital mortality after EVAR (9%) reported in EVAR 2.

They concluded that The EVAR procedure is currently being performed in the United States with low in-hospital mortality, even in patients with the highest risk. Therefore, EVAR should not be denied to high-risk patients with abdominal aortic aneurysms in the United States on the basis of the level I evidence from the United Kingdom study.²⁹

Another group utilizing Department of Veteran Affairs data attempted to further investigate this issue by examining the influence of age, aneurysm size, and patient fitness on suitability for endovascular aortic aneurysm repair. They examined 186 male patients referred for evaluation of nonruptured AAAs. Suitability for EVAR was determined by neck anatomy, iliac artery morphology, and total aortic aneurysm angulation and tortuosity according to the clinicians' experience and current practice. They found that aortic neck length (odds ratio [OR]=1.2, 95% confidence interval [CI] 1.1-1.2) and diameter (OR=0.78, 95% CI 0.63-0.96) were the only independent predictors for EVAR suitability and concluded that Overall, EVAR suitability is not influenced by age, aneurysm size, or patient fitness.³⁰

5. The elderly and ethics

5.1 The elderly

The elderly group is a cohort is not well documented in the world literature with relation to management of AAA. There are few large series in this population which may reflect a unique survivability in this population. The average life expectancy has been steadily increasing world wide. The United Nations World Population Prospective 2006 revision showed an average life expectancy from birth in the united states of 77.4 from 2000-to-2005 and predicted an increase to 78.2 from 2005-to-2010 and to 78.9 for 2010-to-2015. Due to the increasingly aging populations of the industrialized countries, the prevalence of vascular disorders is increasing, with an emerging patient subgroup of 80 years and older (octogenarians), often multi-morbid with an increased risk of anaesthesiological and surgical complications³¹. Abdominal aortic aneurysms (AAAs) occur in approximately 5% of the population older than 50 years and up to 10% within the male population over 80 years³². According to the United Nations World Population Prospective 2006 revision globally, the number of persons aged 60 years or over is expected nearly to triple, increasing from 673 million in 2005 to 2 billion by 2050. Over the same period, the share of older persons living in developing countries is expected to rise from 64 per cent in 2005 to nearly 80 per cent in 2050. A recent analysis of the nationwide sample of intact AAA repairs from 2001 to 2006 demonstrated a 69% increase in the total number of asymptomatic AAA repairs in patients more than 85 years of age in comparison to their younger counterparts³³. Moreover the estimated life expectancy of a centenarian in the United States in 2004 was 2.3 years. (National Vitals Statistics System. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_09.pdf. Accessed June 10, 2010.)

The Question of age as a defining category of AAA repair becomes more difficult when analyzing the outcomes of the studies in the literature, many of which demonstrate favorable outcomes. Numerous articles have reported acceptable results for octogenarians treated with both open and endovascular techniques.³⁴ Open repair of AAAs in octogenarians has been associated with increased life expectancy in comparison to untreated AAAs³⁵. With respect to treatment of AAA mortality rate, while higher than in younger patients, is acceptable in carefully selected octogenarians³⁶. While other investigators looking at EVAR vs. Open repair concluded that there was no difference in the long-term survival benefit between open repair

and EVAR in 150 octogenarians.³⁷ With attention to the population of octogenarian-to-nonagenarians (age range 80-95) Prenner et al report a series of 322 patients that underwent elective EVAR from January 1997 to November 2007. The mean age was 84 years +/- 3.4 years. They reported a perioperative 30-day mortality rate of 3.1% with a mean follow-up of 25.7 months. Freedom from aneurysm-related mortality was 95.4% at 1 year and 92.9% at 5 years. They concluded that EVAR in octogenarians is associated with high procedural success and low perioperative morbidity and mortality.³⁸

In the Nonagenarian population Halpern et al report the largest retrospective review of EVAR over a 10-year period. While this remains a small cohort of only 23 patients. The mean age was 91.5 (range 90-94) and the perioperative mortality was only 4.3%. There were no aneurysm-related deaths beyond the 30-day postoperative period. They also reported that the mean survival beyond 30 days was 800 +/-459 days following EVAR. These results suggest that despite their advanced age, these patients benefit from EVAR with low morbidity, low mortality, and mean survival exceeding 2.4 years. Survival appears best in those patients with ≤ 5 comorbidities. With or without symptoms, patients over the age of 90 should be considered for EVAR³⁹. Another relatively large study from a single institution analysis of endovascular repair (EVAR) in nonagenarians analyzed 18 nonagenarians (age range 90-95). They reported 100% technical success with a mortality rate of 5.6%, 41.2% and 58.3% at 30 days, 365 days, and 2 years, respectively. Mean survival of the 11 patients who expired beyond the first 30 days was 17.5 months. EVAR is safe in nonagenarians despite their advanced age and significant surgical risk factor profile. The procedure can be performed with excellent technical success and a low rate of perioperative complications. However, mortality rates after 30 days are significant. The substantial long-term mortality raises the question of possible treatment futility in this unique population. While age should not be a contraindication for EVAR, recommendations for the procedure should be based on individual patient selection.⁴⁰ In a recent review Demirel and colleagues examined Vascular Surgery in the Elderly and made Recommendations for Clinical Practice. They state that with suitable morphology of the aneurysm, endovascular aneurysm repair (EVAR) is the therapy of choice for abdominal aortic aneurysm (AAA). In elderly patients unfit for open repair and with a life expectancy of less than 4 years, EVAR does not offer any survival benefit compared with no intervention. In such patients, conservative therapy should be taken into consideration³¹

