Prognostics in Aortic and Peripheral Artery Disease

Klaas Hendrik Jan Ultee

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Prognostics in Aortic and Peripheral Artery Disease

Prognostische factoren voor ziekten van de aorta en perifere arteriën

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Klaas Hendrik Jan Ultee

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Introduction

INTRODUCTION

Cardiovascular disease

As one of the leading causes of death in the Western world, cardiovascular disease belongs to the biggest health problems in today's society.[1] Moreover, because of our dietary habits, sedentary lifestyle, and the aging of the population, the health hazards of cardiovascular disease only continue to increase. By 2030, the annual national health expenditures towards cardiovascular disease are predicted to have doubled.[2, 3] Cardiovascular disease can be classified into diseases affecting the heart and those affecting the vascular system. Vascular disease may involve the arteries, veins, or lymphatic vessels. Arterial disease constitutes the far majority of life-threatening vascular disease, as the arterial circulation provides the vital organs with oxygen and nutrients, for which deprivation can be fatal within minutes.[4]

Aortic disease

The aorta is the largest artery in the human body, transporting an average of 200 million liters of oxygenated blood from the left ventricle of the heart to the body during a lifetime. Separating from the heart by the aortic valve, the aorta arches over the left main bronchus, after which it extents downwards into the abdominal cavity, where it eventually bifurcates into the two iliac arteries. Histologically, the aortic wall comprises of three layers: the *tunica intima*, which is lined by the endothelium; a thick *tunica media* characterized by concentric sheets of elastin and collagen; and the outer *tunica adventitia* containing mainly collagen, vasa vasorum, and lymphatics.

The aorta may be affected by various pathologies. First, the connective tissue in the *tunica media* may degenerate with age. This weakening causes the aorta to lose its ability to withstand the arterial pressure, resulting in the aorta to gradually dilate. When the diameter of the aorta exceeds the estimated original diameter by more than 50%, it is considered a pathological enlargement, and called an aneurysm. The prevalence of aortic aneurysmal disease is approximately 2% to 4% in the elderly population, and important risk factors include male gender, advanced age, and smoking.[5-12] Aneurysms are usually asymptomatic, and can therefore remain undetected for many years. However, as aneurysms grow, the wall strength decreases, which increases the risk of an aortic rupture to occur. This is a catastrophic complication with mortality exceeding 80%.[13, 14] Once detected, aneurysms are therefore prophylactically treated when the risk of rupture exceeds the operative risk.[15]

Second, a pathologic build-up of white blood cells filled with cholesterol and other lipids called foam cells may accumulate within the aortic wall. This process, known as atherosclerosis, is a slow yet progressive disease that may begin as early as childhood. Due to its systemic nature, not only the aorta, but any artery in the human body may become affected. Over time, the deposits of fats and cellular products harden and narrow the vessel. This limits the flow of oxygen-rich blood to organs distal to the lesion, and eventually causes organ dysfunction. Risk factors for atherosclerosis are well known, and include male gender, high blood pressure, diet high in saturated fat, smoking, insulin resistance, and chronic inflammation.

Less common are aortic dissections, which occur when the layers of the aortic wall become separated resulting from severe long lasting hypertension and/or loss of vessel integrity due to high age or connective tissue disorders.[16, 17] As blood flow separates the layers of the aorta, perfusion to vital organs may become obstructed, and weakening of the aortic wall may result in aortic rupture.[16, 17] In addition to endogenous wall stress, the aorta may also be injured by external high-energetic trauma, most importantly a sudden deceleration.[18] These blunt traumatic aortic injuries are the second leading cause of death after automobile and motorcycle crashes, and have relatively young population.[19-21] The severity of these injuries may vary from a small intimal tear, to pseudoaneurysms, and even full aortic ruptures.

Non-aortic disease

The various pathologies affecting the aorta may occur in all other arteries in the human body as well. However, these vessels –such as the arterial supply to the brain, heart, and limbs– are mostly affected by atherosclerotic disease.[22] When the vessels supplying oxygenated blood to the heart become obstructed, it is known as coronary artery disease. Occlusive vascular disease in all other arterial systems is referred to as peripheral artery disease (PAD), and most commonly involves the arteries in the legs. With 10 to 20% of the population over 65 years affected, atherosclerotic disease in the arteries of the lower extremities is very common.[23, 24] Classic symptoms include leg pain induced by walking, which resolves after rest (intermittent claudication). In more advanced stages, perfusion beyond the obstruction has severely diminished, causing patients to suffer rest pain and even tissue necrosis (critical limb ischemia). Atherosclerotic disease in the arteries to the brain is called cerebrovascular disease. Because the brain receives blood from four separate arteries, narrowing of these vessels is often asymptomatic. However, when an atherosclerotic plaque ruptures, atherothrombic debris causes an obstruction of bloodflow downstream. The consequent oxygen deprivation may

be temporary, resulting in a transient ischemic attack, or cause permanent damage, which is referred to as an ischemic stroke.

The long-term prognosis after vascular surgery for peripheral occlusive disease is generally poor, with 10-year survival rates as low as 25% after 10 years.[25] Cardiovascular causes account for the majority of early and late mortality following vascular surgery, surpassing 60%.[26] This thesis aims to provide new insights in the long-term postoperative prognosis of vascular surgery patients, focusing on the role of conventional, as well as unconventional risk factors for the prediction of long-term outcomes.

Aortic Surgery

Traditionally, aortic disease was surgically treated through open repair, which required a large incision through which the aorta was exposed and the affected segmented was replaced by an interposition graft. As an alternative to open repair, endovascular repair for the treatment of the diseased aorta was first introduced in the early nineties.[27, 28] With endovascular repair, exclusion of the diseased aorta can be achieved with a small incision in the femoral artery in the groin, through which a self-expanding stent graft can be brought up and deployed over the lesion. Owing to the less invasive nature of the procedure, endovascular repair has been associated with lower perioperative mortality, as well as lower rates of complications, need for transfusions, and length of stay compared to open repair for abdominal and thoracic aortic pathologies.[29-36] Because of these benefits, the utilization of endovascular treatment for elective aortic repair has rapidly increased since its introduction.[14, 29, 37-41]

Over the years, numerous studies have clarified many crucial aspects of open and endovascular repair, and the relative performance of these two techniques. However, knowledge gaps in the current literature remain. For acute aortic surgery, for example, the paradigm shift from open towards endovascular repair has not fully caught on yet, most importantly because of a scarcity of evidence supporting a benefit of endovascular treatment over open repair. For elective repair, little is known about the safety of performing concomitant procedures during abdominal aortic aneurysm repair, and whether endovascular repair is also preferable for anatomically complex aneurysms.[42-44] Additionally, is has become apparent that endovascular treatment is associated with more early and late graft-related complications compared to open repair, and that endovascular patients more commonly undergo reinterventions.[45-47] How these complications affect long-term outcome, and whether these reinterventions can be performed safely, remains largely unclear.

By satisfying some of these knowledge gaps in the current literature, this thesis is dedicated to contribute to a better understanding of the prognosis of aortic and peripheral artery disease, and thereby improve patient care.

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THESIS OVERVIEW

Part I is dedicated to determine the current role of endovascular repair for the treatment of acute aortic pathologies, and assess the potential benefit of endovascular repair in the emergent setting. In **Chapter 1**, the rate of adoption and relative effectiveness of endovascular repair for traumatic thoracic aortic injury are assessed in a United States (US) national registry. **Chapter 2** is a US national review of treatment of ruptured thoracic aortic aneurysms, focusing on the age-related utilization and outcome of endovascular repair, open repair, and non-operative treatment. **Chapter 3** is a systematic review attempting to clarify the role of endovascular repair for the treatment of abdominal aortic aneurysms. In **Chapter 4,** an institutional series of ruptured abdominal aortic aneurysm (AAA) repairs is described, attempting to establish risk factors for early mortality following ruptured AAA repair, as well as the impact of treatment approach on outcome. **Chapter 5** focuses on the treatment of symptomatic AAAs, and assesses the applicability endovascular repair in this setting.

In *Part II,* the aim is to clarify, and assess risks associated with operative and postoperative aspects of AAA repair. In **Chapter 6 and Chapter 7**, the authors aim to identify the perioperative risks associated with performing concomitant procedures during endovascular and open AAA repair, respectively. **Chapter 8** is dedicated to assess the perioperative outcome following endovascular repair for anatomically complex abdominal aneurysms, focusing on differences with complex open repair, the alternative treatment option, and standard infrarenal endovascular repair. The purpose of **Chapter 9** is to identify anatomical differences between patients currently selected for transperitoneal versus retroperitoneal AAA repair, and to establish differences in intra-operative characteristics, as well as perioperative outcome. In **Chapter 10**, the authors describe how the introduction of endovascular repair has changed the specialty of surgeons performing AAA repair. **Chapter 11** aims to determine whether differences exist in long-term survival and causes of death between patients undergoing endovascular and open repair for AAA. Additionally, the authors sought out to establish the influence of presentation on the long-term postoperative prognosis.

In *Part III*, various complications encountered after AAA repair were scrutinized to determine their incidence, significance, and risk factors for their occurrence. The purpose of **Chapter 12** is to assess the incidence of postoperative bowel ischemia following AAA repair in the endovascular era, and identify overall and procedure-specific risk factors for its occurrence. **Chapter 13** demonstrates the impact of renal complications following endovascular repair, and provides an analysis of patient-, stent graft-, and procedure-related risk factor for impair-

ment of the postoperative renal function. In **Chapter 14** the incidence and outcome of conversion surgery from endovascular to open repair are described, as well as factors associated with its occurrence.

In *Part IV*, the authors aim to shed unconventional light on long-term prognosis after (vascular) surgery. **Chapter 15** is dedicated to determine the role of socioeconomic status as a predictor for survival following surgical treatment for peripheral artery disease, abdominal aortic aneurysm and carotid artery stenosis, irrespective of healthcare disparities. **Chapter 16** is an attempt to extrapolate the hypothesis on the importance of socioeconomic deprivation for the postoperative prognosis beyond vascular surgery. **Chapter 17** clarifies on the impact of ischemic heart disease and coronary revascularization in vascular surgery patients, focusing on the influence on overall and cause-specific mortality. **Chapter 18** is a comparison between the prognosis of patients with aneurysmal and occlusive disease in order to determine whether these two entities of vascular disease are prognostically different.

Part I

ENDOVASCULAR REPAIR FOR ACUTE AORTIC PATHOLOGIES

Chapter 1

National Trends in Utilization and Outcome of Thoracic Endovascular Aortic Repair for Traumatic Thoracic Aortic Injuries

Klaas H.J. Ultee[1,2]
Peter A. Soden[1]
Victor Chien[1]
Rodney P. Bensley[1]
Sara L. Zettervall[1]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Objective

Endovascular repair of traumatic thoracic aortic injuries (TTAI) is an alternative to conventional open surgical repair. Single institution studies have shown a survival benefit with TEVAR, but it is not clear if this is being realized nationally. The purpose of our study was to document trends in the increase in utilization of TEVAR and its impact on outcomes of TTAI nationally.

Methods

Patients admitted with a traumatic thoracic aortic injury between 2005 and 2011 were identified in the National Inpatient Sample (NIS). Patients were grouped by treatment into TEVAR, open repair, or nonoperative management groups. Primary outcomes were relative utilization over time and in-hospital mortality. Secondary outcomes included postoperative complications and length of stay. Multivariable logistic regression was performed to identify independent predictors of mortality.

Results

A total of 8384 patients were included, with 2492 (29.7%) undergoing TEVAR, 848 (10.1%) open repair, and 5044 (60.2%) managed nonoperatively. TEVAR has become the dominant treatment option for TTAI over the study period, starting at 6.5% of interventions in 2005 and accounting for 86.5% of interventions in 2011 (P<.001). Nonoperative management declined concurrently with the widespread of adoption TEVAR (79.8% to 53.7%, P<.001). In-hospital mortality following TEVAR decreased over the study period (33.3% in 2005 to 4.9% in 2011, P<.001), while an increase in mortality was observed for open repair (13.9% to 19.2%, P<.001). Procedural mortality (either TEVAR or open repair) decreased from 14.9% to 6.7% (P<.001), and mortality following any TTAI admission declined from 24.5% to 13.3% over the study period (P<.001). In addition to lower mortality, TEVAR was followed by fewer cardiac complications (4.1% vs. 8.5%), P<.001), respiratory complications (47.5% vs. 54.8%, P<.001), and shorter length of stay (18.4 vs. 20.2 days, P=.012) compared to open repair. In adjusted mortality analyses, open repair proved to be associated with twice the mortality risk compared to TEVAR (OR: 2.1, 95% CI: 1.6 – 2.7), while nonoperative management was associated with more than a four-fold increase in mortality (OR: 4.5, 95% CI: 3.8 – 5.3).

Conclusions

TEVAR is now the dominant surgical approach in TTAI with substantial perioperative morbidity and mortality benefits over open aortic repair. Overall mortality

following admission for TTAI has declined, which is most likely the result of both the replacement of open repair by TEVAR, as well as the broadened eligibility for operative repair.

INTRODUCTION

Traumatic thoracic aortic injuries (TTAI) remain associated with high morbidity and mortality.[1] Though highly lethal, TTAI has a relatively low incidence within the general population and as such, prior studies were largely limited to single-institution retrospective series. Various studies have suggested an in-hospital mortality of 15% to 30%, beginning with Parmley's 1958 study.[2, 3] Early studies assessing perioperative outcome following open repair showed poor results, with both high surgical mortality and morbidity, of which a high paraplegia rate was most notable.[4]

In 1997, Kato et al. were the first to report on endovascular stent grafting for TTAI.[5] Studies conducted in the following years, which were mostly institutional-based, suggested a substantial reduction in morbidity and mortality associated with TEVAR, compared to open repair and nonoperative treatment.[6-11] The Society for Vascular Surgery determined that endovascular repair of TTAI remained a key area requiring clinical guidelines to aid surgeons, referring physicians, and patients in the process of decision-making. In an effort to provide guidance for clinical practice, a selected panel of experts was tasked with conducting a systematic review and meta-analysis of the existing literature.[12] Although various recommendations were provided, the panel concluded that the available evidence was of very low quality and that further evaluation of operative management of TTAI was warranted.

Hong et al. were the first to utilize a national database to characterize trends in treatment of TTAI and could not confirm the perioperative mortality benefit associated with TEVAR on a national level.[13] Their 2001-2007 Nationwide Inpatient Sample (NIS) data are biased, yielding only 14 TEVAR ICD-9 codes prior to 2006 which underreport its use, as ICD-9 coding did not differentiate a TEVAR from an open repair until October 2005.

Since it remains unclear whether these favorable outcomes demonstrated in institutional series are being realized nationally and the use of endovascular treatment modalities continues to increase, the purpose of our study was to provide a contemporaneous update to the study by Hong et al. using specific TEVAR coding and further assess the relative effectiveness and trends in the use of endovascular repair for traumatic thoracic aortic injury, as well as overall outcome following TTAI admission.

METHODS

Database

For this study, we utilized the NIS. The NIS is the largest US all-payer inpatient database, with over 8 million documented annual hospitalizations. The NIS is maintained by the Agency for Health Care Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project.[14] The NIS represents 20% of all annual U.S. hospitalizations. Through the use of hospital sampling weights, actual annual U.S. hospitalization volumes are approximated. These weighted estimates are utilized throughout this analysis, as recommended by the AHRQ. The database contains de-identified data only without any protected health information. Therefore, Institutional Review Board approval and patient consent were waived.

Patients

Patients were identified using International Classification of Diseases, Ninth Revision (ICD-9). All patients with a diagnosis code for traumatic aortic injury (901.0) between 2005 and 2011 were included. Identified TTAI patients were subsequently grouped by treatment received (TEVAR, open repair, or nonoperative management). Corresponding ICD-9 procedural codes and descriptions were: endovascular graft implantation to the thoracic aorta (39.73), open thoracic vessel replacement (38.45), or nonoperative management when neither of the procedure codes was mentioned.

Documented patient characteristics included demographics (age, sex, race), comorbid conditions (coronary artery disease, diabetes, hypertension, heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and cerebrovascular disease) and concomitant injuries (brain, hemothorax, cardiac, pulmonary, liver, spleen, kidney, pelvic organs, gastro-intestinal, skull fracture, vertebral fracture, and major orthopedic fracture). Brain injury was defined as loss of consciousness lasting longer than 24 hours, brain laceration or contusion, or intracerebral hemorrhage. Cardiac and pulmonary injury included both contusion and laceration. A major orthopedic fracture was defined as a fracture of the spine, pelvis, or femur. Interventions to treat concurrent injuries were grouped into intracranial, thoracic, and abdominal procedures. These interventions did not include diagnostic procedures, and were only considered for patients with a reported traumatic injury in the corresponding organ. Hospital characteristics included hospital setting (rural, urban non-teaching, urban teaching) and hospital bedsize (small medium large). A hospital's bedsize category is nested within location and teaching status. Small hospital bedsize is defined as 1-49, 50-99 and 1-299 beds, respectively for rural, urban non-teaching and urban

teaching hospitals, medium bedsize as 50-99, 100-199, 300-499, respectively, and 100+, 200+, and 500+ beds is considered a large bedsize hospital, respectively. Adverse in-hospital outcomes included death, cardiac or respiratory complications, paraplegia, stroke, acute renal failure, wound dehiscence, infection, discharge to home, and length of stay. Cardiac complications include postoperative myocardial infarction, cardiac arrest, cardiogenic shock, and ventricular fibrillation (Supplemental Table 1). A respiratory complication was defined as a postoperative pneumonia, pulmonary insufficiency after trauma or surgery, transfusion-related acute lung injury, or acute respiratory failure. For paraplegia as a postoperative adverse outcome, patients admitted with vertebral fractures with spinal cord injury were not included. National cause-specific age-adjusted death rates due to traumatic aortic injuries (ICD-10 code: S25.0) were also obtained from Wide-ranging Online Data for Epidemiologic Research (WONDER), an epidemiological internet based database maintained by Centers for Disease Control and Prevention (CDC).[15] More information on WONDER can be found on http://wonder.cdc.gov/.

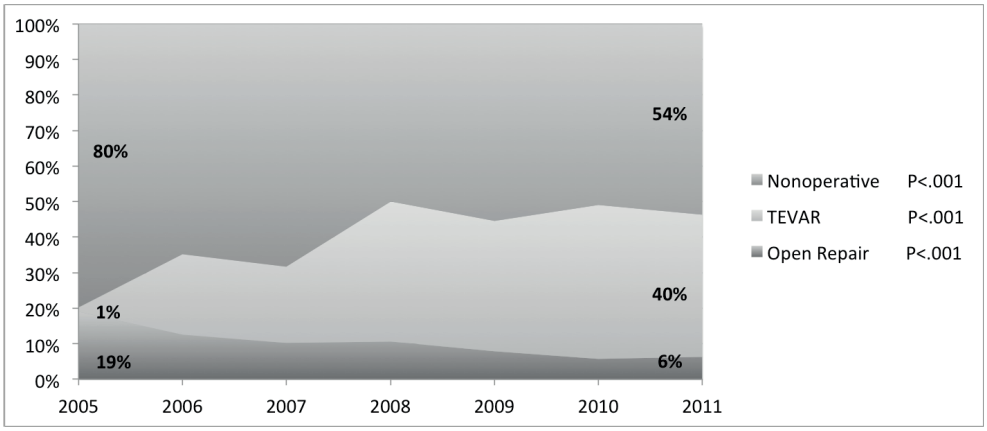
Statistical analysis

Categorical variables are presented as counts and percentages and continuous variables as mean ± standard deviation. Trends over time were assessed using the Cochran-Armitage test for trend. Differences were determined using χ^2 and Fisher's exact testing for categorical variables, and Student's t-test and Kruskal-Wallis test for continuous variables, where appropriate. These analyses included an overall test of the three treatment groups, as well as a separate analysis comparing TEVAR and open repair patients only. In order to identify risk factors for mortality, all variables were first univariately tested using logistic regression analysis. Predictors with a p-value ≤ .1 were subsequently entered into a multivariable model to identify independent risk factors for mortality. Due to the limited number of diagnoses that can be provided per patient in this dataset, less life-threatening comorbid conditions and concomitant injuries are underreported in more complex cases. Since these conditions act as confounders for less severe cases, we chose not to include comorbidities and injuries with protective risk estimates. All tests were two-sided and significance was considered when p-value <0.05. Statistical analysis was performed using the SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 8384 patients were included, with 2492 (30%) undergoing TEVAR, 848 (10%) open repair, and 5044 (60%) undergoing no operative treatment for TTAI. Over the study period, the utilization of TEVAR increased from 6.5% of the operative volume in 2005 to 87% in 2011 (P<.001, Figure 1). Concurrently, the proportion of interventions performed with open repair decreased from 94% to 14% (P<.001), while the number of patients managed nonoperatively declined from 80% to 54% (P<.001).

Figure 1. Annual proportions of the various treatment strategies for the treatment of TTAI



Baseline and hospital characteristics

Baseline characteristics are detailed in Table 1. TEVAR patients were generally older than those undergoing open repair (42.2 vs. 38.4 years, respectively, P<.001). Additionally, the TEVAR group included more non-white patients (33% vs. 28%, P=.030). TEVAR patients more commonly had coronary artery disease (3.0% vs. 1.3%, P=.007), diabetes (4.9% vs. 0.6% P<.001), hypertension (20% vs. 16%, P=.004), and cerebrovascular disease (P=5.3% vs. 2.9%, P=.005) compared to those undergoing open repair. Regarding hospital characteristics, TEVAR was more likely to be performed in urban teaching hospitals (91% vs. 85%, P<.001), while open repair was more likely performed in large bedsize centers (79% vs. 91%, P<.001). As TEVAR became more widely utilized, the proportion of patients undergoing TEVAR in small or medium bedsize hospitals increased (0% in 2005 to 28% in 2011, P<.001). For open repair, however, no changes in hospital bedsize were observed over time (7% to 8%, P=.635). No difference existed in the proportion of patients transferred from other hospitals between patients undergoing

Table 1. Baseline and hospital characteristics

Procedure	TEVAR (N=2492)	Open Repair (N=848)	Nonoperative (N=5044)	P-value Overall	P-value TEVAR vs. OR
Demographics					
Age – years (SD)	42.2 (18.3)	38.4 (18.2)	44.6 (20.7)	<.001	<.001
Male gender – %	75.2%	72.5%	71.2%	.001	.117
Non-white race – %	32.8%	28.1%	32.4%	.080	.030
Comorbidities					
Coronary disease – %	3.0%	1.3%	6.5%	<.001	.007
Diabetes – %	4.9%	0.6%	5.3%	<.001	<.001
Hypertension – %	20.2%	15.8%	19.5%	.016	.004
Heart Failure – %	1.0%	1.1%	4.2%	<.001	.803
COPD – %	3.0%	3.4%	3.3%	.726	.553
Chronic kidney disease – %	1.2%	1.1%	1.3%	.765	.809
Cerebrovasc disease – %	5.3%	2.9%	2.2%	<.001	.005
Hospital Characteristics					
Hospital Setting – %				<.001	<.001
Rural	2.4%	1.2%	2.8%		
Urban non-teaching	6.2%	13.9%	14.2%		
Urban teaching	91.4%	85.0%	83.0%		
Hospital Bedsize – %				<.001	<.001
Small	2.6%	0.5%	2.3%		
Medium	18.1%	8.2%	19.6%		
Large	79.3%	91.4%	78.1%		
Transf. from other hospital	17.5%	18.6%	12.3%	<.001	.456
Emergency admission	91.8%	91.1%	93.5%	.004	.550
Surgery on day of admission[a] – %	57.0%	65.6%	-	-	<.001

COPD: chronic obstructive pulmonary disease
[a] among emergent admissions only (10% missing cases)

TEVAR and open repair (18% vs. 19%, P=.456). However, TEVAR was less often performed on the day of admission (57% vs. 66%, P<.001).

Concomitant injuries and interventions

Concomitant injuries were more pronounced in TEVAR patients as compared to open repair patients (Table 2). Brain injuries were diagnosed concomitantly in 26% of TEVAR patients vs. 17% of open repair patients (P<.001). Similarly, the TEVAR group more commonly had cardiac injuries (3.9% vs. 1.1%, P<.001), pulmonary

Table 2. Concomitant injuries and interventions

Procedure	TEVAR (N=2492)	Open Repair (N=848)	Nonoperative (N=5044)	P-value Overall	P-value TEVAR vs. OR
Number of injuries – median (IQR)	3 (1-4)	2 (1-4)	2 (1-3)	<.001	<.001
Brain – %	26.2%	17.2%	24.4%	<.001	<.001
Thoracic					
Hemothorax – %	11.2%	11.8%	10.4%	.341	.659
Cardiac – %	3.9%	1.1%	3.8%	<.001	<.001
Pulmonary – %	31.6%	22.4%	24.6%	<.001	<.001
Abdominal					
Liver – %	24.1%	21.3%	21.4%	.028	.104
Spleen – %	25.4%	20.9%	22.3%	.003	.007
Kidney – %	13.5%	12.0%	9.6%	<.001	.278
Pelvic organs – %	3.1%	2.2%	2.6%	.284	.201
GI-tract – %	9.7%	9.5%	8.9%	.482	.912
Fractures					
Skull fracture – %	18.7%	15.1%	14.2%	<.001	.017
Vertebral fracture – %	37.4%	32.1%	31.2%	<.001	.005
Spinal involv – %	3.7%	3.4%	4.9%	.023	.671
No spinal involv – %	34.7%	28.7%	27.6%	<.001	.002
Major orthopedic – %	57.9%	56.8%	48.0%	<.001	.587
Interventions					
Intracranial – %	4.8%	2.5%	2.6%	<.001	.003
Thoracic – %	16.9%	18.9%	17.2%	.405	.190
Abdominal – %	13.7%	13.5%	13.7%	.991	.954

injuries (32% vs. 22%, P<.001), and spleen juries (25% vs. 21%, P=.007). Also, patients undergoing TEVAR more frequently suffered a skull fracture (19% vs. 15%, P=.017), and vertebral fractures without spinal cord injury (35% vs. 29%, P=.002). Regarding the treatment of concurrent injuries, TEVAR patients more often underwent intracranial interventions (4.8% vs. 2.5%, P<.001), while no difference was observed in the frequency of thoracic (16.9% vs. 18.9%, P=.405), and abdominal interventions (13.7% vs. 13.5%, P=.991).

Perioperative outcomes

With an average of 7.8% over the study period, death following TEVAR was considerably lower compared to open repair (13%, P<.001, Table 3), and nonoperative management (24% P<.001). This mortality difference held when comparing

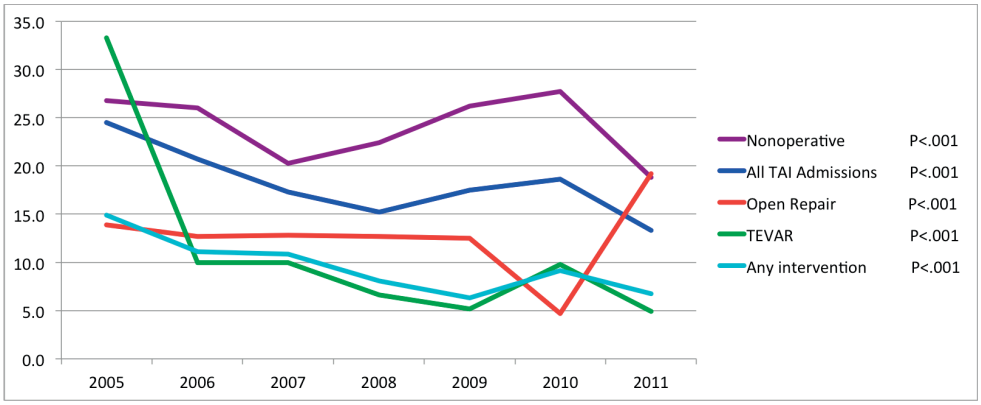
Table 3. Postoperative outcomes

Procedure	TEVAR (N=2492)	Open Repair (N=848)	Nonoperative (N=5044)	P-value Overall	P-value TEVAR vs. OR
Death – %	7.8%	12.7%	24.2%	<.001	<.001
Death surgery on day 1 – %	8.5%	13.4%	-	-	.003
Cardiac complication – %	4.1%	8.5%	13.0%	<.001	<.001
Paraplegia [a] – %	0.8%	0.5%	0.6%	.428	.480
Stroke complication – %	0.6%	0.6%	0.5%	.711	.867
Acute renal failure – %	9.7%	10.0%	10.5%	.584	.791
Respiratory – %	47.5%	54.8%	38.3%	<.001	<.001
Wound Dehiscence – %	1.2%	1.2%	0.9%	.357	.974
Postoperative infection – %	1.8%	2.8%	1.8%	.117	.070
Length of stay – days (SD)	18.4 (18.6)	20.2 (18.1)	14.8 (18.8)	<.001	.012
Discharge to home – %	64.0%	65.8%	68.5%	<.001	.336
Total hospital charges – $	279,828	238,392	182,403	<.001	<.001

[a] excluding patients admitted with spinal involved vertebral fractures

TEVAR versus open repair for procedures performed on day of admission (8.5% vs. 13%, P=.003). Over time, in-hospital mortality after TEVAR decreased from 33% in 2005 to 4.9% in 2011 (P<.001, Figure 2). Death among patients who underwent open repair remained stable at first, but as the proportion of patients undergoing open repair further declined, mortality increased (14% to 19%, P<.001). Concurrently with the widespread adoption of TEVAR, death following any intervention (i.e. either TEVAR or open repair) decreased from 15% to 6.7% (P<.001). Nonoperative management remained associated with the highest mortality with a general trend towards lower mortality, although there was random variation over time (27% to 19%, P<.001). Overall mortality following admission for TTAI decreased from 25% to 13% (P<.001). A similar decrease in death due to TTAI was seen in national CDC data, with mortality declining from 5 to 3 per 10,000 (40%) between 2000 and 2011 with a continuing downward trend in more recent years.[15] In addition to lower mortality, TEVAR was associated with fewer cardiac complications (4.1% vs. 8.5%, P<.001), and respiratory complications (48% vs. 55%, P<.001) compared to open repair. Furthermore, TEVAR was associated with a shorter length of stay (18.4 vs. 20.2 days, P=.012). Hospital charges, however, were significantly higher for TEVAR compared to open repair ($238,392 vs. $182,403, P<.001). No differences were found in rates of paraplegia, stroke, acute renal failure, postoperative infection, and wound dehiscence (Table 3).

Figure 2. Changes in in-hospital mortality over time according to treatment received



Independent predictors of mortality

Predictors of mortality are listed in Table 4 In adjusted analyses, open repair had twice the mortality risk compared to TEVAR (OR: 2.1, 95% CI: 1.6 – 2.7), while nonoperative management was associated with a four fold higher mortality (OR: 4.5, 95% CI: 3.8 – 5.3). Other risk factors for mortality included age (OR: 1.1 per 10 years of age, 95% CI: 1.1 – 1.2), male gender (OR: 1.3, 95% CI: 1.1 – 1.5), and cerebrovascular disease (OR: 2.4, 95% CI: 1.8 – 3.2). Surgery on day of admission was also associated with higher mortality risks (OR: 1.6, 95% CI: 1.2 – 2.2). Concomitant injuries predictive of mortality included brain injury (OR: 1.4, 95% CI: 1.2 – 1.6), hemothorax (OR: 1.6, 95% CI: 1.3 – 1.9), cardiac injury (OR: 1.5, 95% CI: 1.1 – 2.0), and major orthopedic injury (OR: 1.3, 95% CI: 1.1 – 1.5). In addition, intracranial (OR: 3.0, 95% CI: 2.2 – 4.0), thoracic (OR: 1.9, 95% CI: 1.6 – 2.2), and abdominal interventions (OR: 2.1, 95% CI: 1.8 – 2.5) were established as risk factors for mortality.

We were unable to differentiate between emergent admissions and relatively stable patients (e.g., transferred and readmitted patients). However, sensitivity analyses were performed among all patients coded as non-elective (93% of the total cohort), and no notable differences were observed compared to the multivariable model for the cohort as a whole.

DISCUSSION

This study demonstrates that TEVAR is now the dominant treatment modality for TTAI, with open repair only rarely being performed in recent years. Since the proportion of patients managed nonoperatively decreased by 26% (80% to

Table 4. Multivariable predictors of mortality after thoracic aortic injury

Management	**OR**	**95% CI**	**P-value**
TEVAR	*Reference*	-	-
Open Repair	2.1	1.6 – 2.7	<.001
Nonoperative	4.5	3.8 – 5.3	<.001
Baseline Characteristics	**OR**	**95% CI**	**P-value**
Age (per 10 years)	1.1	1.1 – 1.2	<.001
Male gender	1.3	1.1 – 1.5	.001
Congestive heart failure	1.2	0.9 – 1.6	.299
Cerebrovascular disease	2.4	1.8 – 3.2	<.001
Concomitant injuries	**OR**	**95% CI**	**P-value**
Brain injury	1.4	1.2 – 1.6	<.001
Hemothorax	1.6	1.3 – 1.9	<.001
Cardiac injury	1.5	1.1 – 2.0	.006
Major orthopedic injury	1.3	1.1 – 1.5	<.001
Other interventions	**OR**	**95% CI**	**P-value**
Intracranial intervention	3.0	2.2 – 4.0	<.001
Thoracic intervention	1.9	1.6 – 2.2	<.001
Abdominal intervention	2.1	1.8 – 2.5	<.001
Timing	**OR**	**95% CI**	**P-value**
Surgery on day of admission	1.6	1.2 – 2.2	.002

54%), our study indicates that TEVAR may have broadened patient eligibility for surgical repair, which has been suggested previously.[13] This is also supported by the observation that TEVAR patients had more pre-operative comorbidities and concomitant injuries compared to patients undergoing open repair. Despite their worse condition at admission, this study demonstrates that in-hospital mortality and postoperative morbidity of patients selected for TEVAR are substantially lower compared to open repair. Due to the shift from open repair towards TEVAR, overall procedural mortality has declined, which was confirmed with national CDC data. In addition, as TEVAR became more widely used and the proportion of patients managed nonoperatively decreased, total mortality following admission for TTAI declined as well.

The first comprehensive study on TTAI was carried out in 1958, which defined the pathological mechanisms, histopathology, and epidemiologic characteristics of the untreated TTAI and was the first to propose management strategies for this highly lethal injury.[2] Subsequently, open repair became the standard of care. In 1997, a large prospective multicenter trial conducted by the American Association for the Surgery of Trauma (AAST) reported that the operative mortality after

open repair was 31%, with paraplegia occurring in 9% of patients.[3] These rates are substantially higher than those for open repair in the present study where mortality was 12.7% and paraplegia was 0.8%. In that same year, endovascular stent-graft placement for TTAI was first described.[5] The comparative literature of open repair vs. TEVAR has largely been at the institutional level. These studies consistently determined that TEVAR was associated with substantial decreases in perioperative morbidity and mortality compared to open repair.[7-9, 11, 16-19] A second AAST analysis was published in 2008, in which 65% of patients were treated using endovascular repair.[20] With an operative mortality of 7.2% and an incidence of paraplegia lower than 1%, perioperative outcomes following TEVAR were comparable to our study. In line with the institutional series, this AAST follow-up study found favorable perioperative results for TEVAR.[20] Yet, Hong et al. could not confirm the perioperative mortality benefits associated with TEVAR on a national level utilizing the NIS for the years 2001 to 2007.[13] The conflicting results between these data and the present study may be explained by lower patient numbers in the Hong et al. study, as well as confounding resulting from the inclusion of data from 2001-2005, prior to the introduction of a specific ICD-9 procedure code for TEVAR. In addition, mortality trend analysis showed a dramatic decrease in perioperative mortality for TEVAR in the later years of our analysis, during which more TEVARs were performed as a proportion of total interventions. This could represent a learning curve for both surgeons and hospitals,[21-23] and may also explain why the earlier NIS study did not find such a difference between TEVAR and open repair. Similar to the present study, de Mestral et al. showed a rapid increase in the utilization of endovascular repair for TTAI using the Canadian National Trauma Registry.[24] Interestingly, they reported a concurrent increase in nonoperative treatment that was associated with a decline in mortality. As a result, de Mestral et al. recommended that nonoperative treatment for TTAI should be a major focus in the endovascular era. In our study, however, the proportion of patients treated nonoperatively decreased, and the associated mortality remained substantially higher compared to TEVAR over the entire length of the study. Further data are needed comparing outcomes of patients undergoing TEVAR and those treated nonoperatively stratified by grade of the aortic injury.

An unadjusted comparison of adverse postoperative events between TEVAR and open repair is complicated by the high diversity and prevalence of concomitant injuries. However, as length of stay was shorter, and the incidence of postoperative complications such as cardiac and respiratory complications was lower among TEVAR patients despite comorbidities and concomitant injuries being more pronounced, this further supports the benefits of TEVAR over open

repair in the perioperative period. Earlier series showed high rates of paraplegia following open repair.[3] Our results demonstrated similar low occurrence rates for paraplegia, as well as acute renal failure, for open repair and TEVAR, which is in line with more recent studies.[16, 20] Shorter length of stay after TEVAR has also been reported previously.[8, 18]

In regards to the clinical practice guideline from the SVS selected expert committee, our results confirm the recommendation that TEVAR should be preferentially performed over open surgical repair and nonoperative management.[12] The use of TEVAR is further supported by recent studies demonstrating good long-term results of endovascular repair for TTAI.[25-27] The expert panel additionally advised that aortic repair should be performed within 24 hours after admission barring other serious concomitant nonaortic injuries. However, our results showed that surgery on the day of admission was an independent risk factor for in-hospital mortality. Since this increased risk may very well be driven by patients with relatively severe aortic injuries requiring more urgent treatment, we believe that these data should not be used for deriving recommendations in regards to the timing of surgery.