5.2 The ethical dilemma

The ethical dilemma of age is mirrored on every level of patient treatment and the decision for any surgery. The question of age however perhaps underscores these considerations more strongly than any other patient related characteristics because the emphasis must be placed on the individual. There are patients that are in the most advanced chronological category that are much healthier from a physiological stand point than some patients that are very much younger in years. This gives rise to the concept of physiological age of the patient, which is far more important than the chronological age when considering surgery. The ethical discussion in the health care arena centers around 4 main concepts. These briefly outlined are as follows. First are the basic ethical principals of beneficence and nonmaleficence. These state that the procedure or treatment in question should be beneficial and not do harm. While this is often not totally possible it may be extended in thought and practice to have the potential benefits outweigh the potential risks. Second is the principal of autonomy. This simply stated is the

patients right to make decisions for themselves and has been expanded in modern medicine to be the basis of the informed consent. Given all of the information available and a clear understanding of the first principle the patient has the right to guide his or her own care. The third principle is that of justice. This principle brings into account the population or community as a whole. It is concerned with the allocation of limited vital healthcare resources and whom these should be made available to. The dichotomy of this prospective, simply stated, is should valuable resources be adjudicated to the largest amount of people that could benefit from them or on the people that need them most. The final issue is the respect for human life. This brings into account religion, cultural beliefs, and moral values both of the individual and of society and may differ around the world.

Abdominal aortic aneurysms (AAAs) occur in approximately 5% of the population older than 50 years and up to 10% within the male population over 80 years. (Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2007;2:CD002945.)

Schwarze et al⁵ analyzed a nationwide sample of intact AAA repairs from 2001 to 2006 and demonstrated a 69% increase in the total number of asymptomatic AAA repairs in patients more than 85 years of age in comparison to their younger counterparts.³³

6. Nonagenarians

Jim et al⁶ reported a single institution analysis of endovascular repair (EVAR) in nonagenarians. The study analyzed 18 nonagenarians (age range 90-95) and reported 100% technical success with a mortality rate of 5.6%, 41.2% and 58.3% at 30 days, 365 days, and 2 years, respectively. Mean survival of the 11 patients who expired beyond the first 30 days was 17.5 months. They concluded that EVAR is safe in nonagenarians despite their advanced age and significant surgical risk factor profile.³⁴

Halpern et al reported a largest retrospective review of nonagenarians that underwent EVAR over a 10-year period. They analyzed 23 patients with mean age of 91.5 (range 90-94) and reported a perioperative mortality of 4.3%. There were no aneurysm-related deaths beyond the 30-day postoperative period. Mean survival beyond 30 days was 800 +/- 459 days following EVAR. Their results demonstrated nonagenarians' benefit from EVAR with low morbidity, low mortality, and survival exceeding 2.2 years despite their advanced age and, therefore, they should be considered for EVAR with or without symptoms.³⁹

7. Octogenarians-to-nonagenarians

A series of 322 patients that underwent open and EVAR in octogenarians and nonagenarians (age range 80-95) was reported by Stuart Prenner and colleagues.⁸ The perioperative 30-day mortality rate was 3.1% with a mean follow-up of 25.7 months. Freedom from aneurysm-related mortality was 95.4% at 1 year and 92.9% at 5 years. Their results demonstrated EVAR in octogenarians is associated with low rates of perioperative morbidity and mortality and low long-term aneurysm-related mortality despite the high rates of comorbidities in these patients.³⁸

8. The ruptured aneurysm

An interesting and natural advancement to endovascular technology has resulted in another group not previously mentioned which has benefited from EVAR with increasingly

promising results in the literature. This is the rupture population. EVAR has now been used with excellent results in some centers not only for prevention rupture, but also for the treatment of ruptured abdominal aortic aneurysms, and is now growing in acceptance as a life saving procedure. Foster and colleagues reviewed the literature to answer the question whether a policy for endovascular repair as the primary mode of treatment for ruptured abdominal aortic aneurysms (rAAAs) would improve outcomes. They reviewed One thousand three hundred and twenty-eight papers and concluded that conclude that, within the limitations of the published literature to date, endovascular repair as the primary treatment for rAAA is achievable and appears to be associated with favorable mortality over open repair with appropriate case selection.⁴¹ More recently Bosch et al reviewed their results from April 2002 until March 2008 from a single center in the Netherlands comparing their open to their EVAR experience in the ruptured setting and concluded that In EVAR-suitable patients, an absolute perioperative mortality reduction of 25.5% of rEVAR over open surgery was found, which was still present at 6 months of follow-up. These data suggest that rEVAR is a superior treatment option for EVAR-suitable patients with an rAAA compared with an open surgery.⁴² Setacci and the university of Siena group reported that despite this evidence, EVAR for rAAA remains prerogative of few centers worldwide. In conclusion only larger study or registry could assess the real role of EVAR in the management of rAAA.⁴³ In an attempt to further explore this question Davenport et al from the University of Kentucky examined the Thirty-day NSQIP database outcomes of open versus endoluminal repair of ruptured abdominal aortic aneurysms. They identified A total of 427 patients the majority of which (76.8%) underwent open repair. However in review of the data they found that composite 30-day morbidity risk is lower after EVAR vs open repair of rAAA. Open repair is associated with increased transfusion requirements. Performance of EVAR in rAAA patients with favorable anatomy could potentially result in improved outcome as compared with open repair.⁴⁴

9. Inherent problems in study design

In the era of clinical and research based medicine otherwise known as evidence based medicine a great deal of positive information and tools to assist in clinical judgment have been generated. However along with the need for research to both explain what we do and document its positive or negative effects there has evolved an overwhelming amount of information. This information is not free of error and in even the gold standard randomized control study can be manipulated. While these statistical acrobatics are generally not malicious in intent a lot can ride on the outcome of study both with respect to surgical and to a broader extent medical decision making and to the bottom line of reimbursement which drive the hospitals and clinics. Whatever the reason it is important to recognize that in particular many of the "land mark studies" in AAA have a very serious problem associated with their general design, despite the fact that superficially these appear to represent the "gold standard." These studies are the randomized clinical trials (RCTs) offering an observation/no treatment (OBS/NoRx) arm as control and which are focused on the management of a condition with potentially life-threatening consequences, however small the risk, often experience a significant rate of crossover to treatment by those randomized to the OBS/NoRx arm.⁴⁵ this type of design was initially designed for Medication and drug testing. Intent-to-treat data analytic strategy was developed for drug trials in which some patients dropped out (after 10-12 weeks) before receiving full treatment. To determine

whether the full treatment worked, you could just use the subjects who completed treatment when analyzing outcome data for these studies. Hence preserving data for the statistical analysis, however in a life threatening, or perceived life threatening condition, where there can be no “blinding” of the patient this type of design often leads to a significant degree of error in the form of the cross over effect. The frequency with which patients cross over may either confound the outcomes of these trials and/or undermine the acceptance of conclusions based on an intent-to-treat analysis, which should not be used in this situation.⁴⁵ Yet the very fabric on which a great many of our clinical decisions are based is from just such studies. Studies of abdominal aortic aneurysms with this design that exemplify this dilemma, with crossovers ranging from 27% to over 60% include EVAR II, UKSAT, ADAM, and PIVOTAL. Results of these trials are frequently used as level I medical evidence and their potential impact on clinical decision-making and reimbursement can be quite significant and long-lasting.⁴⁵

10. Analysis of available studies

In 2005 the findings from the United Kingdom EVAR 1 Trial were released in the British journal, the *Lancet* titled “Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomized controlled trial”. This randomized controlled trial prospectively randomized 1082 patients aged 60 years or older who had aneurysms of at least 5.5 cm in diameter and who had been referred to one of 34 hospitals proficient in the EVAR technique. The patients were both anatomically suitable for EVAR and fit for an open repair to EVAR or open repair cohorts.²⁴ The primary endpoint was all-cause mortality at 4 years and EVAR and OPEN were found to be similar in this regard, with mortality rates of approximately 28% (hazard ratio, 0.90; 95% CI, 0.69–1.18; $P = 0.46$). One of the secondary endpoints, AAA-related death, showed a 3% advantage to EVAR, which was maintained for 4 years (perioperative mortality: EVAR 1.7% versus OPEN 4.7%; midterm mortality: EVAR 26% versus OPEN 29%). Other secondary endpoints showed that patients undergoing EVAR had a much higher complication rate (41% versus 9%, $P < 0.0001$) and reintervention rate (20% versus 6%) than those having OPEN. Mean hospital (not total) costs were roughly estimated to be about 30% higher in the EVAR group. Additionally, at 12 months follow-up, there was no difference in health-related quality of life. The Authors concluded that Compared with open repair, EVAR offers no advantage with respect to all-cause mortality and HRQL, is more expensive, and leads to a greater number of complications and reinterventions. However, it does result in a 3% better aneurysm-related survival. The continuing need for interventions mandates ongoing surveillance and longer follow-up of EVAR for detailed cost-effectiveness assessment.

However a closer examination of the statistical breakdown of the EVAR 1 protocol raises several issues with regards cohort assignments. Of the 1082 patients ultimately randomized from the original 4799 persons assessed for the study, 453 were assigned to EVAR and 539 were assigned to open repair. Thus, only 23% of those assessed for eligibility were ultimately randomized. This eliminated close to two thirds of the candidates from the EVAR group. Reasons for exclusion included AAA was considered too small for repair in 9%; the AAA morphology was unsuitable for EVAR in 54%, and the patients were unfit for open repair in 1.5%. Adding further confusion is the all cause mortality. As demonstrated in the EVAR cohort where 10 patients died while waiting EVAR, in effect they were randomized to this group, but never availed the benefit of the intervention. Another 15 patients

randomized to the EVAR group had OPEN repair. Three of these deaths were directly ascribed to AAA rupture. In the OPEN group, there were 13 deaths, of which 7 had ruptured AAAs and 18 patients received EVAR. This demonstrates a significant cross-over effect between the groups and further clouds the final analysis. The average delay from randomization to actual treatment was 57 days, despite a mean AAA size of 6.7 cm, which provides a likely explanation for the high pretreatment rupture rates. The increased availability of devices and the "off-the shelf" combinations in most large center stocks as well as the more expedient progression from diagnosis to treatment in the United States as well as many other countries world wide make delayed treatment extremely unlikely or even unacceptable in this day and age.

Another problem with the initial reporting in EVAR 1 is that only 24% of participants' data were included in the 4-year cutoff point for analysis, with 72% being still alive and uncensored at 4 years. Indeed, 25.3% of the open cohort and 21.6% of the EVAR cohort were ASA class 1; thus, this trial represented relatively healthy individuals.⁴⁶ View of the above, these results, although contributory to the current body of knowledge, really only represent midterm outcomes.