TEVAR was more commonly performed in urban teaching hospitals. This was anticipated, as novel techniques and technologies such as TEVAR are typically introduced first to high volume academic centers. Also, the majority of these patients were likely transferred or brought directly to Level 1 trauma centers, which are predominantly urban and teaching. Prior literature evaluating differences in hospital costs between TEVAR and open repair is conflicting. While a study from Canada found comparable procedural costs between TEVAR and open repair,[28] a recent study conducted in Houston found higher hospital charges for patients who underwent TEVAR.[16] Although procedural costs are not documented in the database that was used, the NIS does provide total hospital charges for the hospitalization. In line with the more recent study, we found that TEVAR was associated with higher total charges. However, treatment of concomitant injuries, which were more pronounced among TEVAR patients, may have contributed to this cost difference.

This study has several limitations that should be considered. First, as with every ICD-9 based database, the NIS lacks clinically relevant data such as the grade of the aortic injury, and hemodynamic status at admission. This lack of specificity should be kept in mind when comparing outcome differences between treatment strategies, as confounding by indication may influence results. The lack of these data may have resulted in heterogeneity particularly in the nonoperative treatment group, as we were unable to differentiate between patients who were turned down for surgery due to the severity of the aortic injury or

because of prohibitive surgical risks resulting from comorbidities. Additionally, the nonoperative treatment group may have included patients that did not undergo aortic repair because the low grade of the aortic injury did not warrant repair or because concomitant injuries required more immediate medical attention. In addition, previous studies have indicated that results on surgical complications from administrative databases should be interpreted with caution, since these data resources have problems in regards to documentation of non-fatal perioperative outcomes.[29-31] Furthermore, due to the limited number of diagnoses that can be reported per case, common comorbidities and less threatening concomitant injuries are underreported in more complex patients. As a result, these conditions act as confounders for less severe cases, resulting in protective risk estimates in regression analyses. As these estimates did not accurately reflect the association with mortality, we decided to exclude these variables from further analyses. Also, we were unable to differentiate between emergent admissions, and those (re)admitted for their procedure. However, sensitivity analyses among all patients coded as non-elective showed no notable differences in the multivariable model. Finally, we could not distinguish between blunt and penetrating thoracic aortic injuries using ICD-9 coding. However, since the majority of chest traumas are of blunt nature,[32] we presume our cohort to predominantly consist of blunt TTAI patients. Also, the observed high prevalence of orthopedic injuries is often observed in blunt trauma patients, and is in line with prior studies reporting on blunt TTAI.[3]

In conclusion, traumatic thoracic aortic injury continues to be a highly lethal injury. TEVAR is now the dominant surgical approach in TTAI with substantial perioperative morbidity and mortality benefits over open aortic repair. Overall mortality following admission for TTAI has declined, which is most likely the result of both the replacement of open repair by TEVAR, as well as the broadened eligibility for operative repair.

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Supplemental Table 1. ICD-9 definitions for comorbid conditions, concomitant injuries, other interventions, and adverse outcomes

Baseline characteristics	**ICD-9 codes**
Hypertension	401.0-405.11
Coronary artery disease	412-414
Diabetes	250.x
Heart failure	428.x
COPD	492.x, 496.x
Chronic kidney disease	585.x
Cerebrovascular disease	433-438
Concomitant injuries	**ICD-9 codes**
Brain injury	850.3-850.5, 850.9, 851-854.x
Hemothorax	860.2-860.5
Cardiac injury	861.00-861.13
Pulmonary injury	861.20-861.32
Liver injury	864.x
Spleen injury	865.x
Kidney injury	866.x
Pelvic injury	867.x
GI-tract injury	863.x
Skull fracture	800.x-804.x
Vertebral fracture without SCI	805.x
Vertebral fracture with SCI	806.x
Major orthopedic injury	805.x-806.x, 808.x, 820.x, 821.x
Other interventions	**ICD-9 codes**
Intracranial	01.x-02.x (excl.: 01.1)
Thoracic	
Cardiac	32.x-34.x (excl.: 33.2, 34.2)
Lung	35.x-37.x (excl.: 37.2)
Abdominal	
Liver	50.x (excl.: 50.1)
Spleen	41.1-41.2, 41.4-41.5
Kidney	55.0x (excl.: 55.2)
Pelvic organs	56.x-57.x, 65.x-71.x (excl.: 56.3, 57.3, 65.1, 66.1, 67.1, 68.1, 70.2, 71.1)
GI-tract	42.x-54.x (excl.: 42.2, 44.1, 45.1, 48.2, 49.2, 50.1, 51.1, 52.2, 54.2)
Complications	**ICD-9 codes**
Cardiac complication	997.1, 785.51, 427.41, 427.5, 410
Paraplegia	344.1
Stroke complication	997.02
Acute renal failure	584.5-584.9
Respiratory	481, 482, 518.5x, 518.7 518.81, 997.3x,
Wound dehiscence	998.30, 998.31, 998.32
Postoperative infection	998.51, 998.59

Chapter 2

Age-related Trends in Adoption and Outcome of Endovascular Repair for Ruptured Thoracic Aortic Aneurysms

Klaas H.J. Ultee[1,2]
Sara L. Zettervall[1]
Peter A. Soden[1]
Dominique B. Buck[1]
Sarah E. Deery[1]
Katie E. Shean[1]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

Submitted

ABSTRACT

Objective

Endovascular repair (TEVAR) has become an alternative to open repair for the treatment of ruptured thoracic aortic aneurysms (rTAA). The aim of this study was to assess national trends in the utilization of TEVAR for the treatment of rTAA and determine its impact on perioperative outcomes.

Methods

Patients admitted with a ruptured thoracic aortic aneurysm between 1993 and 2012 were identified from the Nationwide Inpatient Sample (NIS). Patients were grouped in accordance with their treatment: TEVAR, open repair, or nonoperative treatment. The primary outcomes were treatment trends over time and in-hospital death. Secondary outcomes included perioperative complications and length of stay. Trend analyses were performed using the Cochran-Armitage test for trend, and adjusted mortality risks were established using multivariable logistic regression analysis.

Results

A total of 12,399 patients were included, with 1622 (13%) undergoing TEVAR, 2808 (23%) undergoing open repair, and 7969 (64%) not undergoing surgical treatment. TEVAR has been increasingly utilized from 2% in 2003-2004 of total admissions to 43% in 2011-2012 (P<.001). Concurrently, there was a decline in the proportion of patients undergoing open repair (29% to 12%, P<.001) and nonoperative treatment (69% to 45%, P<.001). The proportion of patients undergoing surgical repair has increased for all age groups since 1993-1994 (P<.001 for all), but was most pronounced among those aged 80 years with a 7.5 fold increase. After TEVAR was introduced, procedural mortality decreased from 36% to 27% (P<.001), while mortality among those undergoing nonoperative remained stable between 63% and 60% (P=.167). Overall mortality following rTAA admission decreased from 55% to 42% (P<.001). Since 2005, mortality for open repair was 33% and 22% for TEVAR (P<.001). In adjusted analysis, open repair was associated with a two-fold higher mortality than TEVAR (OR: 2.0, 95% CI: 1.7 – 2.5).

Conclusion

TEVAR has replaced open repair as primary surgical treatment for rTAA. The introduction of endovascular treatment appears to have broadened patient eligibility for surgical treatment, particularly among the elderly. Mortality following rTAA admission has declined since the introduction of TEVAR, which is the result of improved operative mortality, as well as the increased proportion of patients undergoing surgical repair.

INTRODUCTION

A ruptured descending thoracic aortic aneurysm (rTAA) is a life-threatening diagnosis, with an estimated mortality exceeding 90%.[1] The majority of patients die before making it to the emergency department. For those hemodynamically stable enough to reach the hospital and undergo surgery,[1] traditional open repair requires an emergency thoracotomy to replace the diseased aorta with an interposition graft. Despite the fact that hospitalized patients are presumed to have a better prognosis, mortality following surgery is as high as 45%,[2, 3] with surviving patients often suffering disabling complications such as paraplegia and stroke.[2, 4-6]

As a minimally invasive alternative, endovascular repair (TEVAR) for rTAA was first introduced and described by Semba et al in 1997.[7, 8] In subsequent years, single institution studies were performed to evaluate its feasibility, and performance compared to conventional open repair.[4, 9-14] Although some of these studies showed encouraging perioperative results favoring TEVAR, they were often limited by small numbers, and the inclusion of other acute aortic pathologies. Moreover, an absolute perioperative survival benefit of TEVAR over open repair could not be confirmed. [4, 14] Reports on outcome of rTAA using early national data from the Nationwide Inpatient Sample (NIS) yielded conflicting results, despite an identical TEVAR cohort. While Kilic et al. demonstrated that TEVAR for rTAA was associated with significantly lower perioperative in-hospital mortality compared to open repair,[15] Gopaldas et al. concluded equivalent mortality and complication rates for the two treatment approaches.[16] Age-stratified trends in treatment utilization were not explored in these studies.

Previous studies have demonstrated that for patients presenting with a traumatic thoracic aortic injury, the introduction of TEVAR has reduced the proportion of patients managed nonoperatively.[17, 18] For rTAA patients, however, it is unknown whether the introduction TEVAR has broadened their treatment eligibility.[17] The purpose of this study was to assess national trends in the treatment of rTAA, focusing on the relative utilization and outcome of TEVAR, open repair, and nonoperative treatment.

METHODS

For this study, we used the Nationwide Inpatient Sample (NIS). The NIS is the largest US all-payer inpatient database, and is maintained by the Agency for Health Care Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project (HCUP). The NIS represents 20% of all annual U.S. hospitalizations.

Actual annual hospitalization volumes are approximated using hospital sampling weights. The weighted estimates are utilized for all analyses in this study, as recommended by the AHRQ. The Institutional Review Board of Beth Israel Deaconess Medical Center approved this study and patient consent was waived, due to the de-identified nature of the data.

Patients were identified using International Classification of Diseases, Ninth Revision (ICD-9). All patients admitted with a ruptured thoracic aortic aneurysm (411.1) were identified. Patients were subsequently divided in the open repair group (38.35) and the TEVAR group (39.73). Those with a primary diagnosis of a ruptured aneurysm without mention of any procedure were considered nonoperatively treated. In an effort to capture TEVAR cases before TEVAR procedure coding was introduced in 2005, patients with a primary diagnosis of a ruptured thoracic aortic aneurysm in combination with mentioning of EVAR (39.71) or insertion of non-drug eluting peripheral (non-coronary) vessel stent (39.90) were also considered to have undergone endovascular repair. Patients with both a procedure code for open repair and TEVAR were excluded. In addition, those with a concomitant diagnosis for thoracoabdominal aneurysm (diagnosis codes: 441.3-441.9 or procedure codes: 38.44, 39.71), aortic dissection (diagnosis codes: 441.00-441.03), or connective tissue disorder (diagnosis codes: 446.0-446.7, 758.6, 759.82) were excluded from this study. To separate ascending from descending aneurysms, patients with procedure codes for cardioplegia (39.63), valve surgery (35.00-35.99), and procedures on the vessels of the heart (36.00-36.99, 37.0, 37.2, 37.31-37.90, 37.93, 37.99) were also excluded, as they are more likely to represent aneurysms of the ascending aorta.

Patients were compared on demographics (age, gender, race), and comorbid conditions (coronary artery disease, diabetes, hypertension, heart failure, chronic obstructive pulmonary disease [COPD], chronic kidney disease, and cerebrovascular disease). We additionally assessed differences in hospital characteristics, including hospital bedsize (small, medium, large), setting and teaching status (rural, urban non-teaching, urban teaching). Hospital bedsize category varies according to location and teaching status. Small hospital bedsize is defined as 1-49, 50-99 and 1-299 beds, respectively for rural, urban non-teaching and urban teaching hospitals, medium bedsize as 50-99, 100-199, 300-499, respectively, and 100+, 200+, and 500+ beds is considered a large bedsize hospital, respectively. Adverse in-hospital outcomes included death, cardiac or respiratory complications, paraplegia, stroke, acute renal failure, wound dehiscence, infection, discharge to home, and length of stay. Cardiac complications include postoperative myocardial infarction, cardiac arrest, cardiogenic shock, and

ventricular fibrillation (Supplemental Table 1). A respiratory complication was defined as a postoperative pneumonia, pulmonary insufficiency after trauma or surgery, transfusion-related acute lung injury, or acute respiratory failure.

For this study we also utilized the Wide-ranging Online Data for Epidemiologic Research (WONDER), an epidemiological internet based database maintained by Centers for Disease Control and Prevention (CDC)[19], to assess national cause-specific age-adjusted death rates due to thoracic aortic aneurysms (ICD-10 code: S25.0). More information on WONDER can be found on http://wonder.cdc.gov/.

Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were assessed using Pearson's chi-Square or Fisher's exact testing, and Student's t-test, where appropriate. Trend analyses were performed using the Cochran-Armitage test for trend. In order to assess the independent risk associated with treatment option for rTAA, we subsequently performed multivariable logistic regression analysis. Predictors with a P <.1 were entered into the multivariable model, after which the final model was obtained using stepwise backward elimination (exit P > .05). As a result of underreporting of less life-threatening conditions in more acute patients, less life-threatening comorbid conditions act as confounders for less severe cases. Therefore, we chose not to include comorbidities with protective risk estimates on univariate screening. All tests were two-sided and significance was considered when P<.05. Statistical analysis was performed using SPSS Statistics 21 (IBM Inc., Chicago, IL).

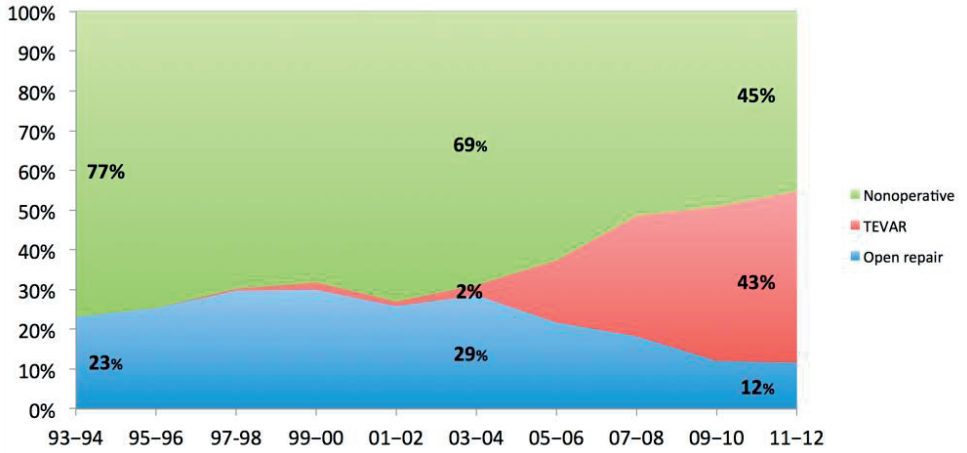
RESULTS

A total of 12,399 patients were included, with 1622 (13%) undergoing TEVAR, 2808 (23%) undergoing open repair, and 7969 (64%) not undergoing surgical treatment.

Epidemiological trends

TEVAR has been increasingly utilized from 2% of total admissions in 2003-2004 to 43% in 2012 (P<.001, Figure 1). Concurrently, the proportion of patients undergoing open repair declined from 29% to 12% (P<.001). Despite a decrease in open repair utilization, the overall proportion of patients undergoing surgical repair dramatically increased once TEVAR received FDA approval in 2005 (31% to 55%, P<.001).

Figure 1. Annual proportions of the treatment strategies for the treatment of rTAA



Although an increase in surgical repair was observed in all age groups, it was not uniform. The utilization of surgical treatment for patients under 70 increased 207% from 1993-1994 to 2011-2012 (P<.001, Figure 2a). For those aged 70-80 years, this was 177% (P<.001). With a 750% increase over the study period, the shift towards operative management was most pronounced among those aged 80 and above. Figure 2b illustrates that the adoption to TEVAR started relatively early among the eldest patients, as 18% of patients aged 80 and over were undergoing TEVAR prior to its FDA approval (<70 years: 3%; 70-80 years: 9%, P=.004). In 2011-2012, only 14% of patients aged 80+ underwent open repair, which was significantly lower compared to the <70 group (24%) and 70-80 group (25%, P=.008)).

When population-adjusted trends were evaluated, an overall decrease in rTAA admissions was observed from 1993 to 2004 (4.7 to 3.6 per million, Figure 3), a rate that stabilized thereafter. The number of patients surgically treated increased since 2003-2004 from 1.4 to 1.9 per million. This was observed among patients under 70 years (0.8 to 1.1 per million), but more strongly among patients aged 80 and above (3.5 to 9.9 per million).

Baseline characteristics

Baseline characteristics are detailed in Table 1. When comparing TEVAR patients to those undergoing open repair, we found that TEVAR patients were substantially older (72 years vs. 66 years, P<.001). In terms of comorbidities, TEVAR patients more often had diabetes (14% vs. 11%, P=.031), and hypertension (75.4% vs. 60.4%, P<.001). Additionally, coronary artery disease (27% vs. 18%, P<.001),

Figure 2a. Changes in rates of surgical repair by age (index volume: 1993-1994)

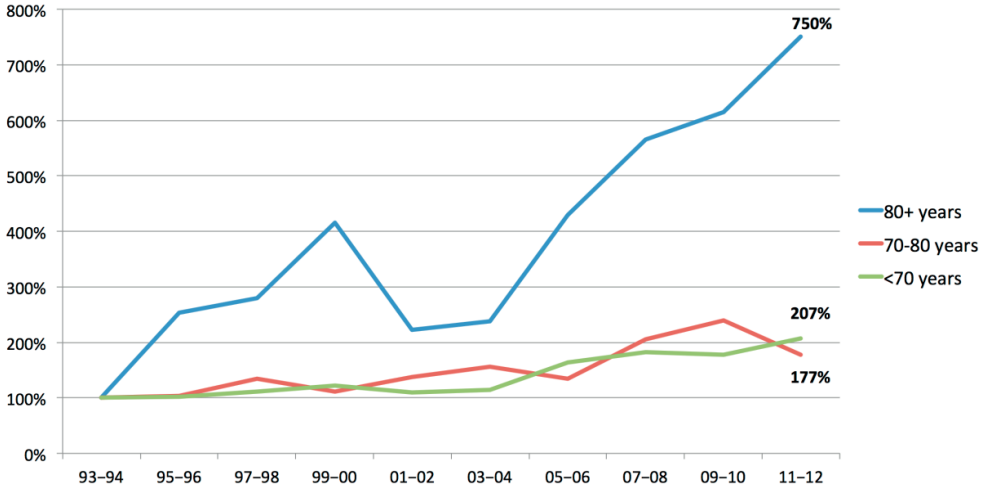
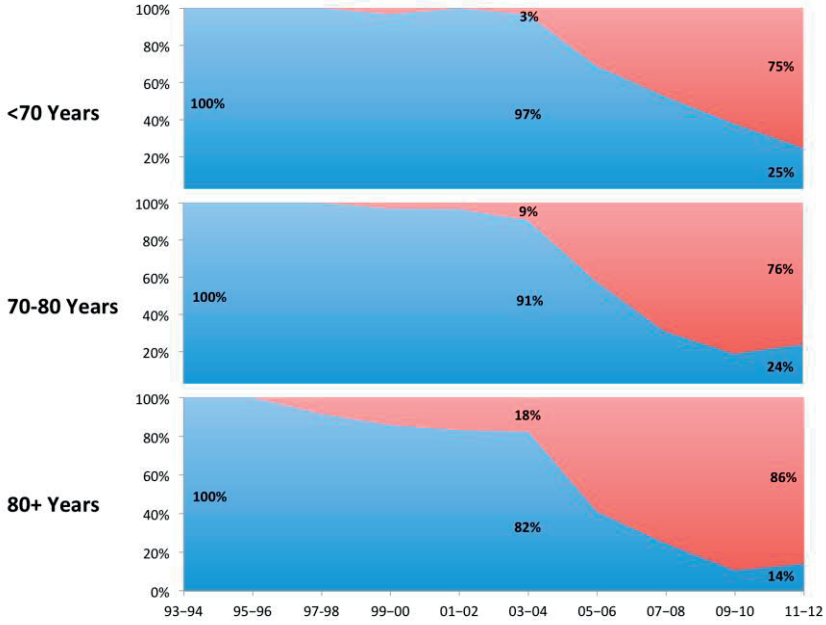


Figure 2b. The proportion of TEVAR vs. open repair per age group



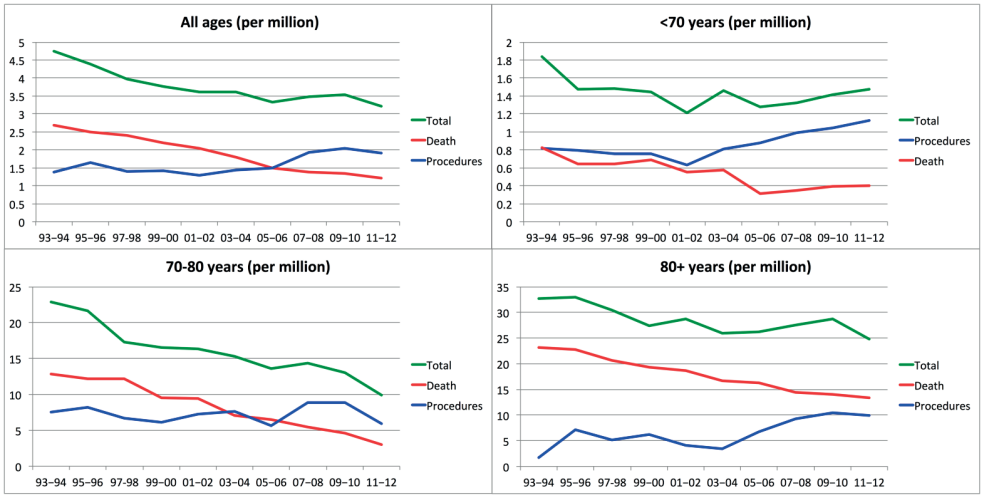
and chronic kidney disease (21% vs. 11%, P<.001) were more common among those undergoing TEVAR compared to open repair. TEVAR was more often performed in academic centers (85% vs. 75%, P<.001), and larger bedsize hospitals (82% vs. 79%, P<.001) compared to open repair.

Table 1. Baseline characteristics of patients admitted with for rTAA

Procedure	TEVAR (N=2492)	Open Repair (N=848)	Nonoperative (N=5043)	P-value Overall	P-value OR vs TEVAR
Demographics					
Age – years (SD)	72.2 (13.2)	66.0 (14.2)	78.2 (12.7)	<.001	<.001
Age category – %				<.001	<.001
<70 years	36.0%	55.0%	16.3%		
70-80 years	30.0%	27.6%	26.3%		
80+ years	34.1%	17.4%	57.5%		
Female gender – %	49.6%	51.0%	58.4%	<.001	.526
Non-white race – %	27.3%	27.1%	23.3%	.016	.922
Comorbidities	**TEVAR**	**Open Repair**	**Nonoperative**	**Overall**	**OR vs TEVAR**
Coronary artery disease – %	27.0%	17.8%	23.9%	<.001	<.001
Old myocardial infarction – %	7.5%	1.3%	4.5%	<.001	<.001
Diabetes – %	14.2%	11.0%	13.4%	.096	.031
Hypertension – %	75.4%	60.4%	73.1%	<.001	<.001
Heart Failure – %	14.5%	13.3%	14.0%	.762	.462
COPD – %	18.7%	17.0%	18.0%	.619	.328
Chronic kidney disease – %	20.8%	11.0%	15.2%	<.001	<.001
Cerebrovasc disease –%	12.3%	14.0%	6.6%	<.001	.263
Socioeconomic status	**TEVAR**	**Open Repair**	**Nonoperative**	**Overall**	**OR vs TEVAR**
Income quartile				.538	.207
First	27.1%	25.9%	27.1%		
Second	26.6%	27.3%	26.9%		
Third	25.6%	22.8%	23.9%		
Fourth	20.7%	24.0%	22.2%		
Hospital Characteristics	**TEVAR**	**Open Repair**	**Nonoperative**	**Overall**	**OR vs TEVAR**
Hospital Setting – %				<.001	<.001
Rural	1.5%	0.7%	11.9%		
Urban non-teaching	13.2%	24.2%	31.5%		
Urban teaching	85.3%	75.2%	56.5%		
Hospital Bedsize – %				<.001	<.001
Small	6.3%	3.9%	13.5%		
Medium	12.2%	17.4%	17.7%		
Large	81.5%	78.7%	68.8%		

COPD: chronic obstructive pulmonary disease

Figure 3. Population-adjusted trends in rTAA death rates, admission rates, and surgical repair utilization (per million)



Perioperative mortality

In-hospital mortality was significantly lower for patients undergoing TEVAR compared to open repair (22% vs. 33%, P<.001, Table 2). Following nonoperative treatment in-hospital mortality was 60%. In adjusted analysis, open repair was associated with a two-fold higher mortality compared to TEVAR (OR: 2.0, 95% CI: 1.7 – 2.5), while nonoperative management was associated with a five-fold increase in mortality (OR: 5.0, 95% CI: 4.3 – 5.9). From 2005 onward, mortality after TEVAR increased non-significantly from 21% to 26% (P=.219, Figure 4), while mortality following open repair decreased significantly between 2003-2004 and 2011-2012 (36% to 29%, P=.005). Overall procedural mortality decreased from 36% to 27% (P<.001), while mortality among those undergoing nonoperative remained stable between 63% and 60% (P=0.167). As TEVAR became more widely adopted –and the proportion of patients undergoing nonoperative treatment decreased– overall mortality following rTAA admission decreased from 55% to 42% (P<.001).

Despite an increase in rTAA admissions among those under age 70 after the introduction of TEVAR, in-hospital deaths declined after 2003-2004 (0.6 to 0.4 per million, Figure 3). Similarly, for those over 80, death following rTAA admission declined (16.7 to 13.3 per million), even though the rTAA admission incidence increased. The population-adjusted incidence of death following rTAA in patients 70-80 years of age also decreased considerably (7.1 to 3.0 per million), although this was concurrent with a strong decline in admission for rTAA. Similar declining trends were seen in the national WONDER data from the CDC,

with rTAA mortality among patients less than 70 years declining from 1.0 to 0.8 per million between 2003-2004 and 2011-2012, and 42 to 22 per million among those aged 80 and above.

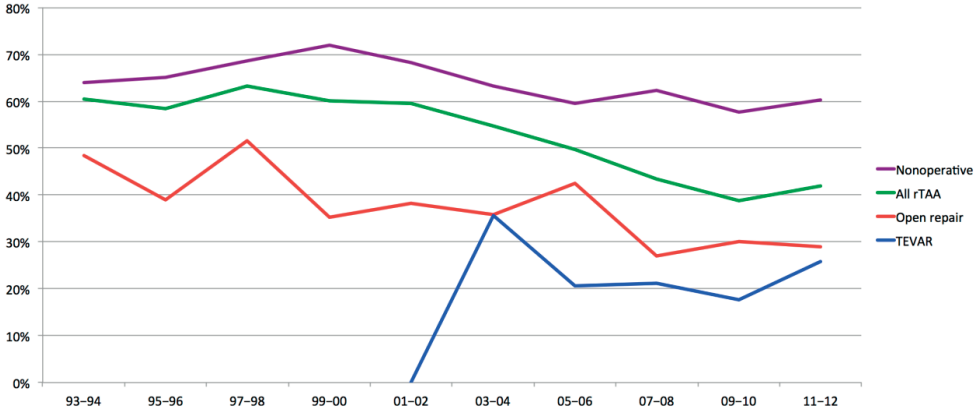
Table 2 Perioperative outcome of patients admitted for rTAA in accordance with treatment strategy.

Procedure	TEVAR (N=2492)	Open Repair (N=848)	Nonoperative (N=5043)	P-value Overall	P-value OR vs TEVAR
Death[α] – %	21.6%	33.2%	59.9%	<.001	<.001
Cardiac complication – %	16.6%	31.2%	17.0%	<.001	<.001
Paraplegia[α] – %	3.7%	5.6%	0.6%	<.001	.031
Stroke complication – %	3.7%	5.0%	0.8%	<.001	.165
Acute renal failure – %	21.8%	25.1%	9.6%	<.001	.072
Respiratory – %	33.4%	43.0%	10.6%	<.001	<.001
Wound Dehiscence – %	0.9%	3.7%	0.2%	<.001	<.001
Postoperative infection – %	0.6%	3.8%	0.2%	<.001	<.001
Bleeding complication	14.3%	18.2%	1.2%	<.001	.015
Length of stay – days (SD)[β]	13.7 (12.7)	17.2 (15.0)	5.2 (7.3)	<.001	<.001
Discharge to home – %	27.2%	21.1%	9.3%	<.001	.002

[α] Odds ratio open repair vs. TEVAR: 2.0 (95% CI: 1.7 – 2.5); Odds ratio Nonoperative treatment vs. TEVAR: 5.0 (95% CI: 4.3 – 5.9) (adjusted for: age, gender, old myocardial infarction, congestive heart failure, obstructive pulmonary disease, ZIP household income quartile)

[β] Length of stay among those who did not die during hospitalization

Figure 4. Trends in in-hospital mortality following rTAA admission



Perioperative complications

In addition to favorable mortality, TEVAR was associated with a lower incidence of cardiac complications (17% vs. 31%, P<.001), paraplegia (4% vs. 6%, P=.031), respiratory complications (33% vs. 43%, P<.001), wound dehiscence (0.9% vs. 4%, P<.001), postoperative infection (0.6% vs. 4%, P<.001), and bleeding complications (14% vs. 18%, P=.015) compared to open repair. Additionally, those undergoing TEVAR had a significantly shorter hospital stay (14 days vs. 17 days, P<.001), and were more likely to be discharged to home (27% vs. 21%, P=.002).

DISCUSSION

This study demonstrates that since its introduction, the utilization of endovascular repair has rapidly increased for the treatment of rTAA, and is currently the primary mode of treatment. Aside from replacing open repair, the use of TEVAR has led to an increase in the proportion of rTAA patients being treated surgically, particularly among patients older than 80. As a result, the majority of patients admitted for rTAA now undergo surgical repair. TEVAR was associated with favorable outcomes compared to open repair, despite TEVAR patients being older and having more comorbidities. Due to the shift from open repair to TEVAR, and the shift from non-operative treatment to TEVAR, overall mortality following rTAA admission declined over the study period.

The feasibility of endovascular repair in an acute setting for rTAA was first described in 1997.[7] In 2004, Scheinert et al. reported a 30-day mortality of 9.7% among a cohort of 31 rTAA patients.[10] Other series reported similar encouraging results, with mortality ranging between 3.1% and 24.6%. Comparing these outcomes to historic results for open repair with mortality of up to 45%,[2, 6] Mitchell et al. concluded that TEVAR has become the treatment of choice for acute thoracic aortic surgical emergencies.[13] However, comparative studies were unable to establish an absolute survival benefit of TEVAR over open repair.[4, 11, 14] Jonker et al. evaluated morbidity and mortality after both operative approaches, and demonstrated that TEVAR was associated with a lower rate of perioperative adverse events in a multi-institutional study. Mortality, however, was not significantly reduced in TEVAR patients.[4] These findings were supported by Patel et al. who also demonstrated a lower incidence of adverse events in a composite outcome measure.[14]

When Gopaldas et al. utilized the NIS in an effort to assess national rTAA outcomes on a national level for the years both treatments were available (2006-2008), neither mortality nor complications rates differed between TEVAR

and open repair.[16]. Conversely, a recent study also utilizing NIS data up until 2008 found that TEVAR was associated with a reduction in perioperative mortality compared to open repair.[15] In this study, however, open repairs as far back as 1998 were compared to TEVAR patients treated in 2008, which resulted in substantially higher in-hospital mortality after open repair (53% vs. 29% in the Gopaldas study). In the present study using more recent data, we limited comparative analysis to data after the introduction of TEVAR. With mortality rates similar to the Gopaldas study, we found that perioperative morbidity and mortality following TEVAR was significantly lower compared to open repair. This in line with a retrospective analysis of Medicare beneficiaries in which Goodney et al. found significantly lower perioperative mortality in TEVAR patients compared to those undergoing open repair.[20]

Our study, similar to previous studies utilizing the NIS, is unable to assess long-term follow-up. However, previous reports have shown equivalent survival at 1- and 5-years, despite a substantially lower perioperative mortality after TEVAR.[20-22] Patel et al. had similar 5-year findings in a cohort of 69 RTAA patients, although no significant differences in survival were observed in the perioperative period either.[14]

While increases in the proportion of patients undergoing surgery were observed in all age groups, patients aged 80 and over benefitted most significantly from the introduction of TEVAR, as surgical treatment more than tripled since its introduction. This is similar to the increase in operative treatment among elderly abdominal aortic aneurysm (AAA) patients observed after the introduction of endovascular repair for AAA.[23] These trends were also apparent after population-adjustment, with substantial increases in the number of surgical interventions per million, and a concurrent decline in in-hospital death. Aside from elderly patients, TEVAR also appeared to be preferred for patients with increased comorbidities, as evidenced by increased rates of coronary artery disease, chronic kidney disease and hypertension among TEVAR patients compared to those undergoing open repair. This phenomenon has been demonstrated for elective abdominal and thoracic aortic surgery, and may explain the improved mortality trend for open repair due to patients with severe comorbidities now offered the endovascular alternative instead of invasive open repair.[24, 25]

This study has several limitations that should be addressed. First, since the NIS is an ICD-9 based database, it does not provide detailed operative or clinical data, including hemodynamic status at admission. Consequently, we are unable to assess the role of hemodynamics on operative selection. Anatomic data are also lacking which may impact the choice of open repair vs. TEVAR and may also impact outcome. Additionally, previous studies have indicated that evaluation

of surgical complications from administrative databases should be interpreted with caution, since documentation of non-fatal perioperative outcomes may be incomplete.[26-28] Furthermore, only a limited number of diagnoses can be reported per patient. As a result, common comorbidities may be underreported in the sickest patients, leading to confounding for less severe cases. Since these protective risk estimates do not accurately reflect the association with mortality, we decided to exclude these variables from further analyses.

In conclusion, this study shows that TEVAR has been increasingly utilized since its introduction, and is associated with significantly lower perioperative morbidity and mortality than traditional open surgical repair. In addition to replacing open repair as the dominant surgical approach for rTAA nationally, TEVAR has broadened treatment eligibility, with the majority of patients presenting with rTAA now undergoing operative intervention. As a result of the shift from open repair and nonoperative treatment to TEVAR, overall mortality following RTAA admission has decreased in recent years.

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Supplemental Table 1. ICD-9 codes used for defining comorbid conditions, and adverse outcomes

Baseline characteristics	**ICD-9 codes**
Hypertension	401.0-405.11
Coronary artery disease	412-414
Old myocardial infarction	412
Diabetes	250.x
Heart failure	428.x
COPD	492.x, 496.x
Chronic kidney disease	585.x
Cerebrovascular disease	433-438
Complications	**ICD-9 codes**
Cardiac complication	997.1, 785.51, 427.41, 427.5, 410
Paraplegia	344.1
Stroke complication	997.02
Acute renal failure	584.5-584.9
Respiratory	481, 482, 518.5x, 518.7 518.81, 997.3x,
Wound dehiscence	998.30, 998.31, 998.32
Postoperative infection	998.51, 998.59
Bleeding complication	998.11-998.12

chapter 3

Ruptured AAA: State of the Art Management

Daniel Eefting[1]
Klaas H.J. Ultee[1]
Gerdine C.I. Meijenfeldt[1]
Sanne E. Hoeks[1]
Sander ten Raa[1]
Joke M. Hendriks[1]
Frederico Bastos Gonçalves[1]
Hence J.M. Verhagen[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Since its introduction more than two decades ago, endovascular aneurysm repair (EVAR) has become the primary choice for elective treatment of abdominal aortic aneurysms (AAA) in many medical centers. The (dis)advantages, including 30-day mortality and long-term survival, of both open and endovascular elective AAA repair have been studied extensively, including four randomized trials. On the contrary, the survival benefit of EVAR for ruptured AAAs is not as well established as in elective situations. In the absence of randomized trials, the best treatment modality for ruptured AAA has not been revealed. In this manuscript, we describe the design and (preliminary) results of recently completed and ongoing randomized trials. Furthermore, the trends in management and the results of the treatment of ruptured AAA in our tertiary center over a 20-year period are presented. In the last decade, a progressive increase in the proportion of patients managed by EVAR was observed. This increase was associated with an overall increase in the number of treated patients and, simultaneously, a decrease in the overall 30-day mortality (53% versus 39%) was seen when comparing the two last decades. The 30-day mortality rates were significantly lower in the patients treated with EVAR (24%) compared to open repair (52%). The survival advantage for EVAR after ruptured AAA persisted during the first 5 years after repair, but was lost after that period. The estimated 5-year survival was 44% and 39% for EVAR and open repair, respectively. These data support that endovascular repair is an effective and safe strategy as a primary treatment modality for ruptured AAA.

INTRODUCTION

After the world's first endovascular aneurysm repair (EVAR) in 1987 by Volodos, this less invasive treatment modality has been adapted in many medical centers and its use has expanded to approximately 60% of all elective abdominal aortic aneurysm (AAA) repairs.[1, 2] Recent multicenter randomized controlled trials have confirmed that EVAR can be performed with three-fold reduction of perioperative mortality compared with open repair.[3] The reported 30-day mortality rates in four randomized trial (EVAR, DREAM, OVER and ACE) was 0.2-1.7% in the EVAR-treated patients versus 0.7- 4.7% after open repair. However, no significant differences were found in the long-term mortality rates (2-6 years).[3]

Since a ruptured aneurysm is nearly always fatal, the primary survival is of utmost importance for the critically ill patient with a ruptured AAA. Intuitively, it could be expected that these patients, in case of anatomical suitability, benefit most from the endovascular approach. However, since its first description, the introduction of endovascular treatment of ruptured AAA has faced significant resistance.[4, 5] Several single-center, mostly observational studies, report superior results, with a mean 38% decrease in 30-day mortality favoring EVAR in patients with ruptured AAAs.[6] However, level I evidence from randomized trials which confirm these survival benefits of endovascular repair is still lacking.

This manuscript outlines the design and results of recently completed and ongoing randomized trials comparing EVAR to open repair for ruptured AAAs, and the most important published data so far will be discussed. Moreover, the trends in management and data of 20 years of ruptured AAA treatment in our tertiary center are discussed.