In 2010 the United Kingdom EVAR trial investigators produced a subsequent analysis in the publication of Endovascular versus open repair of abdominal aortic aneurysm in the *New England Journal of Medicine*. Here the United Kingdom EVAR trial investigators examined their data from 1999 through 2004 at 37 hospitals in the United Kingdom. They randomly assigned 1252 patients with large abdominal aortic aneurysms (≥ 5.5 cm in diameter) to undergo either endovascular or open repair; 626 patients were assigned to each group. Patients were followed for rates of death, graft-related complications, reinterventions, and resource use until the end of 2009. In this group the initial 1082 patients included in a planned midterm analysis that was reported in 2005 and an additional 170 patients who were enrolled between January 2004 and August 2004, who were not included in the midterm analysis. There were no significant differences between the two treatment groups with respect to baseline characteristics. The patients in EVAR 1 were randomly assigned to undergo either open repair or endovascular repair. Patients were encouraged to undergo repair within 1 month after randomization, although such scheduling was not always possible for logistic or other reasons.⁴⁷ Despite this the for patients undergoing aneurysm repair, the median time from randomization to surgery was 44 days (interquartile range, 29 to 70) in the endovascular-repair group and 35 days (interquartile range, 20 to 57) in the open-repair group.⁴⁷ Representing, again, a delay that would still be considered unacceptable by many. Of the 12 patients in the endovascular-repair group who did not undergo aneurysm repair, 7 died within 6 months after randomization (3 as a result of rupture), 3 became physically ineligible, 1 declined surgery, and 1 became anatomically unsuitable because of a change in the shape of the aorta. Of the 24 patients in the open-repair group who did not undergo aneurysm repair, 7 died within 6 months after randomization (3 as a result of rupture), 7 became physically ineligible, 8 declined surgery (of whom 3 died), and 2 had an unknown reason (of whom 2 died).⁴⁷ They report that the 30-day operative mortality was 1.8% in the endovascular-repair group and 4.3% in the open-repair group (adjusted odds ratio for endovascular repair as compared with open repair, 0.39; 95% confidence interval [CI], 0.18 to 0.87; $P=0.02$). The endovascular-repair group had an early benefit with respect to aneurysm-related mortality, but the benefit was lost by the end of the study, at least partially, because of fatal endograft ruptures (adjusted hazard ratio, 0.92; 95% CI, 0.57 to 1.49; $P=0.73$). By the end of follow-up, there was no significant

difference between the two groups in the rate of death from any cause (adjusted hazard ratio, 1.03; 95% CI, 0.86 to 1.23; $P=0.72$). The rates of graft-related complications and reinterventions were higher with endovascular repair, and new complications occurred up to 8 years after randomization, contributing to higher overall costs.⁴⁷

In response to these findings Jetty et al in their manuscript Long-term outcomes and resource utilization of endovascular versus open repair of abdominal aortic aneurysms in Ontario. This retrospective analysis was based on hospital discharge abstracts. They examined all patients who underwent elective AAA repair between April 2002 and March 2007. Clinical outcomes included time to all-cause death and discharge to a nursing home or long-term care facility. Resource utilization outcomes included imaging utilization, hospital utilization, and reintervention rates. They identified 6461 patients underwent treatment of nonruptured AAAs, comprising 888 EVARs and 5573 open repairs. EVAR patients were older and had more comorbidities. The adjusted mortality was significantly lower in the EVAR group at 30 days (adjusted odds ratio [adj-OR], 0.34; 95% confidence interval [95% CI], 0.20-0.59), but long-term mortality was similar (adj-OR, 0.95; 95% CI, 0.81-1.05). EVAR patients were significantly less likely to be discharged to a nursing home or other chronic care facility (adj-OR, 0.55; 95% CI, 0.41-0.74). Imaging utilization as well as urgent and vascular readmissions were significantly higher in the EVAR group. However, the EVAR group had a significantly shorter length of stay and less intensive care unit use for the index hospitalization and decreased hospital length of stay during follow-up. There was a trend toward a slightly increased risk of reintervention with EVAR (adj-OR, 1.3; 95% CI, 0.98-1.75). They concluded that compared with open repair, EVAR significantly reduced short-term but not long-term mortality. The EVAR patients spent less time in health institutions, including long-term care facilities, but underwent more imaging studies. Future improvements in EVAR could result in further decreases in reinterventions and subsequent radiologic monitoring.⁴⁸

The Dutch DREAM trial was similar to EVAR 1 in that it was a prospective randomized study comparing EVAR to OPEN among patients with AAAs 5 cm or greater in diameter who were fit for open repair, but the number recruited was significantly smaller in this trial than in EVAR 1—only 351 patients. This study initially reported its 30-day mortality endpoint but it also performed a composite endpoint analysis of mortality and moderate or severe complications. Much like EVAR 1, there was a roughly 3% advantage to EVAR in perioperative mortality (EVAR 1.2% versus OPEN 4.6%), and interestingly, even though at 1 year the all-cause mortality was not different (EVAR 20.4% versus OPEN 20.3%), AAA-related death was higher for OPEN at 2 years (EVAR 2.1% versus OPEN 5.7%). Health-related quality-of-life measures were improved at 6 months in patients having EVAR; however, they were equivalent thereafter. Also, significantly higher costs were again documented in the EVAR cohort. The authors' conclusion was that the "Initial mortality advantage was lost at one year because of non-aneurysm related deaths."

The Dream trial was also updated in 2010 with a follow up carried out to 6 years titled Long-Term Outcome of Open or Endovascular Repair of Abdominal Aortic Aneurysm published in the New England Journal of medicine. Here they conducted a long-term, multicenter, randomized, controlled trial comparing open repair with endovascular repair in 351 patients with an abdominal aortic aneurysm of at least 5 cm in diameter who were considered suitable candidates for both techniques. They randomly assigned 178 patients to undergo open repair and 173 to undergo endovascular repair. The primary outcomes were rates of death from any cause and reintervention. Six years after randomization, the

cumulative survival rates were 69.9% for open repair and 68.9% for endovascular repair (difference, 1.0 percentage point; 95% confidence interval [CI], -8.8 to 10.8; $P = 0.97$). The cumulative rates of freedom from secondary interventions were 81.9% for open repair and 70.4% for endovascular repair (difference, 11.5 percentage points; 95% CI, 2.0 to 21.0; $P = 0.03$). Further more similar to the original trial Six patients did not undergo aneurysm repair after randomization: four declined treatment (three in the open-repair group and one in the endovascular-repair group), one died from a ruptured abdominal aortic aneurysm before undergoing open repair, and one died from pneumonia before undergoing endovascular repair. There were eight in-hospital deaths after open repair and two after endovascular repair. The median follow-up was 6.4 years (range, 5.1 to 8.2). All patients were followed for 5 years, 79% for 6 years, and 53% for 7 years. The completeness of follow-up was 99.3% (11,589/11,673 months) for open repair and 99.7% (11,193/11,232 months) for endovascular repair. At the date of censoring, 106 patients had died during followup after hospital discharge (51 in the open-repair group and 55 in the endovascular-repair group). Five years after randomization, CT was performed in approximately one fourth of patients in the open-repair group and in almost all patients in the endovascular-repair group. They concluded that Six years after randomization, endovascular and open repair of abdominal aortic aneurysm resulted in similar rates of survival. The rate of secondary interventions was significantly higher for endovascular repair.⁴⁹

Although the DREAM trial was criticized for being underpowered, and drawing this conclusion, most of its findings were in concert with EVAR 1, And subsequently validated in comparison to the EuroStar registry by Leurs et al. Here the Data of 177 patients of the DREAM trial with randomization to EVAR and 856 patients selected in the EUROSTAR-registry were compared. Baseline characteristics were comparable between the EUROSTAR-cohort and EVAR-arm of the DREAM-trial. The 36-month survival-rate was 87.6% for EVAR-arm in the DREAM-trial similar to the 86.8% found in this EUROSTAR-study population. The freedom of secondary procedures reached after 3 years 85.7%, and 86.9% in the DREAM and EUROSTAR-cohort, respectively. They concluded that comparable characteristics and outcomes between patients of comparable risk class of the EUROSTAR-registry and the EVAR-cohort of the DREAM-trial. This demonstrates the following; first, the EUROSTAR-data provide reliable information, and further comparisons of registry data with patients treated by conventional AAA surgery may be justified. Secondly, the various outcomes of the randomised DREAM trial appear generalisable, as it agrees with observations in a broad common practice derived database.⁵⁰ In summary, both EVAR 1 and DREAM showed no difference their primary endpoint of overall mortality but both demonstrated about a 3% advantage for EVAR in perioperative and AAA-related death, at 4 and 2 years, respectively, with similar results over long-term analysis. Complications, reinterventions, and costs were much higher in the studies' EVAR cohorts, with no improvements seen in health-related quality-of-life measures lasting beyond the initial period.

11. EVAR 2 trial

EVAR 2 utilized patients that were excluded from the EVAR1 trial who were considered to be physically ineligible for open repair but who were candidates for endovascular repair were offered enrollment in the EVAR 2 trial^{24,47}. Citing that Endovascular aneurysm repair (EVAR) to exclude abdominal aortic aneurysm (AAA) was introduced for patients of poor health status considered unfit for major surgery. The investigators instigated EVAR trial 2 to

identify whether EVAR improves survival compared with no intervention in patients unfit for open repair of aortic aneurysm. In this randomized controlled trial of 338 patients aged 60 years or older who had aneurysms of at least 5.5 cm in diameter and who had been referred to one of 31 hospitals in the UK. They assigned patients to receive either EVAR (n=166) or no intervention (n=172). Primary endpoint was all-cause mortality, with secondary endpoints of aneurysm-related mortality, health-related quality of life (HRQL), postoperative complications, and hospital costs. Analyses were by intention to treat. The 30-day operative mortality in the EVAR group was 9% (13 of 150, 95% CI 5-15) and the no intervention group had a rupture rate of 9.0 per 100 person years (95% CI 6.0-13.5). By end of follow up 142 patients had died, 42 of aneurysm-related factors; overall mortality after 4 years was 64%. There was no significant difference between the EVAR group and the no intervention group for all-cause mortality (hazard ratio 1.21, 95% CI 0.87-1.69, p=0.25). There was no difference in aneurysm-related mortality. The mean hospital costs per patient over 4 years were UK pound sterling 13,632 in the EVAR group and pound sterling 4983 in the no intervention group (mean difference pound sterling 8649, SE 1248), with no difference in HRQL scores. This data evoked several interpretations and conclusions at variance with those proposed by the trialists, who basically concluded that there was no mortality advantage to EVAR in managing large AAAs in patients unfit for open repair and, since this treatment modality costs much more than observation alone, a policy of no treatment was endorsed. The paradox here is that it is precisely for such high-risk patients that EVAR was first proposed, as a lower risk alternative to open repair, yet the EVAR 2 trial appeared to refute this expectation, concluding it to be no better than no treatment! ¹⁴ Interestingly, the reported 30-day mortality rate of 9% for EVAR and the 4-year mortality of 64% are both much higher than previously reported in high-risk patient cohorts, and, while these observations provided a basis for much criticism, the published results of EVAR 2 have clearly complicated patient and provider decision-making, in addition to potentially influencing policymaking and reimbursement practices.