TRIALS

Currently, the results of one randomized trial have been published, two randomized trials are in progress (IMPROVE and ECAR) and the inclusion of the AJAX trial was completed in March 2011.[5, 7-9]

The Nottingham Trial

Hinchliffe et al.[5] described the results of the first, single-center, prospective randomized controlled trial comparing EVAR with open aneurysm repair in patients with ruptured AAA. The primary endpoint was operative (30-day) mortality and secondary endpoints were moderate or severe operative complications, hospital stay and time between diagnosis and operation. Although 103 patients were admit-

ted to the study between September 2002 and December 2004, only 32 patients were recruited. The trial was stopped because it was underpowered. No significant differences were found between the two groups in the 30-day mortality rates (53% in both groups) or other endpoints. The authors concluded that it is possible to perform a randomized trial of open and endovascular surgery in patients with ruptured AAA and that preoperative CT scanning does not delay treatment.

The Amsterdam Trial

The first results of the Acute Endovascular Treatment to Improve Outcome of Ruptured Aortoiliac Aneurysms (AJAX) Trial were presented at the 34th Charing Cross Symposium in London (April 2012).[9] The objective of this multicenter randomized clinical trial was to study the outcome of open surgery versus endovascular treatment for ruptured AAAs. All patients in the Amsterdam region with a ruptured abdominal aneurysm who were eligible for endovascular and conventional surgery were included. The primary endpoint was a combination of mortality and severe morbidity at 30 days. The secondary endpoints were length of hospital and intensive care unit (ICU) stay, intubation/ventilation and use of blood products.

Between April 2004 and February 2011, 520 patients with ruptured AAAs were enrolled in the trial. Of these cases, 395 patients were evaluated with CT and 155 (39%) were found to have a suitable anatomy for endovascular repair. Eventually, only 116 patients (22%) were randomized (57 to EVAR and 59 to open repair). Other patients were excluded for a variety of reasons. The preliminary data of this trial showed that there was no difference between EVAR, using an aorto-uni-iliac (AUI) graft with contralateral occlude and femorofemoral crossover bypass, and open repair in the treatment of ruptured AAAs. EVAR had a combined and severe complications rate of 42% (24/57) and in the open surgery group this rate was 47% (28/59) at 30 days. Also, the 30-day mortality rates showed no significant differences (EVAR: 21% and open repair: 25%). Regarding some of the secondary endpoints, EVAR performed slightly better. In the open repair group, ICU stay was 48 hours versus 28 hours in the EVAR group (P=0.14); hospital stay 9 days with EVAR and 13 days with open repair (P=0.57); mechanical ventilation: 39 versus 52 patients in the open repair group (P=0.002); blood loss with EVAR was 500 mL while it was 3500 mL with open repair (P<0.001) and 45 EVAR patients needed blood products during surgery versus 56 patients after open repair (P=0.01).

In conclusion, open repair performed much better than expected with low death rates in the randomized controlled trial, but also low death rates in the entire cohort. The absolute risk reduction (ARR) of EVAR versus open repair was 5.4% (95% CI -11 to +23).

It is remarkable that the AJAX Trial was initially based on the recruitment of just 80 patients. With these 80 patients, no significant difference in the primary endpoint was found. Therefore, the recruitment of patients was extended. The low death rates could not be explained by neither a selection of hemodynamically stable patients nor favorable anatomy. Of all patients, 17% was hemodynamically] unstable, versus 20% in the randomized group (23/116). The death rate following open surgery in patients with unfavorable anatomy was 26% in the cohort (58/222) and the 30-day mortality of all patients who underwent surgery was 30% (138/454; 95% CI 26-35%).

The ECAR Trial

The inclusion of the multicentric randomized Endovasculaire vs. Chirurgie dans les Anévrysmes Rompus (ECAR) trial started in January 2008 and is still running.[8] This study was setup on 160 patients to compare EVAR versus open repair in patients with ruptured aortoiliac aneurysms in France. The study is powered for an expected 20% reduction in early mortality after endovascular repair. The design of the study is comparable to the AJAX trial and only patients who are hemodynamic stable and morphologically suitable for EVAR (including an infrarenal neck longer than 10 mm and smaller than 32 mm diameter) are included. Patients are randomized according to the calendar week and the hospital at which they present. The primary endpoint is 30-days mortality.

The IMPROVE Trial

Also the Immediate Management of the Patient with Rupture: Open Versus Endovascular repair (IMPROVE) Aneurysm Trial is still in progress.[7] The objective of this international multicenter study is to determine whether a policy of endovascular repair improves the survival of all patients with ruptured AAA. The recruitment of patients started in October 2009. In this randomized trial, patients with a clinical diagnosis of ruptured AAA are randomized to immediate CT scan and endovascular repair whenever anatomically suitable (endovascular first), or to open repair, with CT scan being optional. The trialists expect that 600 patients are required to show a 14% reduction in 30-days mortality (primary outcome) for the endovascular first policy. Secondary endpoints include 24h, in-hospital and 1 year survival, complications, major morbidities, costs and quality of life.

As compared to the ECAR trial, the IMPROVE trial compares endovascular and open strategies in a more anatomically and hemodynamically heterogeneous group by this approach.

RELEVANT STUDIES

Many centers have published their data on endovascular treatment of rAAAs. In this part, two recent papers are summarized and some management strategies of rAAAs are enumerated.

Veith et al.[10] collected data of 49 centers worldwide, which had used EVAR for rAAAs. The purpose of the study was to examine the role and value of the endovascular treatment of ruptured aneurysms and explain the variable results that have been published. Questionnaires were used to obtain the data. In total, 1037 patients treated by EVAR and 763 patients treated by open repair were included. Overall 30-day mortality after EVAR in 1037 patients was 21.2% versus 36.3% for 763 patients in the open repair group ($P<0.0001$). Centers performing EVAR as primary choice, treated patients with rAAAs endovascular in 28-79% (mean 49%) of all cases. Furthermore, centers with the largest number of patients had a lower 30-day mortality after EVAR as compared to centers with low patient numbers (21% versus 35%). The authors concluded that in patients with a suitable anatomy, EVAR seems to be a superior way to treat rAAAs with lower 30-days mortality than open repair. Especially high risk patients who most probably will not survive open surgery, e.g. hemodynamic instable patients or patients with a hostile abdomen, will benefit most of EVAR. Furthermore, centers that treat this category of patients should be able to perform both techniques and additional surgical procedures. Finally, some recommendations on several key strategies, adjuncts and technical factors to perform EVAR for rAAAs are listed in this publication:

- a standard approach or protocol is indispensable for an efficient treatment and facilitates decision-making;
- hypotensive hemostasis: fluid resuscitation should be restricted and low systolic arterial pressure is well tolerated for short periods and limits internal bleeding;
- for optimal results, EVAR procedures should be performed in well equipped sites where open surgery is also possible;
- catheter-guidewire placement should be performed under local anesthesia. By this, circulatory collapse caused by the induction of general anesthesia can be prevented;
- supraceliac aortic balloon control can be used in case of severe circulatory collapse;
- both bifurcated and AUI grafts can be used successfully;
- a high index of suspicion for abdominal compartment syndrome (ACS) is mandatory as this is a major cause of morbidity and mortality after EVAR for

rAAAs. ACS can be managed by early laparotomy, hematoma evacuation and open abdomen treatment with suction/sponge (VAC) dressings

The group of Schermerhorn published their results on endovascular versus open repair for ruptured AAA very recently.[11] In this study, perioperative mortality, mid-term survival, and morbidity after EVAR and open surgical repair were compared in a period of 10 years (2000-2010). In this period, 74 infrarenal ruptured AAAs were treated (19 by EVAR and 55 by open repair). Although EVAR patients were significant older and faced more comorbidity, a large difference in perioperative mortality was found in favor of the EVAR patients (15.7% versus 49%; P=0.008). Also other endpoint as mid-term and one-year survival, mean length of stay and ventilator-dependent respiratory failure were more advantageous in the EVAR treated patients. Because of these results, EVAR should be considered the standard of care for ruptured AAAs.

The Erasmus University Medical Center Experience: endovascular versus open surgical repair of ruptured AAAs

In the Erasmus University Medical Center (Rotterdam, the Netherlands) we performed a study to determine the trends in management for ruptured AAAs over a 20-year period. We also assessed the impact of treatment modality on early and late survival after ruptured AAA. The Erasmus University Medical Center is a tertiary institution, which provides endovascular and open vascular surgery in its full extent serving about one and a half million people living in the Rotterdam's conurbation. In this study we only included the patients with a true AAA rupture. We defined rupture as either direct visualization of fresh blood in the retroperitoneal or peritoneal compartments during open surgery, or visualization of periaortic hematoma on the immediate preoperative CTA.[12] Patients included were treated between 1991 and June 2012. All possible operation codes were retrieved retrospectively and the hospital charts and stored CTAs were manually searched to assess the presence of rupture. Due to the retrospective nature of this study, we were not able to determine the amount of patients with a ruptured AAA who were not operated on, either because they did not agree to surgery or because their surgical risk was unacceptably high. In the 1990s, open surgery was the only method to treat ruptured AAA but this changed in 2001 with the introduction of endovascular surgery for ruptured AAA in our facility. From the introduction onwards all patients suspected of ruptured AAA got a CTA to determine whether or not the aorta was suitable for endovascular repair, and the decision was individualized, according to anatomical suitability and the surgeon's preference.

In the last 5 years, logistics changed, making it possible to offer EVAR to any anatomically suitable patients at any day or time. This includes a CT scan

present in the emergency department, an endovascular team on call 24/7, and a full stock of endoprosthesis with a large selection of sizes and configurations. By institutional protocol, patients with a suspected ruptured AAA are kept on permissive hypotension and a CTA is performed immediately after confirmation of the presence of an AAA by ultrasound. The images are instantly transferred to the hospital's patient management system, where it can be redirected to a dedicated postprocessing image workstation. If a rupture is confirmed and the patient is anatomically suitable, preference is generally given to endovascular repair. Immediate repair is performed in the operating theatre using a mobile C-arm. Whenever possible, the procedure is performed under local anesthesia.

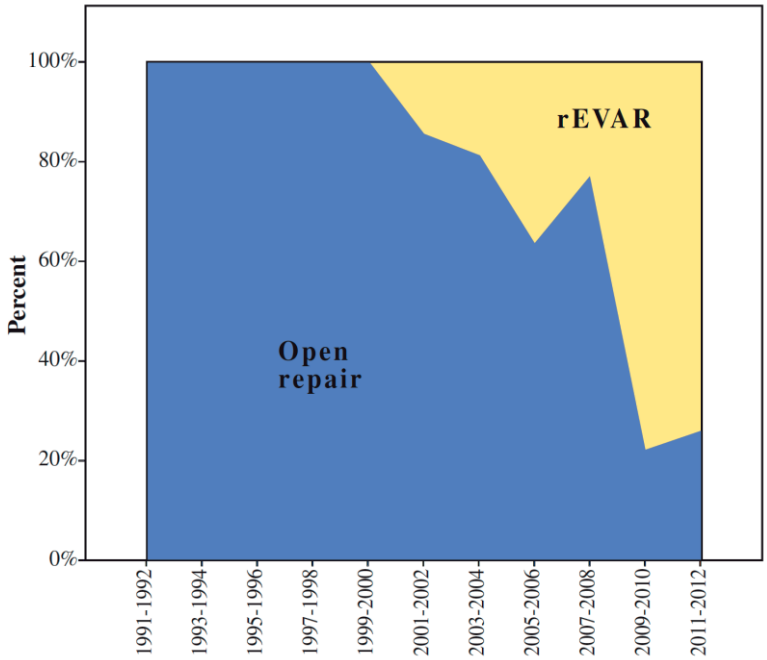
The data from all these patients were retrieved from emergency reports, CT scans, operation — as well as anesthesia reports, patient files and discharge letters. To obtain mortality rates, inquiry of national civil registry data was used to extract dates of death. The study endpoints were 30-day mortality and longterm survival. To compare 30-day mortality between EVAR and open surgery, $\chi 2$ test was used. Significant variables on univariable analysis were subsequently used in a multivariable logistic regression to determine the odds ratio (OR) and 95% confidence interval (CI) for 30-day mortality. Expected survival during follow-up was obtained using Kaplan-Meyer estimates, and survival after EVAR versus open repair was compared using the Log-rank (Mantel-Cox) statistical test. Kaplan-Meyer curves were plotted for 30-day, 5 year and overall survival.

The inclusion criteria were met in 314 patients with a mean age of 72±8 (88% male). Of these cases, 78 patients underwent EVAR and 236 patients open repair (Table 1). The mean age was not significantly different between the two groups. While in the first 10 years of the study open repair was used exclusively, a progressive increase in the proportion of patients managed by EVAR was observed in the last decade (Figure 1). The introduction of endovascular treatment was associated with an overall increase in the number of treated patients (119 in the first 10 years of the study versus 195 in the subsequent decade) and, simultaneously, a decrease in the overall 30-day mortality (from 52.6% in the period of 1991- 2001 to 39.3% from 2002 to 2012). The 30-day mortality rates were significantly lower in the patients treated with EVAR (23.8%) compared to open repair (52.3%; P=0.016, Figure 2a-c). These results support that early survival

Table 1. Baseline characteristics (N=314)

Variable	Open surgery	EVAR	P-value
Age - mean ±SD	71.5±8.1	72.7±7.7	0.24
Female – N. (%)	29 (12.3)	9 (11.5)	0.52

Figure 1. Trends of type of repair for treatment of rAAA (1991-2012).



benefit for EVAR is not restricted to elective repair but also possible of the acute setting. 3 Both open repair (OR: 2.46, 95% CI: 1.29-4.68, P=0.006) and age at repair (OR: 1.08, 95% CI: 1.04-1.12 per year increase) were independent risk factors for 30-day mortality. In Figure 3, one can see the change in use of type of stent in the acute treatment of rAAA. At first, only bifurcated stents were used in rAAAs because those were the only type of stents in stock. In the latter years, this changed by adding the AUI stent, which caused a shift in use from bifurcated to AUI. Aneurysm exclusion using AUI is generally faster as compared with bifurcated stent-grafts, which is potentially advantageous when treating hemodynamically unstable patients. Availability of AUI devices may have resulted in expansion in the range of "amenable" patients for EVAR, and also contribute to the reduction in patients managed by open surgery. Within the open repair group, a shift was seen as well; with an increase of the usage of tube grafts in the latter decade. However, the type of open repair (tube versus bifurcated graft) or endovascular repair (bifurcated versus AUI configuration) was not a significant determinant of 30-day mortality in this study.

The survival advantage for EVAR after ruptured AAA persisted during the first 5 years after repair (Figure 4; P=0.026), but no significant difference was observed when the entire period of follow-up was analyzed (P=0.078). The

Figure 2a. 30-day mortality for all patients (2003-2012)

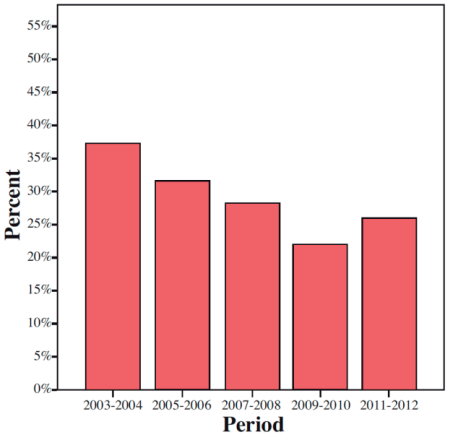


Figure 2b. 30-day mortality for patient treated with open repair (2003-2012)

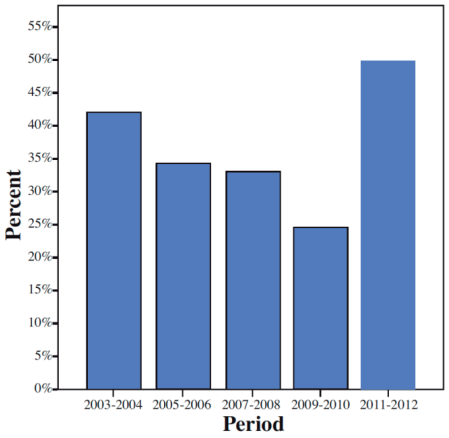
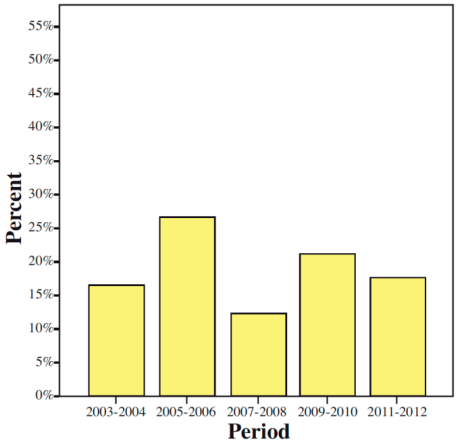


Figure 2c. 30-day mortality for patient treated with EVAR (2003-2012)



estimated 5-year survival was 44.6% and 39.1% for EVAR and open repair, respectively. These late survival rates are remarkably good and compare favorably to current literature.[11-13] Importantly, these late results are encouraging for current management of ruptured AAA. In conclusion, our study shows a significant difference between the endovascular and open repair approach in short-term and long-term mortality for patients with ruptured AAA in favor of endovascular treatment.

Figure 3. Trends of type of operation and type of graft.

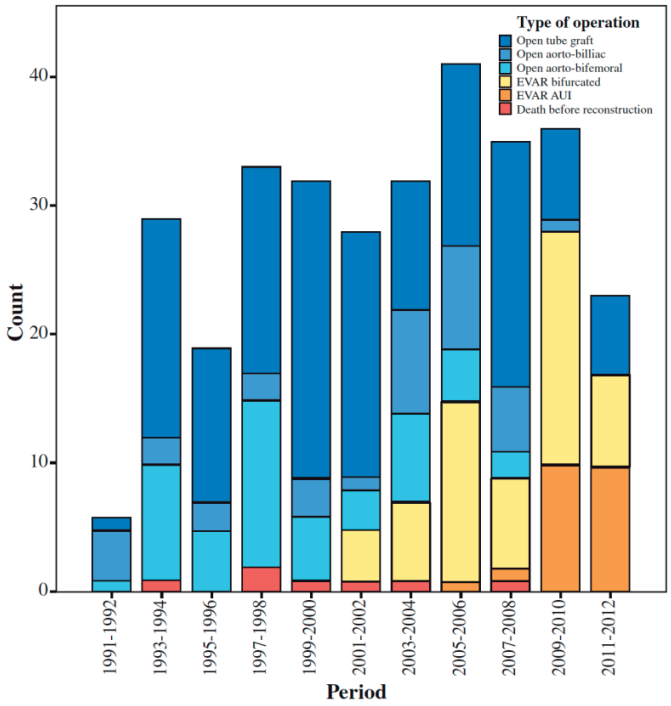
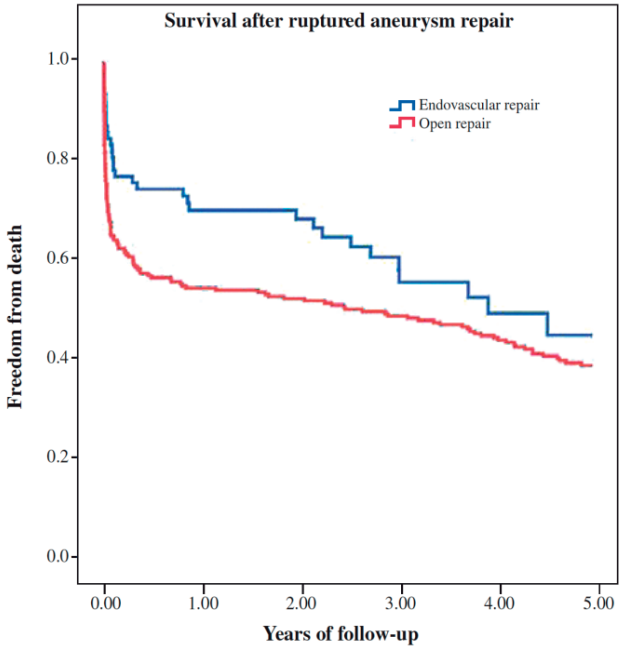


Figure 4. Survival at 5-years (p=0.026)



CONCLUSIONS

With the growing worldwide application of EVAR for the treatment of elective AAAs, this endovascular treatment modality has also been adapted increasingly to the management of patients with ruptured AAAs. In contrast to elective aneurysm repair, up to now, the (short-term) survival benefit of EVAR for rAAAs has not been confirmed by randomized clinical trials. The ECAR and IMPROVE trials are not completed yet and in the Nottingham pilot trial no significant differences in the 30-day mortality rates were found between open surgery and EVAR.[5, 7, 8] However, as this study was underpowered, no final conclusion can be drawn, except that it is possible to perform a randomized controlled trial in patients with ruptured AAAs. Also the authors of the AJAX trial did not succeed to demonstrate the potential benefits of EVAR in ruptured AAA repair.[9] In this study, only 22% (116/520) of all initial enrolled patients were randomized for EVAR or open surgery in a 7-year period. Moreover, in this small group, the open repaired patient performed much better than anticipated. These data endorse that is difficult to perform a randomized trial in patients with ruptured AAAs.

On the other hand, the majority of comparative, mostly observational, single-center studies show a clear trend towards reduced perioperative mortality for endovascular treatment as compared to open repair.[14, 15] The data from our tertiary institute, as described in this chapter, are in line with these reports. With both methods, randomized trials and observational studies, a potential selection bias can occur in selecting more hemodynamically stable patients or patient with a favorable anatomy. For the successful management of rAAAs by EVAR, it is a prerequisite that centers have dedicated teams, an extensive stock of materials and the rapid availability of CT-scan examination with appropriate planning software. Finally, it can be concluded that, within the limitations of the published studies and taking into account that not all patients are suitable for endovascular treatment due to anatomic constraints, endovascular repair is an effective and safe strategy as a primary treatment modality for ruptured AAAs.

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Chapter 4

Differences in Mortality, Risk Factors, and Complications After Open and Endovascular Repair of Ruptured Abdominal Aortic Aneurysms

Gerdine C.I. von Meijenfeldt[1]
Klaas H.J. Ultee[1]
Daniel Eefting[1]
Sander ten Raa[1]
Ellen V. Rouwet[1]
Joke M. Hendriks[1]
Hence J.M. Verhagen[1]
Frederico Bastos Gonçalves[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Objective

Endovascular aneurysm repair (EVAR) for ruptured abdominal aortic aneurysm (rAAA) has faced resistance owing to the marginal evidence of benefit over open surgical repair (OSR). This study aims to determine the impact of treatment modality on early mortality after rAAA, and to assess differences in postoperative complications and long-term survival.

Methods

Patients treated between January 2000 and June 2013 were identified. The primary endpoint was early mortality. Secondary endpoints were postoperative complications and long-term survival. Independent risk factors for early mortality were calculated using multivariate logistic regression. Survival estimates were obtained by means of Kaplan–Meier curves.

Results

Two hundred and twenty-one patients were treated (age 72 ± 8 years, 90% male), 83 (38%) by EVAR and 138 (62%) by OSR. There were no differences between groups at the time of admission. Early mortality was significantly lower for EVAR compared with OSR (odds ratio [OR]: 0.45, 95% confidence interval [CI]: 0.21–0.97). Similarly, EVAR was associated with a threefold risk reduction in major complications (OR: 0.33, 95%CI: 0.15–0.71). Hemoglobin level <11 mg/dL was predictive of early death for patients in both groups. Age greater than 75 years and the presence of shock were significant risk factors for early death after OSR, but not after EVAR. The early survival benefit of EVAR over OSR persisted for up to 3 years.

Conclusion

This study shows an early mortality benefit after EVAR, which persists over the mid-term. It also suggests different prognostic significance for preoperative variables according to the type of repair. Age and the presence of shock were risk factors for early death after OSR, while hemoglobin level on admission was a risk factor for both groups. This information may contribute to repair-specific risk prediction and improved patient selection.

INTRODUCTION

Since the introduction of endovascular aneurysm repair (EVAR) in 1991 by Volodos et al.1 and Parodi et al.,2 the use of this less invasive treatment for infra-renal aortic aneurysms has expanded significantly. Nowadays, >60–70% of all elective abdominal aortic aneurysm (AAA) repairs are performed with EVAR.3 and 4 This is not the case for ruptured AAA (rAAA), for which the use of EVAR has not yet achieved generalized acceptance.5 and 6 In general, rAAA are frequently fatal with a mortality of up to 80%,7 but patients surviving until they receive hospital care, might expect to benefit from a minimally invasive technique.

For elective surgery, randomized trials have demonstrated a nearly uniform threefold reduction in peri-operative mortality and prolonged survival benefit for EVAR over open surgical repair (OSR), which is maintained for at least 2 years.8 and 9 These results, also confirmed by large registries and national audits,10 have justified a shift towards a preferential use of EVAR. For rupture, however, evidence of a similar advantage is still lacking.

The aim of this study was to determine the impact of treatment modality on early mortality after rAAA repair, and to evaluate the differences in the prognostic capacity of preoperative variables in determining early survival for EVAR and OSR. Additionally, we investigated the differences in major postoperative complications and assessed any survival advantage related to treatment modality during follow-up.

METHODS

The study complied with the Declaration of Helsinki. According to our institutional guidelines, no formal ethical approval was required.

Patients

The study population consisted of all consecutive patients who underwent AAA repair between January 2000 and June 2013 at a single, tertiary institution. For this study, only patients with confirmed rAAA were included. Some of these patients have previously been included in a published 20-year overview of institutional trends in the management of rAAA.7 Patients with infected aneurysms and those having had prior aneurysm repair were excluded from the analysis.

Data collection

All possible operation codes and surgical reports were retrospectively retrieved, and hospital charts and computed tomography angiographies (CTAs) were checked for the presence of rupture. If confirmed, patient demographics, clinical baseline characteristics, intraoperative details, and clinical and laboratory outcome were obtained. Baseline characteristics on admission included age, gender, state of consciousness, blood pressure, and pulse rate. Duration from the emergency room (ER) to the operating theatre, operation duration, body temperature, blood pressure and pulse rate during operation, type of anesthesia, blood loss, and usage of blood products and fluids were derived from operative and anesthesia reports. Laboratory results on admission were also obtained. Postoperative complications and events were retrieved from hospital registries. Survival status and the exact date of death of treated patients were obtained via the national civil registry.

Missing data

Baseline data that were not retrievable were analyzed for differences between the OSR and EVAR groups. There were no significant differences in the number of missing data in either group, except for blood loss and the volume of intraoperative transfusion, owing to a lack of documentation about minimal blood loss and transfusions needed with an EVAR procedure. Only variables with <3% missing data were included in multivariate models.

Institutional management of rAAA

The Erasmus University Medical Center is a tertiary teaching institution with full capacity for endovascular and open vascular surgery (24 hours a day/7 days a week), serving about 1.5 million people living in the Rotterdam and surrounding area. Owing to the characteristics of the institution, a relatively high proportion of AAA repairs are done for rupture. Although the logistics involved in EVAR have been adapted and improved over time, the capacity to offer both treatment options was present throughout the entire study period. This made EVAR available for any anatomically suitable patient on any day and at any time. The choice of treatment is individualized, but preference is generally given to EVAR in older patients.

If a patient presents at the ER with a suspected rAAA, the on-call surgical team is informed. On arrival of the patient in the ER, an ultrasound of the abdominal aorta is done to confirm the presence of an aortic aneurysm if the patient is not known to have an AAA. Otherwise, a CTA can be performed immediately. Patients are

managed by permissive hypotension in the ER, and resuscitation is started only if the patient becomes unconscious.

According to protocol, a multi-slice CT scanner is used for rAAA CTA. The patient is scanned from nipple to pubic symphysis with a collimation of 118*0.6, and plain and contrast series are acquired after administering 120 mL of Visipaque 320 contrast. Anatomical suitability for EVAR is determined by the surgeon's expectations and experience. In anatomically complex cases, or whenever time allows, a dedicated post-processing workstation (3Mensio Vascular 4.2 software; 3Mensio Medical Imaging, Bilthoven, the Netherlands) is available for sizing and planning. After diagnosis, informed consent is obtained whenever possible.

Aneurysm repair is performed either by consultant vascular surgeons or by residents during their vascular sub-specialization under the direct supervision of a consultant vascular surgeon. For EVAR, repair is performed in the operating theatre using a mobile C-arm. Preference is given to local anesthesia for EVAR, although the decision depends on the individual case.

For OSR, a midline transperitoneal approach is preferred, and aorto-aortic or aorto-bi-iliac reconstruction is performed depending on the presence of concomitant iliac aneurysms. Postoperatively, intra-abdominal pressure using a vesical pressure probe is only checked when there is clinical suspicion of abdominal compartment syndrome.

Definitions

Rupture was defined by either direct visualization of fresh blood in the retroperitoneal or peritoneal compartments during OSR, or visualization of peri-aortic hematoma on the immediate preoperative CTA.11 Early mortality was defined by in-hospital mortality or death within 30 days of surgery. Major complications were defined as one of the following: respiratory; cardiac; cerebrovascular; renal failure (estimated glomerular filtration rate [eGFR] < 30); abdominal; wound; bleeding-related; lower limb ischemia; graft-related. Endovascular complications and EVAR-related adverse events were classified according to the reporting standards for EVAR by Chaikof et al.12 The shock index was calculated by dividing the heart rate by systolic blood pressure, and was calculated from the first heart rate and blood pressure recorded on arrival in the ER.13

Endpoints

The primary study endpoint was early mortality. Secondary endpoints were early major complications and overall survival during follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages, and compared with chi-square tests. Continuous variables are presented as means ± standard deviation and compared with Student t tests; or as median and interquartile range, and compared with Mann–Whitney U tests if the distribution was non-parametric. The influence of missing data on results was tested by comparing the outcome of patients with missing data to those with complete data sets. A logistic regression model was used to assess the proportional outcome risk associated with EVAR. Variables associated with 30-day in-hospital mortality were tested in univariate analysis by type of repair, and significant variables were introduced in a multivariate logistic regression model to determine independent significance. From the beginning of the study period the implementation of EVAR evolved and the number of patients undergoing the procedure increased. As a result, the year of operation was used as a co-variable to adjust for the growth in patients treated with EVAR every year. A graph of the proportion of the groups per year and the mortality rates per year of both groups is shown to illustrate the changes in both groups during the study period. Overall survival during follow-up was estimated using Kaplan–Meier tables, and survival after EVAR versus open repair was compared using the log-rank (Mantel–Cox) statistical test.

RESULTS

From January 2000 to June 2013, 878 patients underwent AAA repair at our institution. The study sample of rAAA included 221 patients with a mean age of 72 ± 8 years (90% of whom were men). Of these 221 patients, 138 were treated with OSR and 83 with EVAR. The demographics and clinical characteristics of patients on admission did not differ significantly between groups (Table 1).

Intraoperative details

Within the OSR group, 13 (9%) intraoperative deaths occurred, while in the EVAR group four (5%) deaths occurred (p = .21; Table 2). Most deaths occurred as a result of severe hemorrhagic shock. Intraoperative complications were observed in 15 (11%) and 10 (13%) patients after OSR and EVAR, respectively (p = .48). These complications differed significantly between groups. Thrombosis (n = 7) and

iatrogenic arterial lesions or dissection (n = 6) were the most frequent intraoperative complications for the OSR group; in the EVAR group, the main intraoperative complications were type I/III endoleaks (n = 6). Large differences were observed between the two treatment groups regarding the duration of operation, estimated intraoperative blood loss, and the intraoperative consumption of blood products and fluids (p < .001; Table 2).

Table 1. Preoperative baseline characteristics on admission.

Variable	OSR *n* = 138	EVAR *n* = 83	*P*
Age			
Mean ± SD	71.9 ± 7.8	72.1 ± 8.2	.89
>75 y, *n* (%)	46 (33)	29 (35)	.81
Male gender, *n* (%)	123 (89)	68 (93)	.37
Unconsciousness, *n* (%)	4 (3)	1 (1)	.65
Cardiopulmonary resuscitation before OR, *n* (%)	1 (1)	0 (0)	1
Hemodynamic status[a]			
Systolic blood pressure, mean ± SD	114 ± 37	115 ± 37	.81
Diastolic blood pressure, mean ± SD	69 ± 26	67 ± 21	.55
Heart rate (bpm), mean ± SD	85 ± 22	88 ± 25	.37
Shock index > 1[b]	31 (24)	29 (36)	.05
Hemoglobin (g/dL)			
Median (IQR)	11.1 (9.4–12.6)	11.8 (9.6–13.3)	.10
<11, *n* (%)	60 (46)	31 (42)	.59
Coagulation			
INR ≥ 1.5, *n* (%)[c]	33 (28)	24 (33)	.52
Platelet count ($\times 10^3$/μL), median (IQR)[a]	177 (135–235)	196 (154–256)	.008
eGFR			
Median (IQR)	61 (45–77)	63 (46–75)	.96
< 60, *n* (%)	68 (53)	37 (51)	.86
Leukocytes ($\times 10^3$/μL), median (IQR)[c]	12.0 (9.0–16.3)	12.5 (8.5–16.3)	.69
CRP (mg/dL), median (IQR)[c]	11 (5–47)	14 (4–70)	.58
Time from ER to OR (mins)[d]	50	36	.023

Note. OSR = open surgical repair; EVAR = endovascular aneurysm repair; OR = operating room; BPM = beats per minute; IQR = interquartile range; INR = international normalized ratio; eGFR = estimated glomerular filtration rate; CRP = C reactive protein; ER = emergency room.
a Missing 1–3% of baseline data.
b Heart rate/systolic blood pressure.
c Missing 3–15% of baseline data.
d Missing >15% of baseline data.

Table 2. Intraoperative characteristics.

Variable	OSR	EVAR	*p*
Duration of surgery (h), median (IQR)[a]	3.42 (3.07–4.46)	2.46 (2.20–3.57)	<.001
Blood loss (mL), median (IQR)[b]	4,500 (2,050–8,875)	200 (0–500)	<.001
Red blood cell concentrates, median (IQR)[b]	6 (3–11)	2 (0–4.5)	<.001
Plasma units, median (IQR)[b]	6 (2–10)	0 (0–2)	<.001
Platelet units, median (IQR)[b]	1 (0–5)	0 (0–0)	<.001
Crystalloids, median (IQR)[b]	4,000 (2,500–7,000)	1,500 (1,000–2,125)	<.001
Colloids, median (IQR)[b]	1,500 (1,000–2,000)	500 (0–1,000)	<.001
Body temperature at end of surgery, °C, median (IQR)[b]	35.9 (35.0–36.5)	36.00 (35.50–36.25)	.21
Intraoperative death, *n* (%)[a]	13 (9)	4 (5)	.21
Intraoperative complications, *n* (%)[a]	15 (11)	12 (14)	.48
Endoleaks (type I/III), *n* (%)	—	6 (7)	
Graft occlusion	2 (1)	1 (1)	
Peripheral embolization/thrombosis	7 (5)	0 (0)	
Iatrogenic dissection	3 (2)	0 (0)	
Arterial disruption with bleeding	3 (2)	2 (2)	
Unintentional renal artery occlusion	0 (0)	2 (2)	

Note. OSR = open surgical repair; EVAR = endovascular aneurysm repair; IQR = interquartile range.
a Missing 1–3% of baseline data.
b Missing 3–15% of baseline data.

Early survival

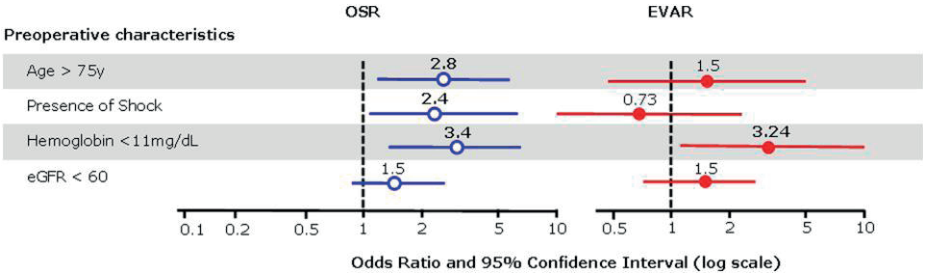
Early death occurred in 55 patients (40%) and 20 patients (24%) for OSR and EVAR, respectively. After adjusting for age, gender, eGFR, hemoglobin (Hgb) and hemodynamic status, and year of operation, EVAR was associated with a twofold risk reduction of early death compared with OSR (odds ratio [OR]: 0.45; 95% confidence interval [CI]: 0.21–0.97; Table 3). In multivariate analysis of risk factors for early mortality (Fig. 1), significant differences were observed between groups. Only a low Hgb level was an independent risk factor for both types of repair. Being older than 75 years and the presence of shock were risk factors for OSR only and not for EVAR. Univariate analysis suggested coagulopathy on admission as a risk factor for EVAR (OR: 4.60, 95%CI: 1.49–14.18) instead of OSR (OR: 1.69, 95%CI: 0.79–3.66), but the high number of missing values (12%) did not allow for inclusion of this variable in the multivariate model. Type of anesthesia (local vs. general) had no effect on mortality for EVAR patients (OR: 1.19, 95%CI: 0.67–2.04). Fig. 2 shows the proportion per year of EVAR- or OSR-treated patients, as well as the 30-day mortality per year per treatment.

Table 3. Thirty-day/in-hospital outcome after ruptured abdominal aortic aneurysm repair.

Variable	OSR	EVAR	OR[a]	95%CI
Mortality	55 (40)	20 (24)	0.45	0.21–0.97
Major complications	95 (76)	46 (58)	0.33	0.15–0.71
Systemic complications	80 (64)	42 (53)	0.69	0.34–1.38
Local complications	38 (30)	15 (19)	0.37	0.16–0.83
Fatal complications	37 (30)	13 (16)	0.39	0.17–0.90
Multiple complications	52 (42)	21 (27)	0.53	0.26–1.08

Note. ORs are given for EVAR compared with OSR. Significant values are presented in bold. OSR = open surgical repair; EVAR = endovascular aneurysm repair; OR = odds ratio; CI = confidence interval.
a Logistic regression is performed for each outcome measure, adjusting for age, gender, estimated glomerular filtration rate, preoperative hemoglobin level, hemodynamic status (shock index), and year of operation.

Figure 1. Multivariate logistic regression analysis of risk factors for early mortality, by type of repair (only including variables with <3% missing data).



Note. eGFR = estimated glomerular filtration rate; OSR = open surgical repair; EVAR = endovascular aneurysm repair.

Major postoperative complications

Median stay in the intensive care unit (ICU) was 4 (1–11) days for OSR and 1 (1–5) days for EVAR (p = .001). Median hospital stay was 14 (6–33) days for OSR and 8.5 (4–21) days for EVAR (p = .001). More major complications occurred after OSR than after EVAR (76% vs. 58%, p = .007). Furthermore, OSR patients were more likely to suffer from more than one complication (42% vs. 24%, p = .047) and have more frequent fatal complications (30% vs. 16%, p = .033). The distribution of complications is shown in Table 4. More abdominal, wound, and bleeding complications occurred after OSR, and more graft-related problems occurred after EVAR. Compared with OSR, EVAR was associated with a threefold risk reduction for major complications (OR: 0.33, 95%CI: 0.15–0.71), after adjusting for age, gender, Hgb, eGFR, hemodynamic status on admission, and year of surgery (Table 3).

Figure 2. Thirty-day mortality and relative amount of open surgical repair (OSR)- or endovascular aneurysm repair (EVAR)-treated patients.

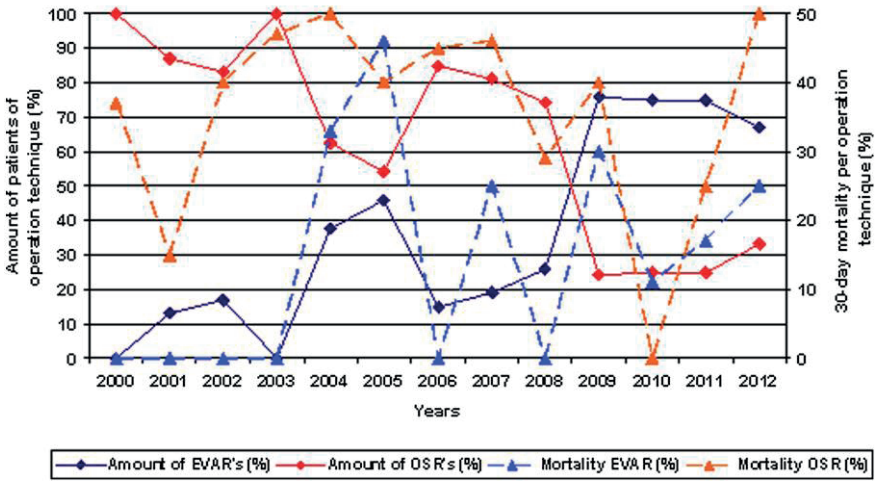


Table 4. Postoperative complications.

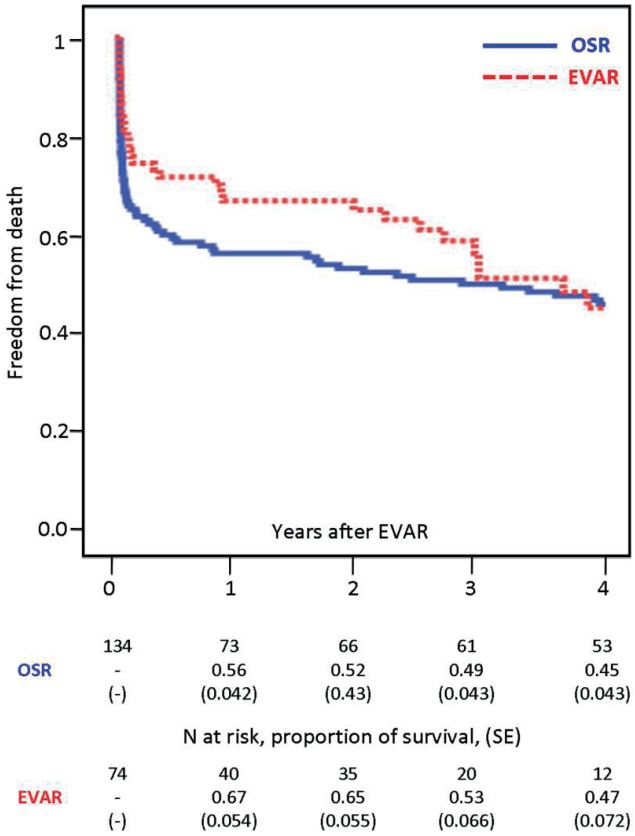
Variable	OSR	EVAR	*p*
Days in ICU, median (IQR)	4 (1–11)	1 (1–5)	.001
Total days of admission, median (IQR)	14 (6–33)	8.5 (4–21)	.001
Major complications	95 (76)	46 (58)	.007
Systemic complications	80 (64)	42 (53)	.124
Cardiac	20 (16)	8 (10)	
Cerebrovascular	6 (5)	3 (4)	
Renal	49 (39)	25 (32)	
Pulmonary	33 (26)	18 (23)	
Local complications	38 (30)	12 (19)	.070
Bowel ischemia	13 (10)	2 (3)	
Abdominal compartment syndrome	10 (8)	4 (5)	
Bleeding	7 (6)	1 (1)	
Distal embolization/thrombosis	5 (4)	1 (1)	
Wound infection	9 (7)	1 (1)	
Graft-related	3 (2)	5 (6)	
Multiple complications	52 (42)	19 (24)	.047
Fatal complications	37 (30)	11 (16)	.033

Note. OSR = open surgical repair; EVAR = endovascular aneurysm repair; ICU = intensive care unit; IQR = interquartile range.

Late survival

The survival benefit after EVAR on early outcome was maintained during the mid-term follow-up. The estimated survival after 2 years was 52% for OSR versus 65% for EVAR ($p < .001$; Fig. 3). After 3 years, the survival benefit after treatment with EVAR was no longer present.

Figure 3. Kaplan–Meier curve of survival after ruptured abdominal aortic aneurysm repair, by type of repair (log rank*p* = .52). *Note*. OSR = open surgical repair; EVAR = endovascular aneurysm repair.



DISCUSSION

In this study, EVAR was associated with a twofold reduction in early mortality after rAAA, after correcting for possible confounders. This benefit persisted for up to 3 years after the index event. Moreover, risk factors for early mortality varied in type and importance according to which treatment modality was selected. These risk factors could have a potential impact on current clinical practice.

In contrast to elective EVAR, which is widely accepted, EVAR for rAAA is far from accepted owing to a significant lack of level A evidence.5 and 6 To date, only two randomized controlled trials have been published on the subject. The Nottingham trial, which was only a pilot study, had difficulties with enrollment and was not able to show any differences in early mortality or complications. Recently, the results of the AJAX trial have been published.14 and 15 In this study, no difference in 30-day mortality and severe complications between EVAR and OSR were found. This could be explained, in part, by the unexpectedly good results from OSR, arguably difficult to achieve in most settings. With regard to the secondary endpoints of the AJAX study, EVAR generally performed better: mean ICU stay, mean hospital stay, mean blood loss, and the need for mechanical ventilation all favored the EVAR group. Both of the aforementioned studies were limited by low inclusion rates, which may result in significant bias, and are both considered to be underpowered.

Two other randomized trials are still in progress (IMPROVE16 and ECAR17). While the results of the ECAR trial are awaited, the IMPROVE investigators recently presented preliminary data.18 They were able to recruit 613 patients (about two-thirds of all eligible patients) with a clinical diagnosis of ruptured aneurysm. Based on intention-to-treat analysis, no significant difference was found between the EVAR and OSR groups for 30-day mortality (35.4% and 37.4%, respectively), but there was a significant number of protocol variations (11%). In the endovascular first strategy group, patients who were actually treated by EVAR (n = 150) had a 30-day mortality of 25% compared with 37% for those treated in the OSR first strategy group (n = 220), results similar to those obtained in our study (24% and 40%, respectively). Subgroup analysis revealed a survival benefit for women treated with EVAR. After EVAR, patients had a shorter stay in hospital than OSR patients, and the costs related to both groups of patients after 30 days was comparable. They also found that the lowest measured systolic blood pressure was an independent risk factor for 30-day mortality, and that the use of local anesthesia during EVAR reduced the 30-day mortality. In this study shock and use of local anesthesia had no effect on mortality after EVAR.

In contrast to published randomized trials, retrospective data are generally more favorable for EVAR. Inclusion of symptomatic non-ruptured aneurysms in retrospective series could contribute to this difference between trials and retrospective studies. To avoid such a bias in our study, we individually assessed the presence of true rupture in all cases. Veith19 has published collected data from 49 institutions that routinely use EVAR for the treatment of rAAA. One thousand and thirty-seven

patients treated by EVAR and 763 patients treated by OSR were included in the review. The study showed a significant reduction in early mortality favoring EVAR (21% vs. 36%, $p < .001$). The author concluded that EVAR is superior to OSR for patients with suitable anatomy, especially those who are more hemodynamically unstable, which is in line with the findings in this study. A population-based study by Mandawat et al. 20 showed that EVAR is superior to OSR in regard to short-term clinical outcomes (36% vs. 18%, $p < .01$). Nedeau et al. 21 published a retrospective study comparing EVAR with OSR. Although their patient sample was smaller than in this study (19 EVAR and 55 OSR patients), their conclusions were very similar, with EVAR conferring an early and mid-term survival benefit. A recent publication by Mehta et al.22 also compared early mortality for EVAR versus OSR in rAAA patients.22 In a sample of 283 patients, of whom 120 underwent EVAR, the authors reached a similar conclusion regarding an early mortality benefit for EVAR, which was maintained over time. However, the study by Mehta et al.22 found a higher risk for EVAR in elderly patients, which was only present for OSR in this study. In addition to survival analysis, more insight is provided into the complications after rAAA, suggesting important differences on the number and type of complications found after OSR and EVAR.

A low Hgb level on admission was associated with adverse early prognosis after rAAA. This seems logical, as it suggests more extensive bleeding and a more prolonged evolution, increasing the chance of cardiac ischemia due to inadequate oxygen delivery. This is potentially aggravated by the fact that OSR is associated with greater blood loss. Age more than 75 years was associated with a higher risk of early death after OSR, but not after EVAR. This could be the result of reduced physiological reserve in elderly patients, which is insufficient to withstand the added insult of open surgery. Similarly, the presence of shock on admission was an independent predictor for early outcome after OSR, but not after EVAR. This interesting observation may be explained by the less invasive nature of EVAR and the maintenance of higher peripheral resistance during endovascular operations. Another interesting observation is that coagulopathy on admission was associated with increased mortality after EVAR, but not after OSR. Although this could not be tested for confounders, it may be explained by persistent bleeding followed by abdominal compartment syndrome, and by a higher threshold for transfusion after EVAR.

The difference in early survival could also be explained by patient selection prior to the operation.22 A common argument is that the most unstable patients would not undergo a CTA and, as a consequence, not be offered EVAR. In our population,

however, admission hemodynamic status was similar for both groups, and the presence of shock was only found to influence outcome after OSR. It could be argued that the difference of admission time suggests that OSR patients are more unstable as theirs is shorter. We think that this difference is mainly due to the need for CTA in EVAR patients and not directly to patients' hemodynamic status. Furthermore, admission information was missing 16.7% of the data, which makes it less reliable than the shock index (<3%). These findings support the prior suggestion by Hinchliffe et al.6 that the most unstable patients may be the ones to obtain the greatest benefit from EVAR. Also, it is possible that anatomically suitable patients for EVAR have a better outcome than those who are anatomically unsuitable, independent of the type of repair, as suggested by Ioannidis et al.23 and Dick et al.24 However, this effect was not observed in a study by Ten Bosch et al.,25 in which anatomical suitability did not influence results in a cohort of patients who all underwent preoperative CTA irrespective of hemodynamic status. We could not confirm the hypothesis of anatomical suitability because some patients undergoing OSR did not undergo a preoperative CTA, and performing this analysis would inevitably incur bias. However, no supra-renal or type IV thoracoabdominal aneurysm patients were included in our series.

Postoperatively, the total admission period and ICU period for patients treated with EVAR was significantly lower than that of OSR-treated patients. This suggests a quicker recovery and less severe postoperative complications for EVAR. In parallel with mortality, EVAR was associated with a threefold reduction in the risk of major complications, and the occurrence of multiple and fatal complications were more frequent after OSR, contributing to better early survival rates for EVAR.

Over time, the prognosis of patients treated with EVAR gradually converged with that of OSR patients. In this series, the benefit of EVAR was maintained up to 3 years; beyond this point, the survival of the two groups was similar. No clear explanation for this effect could be found, but it is hypothesized that it may reflect the less aggressive nature of EVAR, therefore minimizing the "second hit" after rupture. In patients with severe comorbidities, the additional surgical aggression of OSR could result in early death. Similarly, frail patients may survive the acute period after EVAR, but succumb to their comorbidities at mid-term. We found no evidence that EVAR-related complications could explain the observed pattern.

The results of this study are limited by the retrospective design and individualized treatment selection, which could result in bias. Also, the time span of the study may have influenced results, with inevitable management and referral modifica-

tions occurring over time. For the outcome analysis, year of operation was used as a co-variable, therefore adjusting for this potential confounder. Because of the relatively small sample, and because many patients died very early after the start of follow-up owing to the rupture, there was not sufficient statistical power to determine differences in long-term survival, and restricted the analysis to 4 years after repair. Finally, accurate turn-down rates for repair, which are known to significantly influence the overall survival after rAAA, could not be provided. This important limitation probably has less impact on direct comparison between treatment modalities than on the overall results of rAAA repair.

In conclusion, this study shows a twofold early mortality risk reduction for rAAA patients undergoing EVAR, which is maintained over the mid-term. Old age and the presence of shock were significant predictors of early mortality for OSR only, suggesting that EVAR may be particularly beneficial for patients presenting with these factors.26 Also, OSR patients were at higher risk of major postoperative complications, required longer ICU and hospital stays, and appeared more likely to suffer from multiple and fatal complications after surgery. These results support the preferential use of EVAR for rAAA, and suggest a potential improvement in risk prediction by introducing the type of repair into the equation.

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Chapter 5

Outcomes for symptomatic abdominal aortic aneurysms in the American College of Surgeons National Surgical Quality Improvement Program

Peter A. Soden[1]
Sara L. Zettervall[1,2]
Klaas H.J. Ultee[1]
Jeremy D. Darling[1]
Dominique B. Buck[1]
Chantel N. Hile[1,3]
Allen D. Hamdan[1]
Marc L. Schermerhorn[1]

1) Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
2) Division of Surgery, George Washington University, Washington, DC
3) Division of Vascular and Endovascular Surgery, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA

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ABSTRACT

Objective

Historically symptomatic AAAs were found to have intermediate mortality compared to asymptomatic and ruptured AAAs but, with wider EVAR use, a more recent study suggested mortality of symptomatic aneurysms were similar to asymptomatic AAAs. These prior studies were limited by small numbers. The purpose of this study is to evaluate the mortality and morbidity associated with symptomatic AAA repair in a large contemporary population.

Methods

All patients undergoing infrarenal AAA repair were identified in the 2011-2013 ACS-NSQIP, Vascular Surgery targeted module. We excluded acute conversions to open repair and those for whom the surgical indication was embolization, dissection, thrombosis, or not documented. We compared 30-day mortality and major adverse events (MAE) for asymptomatic, symptomatic, and ruptured AAA repair, stratified by EVAR and open repair, with univariate analysis and multivariable logistic regression.

Results

5502 infrarenal AAAs were identified, 4495 asymptomatic (830 open repair, 3665 [82%] EVAR), 455 symptomatic (143 open, 312 [69%] EVAR), and 552 ruptured aneurysms (263 open, 289 [52%] EVAR). Aneurysm diameter was similar between asymptomatic and symptomatic AAAs, when stratified by procedure type, but larger for ruptured aneurysms (EVAR symptomatic 5.8cm ±1.6 vs. ruptured 7.5cm ±2.0, P<.001; open repair symptomatic 6.4cm ±1.9 vs. ruptured 8.0cm ±1.9, P<.001). The proportion of females was similar in symptomatic and ruptured AAA (27% vs. 23%, P=.14, respectively), but lower in asymptomatic AAA (20%, P<.001). Symptomatic AAAs had intermediate 30-day mortality compared to asymptomatic and ruptured aneurysms after both EVAR (asymptomatic 1.4% vs. symptomatic 3.8%, P=.001; symptomatic vs. 22% ruptured, P<.001) and open repair (asymptomatic 4.3% vs. symptomatic 7.7% , P=.08; symptomatic vs. 57% ruptured, P<.001). After adjustment for age, gender, repair type, dialysis dependence, and history of severe COPD, patients undergoing repair of symptomatic AAAs were twice as likely to die within 30-days compared to those with asymptomatic aneurysms (OR 2.1, 95%CI 1.3-3.5). When stratified by repair type the effect size and direction of the odds ratios were similar (EVAR OR 2.4, CI 1.2-4.7; open repair OR 1.8, CI 0.86-3.9), although not significant for open

repair. Patients with ruptured aneurysms had a seven-fold increased risk of 30-day mortality compared to symptomatic patients (OR 6.5, CI 4.1-10.6).

Conclusion

Patients with symptomatic AAAs had a two-fold increased risk of perioperative mortality, compared to asymptomatic aneurysms undergoing repair. Furthermore, patients with ruptured aneurysms have a seven-fold increased risk of mortality compared to symptomatic aneurysms.

INTRODUCTION

The 30-day mortality rate for abdominal aortic aneurysm (AAA) repair can range from approximately 1% to over 70% depending on whether the aneurysm is intact, symptomatic, or ruptured.[1-6] 3% to 15% of treated aneurysms have been described as symptomatic in prior studies.[7-10] Symptomatic abdominal aortic aneurysms present with symptoms of abdominal or back pain, often associated with tenderness to palpation of the aneurysm itself, and are thought to represent an intermediate risk group between elective and ruptured aneurysms.

Historically, many single institution studies showed that patients with symptomatic AAAs had higher rates of mortality and major adverse events compared to asymptomatic AAA repairs.[7, 10-14] However, most of these studies predated the wide use of EVAR and had small numbers of symptomatic AAAs. De Martino et al, using a contemporary clinical registry, the Vascular *Study* Group of New England (VSGNE), from 2003-2009, showed that there was no difference in in-hospital mortality between symptomatic and elective infrarenal AAA repairs, when stratified by procedure type.[8] This study had the largest cohort of symptomatic AAAs treated with EVAR at the time. Prior to this study, Cambria et al. reported that deferral of operation to medically optimize the patient and ensure appropriate staff are available, instead of immediate repair within the first 4 hours, improved outcomes for the symptomatic AAAs.[7] This led to an increased focus on preoperative management of the symptomatic patient and was thought to contribute to the lack of difference in perioperative mortality between elective and symptomatic patients in De Martino's study. However, many still believe that symptomatic AAAs continue to have an intermediate operative mortality risk in the short-term but there have been no studies with a current-practice distribution of EVAR and open repair and an adequate number of symptomatic AAA patients to address this ongoing question.

The purpose of this study was to analyze the differences in mortality and morbidity between patients with symptomatic AAAs compared to both asymptomatic and ruptured aneurysms in a contemporary population where EVAR was the preferred treatment modality for elective repair.

METHODS

Dataset

Using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Vascular Surgery targeted module from 2011-2013, we identi-

fied all patients undergoing endovascular (EVAR) and open AAA repair. The NSQIP vascular targeted module is an extension of the original NSQIP with 72 participating hospitals in the AAA module as of 2013. It is a multi-institutional collaboration that continues to collect all the preoperative, intraoperative, and 30-day outcomes that were contained in the original NSQIP as well as further clinical detail selected by vascular surgeons in an effort to better risk adjust and determine best practices. Trained clinical nurse reviewers complete all data collection, and each hospital has a surgeon champion, available to answer any questions related to data entry for cases submitted. Additional information on the NSQIP is available at www.facs.org/quality-programs/acs-nsqip.

Patients and Cohorts

All 6703 patients undergoing AAA repair in the targeted NSQIP were identified. For direct comparison to prior studies the primary analysis of this paper focused on repair of infrarenal aneurysms, as identified by proximal aneurysm extent. Juxtarenal aneurysms were included in the analysis with adjustment in multivariable analysis. A subset of patients who were documented to have infrarenal aneurysm extent yet had a suprarenal clamp position were re-classified as juxtarenal. All those with a proximal aneurysm extent listed as pararenal, suprarenal, or Type IV thoracoabdominal were excluded from the analysis. Patients with no documented proximal aneurysm extent or operative indication were excluded (n= 439 and n= 81 respectively). Patients with an operative indication of dissection, thrombosis, or embolization or those undergoing conversion from EVAR to open repair (n=33) were also excluded.

Patients with symptomatic AAAs were defined as those without evidence of rupture but presenting with abdominal or back pain, or symptoms from local compression by the aneurysm causing early satiety, hydronephrosis, or deep venous thrombosis. Ruptured aneurysms were divided into 2 groups based on hemodynamic status: hypotensive (defined as systolic blood pressure <90mmHg or drop in systolic blood pressure of >40mmHg from baseline or need for pressors preoperatively), and non-hypotensive. The asymptomatic non-ruptured group consisted of those with a surgical indication for repair listed as diameter, prior open repair with unsatisfactory result, or prior endovascular repair with unsatisfactory result. The latter two indications were accepted because it was thought likely that the symptomatic and rupture groups contained some of these patients as well, as only one indication can be entered per patient.

All variable definitions captured by the NSQIP can be found at www.facs.org/quality-programs/acs-nsqip. New or aggregate variables used in this analysis included, obesity, defined as a body mass index >30, and a binary variable for

diabetes mellitus, defined as both insulin and non-insulin dependent diabetes. For EVAR, percutaneous access included attempted but failed percutaneous access attempts. We consolidated the main body devices analyzed and created an "Other" group that included Cook Zenith Fenestrated (1.9%), Cook Zenith Renu (1.4%), Lombard Aorfix (<0.1%), Medtronic Aneurx (0.2%), Medtronic Talent (0.6%), Trivascular Ovation (0.9%), and other (4.1%). 10% of patients were missing data on lower extremity revascularization but these patients were considered as not having revascularization in our analysis. Time from admission to operation was recorded in days with day 0 representing operation on day of admission. We identified patients undergoing surgery after the day of admission to highlight the number of symptomatic patients who have a delay in their repair since this has been shown to affect outcomes in prior literature.[7] Operative details and outcomes were presented for EVAR and open repair separately.

All outcomes were within 30 days of the index operation. A major adverse event was defined as a myocardial infarction (diagnosed as new Q waves on ECG and documentation stating diagnosis of MI), intraoperative cardiac arrest, pneumonia, prolonged intubation (defined as >48 hours), worsening renal function (defined as a rise in creatinine of >2.0mg/dl or new requirement for dialysis), bowel ischemia as stated in the medical record whether intervention was necessary or not, lower extremity ischemia requiring intervention, or subsequent rupture after repair.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, or as median and interquartile range based on distribution. Categorical variables were presented as counts and percentages. Univariate differences between cohorts were assessed using $\chi 2$ and Fisher's exact tests for categorical variables and Student's t-test and Mann Whitney U test for continuous variables, where appropriate. Comparisons were made between asymptomatic and symptomatic AAAs and symptomatic to ruptured AAAs, stratified by repair type. To identify independent risk factors for 30-day mortality *and major adverse events* we used *purposeful selection*, *which utilizes both univariate analysis and* previously *identified* predictors for *the endpoint of interest,* to fill the multivariable model for the comparison of asymptomatic to symptomatic *and symptomatic to ruptured* AAAs.[15] Certain variables, such as emergency repair and aneurysm diameter were not included in the model as they were collinear with symptomatic aneurysms. We listed the Hosmer and Lemeshow statistic for all steps of model optimization to support the stability of our model given the limited number of total events. P-value < .10 *on univariate analysis was* used for inclusion *into each model*. All tests were two-sided and significance was

considered when P-value was < .05. IBM SPSS Statistics version 22.0 (IBM Inc., Chicago, IL) was used for all analysis. Permission to use deidentified data from the NSQIP, without the need for informed consent, was obtained from the Institutional Review Board at Beth Israel Deaconess Medical Center.

RESULTS

From a total of 6703 patients undergoing AAA repair in the vascular targeted NSQIP from 2011-2013, we excluded 516 (7.7% of total) pararenal/suprarenal aneurysms, 439 (6.5%) patients without documentation of aneurysm extent, 213 (3.2%) for indication of dissection, embolization, thrombosis, or no documentation, and 33 (0.5%) for acute conversion from EVAR to open repair. This left 5502 patients undergoing repair of infrarenal (85%, 92% EVAR) or juxtarenal (15%; 20% EVAR) aneurysms. The final cohort included 4495 asymptomatic patients (82% EVAR), 455 symptomatic patients (69% EVAR), and 552 ruptured patients (52% EVAR). Within the asymptomatic group there were 138 (3.1%) patients with prior unsatisfactory endovascular repair (72% EVAR) and 19 (0.4%) with unsatisfactory open repair (79% EVAR).

Patient Characteristics

Asymptomatic vs. Symptomatic

Symptomatic patients in general were younger (mean 72.6 SD ±10.1 vs. 73.6 ±8.6, p=.01), and less likely to be white (80% vs. 87%, P < .001), male (73% vs. 80%, P < .001), or obese (25% vs. 32%, P = .01)(Table 1). They were more likely to be current smokers (43% vs. 32%, P < .001), have preoperative acute renal failure (0.9% vs. 0.2%, P = .03) or hemodialysis (2.6% vs. 0.8%, P < .001), and have a preoperative transfusion (3.1% vs. 0.9%, P < .001). Patients with symptomatic AAAs had larger mean aneurysm diameter overall compared to asymptomatic aneurysms (asymptomatic 5.8 SD ±1.2 vs. 6.0 ±1.7, P = .045). Figure 1 illustrates a higher proportion of asymptomatic AAA repairs occurring between 5.0-5.9cm compared to symptomatic AAAs, which coincides with guidelines for elective repair in this group. As expected there was a higher proportion of symptomatic patients listed as emergent compared to asymptomatic patients (EVAR 26% vs. 2.1% P < .001; open repair 39% vs. 3.0%, P < .001). Symptomatic patients were more likely to have surgery deferred and to not undergo surgical repair on the same calendar day as admission (EVAR 44% vs. 12%, P < .001; open repair 42% vs. 23%, P < .001), which we hypothesized to represent time spent medically optimizing the patient and avoiding off-hour operations, although

Table 1. Preoperative Characteristics

	Asymptomatic %(n)	P-value Asymptomatic vs. Symptomatic	Symptomatic %(n)	P-value Symptomatic vs. Ruptured	Ruptured %(n)
N	**4495**		**455**		**552**
EVAR	82 (3665)	<.001	69 (312)	<.001	52 (289)
Age (years, mean ±SD)	73.6 ±8.6	.01	72.6 ±10.1	.30	73.3 ±10.1
White	87 (3887)	<.001	80 (366)	.62	79 (437)
Male	80 (3604)	<.001	73 (330)	.14	77 (423)
Diabetes	16 (710)	.01	11 (52)	.44	13.0 (72)
Current Smoker	32 (1423)	<.001	43 (197)	.06	38 (207)
Obesity (BMI >30)	32 (1408)	.01	35 (109)	.03	32 (137)
Dyspnea at rest or exertion	19 (851)	.83	19 (88)	<.001	9.6 (53)
Preoperative Intubation	0.1 (5)	.13	0.4 (2)	<.001	11 (60)
Hypertension	82 (3667)	.20	79 (360)	.002	71 (390)
History of					
Severe COPD	19 (837)	.10	22 (99)	.48	20 (110)
CHF exacerbation	1.7 (75)	.26	2.4 (11)	.80	2.2 (12)
Dependent functional status	2.8 (127)	.19	1.8 (8)	.001	5.8 (31)
ASA class > III	24 (1097)	<.001	43 (195)	<.001	86 (469)
Creatinine >1.78 mg/dl[a]	5.1 (225)	.96	5.2 (23)	<.001	17 (85)
Acute renal failure pre-op	0.2 (9)	.03	0.9 (4)	.21	1.8 (10)
On Dialysis pre-op	0.8 (35)	<.001	2.6 (12)	.50	2.0 (11)
Open wound/wound infection	1.0 (47)	.17	1.8 (8)	.70	1.4 (8)
Transfusion	0.9 (40)	<.001	3.1 (14)	<.001	26 (146)
Prior Open Abd. Surgery	23 (979)	.39	25 (104)	.13	21 (100)
Aneurysm Diameter, cm (mean, SD)	5.8 ±1.2	.045	6.0 ±1.7	<.001	7.7 ±2.0
Aneurysm Diameter, cm (median, IQR)	5.5 (5.1-6.2)	.19	5.7 (5.0-6.8)	<.001	7.7 (6.3-9.0)

COPD=Chronic obstrucive pulmonary disease, CHF= Congestive heart failure

[a] Patients on dialysis at baseline are not counted in those with elevated baseline Creatinine

a delay in diagnosis of a symptomatic aneurysm could also be contributing. Out of the 198 symptomatic patients who underwent repair after the day of admission 50% were operated on the next calendar day and 79% were operated on within three calendar days of admission.

Symptomatic vs. Ruptured

When compared to those with ruptured aneurysms, symptomatic patients were less likely to be obese (25% vs. 32%, P = .03), intubated prior to the OR (0.4% vs. 11%, P < .001), have dependent baseline functional status (1.8% vs. 5.8%, P = .001), preoperative creatinine elevation (5.2% vs. 17%, P = .001), preoperative transfusion (3.1% vs. 26%, P < .001), ASA score of 4 or 5 (43% vs. 86 %, P < .001)(Table 1). Symptomatic patients were more likely to have preoperative dyspnea on exertion (19% vs. 10%, P < .001) and hypertension (79% vs. 71%, P < .001). Aneurysm diameter was significantly smaller in symptomatic patients (6.0 ±1.7 vs. 7.7 ±2.0, P < .001), (Figure 1). As expected, there was a lower proportion of emergent cases amongst the symptomatic patients compared to those with rupture (EVAR 26% vs. 88%, P < .001; open repair 39% vs. 92%, P < .001), and greater deferment of cases to the following days after admission (EVAR 44% vs. 13%, P < .001; open repair 42% vs. 12%, P < .001).

Operative details

EVAR

The use of EVAR was highest in asymptomatic patients followed by symptomatic patients (asymptomatic 82% vs. symptomatic 69%, P < .001), and lowest in ruptures (52%, P < .001)(Table 2). Comparing EVAR for asymptomatic and symptomatic presentations, symptomatic patients were less likely to have a percutaneous attempt for access (20% vs. 27%, P = .01), had longer operative times (median 140 minutes [Inter-quartile range 110-178] vs. 133 [102-175], P = .02), and were more likely to require a concomitant access vessel conduit or repair (11% vs. 7.4%, P = .04).

When comparing symptomatic to ruptured EVAR, symptomatic EVAR cases had shorter operative times (140 [110-178] vs. 157 [116-205], P = .01) and were less likely to have an access vessel conduit or repair (11% vs. 18%, P = .01) (Table 2). There was a difference in main body devices used between groups. Excluder was the most common device used for asymptomatic, symptomatic, and ruptured aneurysms. Excluder was followed by Endurant then Zenith for asymptomatic and symptomatic aneurysms, but was followed by Zenith then Endurant for ruptures.

Table 2. Operative details for EVAR

	Asymptomatic %(n)	P-value Asymptomatic vs. Symptomatic	Symptomatic %(n)	P-value Symptomatic vs. Ruptured	Ruptured %(n)
N	**3665**		**312**		**289**
Emergent case	2.1 (76)	<.001	26 (82)	<.001	88 (253)
Distal Extent[a]		.12		.32	
Aortic	47 (1499)		45 (111)		38 (85)
Common Iliac	40 (1280)		39 (96)		42 (94)
External Iliac	5.7 (183)		5.2 (13)		8.6 (19)
Internal Iliac	7.4 (237)		12 (29)		11 (24)
Operation after day of admission	12 (446)	<.001	44 (138)	<.001	13 (36)
Percutaneous Access[b]	27 (972)	.01	20 (61)	.34	23 (66)
Juxtarenal Aneurysm	4.7 (171)	.91	4.8 (15)	.27	6.9 (20)
Main Body Device		.44		.004	
Cook Zenith	21 (752)		18 (56)		24 (70)
Endologix Powerlink	7.4 (270)		9.3 (29)		3.5 (10)
Gore Excluder	33 (1206)		36 (113)		38 (108)
Medtronic Endurant	30 (1088)		28 (88)		22 (64)
Other[c]	8.9 (325)		8.0 (25)		12 (35)
Concommitant Procedures					
Access Vessel Conduit/Repair	7.4 (271)	.04	11 (33)	.01	18 (52)
Hypogastric Embolization	6.6 (241)	.91	6.4 (20)	.23	9.0 (26)
Lower Ext. Revascularization[a]	3.5 (129)	.08	5.4 (312)	.12	8.7 (25)
Aortic Bare Metal Stent	2.1 (78)	.89	2.2 (7)	.55	1.4 (4)
Iliac Bare Metal Stent	3.4 (124)	.87	3.2 (10)	.86	3.5 (10)

[a] Patients missing data (12.7%) for concomitant lower extremity revascularization, defined as any bypass or stent to an infrainguinal artery, coded as "No" because unlikely to have had the procedure and not be captured. The 12.7% missing data from distal extent were kept as missing.

[b]Attempted percutaneous access counted as percutaneous

[c]Other main body device includes: Cook Zenith Fenestrated and Renu, Lombard Aorfix, Medtronic Aneurx, Medtronic Talent, Not documented, Other, Trivascular Ovation

Open Repair

Comparing symptomatic to asymptomatic patients there was no difference in operative time (246 [173-290] vs. 232 [178-302], P = 0.8 respectively), distal aneurysm extent, aneurysm diameter, proportion of juxtarenal aneurysms, or concomitant procedures performed (Table 3).

When comparing symptomatic to ruptured open repairs there was no difference in operative time (246 [173-290] vs. 235 [178-296], P = 0.9 respectively), distal aneurysm extent, proportion of juxtarenal aneurysms, or concomitant procedures performed (Table 3). A retroperitoneal approach was more commonly used in symptomatic patients compared to those with rupture (26% vs. 14%, P = .01).

30-day Outcomes

Symptomatic vs. Asymptomatic

The overall 30-day mortality rate was higher in symptomatic patients (5.1% vs. 1.9%, P < .001). For EVAR, symptomatic patients had a higher 30-day mortality rate (3.8% vs. 1.4%, P = .001) compared to asymptomatic patients (Table 4a). For open repair the mortality difference did not reach statistical significance (7.7% vs. 4.3%, P = .08)(Table 4b). There was also no difference in *30-day* mortality for patients with symptomatic aneurysms whose surgery was not performed on day of admission (EVAR- day of admission 3.4% vs. not on day of admission 4.3%, P = .68; open repair 8.4 vs. 6.7, P = .76).

The rate of major adverse events was higher for symptomatic, compared to asymptomatic, patients after EVAR (9.3% vs. 3.7%, P < .001)(Table 4a). However, no significant difference was seen following open repair (19% vs. 20%, P = .64)(Table 4b). After EVAR, rates of bleeding, myocardial infarction, cardiac arrest, and prolonged intubation were also higher in symptomatic patients. Among those surviving through hospital discharge, symptomatic patients undergoing EVAR had a longer length of stay than asymptomatic patients (3 days [2-6] vs. 2 [1-3], P < .001). After open repair there were no differences in peri-operative morbidity or length of stay.