As an Update to the 2005 Lancet publication EVAR 2 was further examined in the 2010 publication titled Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. Presented in the New England Journal of Medicine. From 1999 through 2004 at 33 hospitals in the United Kingdom, 404 patients with large abdominal aortic aneurysms (> or = 5.5 cm in diameter) who were considered to be physically ineligible for open repair were randomly assigned to undergo either endovascular repair or no repair; 197 patients were assigned to undergo endovascular repair, and 207 were assigned to have no intervention. Patients were followed for rates of death, graft-related complications and reinterventions, and costs until the end of 2009. The 30-day operative mortality was 7.3% in the endovascular-repair group. The overall rate of aneurysm rupture in the no-intervention group was 12.4 (95% confidence interval [CI], 9.6 to 16.2) per 100 person-years. Aneurysm-related mortality was lower in the endovascular-repair group (adjusted hazard ratio, 0.53; 95% CI, 0.32 to 0.89; P=0.02). This advantage did not result in any benefit in terms of total mortality (adjusted hazard ratio, 0.99; 95% CI, 0.78 to 1.27; P=0.97). A total of 48% of patients who survived endovascular repair had graft-related complications, and 27% required reintervention within the first 6 years. During 8 years of follow-up, endovascular repair was considerably more expensive than no repair (cost difference, 9,826 pounds sterling [U.S. \$14,867]; 95% CI, 7,638 to 12,013 [11,556 to 18,176]). The Trialists presented a similar conclusion to their first publication stating that in this randomized trial involving patients who were physically ineligible for open repair, endovascular repair of abdominal aortic

aneurysm was associated with a significantly lower rate of aneurysm-related mortality than no repair. However, endovascular repair was not associated with a reduction in the rate of death from any cause. The rates of graft-related complications and reinterventions were higher with endovascular repair, and it was more costly. Suggesting that observation alone should be considered in patients unfit for open repair which redecorates many of the same arguments previously invoked by the fist publication.

In response to the initial EVAR 2 study data an American group from the University of Texas Southwestern Medical Center performed a Population-based, cross-sectional study analysis to look at The nationwide in-hospital mortality for patients with the highest risk undergoing EVAR in the United States they closely matched the time period of EVAR 2 reviewing the 2001-2004 Nationwide Inpatient Sample identifying EVAR procedures for nonruptured abdominal aortic aneurysms. Risk stratification was based on comorbidities and the Charlson comorbidity index, a validated predictor of in-hospital mortality after abdominal aortic aneurysms repairs. Weighted univariate and logistic regression analyses were used to determine the association between comorbidity measures and risk-adjusted in-hospital mortality. They found that During the 4-year period, 65502 EVARs were performed with an in-hospital mortality of 2.2%. Risk-adjusted in-hospital mortality rates ranged from 1.2% to 3.7%. Stratified analyses, including only elective EVAR procedures, revealed that in-hospital mortality was significantly higher in patients with the most severe comorbidities (1.7%) vs those with lower comorbidity (0.4%; $P < .001$). Patients with high risk had only a 1.6-fold increased risk of adjusted in-hospital mortality (odds ratio, 1.6; 95% confidence interval, 1.2-2.2) compared with patients with low risk. They concluded that the EVAR procedure is currently being performed in the United States with low in-hospital mortality, even in patients with the highest risk. Therefore, EVAR should not be denied to high-risk patients with abdominal aortic aneurysms in the United States on the basis of the level I evidence from the United Kingdom study.²⁹

12. United States experiences with EVAR in high-risk cohorts

Randomized clinical trials had been lacking in the United States, which prompted the V.A. trilists to launch an investigation comparing endovascular to open abdominal aneurysm repair, which was recently published in JAMA. A randomized, multicenter clinical trial of 881 veterans, over the age of 49 years, from 42 Veterans Affairs Medical Centers with AAA that were at least 5 cm in size, or associated with an iliac aneurysm of 3 at least 3 cm in size, or had rapid expansion over a 6-to-12 month period who were candidates for both elective endovascular repair and open repair of AAA. This ongoing report detailed the time period between October 15, 2002, and October 15, 2008 Elective endovascular (n=444) or open (n=437) repair of AAA. Multiple variables and data points were extensively collected which included the main outcome measures, procedure failure, secondary therapeutic procedures, length of stay, quality of life, erectile dysfunction, major morbidity, and mortality. The mean follow-up was 1.8 years after which the American investigators concluded that short-term outcomes after elective AAA repair, perioperative mortality was low for both procedures and lower for endovascular than open repair. The early advantage of endovascular repair was not offset by increased morbidity or mortality in the first 2 years after repair. Longer-term outcome data are needed to fully assess the relative merits of the 2 procedures. The overall study has id still underway with the primary outcome of long-term (5-9 years) all-cause mortality (October 15, 2002-October 15, 2011) and has not yet been

completed. (Outcomes Following Endovascular vs Open Repair of Abdominal Aortic Aneurysm)⁵¹

13. Remaining controversies

Several issues remain unresolved and to a certain extent have been touched on already in this chapter. A clear and comparable system that is widely accepted and used for AAA reporting would greatly forward the global knowledge base and increase understanding and transparency. The issues with randomized control trial and the intention to treat arm have been discussed above. While this practice may improve statistics it does not improve the real numbers that clinicians need when trying to evaluate a patient and determine a care-plan strategy. Another issue is the all cause mortality arm of many studies. This, like the intention to treat, may provide more numbers for statistical analysis and to a certain extent some comparability and useful information however it has been confused in certain situations with aneurysm related death, which would be a much more useful piece of information to know about in the clinical setting.