Table 3. Operative details for Open Repair

	Asymptomatic %(n)	P-value Asymptomatic vs. Symptomatic	Symptomatic %(n)	P-value Symptomatic vs. Ruptured	Ruptured %(n)
N	**830**		**143**		**263**
Emergent case	3.0 (25)	<.001	39 (56)	<.001	92 (241)
Distal Extent		.83		.72	
Aortic	48 (366)		46 (60)		50 (114)
Common Iliac	43 (330)		47 (61)		41 (94)
External Iliac	5.2 (40)		3.8 (5)		3.1 (7)
Internal Iliac	3.5 (27)		3.8 (5)		5.3 (12)
Operation after day of admission	23 (187)	<.001	42 (60)	<.001	12 (32)
Retroperitoneal approach	25 (205)	.82	26 (37)	.002	14 (35)
Juxtarenal Aneurysm	55 (432)	.09	47 (64)	.08	56 (141)
Concomitant Procedures					
Lower Ext. Revascularization	7.6 (63)	.58	6.3 (9)	.32	9.1 (24)
Non-arterial abd. repair/excision	2.5 (21)	.51	3.5 (5)	.21	6.5 (17)

Table 4a. 30-day Outcomes for EVAR

	Asymptomatic %(n)	P-value Asymptomatic vs. Symptomatic	Symptomatic %(n)	P-value Symptomatic vs. Ruptured	Ruptured %(n)
N	**3665**		**312**		**289**
30-day Mortality	1.4 (50)	.001	3.8 (12)	<.001	22 (62)
Major Adverse Event	3.7 (136)	<.001	9.3 (29)	<.001	31 (89)
Return to Operating Room	3.7 (136)	.49	4.5 (14)	<.001	13 (38)
Bleeding	9.9 (364)	<.001	18 (57)	<.001	65 (189)
Cardiac Arrest with CPR	0.4 (14)	<.001	1.9 (6)	<.001	8.7 (25)
Myocardial Infarction	1.2 (45)	.02	2.9 (9)	.05	6.2 (18)
Prolonged Ventilation (> 48hours)	0.7 (27)	<.001	2.9 (9)	<.001	18 (53)
Acute Kidney Injury	0.3 (12)	.11	1.0 (3)	.08	3.1 (9)
New Dialysis	0.5 (18)	1.0	0.3 (1)	<.001	10 (29)
Post-op UTI	1.1 (39)	.77	0.6 (2)	.12	2.1 (6)
Surgical Site Infection	1.7 (61)	1.0	1.6 (5)	.02	4.8 (14)
Pulmonary Embolism	0.2 (7)	.48	0.3 (1)	.36	1.0 (3)
DVT	0.4 (16)	.65	0.6 (2)	.02	3.5 (10)
Lower Extremity Ischemia	1.2 (44)	1.0	1.0 (3)	.08	3.1 (9)
Rupture of Aneurysm after repair	0.1 (4)	1.0	0.0 (0)	<.001	4.8 (14)
Ischemic Colitis	0.5 (17)	.20	1.0 (3)	<.001	8.3 (24)
Length of Stay (days, median (IQR))[a]	2 (1-3)	<.001	3 (2-6)	<.001	7 (4-11)
Readmission[a]	7.7 (276)	.03	11 (34)	.49	9.4 (22)

Bleeding defined as transfusion of 1 or more units of red blood cells from surgical start up to and including 72 hours post-op; Acute kidney injury defined as increase in Creatinine > 2mg/dl from pre-op; Surgical site infection includes superficial, deep, and organ space infection; Ischemic colitis identified by presence of diagnosis on discharge summary or endoscopy for the purpose of diagnosis; UTI=Urinary tract infection (excluded patients with UTI pre-op); DVT=deep venous thrombosis

[a]Excluded patients who died in-hospital; Also data gathered from combination of historical readmission variable and more current one

Table 4b. 30-day Outcomes for Open Repair

	Asymptomatic %(n)	P-value Asymptomatic vs. Symptomatic	Symptomatic %(n)	P-value Symptomatic vs. Ruptured	Ruptured %(n)
N	**830**		**143**		**263**
30-day Mortality	4.3 (36)	.08	7.7 (11)	<.001	34 (89)
Major Adverse Event	20 (165)	.64	18 (26)	<.001	57 (149)
Return to Operating Room	10 (86)	.47	8.4 (12)	.001	22 (57)
Bleeding	73 (602)	.42	69 (99)	<.001	93 (244)
Cardiac Arrest with CPR	2.7 (22)	.79	2.8 (4)	.001	13 (33)
Myocardial Infarction	2.9 (24)	1.0	2.8 (4)	.11	6.8 (18)
Prolonged Ventilation (> 48hours)	11 (91)	.75	12 (17)	<.001	43 (112)
Acute Kidney Injury	1.9 (16)	1.0	1.4 (2)	.15	4.6 (12)
New Dialysis	4.0 (33)	.50	2.8 (4)	<.001	16 (42)
Post-op UTI	1.9 (16)	.67	1.4 (2)	.04	5.7 (15)
Surgical Site Infection	3.4 (28)	.30	1.4 (2)	.34	3.4 (9)
Pulmonary Embolism	0.5 (4)	.55	0.7 (1)	.66	1.5 (4)
DVT	2.3 (19)	.89	2.1 (3)	.13	5.7 (15)
Lower Extremity Ischemia	2.5 (21)	1.0	2.1 (3)	.04	7.2 (19)
Rupture of Aneurysm after repair	0.6 (3)	.30	1.4 (2)	.002	9.1 (24)
Ischemic Colitis	3.9 (32)	.46	2.1 (3)	.001	11 (29)
Length of Stay (days, median (IQR))[a]	7 (6-10)	.14	8 (6-12)	<.001	13 (9-23)
Readmission[a]	7.1 (56)	.81	7.7 (10)	.94	7.5 (13)

[a]Excluded patients who died in-hospital

Symptomatic vs. Ruptured

As expected, patients with symptomatic aneurysms had a lower 30-day mortality rate than those with ruptured aneurysms (5.1% vs. 27%, P < .001; OR 0.14, 95% CI 0.1-0.22). When stratified by type of repair, mortality was lower in the symptomatic group for both EVAR (3.8% vs. 22%, P < .001)(Table 4a) and open repair (7.7% vs. 34%, P < .001)(Table 4b).

Symptomatic patients had lower major adverse event rates compared to ruptured patients (EVAR 9.3% vs. 31%, P < .001 and open repair 18% vs. 57%, P < .001)(Table 4a and 4b respectively). Symptomatic patients also had a lower rate of bowel ischemia (EVAR 1.0% vs. 8.3%, P < .001; Open 2.1% vs. 11%, P = .001) and subsequent rupture after repair (EVAR 0.0% vs. 4.8%, P < .001; Open 1.4% vs. 9.1%, P = .002).

Multivariable Models

After adjustment symptomatic patients had twice the operative mortality compared to asymptomatic patients (OR 2.1, 95% CI 1.3-3.5)(Table 5). Additional predictors included increasing age, female sex, open repair (vs. EVAR), history of severe COPD, and on dialysis preoperatively. When stratified by procedure, this same model showed an increased risk for mortality after EVAR (OR 2.4, CI 1.2-4.7) and a similar effect size and direction for open repair (OR 1.8, CI 0.86-3.9), although not significant in the open repair group. Since method of repair may be influenced by presence of symptoms we ran the overall model without adjusting for this and found a similar risk of 30-day mortality associated with symptomatic

Table 5. Independent Predictors of 30-day Mortality in Elective and Symptomatic AAAs

	OR	95% CI	P-value
Symptomatic aneurysm	1.49	1.07-2.08	.02
EVAR (vs. open)	0.23	0.17-0.30	<.001
Age increase (by decade)	1.25	1.07-1.44	.004
Female	1.51	1.17-1.95	.002
Current smoker	1.24	0.97-1.60	.09
Baseline Cr > 1.78 mg/dl	2.14	1.63-2.82	<.001
Pre-op Wound	2.48	1.11-5.51	.03
Pre-op Transfusion	2.37	1.15-4.88	.02
Juxtarenal aneurysm	1.64	1.22-2.20	.001

*Also adjusted for diabetes, CHF, pre-op dialysis
Hosmer and Lemeshow test .13 (> .13 throughout all steps)
EVAR repairs only: Symptomatic aneurysm OR 2.42 (CI 1.57-3.74, P < .001)
Open repairs only: Symptomatic aneurysm OR 0.91 (CI 0.56-1.48, P = .70)

aneurysms (OR 2.3, CI 1.4-3.8). Symptomatic aneurysm was independently predictive of major adverse events as well (OR 1.5, CI 1.07-2.08)(Table 6).

After similar adjustment for age, repair type, history of congestive heart failure, history of COPD, dialysis dependence, and juxtarenal aneurysms, ruptured aneurysms were at a 7-fold increased risk of 30-day mortality compared to symptomatic aneurysms (OR 6.5,CI 4.1-10.6) and 5-fold increased risk of a major adverse event (OR 5.1, CI 3.6-7.2).

Table 6. Independent Predictors of MAE in Elective and Symptomatic AAAs

	OR	95% CI	P-value
Symptomatic aneurysm	2.14	1.3-3.3	.003
EVAR (vs. open)	0.40	0.2-0.7	.001
Age increase (by decade)	1.81	1.4-2.3	<.001
Female	1.83	1.2-2.8	.004
Dialysis dependent	8.28	3.2-21.2	<.001
Hx of severe COPD	1.85	1.2-2.8	.01
Juxtarenal aneurysm	1.68	0.99-2.9	.06

Initial model also included CHF episode within prior 30 days and elevated baseline creatinine >1.78mg/dl but not on dialysis
Hosmer and Lemeshow test 0.52 (> 0.51 throughout all steps of model optimization)
EVAR repairs only: Symptomatic aneurysm OR 2.42 (CI 1.2-4.7, P=.01)
Open repairs only: Symptomatic aneurysm OR 1.83 (CI 0.9-3.9, P=.12)

DISCUSSION

In this large contemporary series of symptomatic AAAs we found that symptomatic patients have a 2-fold increased risk of 30-day mortality compared to asymptomatic patients. Comparing ruptured and symptomatic patients we also found those with rupture have a 7-fold increased risk of 30-day mortality.

The distribution of symptomatic aneurysms in our study, 8.3%, lies well within the incidence previously reported in the literature, of 3% to 15%.[7-10] Many of the studies on symptomatic AAA repairs are outdated and under-represent the contemporary utilization of EVAR. We found that 69% of patients with symptomatic infrarenal aneurysms had EVAR in the NSQIP from 2011-13, which is quite different from the majority of prior studies on this topic in which open surgery was primarily or solely used.[14, 16-18] Studies that reported higher proportions of EVAR repair for symptomatic AAAs were limited by low numbers and were from single centers.[19, 20] From the Vascular Study Group of New England (VSGNE) in 2010, De Martino et al reported that 38% of symptomatic AAA repairs were completed

using EVAR (60 EVARs of 156 symptomatic AAAs).[8] They found no difference in in-hospital mortality between asymptomatic and symptomatic infrarenal aneurysm repairs, for EVAR (asymptomatic 0.4% and symptomatic 0.0%) and open repair (asymptomatic 2.9% and symptomatic 2.1%). Their study, however, was limited both by smaller numbers and the ability to detect only in-hospital-mortality rather than 30-day. However, over 1- and 4-years they did show reduced survival in symptomatic compared to asymptomatic patients. We have previously demonstrated that in-hospital mortality misses a substantial number of post discharge deaths that occur within 30 days, particularly after EVAR.[21] We found a significant difference in the larger EVAR subgroup (n=312) but not in the open repair subgroup (n=143), likely due to the smaller number of patients. Given the similar magnitude and direction of the effect size (odds ratio) in both the open and EVAR subgroups, it is reasonable to make the general statement from our larger multivariable model, that includes procedure type, that repair of symptomatic AAA is associated with twice the operative mortality compared to asymptomatic AAA repair. Subsequent to the VSGNE study, the ENGAGE registry for Endurant post-market surveillance reported similar 30-day mortality in 185 symptomatic AAAs compared to 1015 asymptomatic AAAs (0.5% vs. 1.5% respectively, p=.31).[9] However, it is difficult to compare real-world results from the NSQIP to a post-marketing surveillance study where most patients met strict eligibility criteria and received the same endograft. Our 30-day mortality rate for patients with asymptomatic aneurysms undergoing EVAR or open repair were consistent with rates previously reported for the NSQIP.[22]

Cambria et al reviewed the Mayo Clinic experience with symptomatic AAA and highlighted the importance of preoperative optimization of patients presenting with symptomatic AAA.[7] In that analysis patients with symptomatic AAAs undergoing operation within the first 4 hours of admission accounted for all deaths compared to those with surgery delayed either 4-24 hours or 24 hours to 7 days. The authors recommended delay to optimize fluid and electrolyte status, evaluation and limited preoperative improvement of cardiac and pulmonary status when necessary, and semi-elective repair when an experienced operating room staff was available. Unfortunately, the NSQIP does not track time from admission to operation in hours but instead by days. We were able to show that 42% of open repair and 44% of EVAR treated symptomatic patients underwent surgery at least one calendar day after the day of admission. We believe this is a surrogate for surgeons choosing to not operate on symptomatic AAAs emergently but allowing optimization and semi-elective repair as advocated by the Mayo Clinic group. We did not find a benefit to delayed surgery, but this may reflect our inability to quantify delay in hours rather than calendar days.

Symptomatic patients had higher rates of major adverse events after EVAR as well, when compared to asymptomatic patients, similar to VSGNE, where major adverse events were found to be approximately 7% and 28% after EVAR in asymptomatic and symptomatic patients respectively.[8]

Similar to prior studies, we had a higher proportion of females in the symptomatic group compared to the asymptomatic but there was no difference between symptomatic and ruptured.[7-9, 23] The reason for this remains unclear from this analysis; however, our previous work has shown that women are being repaired at relatively larger aneurysm sizes when diameter is indexed to body size.[24] Patients presenting with symptomatic or ruptured AAA were also more likely to be non-white. This could be from issues related to unequal access to care, screening, or differences in natural history of aneurysm disease between different races. Unfortunately further delineation between races could not be adequately assessed due to small numbers.

There was a difference in main body device preference between ruptured aneurysm repair and symptomatic/asymptomatic AAAs, with higher rates of the Cook Zenith and "other" devices being used compared to elective utilization, although the Gore Excluder was the most commonly used device for all 3 groups. Whether this is due to surgeon preference related to indication or what is available on the shelf for the more emergent situations is not clear from this analysis.

This study has several limitations. It was a retrospective analysis of a large clinical dataset. Also, despite the large number of symptomatic AAAs our multivariable models were limited by the number of total events. In addition, only one surgical indication could be chosen for recording purposes in the targeted NSQIP and because of this we could not identify the proportion of patients in the symptomatic and ruptured groups who had prior unsuccessful EVAR or open repair. However, those with prior unsuccessful aneurysm repair represented a very small percentage of the asymptomatic group, where it could be identified, and were unlikely to influence the results of this analysis. In addition, the definition of ruptured and symptomatic aneurysms are taken directly from the surgeon's operative note and we believe the larger than expected proportion of non-emergent ruptured aneurysms is likely from miscoding of the emergent status, and may also include some contained ruptures that for undocumented reasons were not repaired emergently. We expected and confirmed that some small aneurysms were being repaired for symptoms but NSQIP lacks data for other potential reasons for repair of small AAA including rapid growth, large concurrent iliac aneurysm, saccular shape, pseudoaneurysm, infected aneurysm, or strong family history of rupture. Similarly, rupture of small AAA could be a result of the above factors as well. Finally, patients could be reported as symptomatic

if their aneurysm caused local compression symptoms; this subgroup of symptomatic patients is presumably not at risk for imminent rupture but we could not differentiate them from the patients presenting with pain. However, inclusion of these patients would likely lower the mortality in this group.

CONCLUSION

In this large contemporary study of symptomatic AAA patients, in which the majority were treated with EVAR, we found that symptomatic patients have twice the perioperative mortality compared to asymptomatic patients. Despite this we also find a reduction in perioperative mortality for symptomatic aneurysms compared to prior reports where the majority were treated by open repair, and believe this supports an EVAR-first approach for symptomatic aneurysms with suitable anatomy.

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Part II

CLARIFYING PROCEDURAL RISK FACTORS FOR AAA REPAIR

chapter 9

The Impact of Concomitant Procedures during Endovascular Abdominal Aortic Aneurysm Repair on Perioperative Outcomes

Klaas H.J. Ultee[1,2]
Sara L. Zettervall[1]
Peter A. Soden[1]
Jeremy Darling[1]
Jeffrey J. Siracuse[3]
Matthew J. Alef[4]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]
on behalf of the Vascular Study Group of New England

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
3) Department of Surgery, Division of Vascular and Endovascular Surgery, Boston University School of Medicine, Boston, MA, USA
4) Department of Surgery, Division of Vascular Surgery, The University of Vermont Medical Center and University of Vermont College of Medicine

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ABSTRACT

Objective

Concomitant procedures during endovascular repair (EVAR) of an abdominal aortic aneurysm (AAA) are performed to either facilitate endograft delivery, simultaneously treat unrelated conditions, or to resolve intraoperative pitfalls. The frequency and perioperative impact of these procedures are not well described. This study aims to assess the frequency and perioperative impact of various concomitant procedures performed at the time of EVAR

Methods

We included all elective EVARs in the Vascular Study Group of New England between January 2003 and November 2014, and identified those with and those without concomitant procedures. Multivariable logistic regression analysis was used to establish the independent association between concomitant procedures and perioperative outcomes.

Results

4033 patients were included in the study, with 1168 (29.0%) patients undergoing one or more additional procedure. Independent risk factors for 30-day mortality were concomitant femoral endarterectomy (OR: 4.8, 95% CI: 2.1-11.2) and renal angioplasty or stenting (3.1, 1.2-8.3). Postoperative bowel ischemia was associated with hypogastric embolization (3.8, 1.1-13.4) and iliac angioplasty or stenting (3.5, 1.3-9.6). Leg ischemia was associated with unplanned graft extension (2.3, 1.02-5.0), other artery reconstruction (5.2, 1.8-15.1), thrombo-embolectomy (5.2, 1.3-20.8), and repair of arterial injury (4.6, 1.2-18.3). Risk factors for deterioration of renal function were ilio-femoral bypass (3.9, 1.3-12.2), other artery reconstruction (2.7, 1.3-5.8), renal angioplasty or stenting (2.5, 1.3-4.6), and repair of arterial injury (4.5, 1.6-12.2). Myocardial infarction was associated with femoro-femoral bypass (3.9, 1.7-8.7), other artery reconstruction (3.9, 1.6-9.2) and repair of arterial injury (6.1, 1.8-21.0). Wound complications were predicted by femoro-femoral bypass (13.4, 5.8-31.1).

Conclusions

Concomitant procedures during EVAR are associated with increased postoperative morbidity and mortality. The need for performing concomitant procedures should be carefully considered. The morbidity associated with intraoperative complications highlights the importance of avoidance of arterial injury and thrombo-embolic events where possible.

INTRODUCTION

Endovascular repair (EVAR) has become the primary mode of treatment for elective abdominal aortic aneurysms (AAA).[1] EVAR is often performed in conjunction with additional procedures. These adjunctive procedures are done for various reasons, such as gaining adequate access to aorto-iliac vessels, establishing adequate endograft seal, but also to resolve intraoperative pitfalls, or to treat unrelated conditions. As EVAR is increasingly utilized for patients with complex anatomy, who more often undergo concomitant procedures, the need for evidence determining the perioperative implications of these interventions is rising.[1, 2]

Several studies have assessed the influence of various types of concomitant procedures on outcome.[3-5] The largest and most recent report by Hobo et al. showed that concomitant endovascular procedures were associated with low additional risks, while surgical interventions for peripheral vascular disease significantly worsened outcome.[6] Although interesting, the clinical implications of these results may be limited, as outcomes were provided for the overall procedural categories only (e.g., endovascular, surgical, etc.), and devices, treatment strategies, and outcomes have changed since the study's last enrollment in 2003.[7, 8] More recently, several studies have reported on the safety of procedures facilitating EVAR, such as concomitant hypogastric embolization and femoral endarterectomy.[9-12] However, these reports described only single institution experiences and were limited to relatively small numbers of patients.

In addition, the role of EVAR as an opportunity to treat concurrent vascular diseases is largely unclear, despite a high prevalence of occlusive vascular disease in the AAA population.[13-16]. Moreover, it has been shown that a substantial proportion of AAA patients later require non-aortic vascular surgery,[17] which will likely increase as life expectancy is improving. By sparing a second operation, total morbidity, hospitalization and costs may decline. The purpose of this study is to assess the frequency and perioperative impact of various concomitant vascular interventions performed at the time of EVAR.

METHODS

Database

For this study, we used data from the Vascular Study Group of New England (VSGNE). The VSGNE is a regional multidisciplinary collaboration of 30 academic and non-academic centers, which prospectively gather data for 12 commonly performed vascular procedures, including EVAR. The group aims to improve regional

outcomes in vascular surgery through monitoring and evaluation of 140 detailed patient demographic, operative, and clinical outcome variables. Trained nurses or clinical data abstractors enter the data in the registry. Surgeons are responsible for the documentation of operative details and intraoperative complications. Researchers employing the VSGNE are blinded to patient, surgeon, and hospital identity. The data are validated through comparisons of submitted hospital data to discharge claims from each of the participating institutions.[18] Patients in the VSGNE are individually matched to administrative data using unique identifiers to assess completeness and accuracy. Previous audits have demonstrated complete data capture for 99% of procedures and in-hospital mortality was correctly entered for all patients. More details on this regional registry can be found at http://www.vsgne.org. As the VSGNE contains de-identified data only without protected health information, Institutional Review Board approval and patient consent were waived.

Patients

We identified all patients undergoing elective endovascular AAA repair between January 2003 and November 2014. Patients with symptomatic AAA were excluded from the analysis. The following concomitant procedures at the time of EVAR are captured by the VSGNE: hypogastric embolization, unplanned graft extension, femoro-femoral bypass, femoral endarterectomy, iliac angioplasty or stenting, ilio-femoral bypass, renal angioplasty or stenting, other artery reconstruction, thrombo-embolectomy and repair of arterial injury. Patients undergoing multiple concomitant procedures were grouped in each of the procedure groups.

Clinical and outcome variables

The additional procedure groups were compared to those without concomitant procedures on baseline characteristics, intraoperative data, and postoperative outcomes. Baseline characteristics consisted of demographics, co-morbidities, and aneurysm diameter. Intraoperative details included operative time, blood loss, contrast media volumes, arterial injury, the occurrence of endoleaks and conversion to open repair. Postoperative outcomes were in-hospital events with the exception of 30-day mortality, and included deterioration of renal function, leg ischemia, cardiac complications, pneumonia, bowel ischemia, wound complications, postoperative blood transfusions, return to the operating room, prolonged postoperative length of stay, and prolonged length of stay in the intensive care unit (ICU). Deterioration of renal function was defined as an increase in postoperative creatinine >0.5mg per dl and/or need for dialysis. Prolonged length of

stay was considered when a patient remained hospitalized longer than 2 days postoperatively.

Statistical analyses

Categorical variables are presented as counts and percentages. Normally distributed continuous variables are presented as mean ± standard deviation and non-parametric distributions as median and interquartile range. Differences between those with and those without concomitant procedures were initially assessed using χ^2 and Fisher's exact testing for categorical variables and Student's t-test, and Mann Whitney U test for continuous variables, where appropriate. Multivariable logistic regression was subsequently used to assess the independent associations between additional procedures and postoperative outcomes. For the adjusted analyses, baseline characteristics were first univariately tested. Variables with a P-value ≤ .1 were subsequently entered into the multivariable model. To avoid overfitting while maintaining adjustment for potential confounding procedures, the concomitant procedures were entered into the multivariate model using a conditional forward inclusion approach (p-value for entry <0.05, exit >0.10). To clarify, the association between all concomitant procedures and the outcome was tested, but only predictive procedures were entered into the multivariable model. Different models were constructed for each of the outcomes. All tests were two-sided and significance was considered when p-value <0.05. Statistical analysis was performed using the SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 4033 patients were included in the study, with 1168 patients (29.0%) undergoing one or more concomitant procedure. In addition to EVAR, 228 (5.7 %) patients received hypogastric embolization, 357 (8.9%) unplanned graft extension, 118 (2.9%) femoro-femoral bypass, 175 (4.3%) femoral endarterectomy, 403 (10.0%) iliac angioplasty or stenting, 29 (0.7%) ilio-femoral bypass, 134 (3.3%) renal angioplasty or stenting, 96 (2.4%) other artery reconstruction, 31 (0.8%) thrombo-embolectomy, and 37 (0.9%) repair of arterial injury. Of the 1168 patients undergoing concomitant procedures, 337 (28.9%) underwent multiple procedures (Supplemental Table 1).

Baseline characteristics

Baseline characteristics are detailed in Table 1. Compared to patients undergoing isolated EVAR, concomitant hypogastric embolization patients were less

Table 1a. Baseline characteristics

	No concomitant procedure	**Hypogastric embolization**		**Unplanned graft extension**		**Femoro-femoral bypass**		**Femoral endarterectomy**		**Iliac angioplasty or stenting**	
	N=2865 (71.0%)	*N=228 (5.7%)*	*P-value*	*N=357 (8.9%)*	*P-value*	*N=118 (2.9%)*	*P-value*	*N=175 (4.3%)*	*P-value*	*N=403 (10.0%)*	*P-value*
Age – (mean ± sd)	73.8 (8.4)	72.8 (8.8)	.075	74.9 (8.8)	.017	73.9 (8.9)	.926	74.8 (8.0)	.117	74.0 (8.3)	.671
Female gender – N (%)	501 (17.5)	26 (11.4)	.019	80 (22.4)	.023	46 (39.0)	<.001	78 (44.6)	<.001	119 (29.5)	<.001
Hypertension – N (%)	2412 (84.2)	185 (81.1)	.218	310 (87.1)	.163	103 (87.3)	.373	153 (87.4)	.260	362 (89.8)	.003
Diabetes – N (%)	551 (19.2)	41 (18.0)	.643	60 (16.8)	.269	22 (18.6)	.872	40 (22.9)	.240	92 (22.8)	.090
CAD – N (%)	932 (32.5)	80 (35.1)	.430	117 (32.9)	.902	45 (38.1)	.205	57 (32.6)	.994	146 (36.2)	.141
COPD – N (%)	957 (33.4)	69 (30.3)	.329	123 (34.5)	.698	48 (40.7)	.102	73 (41.7)	.025	152 (37.7)	.089
Renal insuf – N (%)	148 (5.3)	13 (5.7)	.781	27 (7.8)	.056	8 (6.8)	.475	7 (4.1)	.491	34 (8.5)	.009
Dialysis – N (%)			.367		.266		.595		.685		.944
Working transplant	5 (0.2)	0 (0)		0 (0)		0 (0)		0 (0)		1 (0.2)	
On dialysis	20 (0.7)	0 (0)		5 (1.4)		0 (0)		2 (1.1)		3 (0.7)	
Smoking – N (%)			.106		.144		.096		<.001		.001
Never	373 (13.0)	40 (17.6)		59 (16.6)		13 (11.0)		12 (6.9)		40 (9.9)	
Past	1684 (58.8)	121 (53.3)		195 (54.8)		61 (51.7)		86 (49.1)		215 (53.3)	
Current	805 (28.1)	66 (29.1)		102 (28.7)		44 (37.3)		77 (44.0)		148 (36.7)	
Max diameter (mm, ± sd)	56.5 (20.5)	53.5 (15.2)	.006	57.8 (12.3)	.248	59.0 (14.9)	.084	56.9 (11.8)	.810	55.2 (12.7)	.207

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease

Table 1b. Baseline characteristics

	No concomitant procedure	Ilio-femoral bypass		Renal angioplasty or stenting		Other artery reconstruction		Thrombo-embolectomy		Repair arterial injury	
	N=2865 (71.1%)	*N=29 (0.7%)*	*P-value*	*N=134 (3.3%)*	*P-value*	*N=96 (2.4%)*	*P-value*	*N=31 (0.8%)*	*P-value*	*N=37 (0.9%)*	*P-value*
Age – (mean ± sd)	73.8 (8.4)	74.5 (7.5)	.671	76.6 (7.7)	<.001	75.0 (7.6)	.169	76.7 (6.7)	.024	74.8 (9.8)	.473
Female gender – N (%)	501 (17.5)	13 (44.8)	<.001	41 (30.6)	<.001	19 (19.8)	.559	15 (48.4)	<.001	17 (45.9)	<.001
Hypertension – N (%)	2412 (84.2)	27 (93.1)	.192	123 (91.8)	.018	82 (85.4)	.757	26 (83.9)	.954	34 (91.9)	.204
Diabetes – N (%)	551 (19.2)	4 (13.8)	.636	27 (20.1)	.794	17 (17.7)	.708	5 (16.1)	.662	5 (13.5)	.379
CAD – N (%)	932 (32.5)	9 (31.0)	.863	52 (38.8)	.131	39 (40.6)	.097	10 (32.3)	.973	12 (32.4)	.989
COPD – N (%)	957 (33.4)	14 (48.3)	.092	54 (40.3)	.100	28 (29.2)	.384	15 (48.4)	.079	13 (35.1)	.827
Renal insuf – N (%)	148 (5.3)	2 (7.1)	.658	14 (10.4)	.010	6 (6.3)	.656	3 (10.0)	.212	2 (5.4)	1.000
Dialysis – N (%)			.880		.554		.851		.250		.003
Working transplant	5 (0.2)	0 (0)		0 (0)		0 (0)		0 (0)		1 (2.7)	
On dialysis	20 (0.7)	0 (0)		0 (0)		1 (1.0)		1 (3.2)		0 (0)	
Smoking – N (%)			.391		.377		.988		.112		.220
Never	373 (13.0)	2 (6.9)		23 (17.2)		12 (12.5)		3 (9.7)		5 (13.5)	
Past	1684 (58.8)	16 (55.2)		74 (55.2)		57 (59.4)		14 (45.2)		17 (45.9)	
Current	805 (28.1)	11 (37.9)		37 (27.6)		27 (28.1)		14 (45.2)		15 (40.5)	
Max diameter (mm, ± sd)	56.5 (20.5)	58.6 (13.5)	.582	59.9 (10.6)	.058	54.5 (14.3)	.342	61.5 (13.4)	.181	58.8 (12.6)	.505

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease

often female (17.5% vs. 11.4%, P=.019), while all other concomitant procedure groups –except other artery reconstruction– had a higher proportion of women (22.4% – 48.4%, P-value range <.001 to .023). Also, patients receiving unplanned graft extensions, renal angioplasty or stents, and those undergoing a thrombo-embolectomy were older (73.8 years vs. 74.9, 76.6, and 76.7; P=.017, P<.001, and P=.024, respectively). Patients undergoing additional femoral endarterectomy more often suffered from obstructive pulmonary disease (33.4% vs. 41.7%, P=.025). Iliac and renal angioplasty or stenting patients more commonly had renal insufficiency (5.3% vs. 8.5% and 10.4%, P=.009 and P=.010) and hypertension (84.2% vs. 89.8% and 91.8%, P=.003 and P=.018, respectively). Finally, as expected, smoking was more frequently observed in patients undergoing concurrent treatment of atherosclerotic disease (i.e. femoral endarterectomy: 28.1% vs. 44.0%, P<.001; iliac angioplasty or stenting: 36.7%, P=.001).

Intraoperative characteristics

Operative time was significantly longer (140 min. vs. 193 – 286 min., P<.001 for all, Table 2) and blood loss higher for all concomitant procedure groups (209 mL vs. 297 – 885 mL, P ≤.001 for all). Similarly, patients undergoing combined procedures more often required blood transfusions (3.0% vs. 10.4 – 37.9%, P<.001 for all) and had higher rates arterial injury (0.6% vs. 3.0 – 70.3%, P-value range <.001 to .014). Not surprisingly, type I endoleak occurred more often in patients undergoing concomitant unplanned graft extension (1.9% vs. 7.3%, P<.001), but also in those undergoing iliac angioplasty or stenting (3.5%, P=.032), femoral endarterectomy (4.0%, P=.048), renal angioplasty or stenting (9.0%, P<.001) or repair of arterial injury (13.9%, P<.001). Type III was more common in those undergoing hypogastric embolization (0.2% vs. 1.8%, P=.003) and unplanned graft extension (1.4%, P<.001). In contrast, fewer type II endoleaks were found in patients undergoing procedures to treat atherosclerotic occlusive disease, such as concomitant iliac angioplasty or stenting (22.7% vs. 13.4%, P<.001), iliofemoral bypass (6.9%, P=.044), renal angioplasty or stenting (12.7%, P=.006) and thrombo-embolectomy (6.5%, P=.030).

Postoperative outcomes

Increased 30-day mortality rates were found in patients undergoing concomitant femoro-femoral bypass (0.8% vs. 3.4% P=.018, Table 3), femoral endarterectomy (4.6%, P<.001), iliac angioplasty or stenting (2.7%, P<.001), renal angioplasty or stenting (3.7%, P<.001), other artery reconstruction (3.1%, P=.045), thrombo-embolectomy (6.5%, P=.026), and repair of arterial injury (5.4%, P=.037). Postoperative bowel ischemia was more frequently observed

Table 2a. Intraoperative characteristics

	No concomitant procedure	Hypogastric embolization		Unplanned graft extension		Femoro-femoral bypass		Femoral endarterectomy		Iliac angioplasty or stenting	
	N=2865 (71.0%)	*N=228 (5.7%)*	*P-value*	*N=357 (8.9%)*	*P-value*	*N=118 (2.9%)*	*P-value*	*N=175 (4.3%)*	*P-value*	*N=403 (10.0%)*	*P-value*
Operative time – (min. ± sd)	140 (58)	210 (93)	<.001	193 (83)	<.001	255 (98)	<.001	241 (99)	<.001	199 (93)	<.001
Anesthesia			.028		.396		.193		.197		.603
Local	30 (1.1)	4 (1.8)		2 (0.6)		1 (0.9)		0 (0)		3 (0.7)	
Regional	271 (9.5)	33 (14.5)		28 (7.8)		17 (14.5)		12 (6.9)		33 (8.2)	
General	2555 (89.5)	190 (83.7)		327 (91.6)		99 (84.6)		162 (93.1)		365 (91.0)	
Blood loss (mL, ± sd)	209 (239)	381 (405)	<.001	317 (353)	<.001	543 (585)	<.001	464 (513)	<.001	343 (413)	<.001
≥1 unit transfusion – N (%)	87 (3.0)	26 (11.4)	<.001	40 (11.2)	<.001	29 (24.6)	<.001	29 (16.6)	<.001	42 (10.4)	<.001
Contrast	103 (61)	137 (82)	<.001	131 (72)	<.001	105 (79)	.812	113 (62)	.033	111 (67)	.019
Arterial injury	16 (0.6)	9 (3.9)	<.001	25 (7.0)	<.001	7 (5.9)	<.001	25 (14.3)	<.001	29 (7.2)	<.001
Endoleak I	53 (1.9)	4 (1.8)	1.000	26 (7.3)	<.001	5 (4.2)	.066	7 (4.0)	.048	14 (3.5)	.032
II	650 (22.7)	45 (19.7)	.298	70 (19.6)	.182	23 (19.5)	.410	40 (22.9)	.968	54 (13.4)	<.001
III	5 (0.2)	4 (1.8)	.003	5 (1.4)	<.001	0 (0)	1.000	0 (0)	1.000	2 (0.5)	.210
IV	41 (1.4)	15 (6.6)	<.001	9 (2.5)	.117	4 (3.4)	.101	4 (2.3)	.327	7 (1.7)	.636
Conversion	2 (0.1)	0 (0)	1.000	0 (0)	1.000	0 (0)	1.000	1 (0.9)	.184	2 (0.7)	.119

Table 2b. Intraoperative characteristics

	No concomitant procedure	Ilio-femoral bypass		Renal angioplasty or stenting		Other artery reconstruction		Thrombo-embolectomy		Repair arterial injury	
	N=2865 (71.1%)	*N=29 (0.7%)*	*P-value*	*N=134 (3.3%)*	*P-value*	*N=96 (2.4%)*	*P-value*	*N=31 (0.8%)*	*P-value*	*N=37 (0.9%)*	*P-value*
Operative time – (min. ± sd)	140 (58)	286 (87)	<.001	224 (93)	<.001	254 (111)	<.001	271 (94)	<.001	252 (123)	<.001
Anesthesia			.455		.579		.768		.848		.784
Local	30 (1.0)	0 (0)		1 (0.8)		1 (1.0)		0 (0)		0 (0)	
Regional	271 (9.5)	1 (3.4)		16 (12.1)		7 (7.3)		3 (9.7)		3 (8.1)	
General	2558 (89.5)	28 (96.6)		115 (87.1)		88 (91.7)		28 (90.3)		34 (91.9)	
Blood loss (mL, ± sd)	209 (239)	885 (749)	<.001	297 (260)	<.001	486 (547)	<.001	576 (499)	<.001	774 (970)	.001
≥1 unit transfusion – N (%)	87 (3.0)	11 (37.9)	<.001	19 (14.2)	<.001	13 (13.5)	<.001	9 (29.0)	<.001	12 (32.4)	<.001
Contrast	103 (61)	117 (66)	.218	128 (71)	<.001	116 (72)	.051	145 (100)	.034	121 (61)	.078
Arterial injury	16 (0.6)	4 (13.8)	<.001	4 (3.0)	0.014	6 (6.3)	<.001	6 (19.0)	<.001	26 (70.3)	<.001
Endoleak I	53 (1.9)	2 (6.9)	.104	12 (9.0)	<.001	1 (1.0)	1.000	0 (0)	1.000	5 (13.9)	<.001
II	650 (22.7)	2 (6.9)	.044	17 (12.7)	.006	15 (15.6)	.101	2 (6.5)	.030	5 (13.9)	.208
III	5 (0.2)	0 (0)	1.000	1 (0.7)	.240	1 (1.0)	.180	0 (0)	.1.000	0 (0)	1.000
IV	41 (1.4)	0 (0)	1.000	3 (2.2)	.446	3 (3.1)	.170	0 (0)	1.000	1 (2.8)	.411
Conversion	2 (0.1)	0 (0)	1.000	1 (1.2)	.148	1 (2.0)	.095	0 (0)	1.000	0 (0)	1.000

after unplanned graft extension (0.3% vs. 1.1%, P=.047) and iliac angioplasty or stenting (1.7%, P<.001), with a trend for hypogastric embolization (1.3%, P=.053). Myocardial infarction occurred more often after all concomitant procedures except for iliac angioplasty or stenting (1.0% vs. 2.2 – 10.3%, P-value range: <.001 to .040), and heart failure after all but hypogastric embolization and femoral endarterectomy (0.6% vs. 2.0 – 12.9%, P-value range: <.001 to .015). Postoperative renal function deterioration was more frequently observed in all concomitant procedure groups except for the hypogastric embolization group (2.5% vs. 4.8 – 13.8%, P-value range: <.001 to .022), and leg ischemia in all but the hypogastric embolization and ilio-femoral bypass group (0.6% vs. 2.5 – 9.7% <.001 to P=0.013). Patients undergoing concomitant procedures, except for other artery reconstruction, were also more likely to return to the operating room (1.0% vs. 3.1% – 8.5%, P-value range: <.001 to .045), and all concomitant procedure patients were more likely to be hospitalized for longer than 2 days (17.8% vs. 31.1 – 82.8%, P<.001 for all).

Multivariable analyses

Independent risk factors for 30-day mortality were concomitant femoral endarterectomy (OR: 4.8, 95% CI: 2.1-11.2, Table 4) and renal angioplasty or stenting (OR: 3.1, 95% CI: 1.2-8.3). Risk factors for postoperative bowel ischemia were hypogastric embolization (OR: 3.8, 95% CI: 1.1-13.4) and iliac angioplasty or stenting (OR: 3.5, 95% CI: 1.3-9.6). Leg ischemia was predicted by simultaneous unplanned graft extension (OR: 2.3, 95% CI: 1.02-5.0, P=.046), other artery reconstruction (OR: 5.2, 95% CI: 1.8-15.1), thrombo-embolectomy (OR: 5.2, 95% CI: 1.3-20.8), and repair of arterial injury (OR: 4.6, 95 CI: 1.2-18.3). Risk factors for deterioration of the renal function were ilio-femoral bypass (OR: 3.9, 95% CI: 1.3-12.2), renal angioplasty or stenting (OR: 2.5, 95% CI: 1.3-4.6), other artery reconstruction (OR: 2.7, 95% CI: 1.3-5.8), and repair of arterial injury (OR: 4.5, 95% CI: 1.6-12.2). Postoperative myocardial infarction was associated with femoro-femoral bypass (OR: 3.9, 95% CI: 1.7-8.7), other artery reconstruction (OR: 3.9, 95% CI: 1.6-9.2) and repair of arterial injury (OR: 6.1, 95% CI: 1.8-21.0), while a trend was found for hypogastric embolization (OR: 2.2, 95% CI: 1.0-4.8, p=0.051). Femoro-femoral bypass was additionally predictive of wound complications (OR: 13.5, 95% CI: 5.8-31.1). All concomitant procedures except iliac angioplasty or stenting were predictive of prolonged postoperative length of stay.

Table 3a. Postoperative outcomes

	No concomitant procedure	**Hypogastric embolization**		**Unplanned graft extension**		**Femoro-femoral bypass**		**Femoral endarterectomy**		**Iliac angioplasty or stenting**	
	N=2865 (71.0%)	*N=228 (5.7%)*	*P-value*	*N=357 (8.9%)*	*P-value*	*N=118 (2.9%)*	*P-value*	*N=175 (4.3%)*	*P-value*	*N=403 (10.0%)*	*P-value*
30-day mortality – N (%)	22 (0.8)	1 (0.4)	1.000	5 (1.4)	.216	4 (3.4)	.018	8 (4.6)	<.001	11 (2.7)	<.001
Bowel ischemia – N (%)	9 (0.3)	3 (1.3)	.053	4 (1.1)	.047	0 (0)	1.000	1 (0.6)	.448	7 (1.7)	<.001
Leg ischemia/emboli – N (%)	17 (0.6)	1 (0.4)	1.000	9 (2.5)	<.001	4 (3.4)	.008	5 (2.9)	.001	10 (2.5)	<.001
Renal deterioration – N (%)	70 (2.5)	10 (4.4)	.084	17 (4.8)	.012	7 (5.9)	.022	10 (5.7)	.010	25 (6.2)	<.001
Dialysis – N (%)	12 (0.4)	1 (0.4)	1.000	1 (0.3)	1.000	3 (2.5)	.020	2 (1.1)	.196	3 (0.7)	.421
Wound complication – N (%)	8 (0.3)	1 (0.4)	.449	5 (1.4)	.002	8 (6.8)	<.001	5 (2.9)	<.001	7 (1.7)	<.001
Myocardial infarction – N (%)	28 (1.0)	8 (3.5)	.001	8 (2.2)	.033	8 (6.8)	<.001	7 (4.0)	<.001	8 (2.0)	.070
Heart failure – N (%)	18 (0.6)	4 (1.8)	.074	7 (2.0)	.007	5 (4.2)	<.001	3 (1.7)	.117	10 (2.5)	<.001
Pneumonia – N (%)	25 (0.9)	4 (1.8)	.162	8 (2.2)	.016	7 (5.9)	<.001	9 (5.1)	<.001	13 (3.2)	<.001
>3 transfusions – N (%)	8 (0.3)	7 (3.2)	<.001	13 (3.7)	<.001	13 (11.3)	<.001	13 (7.6)	<.001	14 (3.5)	<.001
Return to OR – N (%)	30 (1.0)	7 (3.1)	.007	12 (3.4)	<.001	10 (8.5)	<.001	8 (4.6)	<.001	16 (4.0)	<.001
Postop. length of stay (days, ± sd)	2.0 (2.7)	3.1 (4.8)	.001	2.7 (2.5)	<.001	5.7 (7.3)	<.001	3.7 (3.7)	<.001	3.1 (4.5)	<.001
> 2 days – N (%)	509 (17.8)	71 (31.1)	<.001	124 (34.7)	<.001	84 (71.8)	<.001	86 (49.1)	<.001	135 (33.6)	<.001

OR: operating room

Table 3b. Postoperative outcomes

	No con-comitant procedure	Ilio-femoral bypass		Renal angioplasty or stenting		Other artery reconstruction		Thrombo-embolectomy		Repair arterial injury	
	N=2865 (71.1%)	*N=29 (0.7%)*	*P-value*	*N=134 (3.3%)*	*P-value*	*N=96 (2.4%)*	*P-value*	*N=31 (0.8%)*	*P-value*	*N=37 (0.9%)*	*P-value*
30-day mortality – N (%)	22 (0.8)	1 (3.4)	.207	5 (3.7)	<.001	3 (3.1)	.045	2 (6.5)	.026	2 (5.4)	.037
Bowel ischemia – N (%)	9 (0.3)	0 (0)	1.000	2 (1.5)	.084	1 (1.0)	.282	1 (3.2)	.102	0 (0)	1.000
Leg ischemia/emboli – N (%)	17 (0.6)	1 (3.4)	.167	4 (3.0)	.013	4 (4.2)	.004	3 (9.7)	.001	3 (8.1)	.002
Renal deterioration – N (%)	70 (2.5)	4 (13.8)	.006	13 (9.7)	<.001	9 (9.5)	<.001	4 (12.9)	.008	5 (13.5)	<.001
Dialysis – N (%)	12 (0.4)	1 (3.4)	.125	0 (0)	1.000	1 (1.1)	.351	1 (3.2)	.133	0 (0)	1.000
Wound complication – N (%)	8 (0.3)	2 (6.9)	.004	2 (1.5)	.071	3 (3.1)	.005	1 (3.2)	.093	0 (0)	1.000
Myocardial infarction – N (%)	28 (1.0)	3 (10.3)	.003	5 (3.7)	.003	7 (7.3)	<.001	2 (6.5)	.040	3 (8.1)	.007
Heart failure – N (%)	18 (0.6)	3 (10.3)	.001	4 (3.0)	.015	5 (5.2)	<.001	4 (12.9)	<.001	4 (10.8)	<.001
Pneumonia – N (%)	25 (0.9)	2 (6.9)	.029	4 (3.0)	.038	7 (7.3)	<.001	3 (9.7)	.003	3 (8.1)	.005
>3 transfusions – N (%)	8 (0.3)	4 (15.4)	<.001	7 (5.2)	<.001	7 (7.7)	<.001	4 (13.8)	<.001	1 (3.0)	.100
Return to OR – N (%)	30 (1.0)	2 (6.9)	.040	6 (4.5)	<.001	3 (3.1)	.090	2 (6.5)	.045	3 (8.1)	.008
Postop. length of stay (days, ± sd)	2.0 (2.7)	5.5 (3.9)	<.001	3.6 (5.6)	.001	4.6 (7.3)	.001	5.1 (5.0)	.002	4.3 (4.4)	.003
>2 days – (%)	509 (17.8)	24 (82.8)	<.001	57 (42.5)	<.001	49 (51.0)	<.001	19 (61.3)	<.001	22 (59.5)	<.001

OR: operating room

Table 4. Adjusted associations between concomitant procedures and postoperative outcomes

	30-day mortality[a]		Bowel ischemia[b]		Leg ischemia[c]		Renal function deterioration[a]		Wound complication[d]		Myocardial infarction[e]		Postoperative length of stay >2 days[f]	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Hypogastric embolization	-	-	3.8	1.1-13.4	-	-	-	-	-	-	2.2	1.0-4.8[h]	1.6	1.2-2.2
Unplanned graft extension	-	-	-	-	2.3	1.0-5.0[g]	-	-	-	-	-	-	1.6	1.3-2.1
Femoro-femoral bypass	-	-	-	-	-	-	-	-	13.5	5.8-31.1	3.9	1.7-8.7	7.1	4.5-11.0
Femoral endarterectomy	4.8	2.1-11.2	-	-	-	-	-	-	-	-	-	-	2.0	1.4-2.9
Iliac angioplasty/stenting	-	-	3.5	1.3-9.6	-	-	-	-	-	-	-	-	-	-
Ilio-femoral bypass	-	-	-	-	-	-	3.9	1.3-12.2	-	-	-	-	13.0	4.1-40.9
Renal angioplasty or stenting	3.1	1.2-8.3	-	-	-	-	2.5	1.3-4.6	-	-	-	-	1.9	1.3-2.8
Other artery reconstr.	-	-	-	-	5.2	1.8-15.1	2.7	1.3-5.8	-	-	3.9	1.6-9.2	2.8	1.8-4.4
Thrombo-embolectomy	-	-	-	-	5.2	1.3-20.8	-	-	-	-	-	-	2.5	1.1-5.8
Repair arterial injury	-	-	-	-	4.6	1.2-18.3	4.5	1.6-12.2	-	-	6.1	1.8-21.0	3.9	1.9-8.1

[a] adjusted for: age, gender, hypertension, coronary disease, renal insufficiency; [b] adjusted for: age, gender, coronary disease, renal insufficiency; [c] adjusted for: gender, obstructive pulmonary disease, current smoking; [d] no baseline characteristics were predictive of postoperative wound complication; [e] adjusted for: age, hypertension, coronary disease; [f] adjusted for: age, gender, hypertension, coronary disease, obstructive pulmonary disease, renal insufficiency;
[g] lower limit of confidence interval is 1.02 (P=.046); [h] lower limit of confidence interval is 0.997 (P=.051).

DISCUSSION

With 29% of patients undergoing one or more additional procedure, this study demonstrates that concomitant procedures are commonly performed during elective EVAR.[6] In line with previous reports, [6, 19-21] we found that women were more likely to undergo concomitant procedures. This is most likely due to smaller artery diameters in women, which more often requires access-related and revascularization procedures.[19-21] Depending on type of intervention, performing concomitant procedures during EVAR proved to be associated with increased intraoperative complications, as well as higher risks of morbidity and mortality in the postoperative period. Femoral endarterectomy and renal angioplasty or stenting were independently associated with perioperative mortality, while hypogastric embolization and iliac angioplasty or stenting were predictors of postoperative bowel ischemia. Unplanned graft extension, other artery reconstruction, and the interventions to treat intraoperative complications (i.e., thrombo-embolectomy and repair of arterial injury) were associated with lower extremity ischemia, and femoro-femoral bypass was a risk factor for wound complications. These, and other concomitant procedures were additionally associated with various other perioperative complications, including renal function deterioration, myocardial infarction, and prolonged length of stay.

Concomitant femoral endarterectomy during EVAR was found to be associated with increased mortality following surgery. While evidence on performing concomitant femoral endarterectomy is limited, one report showed that femoral artery reconstruction (i.e., femoral endarterectomy and femoro-femoral bypass) during EVAR did worsen outcomes as compared to direct closure.[11] However, the conclusions are hampered by limited numbers and consequent lack of statistical power. In line with our study, Nguyen et al. recently reported in a large series that the risks of death following femoral endarterectomy, albeit as an isolated intervention, are not insignificant.[22] In addition, Hobo et al. determined that surgical intervention for PAD, which included femoral endarterectomy, was associated with increased perioperative mortality.[6] The need for femoral endarterectomy is a reflection of extensive PAD, which is a well-established risk for adverse outcomes following surgery. Several other concomitant procedures to treat atherosclerotic occlusive disease (ilio-femoral bypass, iliac angioplasty or stenting, femoro-femoral bypass, renal angioplasty or stenting, other artery reconstruction) were also associated with complications, particularly of ischemic nature. Conversely, these procedure groups had lower rates of type II endoleak, which is likely related to occlusive disease affecting aortic side branches.[23] In addition, procedures that are indicative of extensive atherosclerotic disease,

including femoral endarterectomy, were more likely to have a type I endoleak. This is most likely caused by extensive aortic atherosclerotic disease and particularly calcified aneurysm necks, hampering adequate proximal seal.[24]

The other independent risk factor for 30-day mortality was concomitant renal artery stenting. Renal angioplasty or stenting is performed to either to treat a pre-existing renal artery stenosis, or to preserve renal perfusion after renal artery overstenting (planned or unplanned). In contrast to the present results showing more than 3 times the risk of 30-day mortality, renal stenting has previously been determined a safe and effective means to treat patients with short infrarenal necks and inadvertent renal artery coverage.[12] However, it should be considered that this single center study may not have been adequately powered to detect small differences in outcome, and the lack of single center studies demonstrating increased risk may be due to publication bias. Also, it is likely that apart from the procedure itself, chronic kidney disease, which has been identified as a predictor of worse outcome after EVAR, has contributed to the worse outcome in this particular patient group.[25, 26]

Hypogastric artery embolization and iliac artery stenting were associated with increased risks of bowel ischemia. While complications such as buttock and spinal claudication are well-defined complications of hypogastric embolization, bowel ischemia is not.[27, 28] Several studies have reported on the importance of the hypogastric circulation for mesenteric blood flow.[29, 30] However, it was concluded that bowel ischemia following EVAR is mostly caused by widespread micro-embolization, of which dislodged atheromatous debris from access vessels has been determined an important source. [31, 32] This provides a valid explanation for the increased risks of bowel ischemia after iliac artery angioplasty and stenting. In addition, performing iliac angioplasty o stenting indicates extensive atherosclerotic disease, which is likely to also affect the mesenteric vessels and collaterals. As colonic ischemia significantly worsens the postoperative prognosis, the present data highlight the importance of using caution when performing iliac angioplasty or stenting. Coil embolization of the hypogastric may also cause micro-embolization, in addition to a global decrease in flow. It is unclear whether placement of a more proximal plug has a decreased risk of colonic ischemia compared to placement of coils, but it seems reasonable to try to maintain as much collateral flow as possible. The fact that hypogastric artery embolization was associated with increased risks of bowel ischemia highlights the need to assess patency of the superior mesenteric artery and evaluate any history of colonic surgery that could impact collateral flow in the colon when this procedure is considered.

Apart from planned concomitant procedures, thrombo-embolectomy and repair of arterial injury were also associated with various adverse outcomes, including postoperative leg ischemia, myocardial infarction, and prolonged length of stay. In contrast to most concomitant procedures, consideration of operative risks before intervening is less of an option for these procedures. Therefore, the need for these procedures should be avoided through appropriate patient selection, adequate intraoperative anticoagulation, and careful consideration of performing additional procedures that are associated with increased risks of arterial injury.

This study has several limitations that should be addressed. First, as the VSGNE collects data through a registry, underreporting of events is a possibility. Second, the rates of adverse outcomes following EVAR are generally low, thereby limiting the statistical power of multivariable analyses. As a result, univariate associations between less common procedures and complications, such as the association between ilio-femoral bypass and leg ischemia, could not be established in multivariable analyses. Third, we were unable to distinguish between patients undergoing concomitant renal stenting to treat renal artery stenoses or re-establish blood flow after renal artery coverage (planned or unplanned). As the clinical implications of the procedure depend on the indication, this information would be valuable. Similarly, for several other concomitant procedures we were unable to determine whether the procedure was planned or performed to resolve an intraoperative complication. However, it is unlikely that all planned concomitant procedures were uncomplicated, and only bailout procedures were associated with worse outcome. Therefore, the present data should be considered when a concomitant procedure is planned. Fourth, the lack of data on proximal extent of the aneurysm precluded stratification of outcomes based on the type of aneurysm. Finally, it should be noted that patients were not randomized to undergo concomitant procedures or not. Since the patient dictates which concomitant procedures are indicated, patients undergoing one or more concomitant procedure are more likely to have extensive disease than those not undergoing additional interventions. Therefore, confounding by indication should be considered, despite adjustment for baseline characteristics in multivariable analysis.

In conclusion, this study shows that various additional procedures during EVAR are associated with increased intraoperative complications and postoperative morbidity and mortality. Careful patient selection and deliberation of the need for the intervention are advised for procedures performed electively. The morbidity associated with the treatment of intraoperative complications highlights the importance of avoidance of these events where possible.

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Supplementa Table 1. Incidence of EVAR performed in conjunction with more than one additional procedure

	Hypogastric embolization	*Graft extension*	*Femoro-femoral bypass*	*Femoral endarterectomy*	*Iliac angioplasty or stenting*	*Ilio-femoral bypass*	*Renal angioplasty or stenting*	*Other artery reconstruction*	*Thrombo-embolectomy*	*Repair arterial injury*
Hypogastric embolization	X	31 (13.6)	16 (7.0)	7 (3.1)	35 (15.4)	3 (1.3)	2 (0.9)	16 (7.0)	3 (1.3)	4 (1.8)
Graft extension	31 (8.7)	X	15 (4.2)	20 (5.6)	61 (17.1)	3 (0.8)	26 (7.3)	6 (1.7)	11 (3.1)	10 (2.8)
Femoro-femoral bypass	16 (13.6)	15 (2.7)	X	34 (28.8)	36 (30.5)	8 (6.8)	5 (4.2)	13 (11.0)	3 (2.5)	2 (1.7)
Femoral endarterectomy	7 (4.0)	20 (11.4)	34 (19.4)	X	65 (37.1)	9 (5.1)	7 (4.0)	8 (4.6)	9 (5.1)	7 (4.0)
Iliac angioplasty or stenting	35 (8.7)	61 (15.1)	36 (8.9)	65 (16.1)	X	10 (2.5)	21 (5.2)	21 (5.2)	14 (3.5)	7 (1.7)
Ilio-femoral bypass	3 (10.3)	3 (10.3)	8 (27.6)	9 (31.0)	10 (34.5)	X	1 (3.4)	4 (13.8)	3 (10.3)	1 (3.4)
Renal angioplasty or stenting	2 (1.5)	26 (19.4)	5 (3.7)	7 (5.2)	21 (15.7)	1 (0.7)	X	11 (8.2)	1 (0.7)	2 (1.5)
Other artery reconstruction	16 (16.7)	6 (6.3)	13 (13.5)	8 (8.3)	21 (21.9)	4 (4.2)	11 (11.5)	X	0 (0)	0 (0)
Thrombo-embolectomy	3 (9.7)	11 (35.5)	3 (9.7)	9 (29.0)	14 (45.2)	3 (9.7)	1 (3.2)	0 (0)	X	2 (6.5)
Repair arterial injury	4 (10.8)	10 (27.0)	2 (5.4)	7 (18.9)	7 (18.9)	1 (2.7)	2 (5.4)	0 (0)	2 (5.4)	X

Chapter 7

The Perioperative Impact of Concomitant Procedures during Open Infrarenal Abdominal Aortic Aneurysm Repair

Klaas H.J. Ultee[1,2]
Peter A. Soden[1]
Sara L. Zettervall[1]
John C. McCallum[1]
Jeffrey J. Siracuse[3]
Matthew J. Alef[4]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]
on behalf of the Vascular Study Group of New England

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
3) Department of Surgery, Division of Vascular and Endovascular Surgery, Boston University School of Medicine, Boston, MA, USA
4) Department of Surgery, Division of Vascular Surgery, The University of Vermont Medical Center and University of Vermont College of Medicine

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ABSTRACT

Objective

Open repair of abdominal aortic aneurysms (AAA) is occasionally performed in conjunction with additional procedures. However, it is unclear how these concomitant procedures affect outcome. This study aims to determine the frequency of additional procedures during elective open AAA repair and the impact on perioperative outcomes.

Methods

Between January 2003 and November 2014, all elective infrarenal open AAA repairs in the Vascular Study Group of New England (VSGNE) were identified. Patients were grouped by concomitant procedures, which included: no concomitant procedure, renal artery bypass, lower extremity bypass, other abdominal procedure or thrombo-embolectomy. Analyses were performed using multivariable logistic regression.

Results

1314 patients underwent elective AAA repair, of whom 153 (11.6%) had a concomitant procedure, including renal bypass 27 (2.1%), lower extremity bypass 28 (2.1%), other abdominal procedures 64 (4.9%), and thrombo-embolectomy 48 (3.7%). Independent risk factors for 30-day mortality were renal bypass (OR: 7.2, 95% CI: 1.9 – 27.7), other abdominal procedures (OR: 4.8, 95% CI: 1.6 – 14.1) and thrombo-embolectomy (OR: 8.8, 95% CI: 3.1 – 24.9). Deterioration of renal function was predicted by renal bypass (OR: 5.1, 95% CI: 2.1–12.4) and thrombo-embolectomy (OR: 3.7, 95% CI: 1.8 – 7.6). Lower extremity bypass and thrombo-embolectomy were predictive of postoperative leg ischemia (OR: 8.9, 95% CI: 2.7 – 29.0; OR: 11.2, 95% CI: 4.4 – 28.8, respectively), while thrombo-embolectomy was also predictive of postoperative myocardial infarction (OR: 4.4, 95% CI: 1.6 – 12.0).

Conclusions

Performing additional procedures during infrarenal open AAA repair is associated with increased morbidity and mortality in the postoperative period. Careful deliberation of both the operative risks and the necessity of the additional interventions are therefore advised during operative planning. This study also highlights the importance of avoiding perioperative thrombo-embolic events.

INTRODUCTION

Considering that abdominal aortic aneurysm (AAA) is generally a disease of the elderly,[1] AAA patients commonly have coexisting medical conditions, such as peripheral artery disease and gastrointestinal pathologies.[2-6] Open AAA repair provides the opportunity to simultaneously treat some of these coexisting medical conditions in a single-staged procedure. By sparing the need for a second procedure, outcomes may improve, while total hospital stay and costs decrease.[5, 7] However, clinicians are generally hesitant to attempt one-stage procedures,[4, 5, 8] as evidence supporting the safety and feasibility of contemporaneous procedures is largely lacking.

The prevalence of concurrent nonvascular intra-abdominal pathologies (e.g. malignancies, cholecystopathology) in AAA patients has been reported to be as high as 32%.[3, 4, 6] Several studies have assessed the benefits of a combined procedure over a sequential approach for concomitant nonvascular intra-abdominal disease with mixed conclusions and recommendations.[5, 9-12] With up to one-third of AAA patients suffering from renal artery stenoses and a prevalence of peripheral artery disease (PAD) of over 50%,[13-16] occlusive vascular disease in particular is often present in the AAA population. Despite this high prevalence, the safety and feasibility of concurrent surgical treatments remain largely unclear. The limited studies available for one-stage repairs of AAA and renal artery stenosis are conflicting, with some reporting an increase in adverse events,[16, 17] while others did not.[18-20] Furthermore, these studies mostly described small series of combined procedures and were all conducted prior to the introduction of EVAR, after which the characteristics of patients selected for open repair have likely changed.[21, 22] There are no studies to date investigating the outcomes of open AAA repair with concurrent peripheral revascularization.

The purpose of this study, therefore, is to determine the frequency and outcomes of procedures that are concomitantly performed with open AAA repair and to aid clinicians in deciding whether or not a combined procedure can be safely attempted.

METHODS

Database

Data from the Vascular Study Group of New England (VSGNE) were used for this study. The VSGNE is a regional collaboration of 30 academic and community hospitals in the six New England states, involving more than 180 physicians. The group

aims to study and improve regional outcomes in vascular surgery and documents 140 detailed patient demographic, operative, and clinical outcome variables for 12 commonly performed vascular procedures, including AAA repair.[23] The data are prospectively gathered and entered in the registry by trained nurses or clinical data abstractors. Surgeons enter operative details. Research analysts are blinded to patient, surgeon, and hospital identity. The VSGNE database has been validated for completeness using audits of discharge claims data from each participating institution.[23] Institutional Review Board approval and patient consent were waived, as the VSGNE contains de-identified data only without protected health information. Further details about this registry can be found at http://www.vsgne.org.

Patients

The study cohort included patients undergoing elective open infrarenal AAA repair between January 2003 and November 2014. The following concomitant procedures during open AAA are documented in the VSGNE: 'renal bypass', 'lower extremity bypass', 'other abdominal procedures', and 'thrombo-embolectomy'. Patients undergoing isolated open AAA repair were assigned to the 'no concomitant procedure' group. When a patient underwent more than one concomitant procedure, they were allocated to multiple concomitant procedure groups. Since the incidence of, indication for, and outcomes of concomitant procedures likely differ for juxtarenal and suprarenal aneurysms compared to infrarenal, in particular for renal artery bypass surgery, only patients undergoing infrarenal AAA repair were included.

Clinical and outcome variables

Patients receiving combined surgery were compared to those undergoing infrarenal AAA repair alone on patient characteristics, intraoperative data, and postoperative outcomes. Patient characteristics included age, gender, co-morbidities, and aneurysm diameter. Intraoperative details analyzed were operative time, blood loss, renal/visceral ischemia time, and procedural details, including surgical approach (i.e. transabdominal vs. retroperitoneal), target vessel for the distal anastomosis, and management of the hypogastric and inferior mesenteric artery. Postoperative outcomes were in-hospital events with the exception of 30-day mortality, and included deterioration of renal function, lower extremity ischemia, cardiac complications, pneumonia, bowel ischemia, wound complications, prolonged postoperative length of stay, and prolonged length of stay in an intensive care unit (ICU). Deterioration of renal function was defined as an increase in postoperative creatinine >0.5mg per dl and/or need for dialysis. Myocardial infarction was considered when one of the following was documented: isolated troponin elevation, electrocardiogram change, or clinical evidence of myocardial infarction. Prolonged postoperative length of stay

was defined as longer than 7 days and prolonged length of ICU stay was longer than 2 days, definitions that have been used previously.[24]

Statistical analyses

Discrete variables are presented as counts and percentages, and continuous variables as mean ± standard deviation, if normally distributed, or as median and interquartile range if the distribution is non-parametric. To assess differences between patients undergoing concomitant procedures and those who did not, we used $\chi 2$ and Fisher's exact tests for categorical variables, and Student's t-test for continuous variables, where appropriate. Multivariable logistic regression analysis was used to determine the independent associations between concomitant procedures and outcomes. Baseline characteristics were first univariately tested and significant predictors were added to the multivariable model. Concomitant procedures with a p-value ≤ .1, when compared to the no concomitant procedure group, were subsequently entered. A separate model was constructed for each of the studied outcomes. All tests were two-sided and significance was considered when P-value < .05. Statistical analysis was performed using the SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 1314 patients receiving elective open AAA repair were included in the study, with 153 (11.6%) undergoing one or more additional procedures. Concomitant renal bypass surgery was performed in 27 (2.1%) patients, lower extremity bypass surgery in 28 (2.1%) patients, other additional abdominal procedures in 64 (4.9.%) patients, and thrombo-embolectomy in 48 (3.7%) patients. Of the 153 patients undergoing concomitant procedures, 13 (8.5%) underwent multiple procedures (Supplemental Table 1).

Baseline characteristics

Patients solely treated for AAA and those undergoing additional procedures were generally similar (Table 1). However, concomitant renal bypass patients were more likely to have never smoked compared to those not undergoing concomitant procedures (22.2% vs. 8.2%, P = .020), while lower extremity bypass and thrombo-embolectomy patients were more frequently current smokers (75.0% vs. 40.9%, P = .001; 58.3% vs. 40.9%, P = .051, respectively). In addition, patients requiring a thrombo-embolectomy had a smaller mean aneurysm diameter (52.9 mm vs. 59.2 mm, P = .024).

Table 1. Baseline characteristics

	No concomitant procedure	Renal bypass		Lower extremity bypass		Other abdominal		Thrombo-embolectomy	
	N=1161 (88.4%)	*N=27 (2.1%)*	*p-value*	*N=28 (2.1%)*	*p-value*	*N=64 (4.9%)*	*p-value*	*N=48 (3.7%)*	*p-value*
Age – (mean ± sd)	69.6 (8.4)	71.2 (7.4)	.35	67.0 (7.3)	.11	67.8 (8.2)	.099	69.8 (8.0)	.89
Female gender – N (%)	306 (26.4)	5 (18.5)	.36	10 (35.7)	.27	16 (25.0)	.81	14 (29.2)	.67
Hypertension – N (%)	949 (81.8)	25 (92.6)	.15	24 (85.7)	.60	54 (84.4)	.60	43 (89.6)	.17
Diabetes – N (%)	168 (14.5)	5 (18.5)	.56	6 (21.4)	.30	8 (12.5)	.66	9 (18.8)	.41
CAD – N (%)	351 (30.2)	9 (33.3)	.73	11 (39.3)	.30	15 (23.4)	.25	17 (35.4)	.44
CHF – N (%)	56 (4.8)	2 (7.4)	.38	1 (3.6)	>.99	5 (7.8)	.29	4 (8.3)	.27
CABG/PCI – N (%)	347 (29.9)	5 (18.5)	.20	6 (21.4)	.33	12 (18.8)	.056	11 (22.9)	.30
COPD – N (%)	375 (32.3)	10 (37.0)	.60	10 (35.7)	.70	21 (32.8)	.93	21 (43.8)	.098
Renal insuf – N (%)	62 (5.4)	3 (11.1)	.19	3 (11.1)	.19	6 (9.5)	.17	1 (2.1)	.32
Dialysis – N (%)			.93		.93		.44		.88
Working transplant	1 (.1)	0 (0)		0 (0)		0 (0)		0 (0)	
On dialysis	5 (.4)	0 (0)		0 (0)		1 (1.6)		0 (0)	
Smoking – N (%)			.020		.001		.53		.051
Never	95 (8.2)	6 (22.2)		1 (3.6)		6 (9.4)		2 (4.2)	
Past	591 (50.9)	9 (33.3)		6 (21.4)		28 (43.8)		18 (37.5)	
Current	474 (40.9)	12 (44.4)		21 (75.0)		30 (46.9)		28 (58.3)	
Max diameter (mm, ± sd)	59.2 (12.8)	55.4 (14.5)	.13	54.8 (9.6)	.079	57.2 (12.6)	.22	52.9 (18.5)	.024

CAD: coronary artery disease; CHF: congestive heart failure; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease

Intraoperative characteristics

All combined procedures were accompanied by a longer procedure time, adding between 80 and 121 min. compared to patients with no concomitant procedures (mean: 199 min., P ≤ .001 for all, Table 2). Blood loss more than 1L occurred more frequently with renal bypass surgery (73.1% vs. 46.2, P = .007), other abdominal procedures (60.9%, P = 021) and thrombo-embolectomy (64.6%, P = .012). In lower extremity bypass and thrombo-embolectomy patients the aortic graft was more often anastomosed to vessels distal to the aorta (71.4% vs. 48.5%, P = .016; 68.7% vs. 48.5%, P < .001, respectively). Further, there was a trend for retroperitoneal approach to be more frequently used for simultaneous renal bypass procedures (25.9% vs. 13.3%%, P = .057). Renal and/or visceral ischemia time longer than 30 minutes was observed in 30.8% of renal bypass patients, and 10.6% of those undergoing a thrombo-embolectomy.

Postoperative outcomes

Thirty day mortality ranged from 7.1% to 12.5% for those undergoing concomitant procedures while those without concomitant procedures had a mortality rate of 1.1% (P <.05 for all, Table 3). Similarly, acute kidney failure occurred more often after all concomitant procedures (17.2% – 30.8% vs. 7.2%, P < .05 for all). Patients undergoing lower extremity bypass and thrombo-embolectomy more commonly experienced postoperative leg ischemia (18.5% vs. 1.3%, P < .001; 17.0% vs. 1.3%, P < .001, respectively) and pneumonia (21.4% vs. 5.8%, P = .001; 18.8% vs. 5.8%, P = .001, respectively). Lower extremity bypass was also associated with higher rates of heart failure (17% vs. 4%, P < .001). In addition, thrombo-embolectomy patients more often suffered a postoperative MI (14.6% vs. 4.2%, P = .001) and required an unplanned return to the operating room (14.9% vs. 5.9%, P = .012). Finally, ICU stay was more often prolonged (>2 days) in patients undergoing lower extremity bypass surgery (67.9% vs. 38.7%, P = .002), other abdominal procedures (54.7%, P = .011) and thrombo-embolectomy (62.5%, P = .002), while postoperative length of hospital stay was prolonged (>7 days) in those undergoing other abdominal procedures 50.0% vs. 32.9%, P = .005) and thrombo-embolectomy (58.3%, P < .001).

Multivariable analyses

In adjusted analyses (Table 4), risk factors for 30-day mortality were renal bypass (OR: 7.2, 95% CI: 1.9 – 27.7) other abdominal procedure (OR: 4.8, 95% CI: 1.6 – 14.1) and thrombo-embolectomy (OR: 8.8, 95% CI: 3.1 – 24.9). Concomitant procedures associated with deterioration of renal function were renal bypass surgery (OR: 5.1, 95% CI: 2.1 – 12.4) and thrombo-embolectomy (OR: 3.7,

Table 2. Intraoperative characteristics

	No concomitant procedure	Renal bypass		Lower extremity bypass		Other abdominal		Thrombo-embolectomy	
	N=1161 (88.4%)	*N=27 (2.1%)*	*p-value*	*N=28 (2.1%)*	*p-value*	*N=64 (4.9%)*	*p-value*	*N=48 (3.7%)*	*p-value*
Operative time – (min. ± sd)	198.6 (76.9)	319.3 (158.2)	.001	319.9 (131.2)	<.001	278.2 (120.6)	<.001	313.3 (119.6)	<.001
Blood loss >1L	534 (46.2)	19 (73.1)	.007	16 (57.1)	.25	39 (60.9)	.021	31 (64.6)	.012
Transfusions ≥1 unit	262 (22.6)	10 (37.0)	.079	9 (32.1)	.24	17 (26.6)	.47	20 (41.7)	.002
Retroperitoneal access– N (%)	154 (13.3)	7 (25.9)	.057	7 (25.0)	.073	6 (9.4)	.37	9 (18.8)	.28
Distal anastomosis – N (%)			.43		.016		.088		<.001
Aorta	596 (51.5)	16 (59.3)		8 (28.6)		24 (37.5)		15 (31.3)	
CIA	309 (26.7)	8 (29.6)		7 (25.0)		21 (32.8)		9 (18.8)	
EIA	75 (6.5)	2 (7.4)		4 (14.3)		8 (12.5)		3 (6.3)	
CFA	177 (15.3)	1 (3.7)		9 (32.1)		11 (17.2)		21 (43.8)	
Hypogastric artery occl– N (%)			.19		<.001		.32		.006
Single	81 (7.0)	4 (14.8)		1 (3.6)		7 (11.1)		9 (18.8)	
Both	45 (3.9)	0 (0)		7 (25.0)		1 (1.6)		3 (6.3)	
IMA – N (%)			.96		.65		.16		<.001
Occluded	477 (41.4)	10 38.5)		11 (39.3)		28 (45.2)		29 (61.7)	
Ligated	633 (54.9)	15 (57.7)		15 (53.6)		29 (46.8)		13 (27.7)	
Reimplanted	43 (3.7)	1 (3.8)		2 (7.1)		5 (8.1)		5 (10.6)	

CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery; IMA: inferior mesenteric artery

Table 3. Postoperative outcomes

	No concomitant procedure	Renal bypass		Lower extremity bypass		Other abdominal		Thrombo-embolectomy	
	N=1161 (88.4%)	*N=27 (2.1%)*	*p-value*	*N=28 (2.1%)*	*p-value*	*N=64 (4.9%)*	*p-value*	*N=48 (3.7%)*	*p-value*
30-day Mortality – N (%)	13 (1.1)	3 (11.1)	.005	2 (7.1)	.046	5 (7.8)	<.001	6 (12.5)	<.001
Renal deterioration – N (%)	83 (7.2)	8 (30.8)	<.001	6 (22.2)	.004	11 (17.2)	.004	11 (23.4)	<.001
Dialysis – N (%)	10 (0.9)	1 (3.8)	.22	1 (3.7)	.23	1 (1.6)	.45	2 (4.3)	.077
Leg ischemia – N (%)	15 (1.3)	1 (3.8)	.30	5 (18.5)	<.001	1 (1.6)	.58	8 (17.0)	<.001
Bowel ischemia – N (%)	31 (2.7)	0 (0)	>.99	2 (7.4)	.17	1 (1.6)	>.99	5 (10.6)	.002
Wound complication – N (%)	41 (3.5)	1 (3.8)	.61	1 (3.7)	>.99	5 (7.8)	.080	0 (0)	.40
MI – N (%)	49 (4.2)	2 (7.7)	.31	3 (10.7)	.097	3 (4.7)	.75	7 (14.6)	.001
CHF – N (%)	34 (2.9)	1 (3.7)	.56	6 (21.4)	<.001	1 (1.6)	>.99	3 (6.3)	.18
Pneumonia – N (%)	67 (5.8)	4 (15.4)	.065	6 (21.4)	.001	7 (10.9)	.092	9 (18.8)	.001
Transfusions >3 units – N (%)	38 (3.6)	5 (21.7)	.002	1 (4.3)	.58	6 (10.9)	.007	5 (11.9)	.007
Return to OR – N (%)	68 (5.9)	3 (11.5)	.20	4 (14.8)	.076	5 (7.8)	.52	7 (14.9)	.012
Postop stay >7 days– N (%)	382 (32.9)	10 (37.0)	.65	12 (42.9)	.27	32 (50.0)	.005	28 (58.3)	<.001
ICU stay >2 days – N (%)	449 (38.7)	14 (51.9)	.17	19 (67.9)	.002	35 (54.7)	.011	30 (62.5)	.001

MI: myocardial infarction; CHF: congestive heart failure; OR: operating room

95% CI: 1.8 – 7.6). Predictors for postoperative limb ischemia were concomitant lower extremity bypass surgery (OR: 8.9, 95% CI: 2.7 – 29.0) and thrombo-embolectomy (OR: 11.2, 95% CI: 4.4 – 28.8). Thrombo-embolectomy was additionally found to be a risk factor for bowel ischemia (OR: 4.4, 95% CI: 1.6 – 12.0) and postoperative MI (OR: 3.5, 95% CI: 1.5 – 8.3). ICU stay longer than 2 days was predicted by lower extremity bypass (OR: 3.5, 95% CI: 1.5 – 8.2), other abdominal procedures (OR: 1.9, 95% CI: 1.1 – 3.3) and thrombo-embolectomy (OR: 2.4, 95% CI: 1.3 – 4.5).