Aneurysm-related death can only be accurately determined by directly witnessed objective information, e.g., postmortem examination or rupture seen on an imaging study prior to death¹⁴. This however is difficult to obtain with decreasing numbers of autopsies being performed, deaths outside of the hospital and incomplete communication amongst healthcare systems. One possible solution would be a requirement in study designs for all participants to undergo a postmortem fine cut cat-scan however this has not yet been done. This would have the added benefit of having the patient locked into the system so to speak and could perhaps increase the autopsy rates. Another problem with AAA-related death outside of the above mentioned situation is that, taken alone, is a soft endpoint and one, which tends to preserve any initial/perioperative mortality advantage of one method of repair over another, with respect to aneurysm treatment¹². The data set would have likely been very different in the interpretation of the United Kingdom small aneurysm and Aneurysm Detection and Management trials if AAA-related death had been used as the primary end-point, rather than all-cause mortality. This was the goal of the Positive Impact of endoVascular Options for Treating Aneurysm early trial, or PIVOTAL trial which used as its primary endpoints aneurysm rupture and AAA-related deaths at up to 36 months after randomization⁵². This trial was recently completed after enrolling 728 patients (13.3% women; mean age, 71 +/- 8 years) with 4 to 5 cm AAAs to early endovascular repair (366 patients) or ultrasound surveillance (362 patients). Rupture or aneurysm-related death and overall mortality in the two groups were compared during a mean follow-up of 20 +/- 12 months. The investigators concluded Early treatment with endovascular repair and rigorous surveillance with selective aneurysm treatment as indicated both appear to be safe alternatives for patients with small AAAs, protecting the patient from rupture or aneurysm-related death for at least 3 years¹⁶. Which provided useful information with regards to the size at which aneurysms should be treated with EVAR vs. surveillance. However there was still a significant cross-over rate from surveillance to the interventional arm. Among patients randomized to surveillance, 31% underwent aneurysm repair during the course of the study¹⁶. Cross over-over rates provide useful information as long as the setting is not in the intention to treat model as outlined above⁴⁵. The crossover rates in the PIVOTAL trial were about 1/2 that of the original UKSAT trial⁵³. In the recently published mid-term results of the European-based 17-site Comparison of surveillance vs Aortic Endografting for Small

Aneurysm Repair (CAESAR) of small AAAs (4.1-5.4 cm) for surveillance or EVAR with the Zenith stent-graft with the primary endpoint of all-cause mortality at 54 months. However they included information on Aneurysm-related mortality, aneurysm rupture and major morbidity rates which were similar perhaps indicating a trend towards interpretable information¹⁷ In line with the information provided by the PIVOTAL trial they authors conclude that Mortality and rupture rates in AAA <5.5 cm are low and no clear advantage was shown between early or delayed EVAR strategy. However, within 36 months, three out of every five small aneurysms under surveillance might grow to require repair and one out of every six might lose feasibility for EVAR. Surveillance is safe for small AAA if close supervision is applied.¹⁷ However a clear recommendation can not yet be made on the size for which small aneurysms should be treated, and we are left with the interpretation that aneurysms as seen above and in many other studies have the natural history to continue to increase in size and that many patients in the observation arm of trials, 27% to over 60% (EVAR II, UKSAT, ADAM, PIVOTAL), crossovers to the treatment arm⁴⁵.

Further controversy revolves around large AAA greater than 5.5 cm and the question of treatment in the healthy patient vs the infirmed or unfit for open surgery patients as discussed above. Though the question is somewhat being answered by the trends in AAA management in clinical practice. Studies using large administrative databases in the United States have documented a trend whereby the majority of patients undergoing elective abdominal aortic aneurysm (AAA) repair in the United States are being repaired using endovascular techniques⁵⁴ In a recently published single center study from the United States investigators retrospectively analyzed non-suprarenal AAA repairs between January 1, 1996, and December 31, 2008. Patients were stratified by endovascular AAA repair (EVAR) or open repair and the presence or absence of rupture. During a 13-year period, 721 patients underwent AAA repair, comprising 410 (56.9%) with EVAR and 311 (43.1%) with open repair. This study included a time period prior to the availability of EVAR 1996 through the period when EVAR became widely available 2008, and showed that between 2005 and 2008, average EVAR use increased to 84%.⁵⁵ This is exemplary of the increased use of EVAR over open AAA. Another group analyzed Medicare Part B data sets for 2001 through 2006 with respect to open vs endovascular AAA repair. A total of 31,965 OSRs for AAA were performed in Medicare beneficiaries in 2001, dropping to 15,665 by 2006 (-51%). In contrast, EVAR was carried out in 11,028 instances in 2001, increasing to 28,937 by 2006 (+162%). The utilization rate per 100,000 for OSR dropped from 90 to 42 (a rate decrease of 48) during the study period, while the rate for EVAR increased from 31 to 77 (a rate increase of 46)⁵⁶. The investigators drew the obvious conclusion that the newer, less invasive, and less risky procedure (EVAR) is replacing the older and more invasive procedure (OSR) to a considerable degree⁵⁶. In another study looking at large national administrative in-hospital database to compare utilization and age-specific outcomes between open repair (OAR) and endovascular (EVAR) repair for the treatment of abdominal aortic aneurysm (AAA). The estimated number of elective AAAs treated with EVAR increased from 11,171 in 2001 to 21,725 in 2006 (P = .003). The number of elective AAAs treated with OAR declined from 17,784 to 8451 during the same period (P < .001). By 2006, EVAR was more frequently used than OAR for patients of all ages. Compared with the younger age groups, patients aged >or=85 years had a significant increase in the total number of asymptomatic AAA repairs, driven almost entirely by an increase in the use of EVAR³³. These authors noted that as short-term surgical outcomes are consistently improving for patients undergoing AAA repair, elective EVAR has replaced OAR as the more common method of repair in the

United States. The introduction of this technology has been rapidly adopted, particularly for the oldest-old surgical patients, aged ≥ 85 years, who previously may not have been offered surgical intervention for asymptomatic AAA.³³ This being said there are still significant unknowns with respect to long term outcomes of EVAR despite the trend outlined above. The rapid improvements in EVAR design and deliverability have led to changes in the anatomical criteria, and expanded usage. The EVAR device of today is very different than that of 10 years ago, however the outcomes data for "long-term follow up" is based on these older devices. The durability of these devices is a question that is difficult to answer, as this has been a constantly moving target as improvements to devices are made. Despite the increasing trend to treat all comers with EVAR, or at least the majority, the longitudinal data is not available or appropriate to make a solid recommendation. The durability of open grafts is proven with by the test of time there relatively low-tech nature and static design, this can however not be said about the endograft and the question of placing an endograft in a relatively young or fit patient with the concern that they may outlive the life of the endograft has not yet been answered.

Physician bias and training as well add to the difficulty in patient decision-making. As EVAR has gained in popularity open surgical repair has decreased and younger surgeons have less experience with open repair. The experience gained in many training programs has been that of difficult AAA repair in patients with unsuitable anatomy, which are relatively uncommon. To add to this dilemma as EVAR devices improve the pool of anatomically unfit patients decrease. Another issue is that AAA is no longer solely treated by surgeons and the decision to treat or observe a patient might be made on the clinicians inability to provide both the endovascular and open services.

14. Recommendations for the up-to-date patient decision-making with respect to the repair of abdominal aortic aneurysms

Based on the available literature and the global experience with larger studies and data-base analysis the general principles governing patient selection can be suggested as follows:

(1) in medically fit patients with AAAs large enough to justify consideration of intervention, current-day EVAR is preferable for those with suitable anatomy and with comorbidities likely to limit their longevity commensurate with the estimated durability of the device used. The argument for EVAR in all patients with suitable anatomy has been extended by some prominent figures in the vascular surgery community at recent meetings. The suggestion here is that even the first generation devices have been shown to be durable over time and that with current improvements in device and delivery system that the longevity of these devices has been clearly demonstrated. On the other hand, good risk patients with a projected longevity clearly beyond the known limits of device durability should receive OPEN, has been a standard approach. While this is an acceptable statement, there is no question that EVAR is less invasive, has a faster recovery time and a shorter hospitalization period. The aspect that has generally been looked over is that in a young, fit patient that is a productive member of society, despite their likely ability to heal and continue working with either approach is more likely to be able to do so in a more expeditious way following an endovascular strategy.⁵⁷

(2) High-risk patients with large AAAs, who are unfit for OPEN, first deserve intensive treatment of their comorbidities, followed by EVAR, if they improve, and continued observation if they do not. Here a difficult decision has to be made which brings up

questions of ethical and moral responsibility. While the exact nuances of are left to the practitioner to decide the cautionary note here is not do something like EVAR, or any procedure for that matter, just because it can be done. While this was the patient population in which EVAR was initially studied and designed in we have proven feasibility and this question has been answered. One must look closely at the quality of life and life expectancy as well as comorbidities to make this decision.

(3) Patients with small AAAs deserve continued surveillance, with the threshold diameter being 5.0 cm diameter for males (based on the UKSAT trial follow-up data cited) and even lower, (4.5 cm diameter) for female patients, based on their relatively smaller anatomical dimensions, their attendant higher risk of rupture and higher rupture mortality, and a lower anatomical suitability for EVAR. This being said there appears to be some role in repair of smaller aneurysms in certain patient and closer or more frequent follow up in others. The opportunity for such early decision-making should be afforded by the recently approved national AAA screening program under Medicare, with screening having been shown to not only be cost effective for older men⁵⁸ but also for women as well⁵⁷

15. Conclusions

Trusting as we do in the inevitable progress of newer technology, we believe that, in the future, the great majority of AAAs will be repaired via EVAR. This trend has been demonstrated and to a certain degree the pendulum has been set in motion. EVAR in many institutions world wide is the preferred mode of treatment and the first choice procedure. The de- vices will continue to improve, as will deployment techniques, and hopefully, patient selection will be driven more by evidence than a biased view of the options. EVAR is recommended for most patients with large AAAs and "suitable anatomy," specifically those who are deemed to be poor risk for open repair and/or have a limited life expectancy. Based on the data we have presented and contrary to the conclusions of EVAR 2, we also recommend EVAR for high-risk patients who respond to an intensive treatment of their comorbidities. Ultimately, patient and physician choice must take precedence when deciding between EVAR and no treatment in those with unsuitable anatomy for EVAR who are also unfit for open repair. The treatment of AAA like the treatment of many modern diseases needs to be individualized to the patient taking into account the many complex social and physiological considerations to formulate an appropriate management strategy

16. References

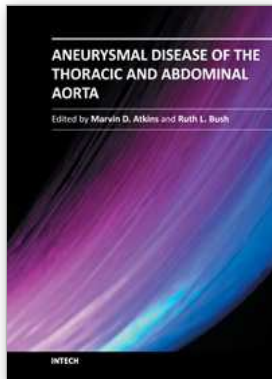
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Aneurysmal Disease of the Thoracic and Abdominal Aorta

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The first successful open surgical repair of an abdominal aortic aneurysm was in 1951 by Dubost and represented a tremendous milestone in the care of this challenging disease. The introduction of endovascular repair in 1991 by Parodi furthered the care of these patients by allowing for lower morbidity and mortality rates and also, enabling surgeons to extend surgical treatment to patients traditionally deemed too high of a surgical risk. This new book on Aortic Disease covers many interesting and vital topics necessary for both the practicing surgeon as well as a student of vascular disease. The book starts with background information on the evolution of aortic management from traditional open surgical repair to modern endovascular therapies. There is also a chapter covering the data supporting current treatment modalities and how these data have supported modern management. Also, the use of endovascular means for care of the challenging situation of ruptured aneurysms is discussed. In addition to management of abdominal aneurysm, there is a chapter on treatment of aneurysms of the ascending aorta. Along with surgical treatment, one must also understand the molecular basis for how blood vessels remodel and thus, the role of cathepsins in aortic disease is elucidated. Lastly, chapters discussing the perioperative management of radiation exposure and ultrasound-guided nerve blocks as well as the need for high-quality postoperative nutrition will lend well to a full understanding of how to management patients from presentation to hospital discharge. We hope you enjoy this book, its variety of topics, and gain a fuller knowledge of Aneurysmal Disease of the Thoracic and Abdominal Aorta.

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