Table 4. Adjusted associations between concomitant procedures and postoperative outcomes

	30-day mortality[α]			**Renal deterioration**[β]		
	OR	**95% CI**	***P-value***	**OR**	**95% CI**	***P-value***
Renal bypass	7.2	1.9 – 27.7	.004	5.1	2.1 – 12.4	<.001
Lower extremity bypass	3.2	0.6 – 17.0	.17	2.5	0.9 – 6.6	.075
Other abdominal	4.8	1.6 – 14.1	.005	2.0	0.9 – 4.0	.070
Thrombo-embolectomy	8.8	3.1 – 24.9	<.001	3.7	1.8 – 7.6	.001
	Leg ischemia[γ]			***Bowel ischemia***[δ]		
	OR	***95% CI***	***P-value***	***OR***	***95% CI***	***P-value***
Renal bypass	-	-	-	-	-	-
Lower extremity bypass	8.9	2.7 – 29.0	<.001	-	-	-
Other abdominal	-	-	-	-	-	-
Thrombo-embolectomy	11.2	4.4 – 28.8	<.001	4.4	1.6 – 12.0	.003
	Myocardial infarction[ε]			***ICU stay >2 days***[ζ]		
	OR	***95% CI***	***P-value***	***OR***	***95% CI***	***P-value***
Renal bypass	-	-	-	-	-	-
Lower extremity bypass	-	-	-	3.5	1.5 – 8.2	.005
Other abdominal	-	-	-	1.9	1.1 – 3.3	.015
Thrombo-embolectomy	3.5	1.5 – 8.3	.005	2.4	1.3 – 4.5	.006

OR: odds ratio; CI: confidence interval
Concomitant procedures without odds ratio's did not reach a p-value ≤ .1 in univariable analysis, and were therefore not included in the
multivariable model.
α adjusted for: age; β adjusted for: diabetes, renal insufficiency; γ adjusted for: gender; δ adjusted for: age; ε adjusted for: age, coronary artery disease, obstructive pulmonary disease; ζ adjusted for: age, gender, renal insufficiency, obstructive pulmonary disease

DISCUSSION

This study demonstrates that performing additional procedures during open AAA surgery is associated with increased morbidity and mortality in the postoperative period. Concomitant renal bypass, other concurrent abdominal procedures, and thrombo-embolectomy were independent predictors for 30-day mortality and multiple other postoperative adverse events. Lower extremity bypass surgery was not established as a risk factor for 30-day mortality, but was associated with postoperative complications, including leg ischemia and prolonged length of ICU stay.

Some studies conducted prior to the introduction of EVAR recommended an aggressive approach towards renal bypass surgery at the time of AAA repair, as they found similar mortality rates between concurrent aortic and renal artery reconstruction versus aortic surgery alone. [18-20, 27, 28] In our study, we found that patients with renal disease severe enough for concomitant renal bypass surgery to be performed, had a 7-fold increase in 30-day mortality risk. This is in agreement with the largest series to date by Benjamin et al,[16] and adds support to performing renal stenting before or after the AAA repair, rather than combined surgery when correction of the renal artery lesion is indicated. Moreover, it has been demonstrated that normotension was less often achieved after combined aortorenal reconstruction as compared to a staged approach.[16, 18] The present results additionally highlight the potential benefit of utilizing endovascular treatment approaches in these patients, which can be performed simultaneously, but also prior or subsequent to the AAA repair. However, two randomized trials comparing endovascular renal artery revascularization to medical therapy recommended a conservative approach over revascularization.[25, 26]

Abdominal aneurysmal disease and PAD share a number of etiologic risk factors.[13] As a result, PAD is present in a majority of AAA patients.[2] Yet, concomitant lower extremity bypass during open AAA repair was only performed in 2.1% of all cases. In addition to treatment of comorbid peripheral artery disease, concomitant lower extremity bypass surgery may be performed to improve outflow following clamp release and prevent graft thrombosis. Although the 30-day mortality rate was significantly higher compared to infrarenal AAA repair only (7.1% vs. 1.1%), no mortality risks associated with concomitant lower extremity bypass could be established in adjusted analyses. A low number of patients and the consequent lack of statistical power, rather than a lack of association, is likely to be responsible for these results. Although extensive occlusive disease in these patients may also have contributed to their poor outcome, we believe a cautionary note on concomitant lower extremity bypass surgery during AAA

repair is fitting. Additionally, the present results warrant consideration of performing angioplasty or stenting rather than bypass surgery, particularly since these interventions can be performed prior or subsequent to the AAA repair with limited additional operative risk.

Since the majority of intra-abdominal procedures involve gastrointestinal structures with potentially infectious contents, the biggest concern of intra-abdominal concomitant procedures is graft contamination.[9] In the present study, performing other abdominal procedures in conjunction with open AAA repair was predictive of increased morbidity and mortality in the perioperative period. The results from prior studies are conflicting. Some studies have demonstrated that additional intra-abdominal interventions during open AAA repair, such as colorectal resections and cholecystectomies, worsen the perioperative outcome.[9, 11, 12] As a result, Lin et al. recommended treating the symptomatic lesion first in case of concurrent colorectal cancer.[12] Conversely, other studies that covered similar concomitant interventions encouraged combined surgery, as they deemed it safe and went a step further to say it reduces the risk of AAA rupture between operative procedures.[5, 9, 10] Unfortunately, we were unable to obtain further details on the nature of the interventions included in the other abdominal procedures group as we do not know what procedures were performed. Nevertheless, the fact that these procedures were associated with such a clear increase in perioperative mortality warrants careful deliberation by the surgeon when considering performing any additional abdominal procedure during open AAA repair.

Apart from other abdominal procedures, concomitant thrombo-embolectomy was a major risk factor for multiple adverse outcomes in the postoperative period, including death. Since the need for thrombo-embolectomy is not something planned pre-operatively, this demonstrates the problems associated with thrombo-embolic events that complicate open AAA repair. The results from this study highlight the importance of minimizing the likelihood of thrombo-embolic events. Patients undergoing a thrombo-embolectomy were more severely burdened by occlusive disease in addition to their known aneurysmal disease, as indicated by the fact that in these patients the prosthesis was more often anastomosed to vessels distal to the aorta. Since dislodged atherothrombotic debris is often the cause of thrombo-embolic events, careful consideration should be given to the clamp location in order to reduce clamp trauma and consequent plaque embolism. Inadequate intraoperative anticoagulation may also play a role. However, heparin dose and activated clotting time were not documented in this data set.

This study has several potential limitations that must be addressed. First, as the VSGNE collects data through a registry, underreporting of events is possible.

Second, since endovascular repair is currently the primary mode of treatment for infrarenal AAA, it is likely that certain patient characteristics either precluded an endovascular approach, or made open repair the better alternative for these patients. Unfortunately, these reasons for performing open repair instead of EVAR are not documented in this data set. Third, concomitant procedures during open repair are grouped into only four categories, with one category consisting of all other abdominal procedures. As a result of the limited specificity of this group, the conclusions and clinical implications are bounded. In addition, this data set does not include operative characteristics specific to each of the concomitant procedures, which precluded us from performing subanalyses within the different concomitant procedure categories. Similarly, data on whether the procedure was planned or not were not documented. However, it is unlikely that all planned concomitant procedures were uncomplicated, and only procedures to resolve intraoperative complications were associated with worse outcome. Therefore, the present data should be considered when a concomitant procedure is planned. Due to the lack of adverse outcome data, we were unable to determine whether any differences in outcomes existed outside the in-hospital period with the exception of mortality. Finally, it should be noted that patients were not randomized to undergo either AAA repair only or combined surgery. Despite the use of multivariable analysis to minimize the potential of confounding by indication, residual confounding should always be considered.

In conclusion, this study demonstrates that combining open AAA repair with additional interventions is associated with increased morbidity and mortality in the perioperative period. Renal bypass surgery, other abdominal procedures and the need for concurrent thrombo-embolectomy were all independent risk factors for mortality and multiple other in-hospital complications. Concomitant lower extremity bypass surgery was also associated with worse mortality and in-hospital outcomes, although the independent risks could not be established for mortality. Careful deliberation of the operative risks and the necessity of additional procedures is advised during operative planning. The poor outcome of thrombo-embolectomy highlights the importance of adequate intraoperative anticoagulation and prevention of intraoperative thrombo-embolic events where possible.

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Supplemental Table 1. Incidence of infrarenal AAA repairs performed in conjunction with more than one concomitant procedure

	Renal bypass	*Lower extremity bypass*	*Other abdominal*	*Thrombo-embolectomy*	*One concomitant procedure*	**Total**
Renal bypass	-	0	4 (15%)	0	23 (85%)	27 (100%)
Lower extremity bypass	0	-	2 (7%)	5 (18%)	21 (75%)	28 (100%)
Other abdominal	4 (6%)	2 (3%)	-	4 (6%)	54 (84%)	64 (100%)
Thrombo-embolectomy	0 (0)	5 (10%)	4 (8%)	-	39 (81%)	48 (100%)

chapter 8

Perioperative Outcome of Endovascular Repair for Complex Abdominal Aortic Aneurysms

Klaas H.J. Ultee[1,2]
Sara L. Zettervall[1]
Peter A. Soden[1]
Jeremy Darling[1]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Objective

As endovascular techniques (EVAR) continue to advance, eligibility of patients with anatomically complex abdominal aortic aneurysms (AAA) for EVAR is increasing. However, it remains largely unclear whether complex EVAR is associated with favorable outcome over conventional open repair and how outcomes compare to infrarenal EVAR. The purpose of this study was to examine perioperative outcomes of patients undergoing complex EVAR, focusing on differences with complex open repair and standard infrarenal EVAR.

Methods

We identified all patients undergoing non-ruptured complex EVAR, complex open repair, and infrarenal EVAR in the Targeted Vascular Module from the American College of Surgeons National Surgical Quality Improvement Program. Aneurysms were considered complex if the proximal extent was juxta- or suprarenal, and/or when the Cook Zenith Fenestrated endograft was used. Independent risks were established using multivariable logistic regression analysis.

Results

A total of 4584 patients were included, with 411 (9.0%) undergoing complex EVAR, 395 (8.6%) complex open repair, and 3778 (82.4%) infrarenal EVAR. Perioperative mortality following complex EVAR was 3.4% vs. 6.6% after open repair (P=.038), and 1.5% after infrarenal EVAR (P=.005). Postoperative acute kidney injuries occurred in 2.3% of complex EVAR patients vs. 9.5% of those undergoing complex open repair (P<.001), and 0.9% of infrarenal EVAR patients (P=.007). Compared to complex EVAR, complex open repair was an independent predictor of 30-day mortality (OR: 2.2, 95% CI:1.1–4.4), renal function deterioration (5.0, 2.3–10.7), and any complication (3.9, 2.7–5.8). When comparing complex to infrarenal EVAR, infrarenal EVAR was associated with favorable 30-day mortality (0.5, 0.3–0.9), and renal outcome (0.4, 0.2–0.9).

Conclusions

Complex EVAR has fewer perioperative complications compared to complex open repair, but –in turn– does carry a higher risk of adverse outcomes than infrarenal EVAR. Further research is warranted to determine whether the benefits of EVAR compared to open repair for complex AAA treatment are maintained during long-term follow-up.

INTRODUCTION

Endovascular repair (EVAR) of an abdominal aortic aneurysm (AAA) is associated with lower perioperative mortality, as well as lower rates of complications, need for transfusions, and length of stay compared to open repair.[1-4] Because of these benefits, the utilization of EVAR has rapidly increased since its introduction in 1996,[5] with over 80% of infrarenal AAA repairs now being performed using endovascular treatment.[6-8] Due to inadequate proximal seal zone, standard endovascular repair cannot be used for juxta- and suprarenal aneurysms (complex AAA), which has been reported to make up as much as 20% of all AAAs.[9-11]

Through advancements in endovascular treatment techniques, including chimney, fenestrated and branched stent grafts, EVAR can now be offered to patients with complex proximal neck anatomy.[12] A large national series from the United Kingdom demonstrated that fenestrated endovascular repair can be performed with a high degree of technical and clinical success.[13] However, most feasibility studies are institutional based and therefore often limited to small numbers of patients.[14-18] Moreover, they usually did not compare outcome of complex EVAR to that of conventional open repair. Efforts that did compare complex EVAR to open repair yielded conflicting results. While one study demonstrated favorable perioperative outcomes after open repair,[19] two other studies showed reduced 30-day morbidity and mortality associated with EVAR.[20, 21] Adding to the confusion, two systematic reviews found perioperative benefits favoring EVAR,[22, 23] while another review demonstrated a pooled perioperative mortality of 4.1% after both EVAR and open repair, with no difference in the complication rate.[24]

In addition, it has been suggested that complex EVAR is associated with increased risk of postoperative renal failure compared to uncomplicated infrarenal EVAR.[25, 26] However, limited comparative data exist for infrarenal versus complex EVAR, and the presumed differences in renal complications could previously not be confirmed.[27]

The purpose of this study was to assess the perioperative outcome following EVAR for complex aneurysms, focusing on differences with complex open repair, the alternative treatment option, and standard infrarenal EVAR using the newly available Targeted Vascular data set of the National Surgical Quality Improvement Program.

METHODS

For this study, we used the Targeted Vascular data set from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. The ACS NSQIP is a multi-institutional collaboration with 102 participating hospitals in the United States that prospectively collect clinical data of patients undergoing major surgery. The NSQIP database includes demographics, comorbidities, intraoperative characteristics, and 30-day postoperative outcomes. The Targeted Vascular data set is a recently added module, which includes additional disease and procedure specific characteristics, and procedure-related outcomes chosen by vascular surgeons. All data collection is performed by trained clinical nurse reviewers and data abstractors. The validity of the ACS NSQIP has been confirmed in previous reports.[28-30] The database contains de-identified data only without any protected health information. Therefore, Institutional Review Board approval and patient consent were waived. Additional information on the ACS NSQIP and the Targeted Vascular data set are available on www.acsnsqip.org.

From the Targeted Vascular data set for years 2011 to 2013, we identified all elective open and endovascular abdominal aortic aneurysm repairs, by the treatment indication variable. Thoracoabdominal aneurysms were excluded from this study. Additionally, procedures coded as repair of a ruptured AAA (CPT: 38082, 35092, 35103), cases with a postoperative diagnosis code for a ruptured AAA (ICD-9: 441.3), and procedures coded as conversions to open repair (CPT: 34830, 34831, 34832) were excluded. The remaining cohort was subsequently divided in three groups in accordance with both treatment modality and proximal aneurysm extent: complex EVAR, complex open repair, and infrarenal EVAR. A complex aneurysm was defined as an aneurysm with either a juxtarenal or suprarenal proximal extent (i.e. all pararenal AAA). All aneurysms treated using the Cook Zenith Fenestrated endograft, which is currently the only fenestrated graft approved by the Food and Drug Administration, were considered complex. Complex open repair patients with infrarenal aortic clamping were excluded. For patients undergoing open repair, a visceral vessel reconstruction was defined as mentioning of a CPT code for visceral vessel reconstruction (CPT: 35361), or mentioning of a visceral vessel reconstruction in the Targeted module.

Groups were compared on baseline and operative characteristics, as well as postoperative outcomes. Postoperative outcomes included 30-day mortality, and in-hospital adverse outcomes such renal function deterioration, ischemic colitis, leg ischemia, wound complications, shock, sepsis, and length of ICU and hospital

stay. Renal function deterioration was defined as a rise in creatinine of >2 mg/dl from preoperative value, and/or requirement of hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration, or ultrafiltration within 30 days of the operation. Patients on dialysis preoperatively were excluded for analysis of renal outcomes. Ischemic colitis was defined as having symptoms of ischemic colitis and/or confirmation of the diagnosis on diagnostic sigmoidoscopy or colonoscopy. Patients with SIRS, sepsis, or septic shock prior to surgery were not included for postoperative sepsis and shock analysis. Wound complications included superficial, deep, and organ space infections. In order to identify differences in postoperative morbidity aside from death, 30-day mortality was not included in the any complication variable.

Statistical analyses

Categorical variables are presented as counts and percentages, and continuous variables as mean ± standard deviation. Differences between treatment groups were assessed using $\chi 2$ and Fisher's exact tests for categorical variables and Student's t-test for continuous variables, where appropriate. To assess independent risks associated with treatment approaches, we used multivariable logistic regression analysis. Baseline characteristics were univariately tested, and predictors with a P-value <.1 were added to the multivariable model. Age was included in all models, regardless of the univariable association. Risk-adjusted comparisons of complex EVAR to complex open repair and infrarenal EVAR were performed separately, and different models were constructed for each analysis. All tests were two-sided and significance was considered when P-value < .05. Statistical analysis was performed using the IBM SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 4584 patients were included, with 411 (9.0%) undergoing complex EVAR, 395 (8.6%) complex open repair, and 3778 (82.4%) underwent EVAR for an infrarenal (noncomplex) AAA.

Baseline characteristics

Baseline characteristics are detailed in Table 1. The complex EVAR group was older than the complex open repair group (74.9 vs. 72.2 years, P<.001), consisted of fewer females (22.4% vs. 33.2%, P=.001), and more non-white patients (11.1% vs. 5.4%, P=.005). In terms of comorbidities, we found that complex EVAR patients more often had insulin-dependent diabetes (3.9% vs. 1.3% P=.019),

had a higher preoperative creatinine (1.22 vs. 1.09 mg/dl, P=.006), and were more commonly on dialysis (2.9% vs. 0.8%, P=.034). Conversely, complex EVAR patients were less often current smokers (29.2% vs. 45.6%, P<.001).

Comparing the complex EVAR patients to the infrarenal EVAR patients, those undergoing repair for a complex AAA were more commonly dialysis depen-

Table 1. Baseline characteristics

	EVAR complex	**OR complex**	**EVAR infra**	**p-value**	
	N=411	*N=395*	*N=3778*	*Complex EVAR vs. OR*	*Infra vs. complex EVAR*
Age – years (sd)	74.9 (8.1)	72.2 (8.3)	74.2 (8.6)	<.001	.160
Categories – N (%)				<.001	.788
<59 years	17 (4.1)	24 (6.1)	191 (5.1)	<.001	.788
60-69	90 (21.9)	125 (31.6)	898 (23.8)		
70-79	181 (44.0)	165 (41.8)	1573 (41.6)		
80-89	112 (27.3)	80 (20.3)	1015 (26.9)		
90+	11 (2.7)	1 (0.3)	101 (2.7)		
Female gender – N (%)	92 (22.4)	131 (33.2)	699 (18.5)	.001	.056
Race				.007	.006
American Indian/ Alaska Native	1 (0.2)	2 (0.5)	3 (0.1)		
Asian	15 (3.6)	4 (1.0)	85 (2.2)		
Black or African American	26 (6.3)	14 (3.5)	185 (4.9)		
Native Hawaiian or Pacific Islander	2 (0.5)	0 (0)	2 (0.1)		
White	352 (85.6)	347 (87.8)	3255 (86.2)		
Unknown	15 (3.6)	28 (7.1)	248 (6.6)		
Comorbidities					
Hypertension – N (%)	343 (83.5)	336 (85.1)	3046 (80.6)	.531	.166
Diabetes – N (%)	63 (15.3)	44 (11.1)	618 (16.4)	.080	.591
Insulin-dependent diabetes – N (%)	16 (3.9)	5 (1.3)	105 (2.8)	.019	0.20
COPD – N (%)	80 (19.5)	93 (23.5)	674 (17.8)	.158	.416
Heart failure – N (%)	17 (4.1)	8 (2.0)	62 (1.6)	.084	<.001
Renal insufficiency – N (%)	79 (19.7)	59 (15.1)	622 (16.9)	.087	.167
Preoperative creatinine – N (%)	1.22 (.85)	1.09 (.43)	1.14 (.57)	.006	.055
Dialysis– N (%)	12 (2.9)	3 (0.8)	34 (0.9)	.034	<.001
BMI >30 – N (%)	110 (26.8)	99 (25.1)	1198 (31.7)	.582	.040
Current smoking – N (%)	120 (29.2)	180 (45.6)	1137 (30.1)	<.001	.706

OR: open repair; COPD: chronic obstructive pulmonary disease; BMI: Body Mass Index

dent (2.9% vs. 0.9%, P<.001), more often had heart failure (4.1% vs. 1.6%, P<.001), and tended towards a higher preoperative creatinine (1.22 vs. 1.14 mg/dl, P=.055). In addition, obesity, defined as a BMI higher than 30 kg/m^2, was less common among complex EVAR patients compared to infrarenal EVAR patients (26.8% vs. 31.7%, P=.040).

Operative and anatomical characteristics

Complex EVAR was associated with shorter operative time compared to complex open repair (184 vs. 269 min., P<.001), while taking significantly longer than infrarenal EVAR (146 min, P<.001, Table 2a). Complex EVAR patients had a smaller aneurysm diameter compared to complex open repair patients (5.9 vs. 6.2 cm, P=.015), but not significantly different from those undergoing infrarenal EVAR (5.7 cm, P=.058). In addition, the aneurysm of complex EVAR patients more often extended into the iliac arteries compared to open complex repair (69.7% vs. 43.2%, P<.001), and infrarenal EVAR (52.9%, P<.001). The complex EVAR group included 22 (5.4%) patients with an infrarenal aneurysm treated using the Cook Zenith Fenestrated graft. Among complex AAA patients undergoing open repair,

Table 2a. Anatomical and intraoperative characteristics for all study groups

	EVAR complex	**OR complex**	**EVAR infra**	**p-value**	
	N=411	*N=395*	*N=3778*	*Complex EVAR vs. OR*	*Infra vs. complex EVAR*
Operative time – min (sd)	184 (100)	269 (108)	146 (70)	<.001	<.001
Diameter – cm (sd)	5.9 (2.6)	6.2 (1.4)	5.7 (1.6)	.015	.058
Indication – N (%)				.074	.108
Diameter	348 (88.1)	328 (83.9)	3304 (88.6)		
Dissection	2 (0.5)	1 (0.3)	28 (0.8)		
Embolization	2 (0.5)	1 (0.3)	20 (0.5)		
Symptomatic	23 (5.8)	47 (12.0)	281 (7.5)		
Thrombosis	10 (2.5)	9 (2.3)	43 (1.2)		
Prior unsatisf. EVAR	7 (1.8)	0 (0)	40 (1.1)		
Prior unsatisf. OR	3 (0.8)	5 (1.3)	12 (0.3)		
Distal extent – N (%)				<.001	<.001
Aortic	112 (30.3)	204 (56.8)	1539 (47.1)		
Common iliac	171 (46.2)	137 (38.2)	1304 (39.9)		
External iliac	38 (10.3)	9 (2.5)	181 (5.5)		
Internal iliac	49 (13.2)	9 (2.5)	242 (7.4)		

18.8% had a clamp location above the celiac artery, 45.4% between the superior mesenteric artery and the renal arteries, and 35.9% above one renal artery. A visceral vessel reconstruction during open repair was performed in 27.1% of patients.

Not surprisingly, complex EVAR patients more often received renal revascularization than those undergoing EVAR for an infrarenal AAA (30.4% vs. 4.1%, P<.001, Table 2b). No difference existed in main body device used between complex and infrarenal EVAR patients (P=.121).

Table 2b. EVAR specific intraoperative characteristics

	EVAR complex	**OR complex**	**EVAR infra**	**p-value**
	N=411	*N=395*	*N=3778*	*Infra vs. complex EVAR*
Acute conversion – N (%)	3 (0.7)	-	21 (0.6)	.506
Access – N (%)				.100
Attempted percutaneous	5 (1.2)	-	33 (0.9)	
Bilateral cutdown	277 (67.4)	-	2441 (64.7)	
One groin cutdown	23 (5.6)	-	348 (9.2)	
Percutaneous bilateral	106 (25.8)	-	950 (25.2)	
Renal revascularization – N (%)	125 (30.4)	-	156 (4.1)	<.001
Lower extrem revasc – N (%)	19 (5.5)	-	138 (4.2)	.247
Access vessel repair – N (%)	42 (10.2)	-	284 (7.5)	.052
Hypogastric embolization – N (%)	27 (6.6)	-	248 (6.6)	.997
Main body device – N (%)				.121[α]
Cook Zenith	72 (17.5)	-	795 (21.0)	
Cook Zenith Fenestrated	84 (20.4)	-	0 (0)	
Cook Zenith Renu	3 (0.7)	-	39 (1.0)	
Endologix Powerlink	26 (6.3)	-	292 (7.7)	
Gore Excluder	95 (23.1)	-	1281 (33.9)	
Lobard Aorfix	0 (0)	-	2 (0.1)	
Medtronic AneuRx	1 (0.3)	-	7 (0.2)	
Medtronic Endurant	95 (23.1)	-	1130 (29.9)	
Medtronic TALENT	1 (0.2)	-	18 (0.5)	
TriVascular Ovation	4 (1.0)	-	36 (1.0)	
other	26 (6.3)	-	149 (3.9)	
not documented	4 (1.0)	-	29 (0.8)	

α analysis did not include patients receiving a Cook Zenith Fenestrated endograft.

Postoperative outcomes

Postoperative outcomes are detailed in Table 3a. Mortality within 30-days was significantly lower after complex EVAR compared to complex open repair (3.4% vs. 6.6%, P=.038). Similarly, deterioration of renal function (2.3% vs. 9.5%, P<.001) and new dialysis requirement (1.3% vs. 6.1%, P<.001) occurred less frequently after complex EVAR than complex open repair. In addition, complex EVAR was associated with lower rates of ischemic colitis (1.0% vs. 4.6%, P=.002), myocardial infarction (0.7% vs. 4.3%, P=.001), pneumonia (1.2 vs. 7.6%, P<.001), prolonged ventilator dependence (1.9% vs. 14.4%, P<.001), reintubation (2.2% vs. 9.4%, P<.001), wound dehiscence (0.2% vs. 3.0%, P=.001), shock (0.7% vs. 2.8%, P=.031, respectively), return to the operating room (5.4% vs. 13.9%, P<.001), and postoperative blood transfusions (16.3% vs. 78.7%, P<.001). Also, length of ICU stay and hospital stay were significantly shorter for those undergoing complex EVAR compared to complex open repair (1.0 vs. 4.7, P<.001; 4.1 days vs. 11.3 days, P<.001, respectively).

In comparison to infrarenal EVAR, 30-day mortality was significantly higher after complex EVAR (3.4% vs. 1.5%, P=.005). Similarly, complex EVAR was associated with a higher rate of renal function deterioration (2.3 % vs. 0.9%, P=.007), postoperative blood transfusion (16.3%, vs. 10.2%, P<.001), and prolonged ventilator dependence (1.9% vs. 0.9%, P=.036). In addition, ICU length of stay (1.0 vs. 0.6, P=.003), and hospital length of stay (4.1 days vs. 2.9 days, P=.001) were both significantly longer after complex EVAR compared to infrarenal EVAR.

Outcomes of patients receiving the Cook Zenith Fenestrated endograft are shown in Table 3b. Although not significant, this subanalysis demonstrated that patients undergoing placement of a Cook Zenith fenestrated graft had a similar, if not lower, 30-day mortality rate compared to all other complex EVAR patients (1.2% vs. 4.0%, P=.318). However, patients treated with the Cook Zenith Fenestrated endograft more frequently received blood transfusions postoperatively (25.0% vs. 14.1%, P=.016). Similar to the other complex EVAR patients, low occurrence rates were found for various adverse outcomes, such as renal function deterioration (2.4% vs. 2.2%, P=1.000), ischemic colitis (1.2% vs. 0.9%, P=1.000), leg ischemia (0% vs. 1.8%, P=.354), and pneumonia (1.2% vs. 1.2%, P=1.000). Hospital and ICU length of stay were also comparable to the other complex EVAR patients (4.6 vs. 4.0 days, P=.488; 1.4 vs. 0.9 days, P=.208, respectively).

Table 3a. Postoperative outcomes for all study groups

	EVAR complex	OR complex	EVAR infra	p-value	
	N=411	*N=395*	*N=3778*	*Complex EVAR vs. OR*	*Infra vs. complex EVAR*
30-day mortality	14 (3.4)	26 (6.6)	57 (1.5)	0.038	.005
Creat rise >2 mg/dl – N (%)	9 (2.3)	37 (9.5)	32 (0.9)	<.001	.007
Requiring dialysis – N (%)	5 (1.3)	24 (6.1)	21 (0.6)	<.001	.096
Ischemic colitis – N (%)	4 (1.0)	18 (4.6)	19 (0.5)	.002	.276
Leg ischemia – N (%)	6 (1.5)	7 (1.8)	49 (1.3)	.725	.783
Pneumonia – N (%)	5 (1.2)	30 (7.6)	32 (0.8)	<.001	.447
>48 hour on ventilator	8 (1.9)	57 (14.4)	33 (0.9)	<.001	.036
Reintubation – N (%)	9 (2.2)	37 (9.4)	51 (1.3)	<.001	.174
Myocardial infarction – N (%)	3 (0.7)	17 (4.3)	52 (1.4)	.001	.364
CPR – N (%)	2 (0.5)	10 (2.5)	22 (0.6)	.019	1.000
Wound infection – N (%)	6 (1.5)	11 (2.8)	60 (1.6)	.191	.860
Wound dehiscence – N (%)	1 (0.2)	12 (3.0)	8 (0.2)	.001	.606
Return to OR – N (%)	22 (5.4)	55 (13.9)	148 (3.9)	<.001	.161
Pulmonary embolism	1 (0.2)	2 (0.5)	8 (0.2)	.617	.606
Stroke – N (%)	3 (0.7)	3 (0.8)	9 (0.2)	1.000	.106
Sepsis – N (%)	3 (0.7)	10 (2.5)	22 (0.6)	.051	.731
Shock – N (%)	3 (0.7)	11 (2.8)	14 (0.4)	.031	.229
Rupture 30-day – N (%)	0 (0)	1 (0.3)	2 (0.1)	.490	1.000
≥1 postoperative transfusion	67 (16.3)	311 (78.7)	385 (10.2)	<.001	<.001
Any complication – N (%)	47 (11.4)	133 (33.7)	333 (8.8)	<.001	.085
Any complication – N (%)[α]	97 (23.6)	328 (83.0)	614 (16.3)	<.001	<.001
Hospital length of stay – days (sd)	4.1 (6.8)	11.3 (10.0)	2.9 (5.1)	<.001	.001
ICU length of stay – days (sd)	1.0 (2.4)	4.7 (4.9)	0.6 (1.7)	<.001	.003

α incidence of any complication when postoperative blood transfusions are included

Multivariable analyses

In multivariable analysis (Table 4), open repair for complex AAA was found to be an independent predictor of 30-day mortality (OR: 2.2, 95% CI: 1.1 – 4.4), renal function deterioration (OR: 5.0, 95% CI: 2.3 – 10.7), and any complication (OR: 3.9, 95% CI: 2.7 – 5.8) compared to complex EVAR. When comparing complex to infrarenal EVAR, infrarenal EVAR was associated with favorable 30-day mortality (OR: 0.5, 95% CI: 0.3 – 0.9), and renal outcome (OR: 0.4, 95% CI: 0.2 – 0.9), while no difference was found in the occurrence of any complication (OR: 0.9,

Table 3b. Postoperative outcomes for complex EVAR patients treated with the Cook Zenith Fenestrated graft and those treated otherwise

	Cook Zenith Fenestrated	Other Complex EVAR	
	N=84	*N=327*	**P-value**
30-day mortality	1 (1.2)	13 (4.0)	.318
Creat rise >2 mg/dl – N (%)	2 (2.4)	7 (2.2)	1.000
Requiring dialysis – N (%)	2 (2.4)	3 (1.0)	.284
Ischemic colitis – N (%)	1 (1.2)	3 (0.9)	1.000
Leg ischemia – N (%)	0 (0)	6 (1.8)	.354
Pneumonia – N (%)	1 (1.2)	4 (1.2)	1.000
>48 hour on ventilator	2 (2.4)	6 (1.8)	.669
Reintubation – N (%)	3 (3.6)	6 (1.8)	.397
Myocardial infarction – N (%)	1 (1.2)	2 (0.6)	.497
CPR – N (%)	0 (0)	2 (0.6)	1.000
Wound infection – N (%)	1 (1.2)	6 (1.8)	1.000
Wound dehiscence – N (%)	0 (0)	1 (0.3)	1.000
Return to OR – N (%)	5 (6.0)	17 (5.2)	.784
Pulmonary embolism	0 (0)	1 (0.3)	1.000
Stroke – N (%)	1 (1.2)	2 (0.6)	.497
Sepsis – N (%)	2 (2.4)	1 (0.3)	.108
Shock – N (%)	1 (1.2)	2 (0.6)	.497
Rupture 30-day – N (%)	0 (0)	0 (0)	1.000
≥1 postoperative transfusion	21 (25.0)	46 (14.1)	.016
Any complication – N (%)	10 (11.9)	37 (11.3)	.880
Any complication – N (%)[α]	25 (29.8)	72 (22.0)	.136
Hospital length of stay – days (sd)	4.6 (6.5)	4.0 (6.9)	.488
ICU length of stay – days (sd)	1.4 (3.5)	0.9 (2.1)	.208

α incidence of any complication when postoperative blood transfusions are included

95% CI: 0.6 – 1.2). Given the invasive nature of open AAA repair and the routine need for postoperative blood transfusions, a postoperative transfusion was not included as a complication in this analysis. However, when a blood transfusion is considered a complication, complex EVAR is associated with an increased risk of any complication compared to infrarenal EVAR as well (OR: 0.7, 95% CI: 0.5 – 0.9). Within the complex EVAR group, no differences were found between patients treated with the Cook Zenith Fenestrated endograft and those treated using other grafts in multivariable analysis.

Table 4. Adjusted associations between treatment groups and outcomes

30-day mortality[α]	***OR***	***95% CI***	***p-value***
EVAR complex	*Reference*	-	-
Open complex[α]	2.2	1.1 – 4.4	0.025
EVAR infrarenal[β]	0.5	0.3 – 0.9	0.019
Renal complication[β]	***OR***	***95% CI***	***p-value***
EVAR complex	*Reference*	-	-
Open complex[γ]	5.0	2.3 – 10.7	<.001
EVAR infrarenal[δ]	0.4	0.2 – 0.9	.017
Any complication[γ]	***OR***	***95% CI***	***p-value***
EVAR complex	*Reference*	-	-
Open complex[ε]	3.9	2.7 – 5.8	<.001
EVAR infrarenal[ζ]	0.9	0.6 – 1.2	.369

α: adjusted for: age, gender, obstructive pulmonary disease
β adjusted for: age, gender, hypertension, insulin-dependent diabetes, preoperative renal insufficiency, preoperative dialysis, heart failure, obstructive pulmonary disease, obesity, current smoking
γ adjusted for: age, preoperative renal insufficiency, obstructive pulmonary disease, obesity
δ adjusted for: age, gender, insulin-dependent diabetes, preoperative renal insufficiency, obstructive pulmonary disease, obesity
ε adjusted for: age, gender, hypertension, preoperative renal insufficiency, obstructive pulmonary disease
ζ adjusted for: age, gender, nonwhite race, hypertension, insulin-dependent diabetes, preoperative renal insufficiency, preoperative dialysis, heart failure, obstructive pulmonary disease, obesity

DISCUSSION

This study demonstrates that endovascular repair provides a good alternative to open repair for the treatment of complex AAA. In addition to lower 30-day mortality, we found that EVAR was associated with a lower incidence of various adverse outcomes, including acute renal failure, ischemic colitis, return to the operating room, and length of stay. In comparison to infrarenal EVAR, complex EVAR was associated with a significantly increased perioperative mortality risk, as well as a higher frequency of several other adverse outcomes, most importantly an increased incidence of postoperative renal dysfunction.

At 3.4%, the mortality following complex EVAR is comparable to previous reports.[22, 31-33] Despite the fact that complex EVAR patients were older and in more frail health than those undergoing open repair, mortality was almost half of that following open repair (3.4% vs. 6.6%). After adjustment for the various health disparities, treatment of a complex AAA through open repair proved to

be associated with two-and-half times higher mortality risk compared to EVAR. This is in line with the results of previously conducted studies by Canavati et al. and Tsilimparis et al., which found a similar mortality benefit for fenestrated EVAR.[20, 34] In contrast to what has been shown for open repair,[35] endovascular complex AAA repair was associated with increased mortality risks over infrarenal EVAR. A difference in operative stress between EVAR for infrarenal and complex AAA, as indicated by the longer operative time, may have contributed to the observed difference in occurrence of adverse outcomes in the perioperative period.

Our results indicated that complex EVAR was associated with lower rates of complications compared to complex open repair. Despite worse preoperative renal function, the avoidance of suprarenal clamping and the resulting renal ischemia led to fewer kidney injuries and fewer patients requiring new dialysis with complex EVAR. This favorable renal outcome of EVAR for complex AAA is in line with previous studies.[22, 23] A recent case-controlled study, however, demonstrated a higher frequency of acute kidney injury after complex endovascular repair with similar 1-year results as open repair.[36] When comparing absolute rates of postoperative renal dysfunction to prior reports, the occurrence of kidney injuries in this study is relatively low.[22, 23, 37, 38] The present results most likely underestimate the actual incidence in our cohort, which is the result of the relative strict definition for postoperative renal dysfunction employed by the NSQIP. In regards to mid-term and late renal outcomes, previous studies have reported good patency results of renal stents and chimneys.[13, 25, 26, 37, 39] Although close monitoring of the renal function is required, this further highlights the benefit of EVAR over open repair, particularly for patients with renal impairment.[40]

Similar to established short-term perioperative benefits of EVAR for infrarenal AAA, the incidence of adverse events such as respiratory and wound complications, ischemic colitis, leg ischemia, myocardial infarction, and return to the operating room were lower for complex EVAR versus open repair. Due to the less complicated postoperative period and invasiveness of procedure, length of stay following complex EVAR was almost one-third of that following open repair. It should be noted that as a result of the exclusion of conversions, the incidence of adverse outcomes in the complex open repair might be relatively low. However, since complex EVAR was superior over open repair despite the exclusion of these patients, this only strengthens the conclusions of this study. As previously suggested,[25, 26] complex EVAR was associated with a higher frequency of postoperative renal dysfunction compared to infrarenal EVAR, although this did not translate into a higher need for dialysis in the postoperative period. This is in contrast to the study by Glebova et al., which showed no difference in renal complications between infrarenal EVAR and fenestrated EVAR using the

non-Targeted NSQIP dataset.[27] This difference may be related to the fact that the definition for complex EVAR in the present study is based on the specific Targeted NSQIP variable for proximal aneurysm extent, while the definition in the Glebova study was established from billing coding prior to the commercial availability of fenestrated endografts.

Several studies have reported on differences in outcome between chimney and fenestrated grafts. These studies determined that no difference exists in mortality or in renal endpoints between chimneys and fenestrated endografts.[32, 41] Unfortunately, we were unable to identify the exact technical approach that was used beyond the type of main body device. Although not significantly different, selective analysis of patients receiving the Cook Zenith Fenestrated graft revealed that these patients had a similar to lower mortality rate as compared to the other complex EVAR patients. However, this may simply reflect that those treated otherwise have more complex anatomy, and were therefore ineligible for the Cook Zenith Fenestrated graft, which led to the trend towards worse outcomes. Unfortunately we did not have this level of anatomic detail. For other perioperative complications, we found that the Cook Zenith Fenestrated patients had comparable occurrence rates to other complex EVAR patients, including adverse renal outcomes, despite an increased transfusion requirement. This is in line with results from a pooled data analysis on fenestrated stent grafts.[32]

This study has several limitations. First, since the Targeted Vascular dataset of the NSQIP is gathered through a registry, underreporting of events is possible. Second, we were unable to fully distinguish between treatment approaches in patients undergoing complex EVAR. However, as previously addressed, reports have shown no differences in perioperative outcomes between fenestrated endografts and chimney grafts, making the group more generalizable.[32, 41] Third, as evidenced by the lower than expected proportion of complex EVARs undergoing concurrent renal stenting, the capture of this data point was thought to be unreliable and therefore limited our ability to identify snorkel repairs. However, we know they are complex aneurysms because of the clearly defined proximal extent of the aneurysm in this data set, as captured by operative report review. Furthermore, NSQIP clinical reviewers are instructed to capture renal revascularization for renal artery stenosis, which we believe leads to variable reporting based on interpretation of this definition. For complex open repair, we found that 27% of patients underwent visceral artery reconstruction, which is similar to previous reports.[42] Unfortunately, the exact number of visceral artery reconstructions is not documented in this data set. Fourth, the NSQIP database lacks data on perioperative endoleaks and long-term outcomes, which precluded us from assessing differences in the occurrence of endoleaks and late reinter-

ventions, as well as long-term renal function. This highlights the need for future studies investigating the long-term outcome of EVAR for complex AAA. Also, since we did not have access to postoperative serum creatinine values, we were unable to redefine renal dysfunction or use standardized formulas consistent with previous studies. In addition, due to the novelty of this recently added vascular module, validation studies have yet to be conducted for it. However, the ability of these same nurse reviewers to accurately abstract data from the medical record for the NSQIP in general has been confirmed previously.[28-30] Finally, it should be noted that patients were not randomized to undergo open repair or EVAR. Nevertheless, this study provides valuable new data on the operative outcome of complex AAA repair in both the open and endovascular setting, which may add to prospectively conducted research efforts.

In conclusion, this study demonstrates that as a result of advancements in endovascular treatment techniques, EVAR has become a good alternative to conventional open repair for treatment of anatomically complex aneurysms. Complex EVAR has fewer perioperative complications compared to complex open repair, but –in turn– is associated with increased perioperative risks compared to infrarenal EVAR. Further research is warranted to determine whether the favorable outcome of EVAR for complex AAA is maintained during long-term follow-up.

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Chapter 6

Transperitoneal vs. Retroperitoneal Approach for Open Abdominal Aortic Aneurysm Repair in the Targeted Vascular NSQIP

Dominique B. Buck[1,2]
Klaas H.J. Ultee[1]
Sara L. Zettervall[1]
Pete A. Soden[1]
Jeremy Darling[1]
Mark C. Wyers[1]
Joost A. van Herwaarden[2]
Marc L. Schermerhorn[1]

1) Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA, USA
2) Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

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ABSTRACT

Objective

We sought to compare current practices in patient selection and 30-day outcomes for transperitoneal and retroperitoneal abdominal aortic aneurysm (AAA) repairs.

Methods

All patients undergoing elective transperitoneal or retroperitoneal surgical repair for AAA between January 2011 and December 2013 were identified in the Targeted Vascular National Surgical Quality Improvement Program database. Emergency cases were excluded. Baseline characteristics, anatomic details, and intraoperative and postoperative outcomes were evaluated among those with infrarenal or juxtarenal AAA only.

Results

We identified 1135 patients: 788 transperitoneal (69%) and 347 retroperitoneal (31%). When only infrarenal and juxtarenal AAAs were evaluated, the retroperitoneal patients were less likely to have an infrarenal clamp location (43% vs 68%) and had more renal revascularizations (15% vs 6%; $P < .001$), more visceral revascularizations (5.6% vs 2.4%; $P = .014$), and more lower extremity revascularizations (11% vs 7%; $P = .021$) compared with the transperitoneal approach. Postoperative mortality and return to the operating room were similar. Transperitoneal patients had a higher rate of wound dehiscence (2.4% vs 0.4%; $P = .045$), and retroperitoneal patients had higher incidence of pneumonia (9% vs 5%; $P = .034$), transfusion (77% vs 71%; $P = .037$), and reintubation (11% vs 7%; $P = .034$), and a longer median length of stay (8 vs 7 days; $P = .048$). After exclusion of all concomitant procedures, only transfusions remained more common in the retroperitoneal approach (78% vs 70%; $P = .036$). Multivariable analyses showed only higher rates of reintubation in the retroperitoneal group (odds ratio, 1.7; 95% confidence interval, 1.0-3.0; $P = .047$).

Conclusions

The retroperitoneal approach is more commonly used for more proximal aneurysms and was associated with higher rates of pneumonia, reintubation, and transfusion, and a longer length of stay on univariate analyses. However, multivariable analysis demonstrated similar results between groups. The long-term benefits and frequency of reinterventions remain to be proven.

INTRODUCTION

Despite the development of endovascular techniques for abdominal aortic aneurysm (AAA) repair in recent years, open surgical repair remains necessary to treat anatomically complex aneurysms and may be beneficial for younger patients and those unable to comply with long-term surveillance.[1] Medicare data show that open surgical repair was used in 23% of intact AAA repairs in the United States in 2008, but also highlighted higher rates of medical and surgical complications compared with endovascular AAA repair.[2, 3] In addition, lower rates of late bowel and hernia complications were demonstrated with retroperitoneal surgery compared with intraperitoneal surgery for nonaortic surgical procedures.[4]

The transperitoneal approach is most familiar to surgeonsand provides extensive intra-abdominal access.[5, 6] The time from skin incision to aortic clamping was shown to be shorter in the transperitoneal group than in the retroperitoneal group.[7, 8] However, complications associated with this approach leading to prolonged ileus have been reported.[9] In an attempt to avoid complications associated with entrance into the peritoneal cavity, the retroperitoneal approach was adopted and also offers improved access to the suprarenal and supraceliac aorta.[5, 10]

Several studies comparing perioperative outcomes of the transperitoneal and retroperitoneal approach for AAA repair suggest that the retroperitoneal approach may result in lower rates of ileus, shortened hospital length of stay, and improved respiratory function than transperitoneal procedures.[6, 7, 9, 11, 12, 13, 14, 15] Conversely, other studies have found no differences in respiratory complications, return of bowel function, and length of stay.[16, 17] This study aimed to identify the demographic and anatomic differences between patients currently selected for elective transperitoneal vs retroperitoneal AAA repair and to assess differences in intraoperative details, perioperative mortality, and complications.

METHODS

Data source

The patient cohort for this study was identified using the Targeted Vascular American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. The NSQIP is a national clinical registry of self-selected hospitals with an interest in quality improvement and improved risk adjustment. This data set contains prospectively collected clinical data on preoperative, operative, and postoperative variables. To ensure quality, data are collected by trained clinical nurse reviewers.

The more clinically detailed Targeted Vascular module was created from the general NSQIP in 2011 to collect additional anatomic and operative characteristics from >60 participating hospitals. The Targeted Vascular ACS NSQIP database contains unidentifiable patients only; therefore, Institutional Review Board approval and patient consent were waived. Details of quality control and data collection have been described extensively on the ACS NSQIP Web site.[18] Definitions for the specific Targeted Vascular ACS NSQIP collected data points may be found in the user guide available online.[19]

We identified all patients undergoing elective transperitoneal or retroperitoneal open surgical repair for AAA from January 2011 to December 2013. Emergency cases were excluded from analyses.

Outcomes

Patients with transperitoneal surgical repair (midline and transverse incisions) were compared with patients undergoing retroperitoneal repair. A subgroup analysis found no differences between midline and transverse incisions; therefore, they were grouped for this analysis. Data were collected on relevant patient demographics, comorbidities, operative details, and postoperative course. Obesity was defined at body mass index >30 kg/m2. Baseline characteristics were compared for all AAA, including infrarenal, juxtarenal, pararenal, suprarenal, and type IV thoracoabdominal aneurysms. This database defines pararenal as AAAs that involve the origin of the renal arteries and is distinct from juxtarenal (AAAs that do not involve the renal arteries but because of proximity require clamping above the renal arteries to complete the proximal anastomosis) and suprarenal (AAAs that begin above at least one main renal artery but below the visceral segment).

Renal revascularization included bypass or reimplantation of one or both of the renal arteries. Visceral revascularization included endarterectomy of celiac or superior mesenteric artery or reimplantation of a visceral vessel. Lower extremity revascularizations were defined as infrainguinal bypass or endovascular stent placement. All lower extremity, renal, and visceral revascularizations were considered concomitant procedures.

Operative time was defined as the time from incision to skin closure. For comparison of intraoperative and postoperative outcomes, pararenal, suprarenal, and thoracoabdominal aneurysms were excluded. Intraoperative anatomic details included clamp location, extent of aneurysm, and extent of distal iliac involvement, and concomitant renal, visceral, or lower extremity revascularization performed. Concomitant procedures were excluded in the comparison of operative time. Any wound complication was defined as a composite variable inclusive of any surgical site infection (SSI), superficial SSI, deep SSI, organ/space SSI, or dehiscence.

Statistical analysis

Analyses were conducted with SPSS 20 software (IBM Corp, Armonk, NY). Categorical variables were compared using the Pearson $\chi 2$ or Fisher exact test, and continuous variables were analyzed by two-tailed independent samples t-test or the Mann-Whitney test, where appropriate. Clinically relevant factors shown to be predictive of adverse outcomes in previous studies were selected for inclusion in multivariable logistic regression. These factors included gender, age, race, prior abdominal surgery, concomitant procedure, aneurysm extent, bifurcated grafts, and management of the inferior mesenteric artery. To evaluate potential interaction between outcomes and concomitant procedures, multivariable models were run with and without adjusting for concomitant procedures, with no significant differences identified. Statistical significance was defined as $P < .05$.

RESULTS

A cohort of 1135 patients was identified, including 788 patients (69%) with a transperitoneal approach, and 347 (31%) with a retroperitoneal approach for repair. Patients who underwent the retroperitoneal approach were less likely to have an infrarenal aneurysm (31% vs 61%) and more likely to have juxtarenal (41% vs 28%), pararenal (9% vs 4%), suprarenal (14% vs 5%), and type IV thoracoabdominal aneurysms (5% vs 1%; Table 1).

Baseline characteristics

The retroperitoneal approach was used less often in men (67% vs 74%; P = .018) and more often in those of white race (90% vs 81%; P < .001) or with prior abdominal operations (35% vs 21%; P < .001). There were no significant differences in mean age (71 vs 71 years; P = .228), American Society of Anesthesiologists (ASA) Physical Status Classification ≥4 (36 % vs 34%; P = .505), or mean aneurysm diameter (6.3 vs 6.2 cm;P = .261). The same significant differences in baseline characteristics persisted when the analysis was confined to infrarenal and juxtarenal aneurysms only.

Analysis of intraoperative characteristics among infrarenal and juxtarenal repairs only (Table 2) indicated that patients undergoing retroperitoneal repairs were more likely to have a more renal revascularization (15% vs 6%; P < .001), lower extremity revascularization (11% vs 7%; P = .021), and visceral revascularization (6% vs 2%; P = .014). When all concomitant procedures were combined, this rate was higher in the retroperitoneal approach (26% vs 16%; P = .001). There was no difference in the management of the inferior mesen-

teric artery, whether reimplantation (2.8% vs 6.0%), ligation, or observation of chronic occlusion.

Table 1. Baseline characteristics of patients with abdominal aortic aneurysms undergoing open repair (transperitoneal vs. retroperitoneal approach)

Variable	Transperitoneal (n=788)	Retroperitoneal (n=347)	P Value
Male gender	74%	67%	0.02
Race or ethnic group			<.001
Other/Unkown	12%	5%	
White	81%	90%	
Black/African American	4.7%	4.0%	
American Indian/Alaska Native	0.4%	0.6%	
Asian	2.8%	0.6%	
White Race	81%	90%	<.001
Age (mean)	70.6	71.3	0.23
Age Category (years)			0.31
18-59	11%	7.8%	
60-69	33%	33%	
70-79	39%	42%	
80+	17%	18%	
Prior Open Abdominal Surgery	21%	35%	<.001
ASA 4 Classification	34%	36%	0.51
Aneurysm diameter (cm)	6.16	6.27	0.26
Coexisting conditions			
Congestive heart failure	2.2%	1.4%	0.42
Hypertension	84%	83%	0.62
Diabetes	13%	12%	0.84
History of severe COPD *	20%	22%	0.48
Dialysis (pre-op)	0.8%	0.9%	0.86
Obesity	27%	30%	0.29
Proximal Aneurysm Extent			<.001
Infrarenal	61%	31%	
Juxtarenal	28%	41%	
Pararenal	4.3%	9.2%	
Supra-renal	5.2%	14%	
Type IV Thoracoabdominal aneurysm	1.4%	4.9%	

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

Table 2. Intra-operative outcomes of patients with infrarenal or juxtarenal abdominal aortic aneurysms undergoing transperitoneal vs. retroperitoneal open surgical repair

Outcomes	Transperitoneal (n=702)	Retroperitoneal (n=248)	P Value
Surgical Approach			<.001
Retroperitoneal		100%	
Transperitoneal-midline	95%		
Transperitoneal-transverse	5%		
Aneurysm Extent			<.001
Infrarenal	68%	43%	
Juxtarenal	32%	57%	
Indication for surgery			0.21
Diameter	81%	78%	
Dissection	0.9%	0.4%	
Embolization	0.3%	1.6%	
Non-ruptured symptomatic	8.5%	11%	
Not documented	0.6%	0.8%	
Prior endovascular intervention w/ unsatisfactory result	3.1%	4.4%	
Prior open intervention w/ unsatisfactory result	0.6%	0%	
Rupture w/ or w/out hypotension	2.3%	2.0%	
Thrombosis	3.3%	2.0%	
Proximal Clamp Location			<.001
Supraceliac	4.6%	15%	
Between SMA & renals	16%	28%	
Above one renal	16%	17%	
Infrarenal	58%	34%	
Not documented	6.0%	6.9%	
Distal Extent			<.001
Aortic	39%	53%	
Common Iliac	44%	30%	
External Iliac	4.4%	6.5%	
Internal Iliac	4.1%	1.2%	
Not documented	8.4%	9.3%	
Management of Inferior Mesenteric Artery			<.001
Chronically occluded	11%	4.8%	
Implanted	6.0%	2.8%	
Ligated	42%	36%	
Not documented	41%	57%	
Renal Revascularization	6.4%	15%	<.001

Table 2. (continued)

Outcomes	Transperitoneal (n=702)	Retroperitoneal (n=248)	P Value
Visceral (SMA & Celiac) Revascularization	2.4%	5.6%	0.01
Lower Extremity Revascularization	6.7%	11%	0.02
Abdominal, non-arterial repair or excision	3.3%	1.6%	0.18
Any Concomitant Procedure	16.2%	25.8%	0.001
Median OR time (min)	234	238	0.12
Median OR time (all concomitant procedures excluded)	219	227	0.25
Median OR time for bifurcated grafts only	243	250	0.18
Median OR time for bifurcated grafts only (all concomitant procedures excluded)	235	236	0.42
Median OR time for tubegrafts only	211	235	0.03
Median OR time for tubegrafts only (all concomitant procedures excluded)	193	223	0.02

SMA = superior mesenteric artery,

Intra-operative characteristics

The overall operative time was similar in the two cohorts. However, more tube grafts were placed in the retroperitoneal group. Median operative time was significantly longer for the retroperitoneal approach among patients with tube grafts alone (235 vs 211 minutes;P = .027). Operative time was 250 vs 243 minutes (P = .180) for bifurcated configurations without concomitant procedures.

Post-operative outcomes

Analysis of the unadjusted postoperative outcomes demonstrated that the retroperitoneal group had significantly higher rates of transfusion (77% vs 71%;P = .037), sepsis (3.2% vs 1.3%; P = .047), pneumonia (8.9% vs 5.1%; P = .034), reintubation (11% vs 7%; P = .034), and median length of stay (8 vs 7 days; P = .048;Table 3a). Prolonged length of stay >10 days was similar in both groups (28% vs 27%;P = .735). The rate of wound dehiscence was lower in the retroperitoneal cohort (0.4% vs 2.4%; P = .045). There were no significant differences in mortality (3.6% vs 3.8%; P = .878) or return to the operating room (12% vs 10%; P = .382).

Multivariable analysis

Because concomitant procedures were more common in the retroperitoneal patients, we performed an analysis limited to those without concomitant procedures. After exclusion of any concomitant procedures during AAA repair, only the

transfusion rate remained higher in the retroperitoneal group (78% vs 70%; P = .036; Table 3b). A separate multivariable analyses, with adjustment for baseline characteristics, showed that only reintubation remained significantly higher with the retroperitoneal approach (odds ratio, 1.7; 95% confidence interval, 1.0-3.0;

Table 3a. Post-operative outcomes of patients with infrarenal and juxtarenal abdominal aortic aneurysms undergoing transperitoneal vs. retroperitoneal open surgical repair

Outcomes	Transperitoneal (n=702)	Retroperitoneal (n=248)	P Value	Odds Ratio (95% CI)
Mortality	3.8%	3.6%	0.88	0.9 (0.4-2.0)
Medical complications (% of patients)				
Myocardial Infarction	2.6%	2.8%	0.83	1.1 (0.5-2.7)
Cardiac Arrest requiring CPR	2.1%	2.8%	0.54	1.3 (0.5-3.3)
Pneumonia	5.1%	8.9%	0.03	1.8 (1.0-3.1)
Pulmonary Embolism	0.4%	0.4%	0.96	0.9 (0.1-9.1)
Progressive Renal Insufficiency	1.7%	2.4%	0.48	1.4 (0.5-3.8)
Acute Renal Failure	3.4%	6.0%	0.07	1.8 (0.9-3.5)
Urinary Tract Infection	3.0%	1.6%	0.24	0.5 (0.2-1.6)
Stroke / CVA	0.4%	0.8%	0.48	1.9 (0.3-11.4)
DVT	2.1%	1.6%	0.61	0.8 (0.2-2.3)
Transfusion	71%	77%	0.04	1.4 (1.0-2.0)
Sepsis	1.3%	3.2%	0.05	2.6 (1.0-6.7)
Surgical complications (% of patients)				
Prolonged Intubation > 48 hours	9.1%	13%	0.06	1.5 (1.0-2.4)
Reintubation	6.7%	11%	0.03	1.7 (1.0-2.8)
Return to OR	9.5%	12%	0.25	1.3 (0.8-2.1)
Any Wound Complication	5.6%	2.8%	0.09	0.5 (0.2-1.1)
Wound dehiscence	2.4%	0.4%	0.05	0.2 (0.0-1.2)
Superficial SSI	2.1%	1.6%	0.61	0.8 (0.2-2.3)
Deep SSI	0.7%	0.4%	0.58	0.6 (0.1-4.9)
Organ/Space SSI	1.1%	0.4%	0.30	0.4 (0.0-2.8)
Ischeamic colitis	3.7%	2.4%	0.34	0.6 (0.3-1.6)
Lower Extremity Ischemia	2.4%	2.0%	0.72	0.8 (0.3-2.3)
Mean length of hospital stay (no. of days)	9.6	10.5	0.17	
Median length of hospital stay (no. of days)	7	8	0.05	
Length of stay ≥ 10 days	28%	27%	0.74	1.3 (0.9-1.7)
Discharged home	77%	74%	0.34	0.9 (0.6-1.2)

CI, Confidence interval; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; OR, odds ratio; SSI, surgical site infection.

P = .047; Table 4a). After adjusting for baseline characteristics and concomitant procedures, there were no differences between groups (Table 4b).

Table 3b. Post-operative outcomes of patients with infrarenal and juxtarenal abdominal aortic aneurysms undergoing transperitoneal vs. retroperitoneal open surgical repair (all concomitant procedures excluded)

Outcomes	Transperitoneal (n=588)	Retroperitoneal (n=184)	P Value
Mortality	4.6%	2.7%	0.27
Rupture of Aneurysm	0.9%	0.5%	0.68
Medical complications (% of patients)			
Myocardial Infarction	2.0%	2.2%	0.91
Cardiac Arrest requiring CPR	2.2%	2.2%	0.98
Pneumonia	4.9%	7.1%	0.27
Pulmonary Embolism	0.3%	0.5%	0.70
Progressive Renal Insufficiency	1.9%	1.6%	0.83
Acute Renal Failure	3.6%	4.3%	0.63
Urinary Tract Infection	2.7%	1.6%	0.41
Stroke / CVA	0.3%	0.5%	0.70
DVT	2.2%	1.1%	0.34
Bleeding Transfusions	69.7%	77.7%	0.04
Sepsis	1.0%	2.7%	0.09
Surgical complications (% of patients)			
Prolonged Intubation > 48 hours	9.2%	9.8%	0.81
Reintubation	6.8%	8.7%	0.39
Return to OR	9.0%	8.2%	0.72
Any Wound Complication	5.4%	2.7%	0.13
Wound dehiscence	2.4%	0.5%	0.12
Superficial SSI	1.9%	1.6%	0.83
Deep SSI	0.9%	0.5%	0.68
Organ/Space SSI	1	0	0.17
Ischeamic colitis	3.2%	2.2%	0.46
Lower Extremity Ischemia	2.2%	1.6%	0.63
Mean length of hospital stay (no. of days)	239.9	244.2	0.63
Median length of hospital stay (no. of days)	219.0	227.0	0.34
LOS ≥ 8 days	40.5%	46.2%	0.17
Discharged home	76.5%	78.1%	0.65

CPR, Cardiopulmonary resuscitation; CVA, cerebrovascular accident; SSI, surgical site infection.

Table 4a. Adjusted outcomes of patients with infrarenal and juxtarenal abdominal aortic aneurysms undergoing transperitoneal vs. retroperitoneal open surgical repair

Outcome	Odds Ratio	(95% CI)	P-value
Mortality	0.9	0.4-2.1	0.89
Pneumonia	1.8	1.0-3.2	0.07
Reintubation	1.7	1.0-3.0	0.05
Acute Renal Failure	1.8	0.8-3.9	0.14
Return to the OR	0.7	0.4-1.3	0.27
Any Wound Complication	0.7	0.3-1.6	0.40
Wound Infection	0.9	0.1-8.3	0.94
Length of stay ≥ 10 days	1.4	1.0-2.0	0.08

CI, Confidence interval; OR, odds ratio.
a Variables included in the regression were male gender, age, white race, prior abdominal surgery, any concomitant procedure, aneurysm extent, bifurcated graft, management of inferior mesenteric artery, and retroperitoneal approach.

Table 4b. Adjusted outcomes of patients with infrarenal and juxtarenal abdominal aortic aneurysms undergoing transperitoneal vs. retroperitoneal open surgical repair (all concomitant procedures excluded)

Outcome	Odds Ratio	(95% CI)	P-value
Mortality	0.6	0.2-1.6	0.27
Pneumonia	1.5	0.7-3.1	0.27
Reintubation	1.3	0.7-2.5	0.47
Acute Renal Failure	1.2	0.5-3.1	0.72
Return to the OR	0.9	0.5-1.7	0.76
Any Wound Complication	0.7	0.3-1.9	0.46
Wound Infection	0.9	0.1-8.4	0.95
Length of stay ≥ 10 days	1.3	0.8-1.9	0.30

CI, Confidence interval; OR, odds ratio.
a Variables included in the regression were male gender, age, white race, prior abdominal surgery, any concomitant procedure, aneurysm extent, bifurcated graft, management of inferior mesenteric artery, and retroperitoneal approach.

DISCUSSION

Our study found that as expected, the retroperitoneal approach was more commonly used for aneurysms with more proximal extent and was associated with higher rates of concomitant procedures as well as pneumonia, reintubation, and transfusion, and longer length of stay. The transperitoneal approach, however,

had a higher rate of wound dehiscence. After multivariable analysis, however, most of these differences were simply related to concomitant procedures.

Data from previous randomized control trials have demonstrated antithetical outcomes.[9, 17, 20, 21, 22] Arya et al found that retroperitoneal surgery shortened the length of stay in a study of 35 patients,[20] whereas Sieunarine et al (n = 100) found no differences in length of stay.[17] Sicard et al,[9] (n = 145) also found that retroperitoneal surgery was associated with shorter hospial stays and excluded patients who required concomitant mesenteric or renal artery revascularization in their analysis. Our analysis found no differences in length of stay between surgical groups, emphasizing that this difference was after adjustment for concomitant procedures.

Sicard et al demonstrated that patients undergoing the retroperitoneal approach had fewer postoperative complications (including bowel obstruction, wound, pulmonary, and cardiac complications).[9] Sieunarine et al found higher rates of wound complications in the retroperitoneal group but no differences in any other postoperative complication.[17] Our data showed lower rates of wound dehiscence with the retroperitoneal approach, higher rates of pneumonia, reintubation, and transfusion, and longer length of stay. However, only reintubation was significantly higher in the retroperitoneal group after accounting for other patient and procedural characteristics.

Although published before 1990, several larger retrospective reviews of 299, 270, and 213 patients have also demonstrated mixed results.[23, 24, 25] Leather et al (n = 299) demonstrated a reduction of pulmonary complications and length of stay favorable for the retroperitoneal approach.[23] Peck et al (n = 270) also showed a shorter length of stay with the retroperitoneal approach and fewer complications, including pneumonia, the need for nasogastric suction, and atelectasis, in the retroperitoneal group.[25] They did not demonstrate significant differences in wound infections or postoperative myocardial infarctions.[25] Sicard et al (n = 213) showed that the retroperitoneal approach was preferable with respect to blood loss.[24]

Our study demonstrates that the retroperitoneal approach is more commonly used for more proximal aneurysms because this approach is generally considered to provide better exposure of the suprarenal abdominal aorta. Our analysis showed that concomitant procedures were more common in the retroperitoneal group. After excluding all concomitant procedures, all differences in outcomes were similar except for transfusion. In our multivariable model, which allowed inclusion of greater numbers and still accounted for concomitant procedures as well as differences in anatomic and comorbid conditions, there were no differ-

ences in outcomes. These results suggest that concomitant procedures drive the observed increase in complications and length of stay.

The use of the Targeted Vascular ACS NSQIP database is limited by the lack of randomization and defined variables. The surgeon's preference and the experience of the surgeon or center performing open AAA repair cannot be captured with this database but likely played a roll in the choice of treatment. In addition, data on choice of anesthesia and the use of epidurals, which may affect outcomes, are not available in the NSQIP. The NSQIP also does not have data describing postoperative ileus or bowel obstruction. However, length of stay is likely a reasonable proxy for this, and we did not see any difference. Finally, the database does not provide information on outcomes >30 postoperative days. As a result, we are unable to draw conclusions on the potential late effects of open surgical approach on hernia and bowel obstruction or on survival. Despite these limitations, our study provides a large cohort, including anatomic detail, and demonstrates current outcomes with open AAA repair in centers participating in the recently released Targeted Vascular ACS NSQIP.

Conclusions

The retroperitoneal surgery was more commonly used for a more proximal aneurysm extent and with concomitant renal, visceral, and lower extremity revascularization procedures. When controlling for concomitant procedures, no significant differences were found between the transperitoneal and retroperitoneal approach for AAA repair. Further long-term data regarding late survival, bowel obstruction, and hernia formation will be useful to guide treatment selection. For the time being, the choice should be driven by anatomy and surgeon preference.

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Chapter 10

The Impact of Endovascular Repair on Specialties Performing Abdominal Aortic Aneurysm Repair

Klaas H.J. Ultee[1,2*]
Rob Hurks[1*]
Dominique B. Buck[1,3]
George S. DaSilva[4]
Peter A. Soden[1]
Joost A. van Herwaarden[3]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]
* the authors have contributed equally to this work

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
3) Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands
4) Critical Care Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective

Abdominal aortic aneurysm (AAA) repair has been performed by various surgical specialties for many years. Endovascular aneurysm repair (EVAR) may be a disruptive technology, impacting which specialties care for patients with AAA. Therefore, we examined the proportion of AAA repairs performed by various specialties over time in the United States and evaluated the impact of the introduction of EVAR.

Methods

The Nationwide Inpatient Sample, 2001-2009, was queried for intact and ruptured AAA and for open repair and EVAR. Specific procedures were used to identify vascular surgeons (VS), cardiac surgeons (CS), and general surgeons (GS) as well as interventional cardiologists (IC), and interventional radiologists (IR) for states that reported unique treating physician identifiers. Annual procedure volumes were subsequently calculated for each specialty.

Results

We identified 108,587 EVAR and 85,080 open AAA repairs (3,011 EVAR and 12,811 open repairs for ruptured AAA). VS performed an increasing proportion of AAA repairs over the study period (52% in 2001 to 66% in 2009, $P < .001$). GS and CS performed fewer repairs over the same period (25% to 17%, $P < .001$ and 19% to 13%, $P < .001$, respectively). EVAR was increasingly utilized for intact (33% to 78% of annual cases, $P < .001$) as well as ruptured AAA repair (5% to 28%, $P < .001$). The proportion of intact open repairs performed by VS increased from 52% to 65% ($P < .001$), while for EVAR the proportion went from 60% to 67% ($P < .001$). For ruptured open repairs, the proportion performed by VS increased from 37% to 53% ($P < .001$) and for ruptured EVAR repairs from 28% to 73% ($P < .001$). Compared to treatment by VS, treatment by a CS (0.55 [0.53-0.56]) and GS (0.66 [0.64-0.68]) was associated with a decreased likelihood of undergoing endovascular rather than open AAA repair.

Conclusions

VS are performing an increasing majority of AAA repairs, in large part driven by the increased utilization of EVAR for both intact and ruptured AAA repair. However, GS and CS still perform AAA repair. Further studies should examine the implications of these national trends on the outcome of AAA repair.

INTRODUCTION

During the late 20th century, surgery has become a technology driven profession.[1] Since then, innovations such as endoscopic and endovascular surgery have transformed clinical medicine. Besides changing the procedure itself, these disruptive technologies have had their effect on the type of physicians performing the procedures. Percutaneous coronary intervention, for example, has diminished the proportion of coronary revascularizations performed by cardiac surgeons, while the proportion of interventional cardiologists increased dramatically with the use of this technique.[2] For abdominal aortic aneurysm (AAA) repair, it is unclear how the introduction and widespread adoption of endovascular repair (EVAR) has changed the distribution of specialties performing elective and ruptured AAA repair.

Prior to the introduction of EVAR, open surgical repair was the primary method of treatment. Using Medicare data, Birkmeyer et al. showed that between 1998 and 1999, prior to the widespread adoption of EVAR, vascular surgeons (VS) performed 39% of all elective AAA repairs, while cardiac and general surgeons (CS, GS) performed 33% and 28%, respectively.[3] In contrast to elective AAA repair, general surgeons performed the largest proportion of ruptured AAA repairs at 39%, followed by vascular surgeons at 33% and cardiac surgeons at 29%.[4] Currently, as with coronary revascularization, the endovascular approach has also led to the inclusion of nonsurgical specialties in treating patients with AAA, such as interventional cardiology (IC) and interventional radiology (IR). Since the performance of EVAR requires a specific skill set that has not been mastered by many surgeons from other specialties, we hypothesize that the proportion of surgical specialties other than VS (i.e., GS and CS) has declined, while VS, IR, and IC are responsible for an increasing number of patients due to a shift from open repair towards EVAR.

The purpose of this study is to analyze how the introduction of EVAR has influenced which specialties are providing care for AAA patients for both elective and ruptured AAA repair in the United States.

METHODS

Database

The Nationwide Inpatient Sample (NIS) is the largest national administrative database and represents a 20% sample of all payer (insured and uninsured) hospitalizations. The NIS is maintained by the Agency for Health Care Research and Quality as part of the Healthcare Cost and Utilization Project. Years 2001

to 2009 were queried using *International Classification of Diseases, 9th revision* (ICD-9) codes to identify patients with diagnosis codes for intact (i.e. elective, symptomatic and mycotic aneurysms) AAA (441.4) and ruptured AAA (441.3). ICD-9 coding does not distinguish infrarenal from juxtarenal or suprarenal AAA. More recent years could not be interrogated due to discontinuation of the surgeon identification variables in the NIS database after 2009.[5] Patients who underwent open AAA repair (38.44, 39.25) or EVAR (39.71) were selected. Patients with procedural codes for both open repair and EVAR were considered to have undergone EVAR, as they likely represent conversions to open repair. Patients with codes for a thoracic aneurysm (441.1 or 441.2), thoracoabdominal aneurysm (441.6 or 441.7) or aortic dissection (441.00-441.03) were excluded. As the NIS contains de-identified data only without protected health information, Institutional Review Board approval and patient consent were waived.

The primary outcome was proportional procedure volume by physician specialty over time for intact and ruptured AAA repair. We evaluated the uptake of EVAR overall and by specialty over time. Additionally, we assessed the likelihood of receiving EVAR rather than open repair by specialty.

Physician specialty

For AAA repair, we were interested in the following type physicians: vascular surgeons (VS), general surgeons (GS), cardiac surgeons (CS), interventional cardiologists (IC), and interventional radiologists (IR). The NIS provides unique physician identifiers per state that allow tracking of procedures performed by that physician during that specific year in that state. Of the available states, 27 provide 2 unique physician identifiers, with 22 of the 27 specifically detailing which physician performed the primary procedure (Supplemental Table 3). For the remaining 5 states, the identifiers were only used when both identifiers were the same to ensure that the identified physician was the one performing the primary procedure. We composed a list of specific procedures (Supplemental Table 1) that we used to determine the specialty of each physician (VS, GS, CS, IC, or IR). The top 15 procedures identified for each of the physician specialties are listed in Supplemental Table 2. Similar approaches have been previously reported.[6-8] Subsequently, a hierarchical model was created: each physician that performed >10 cardiac surgery procedures was labeled a CS; the remaining physicians that performed >10 interventional cardiology procedures (e.g. coronary stenting) were labeled IC; physicians with >10 interventional radiology procedures not typically performed by VS (e.g. liver biopsy, nephrostomy, etc.) were identified as IR; the remaining physicians whose procedures consisted of 75%-100% of vascular pro-

cedures with >10 in number, were classified as VS; physicians whose procedures consisted of 0-75% of vascular procedures and performed >10 general surgery procedures were classified as GS. Similar approaches have been previously described.[9, 10] Two hundred and ten procedures labeled as open repairs were coded as being performed by IC or IR (0.1% of total procedures). We felt these were most likely miscoded endovascular procedures and excluded these patients from further analyses.

Statistical approach

Mean and standard deviation are reported for parametric data. Baseline variables were compared using Chi-square tests or t-tests, where appropriate. We examined the proportional volume of open AAA repairs and EVAR for each specialty and how this changed over the study period. Trends over time were assessed using the Cochran-Armitage test for trend. A P-value less than .05 indicates that annual procedural volumes followed a significant upward or downward (i.e., non-random) trend over time. Multivariable logistic regression analysis was conducted to examine the influence of physician specialty type on the type of procedure performed, whether open or endovascular. Analyses were considered statistically significant when $P < .05$. Statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC) and SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

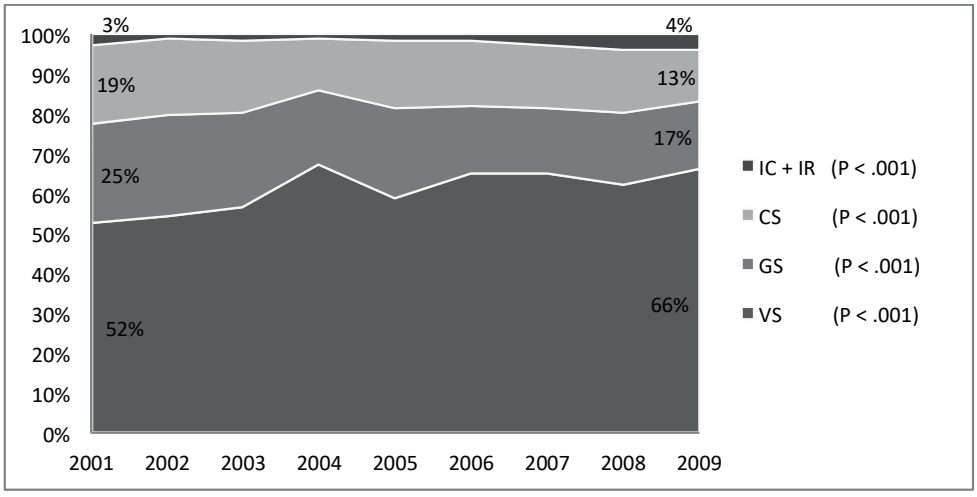
Overall, 108,587 EVAR and 85,080 open AAA repairs were identified in the study period, of which 3,011 EVAR and 12,811 open repairs were for ruptured AAA. The annual overall volume increased from 20,134 in 2001 to 22,541 in 2009 ($P < .001$). Patient and hospital characteristics are detailed in Table 1. Of all AAA repairs, 61% of AAA repairs were performed by VS, 20% by GS and 16% by CS, while the remainder was performed by IC and IR (3% combined). Figure 1 illustrates changes over time for each physician specialty. VS performed an increasing proportion of AAA repairs over the study period (52% in 2001 to 66% in 2009, $P < .001$, Supplemental Table 4). During the same period, GS and CS performed fewer repairs (25% to 17%, $P < .001$ and 19% to 13%, $P < .001$, respectively). Similarly, the absolute number of VS performing AAA repair increased with 30% over the study period, while the number of GS and CS decreased over time (46% and 30%, respectively).

Table 1. Demographic and comorbidity characteristics of patients undergoing open aortic aneurysm repair or endovascular aneurysm repair per physician specialty.

	Open Repair				Endovascular Repair						Open	EVAR	
	VS	GS	CS	P-value	VS	GS	CS	IC	IR	P-value	Overall		P-value
Number	45,804	21,625	17,651		72,489	17,500	14,033	3,055	1,510		85,080	108,587	
Age (years)	71.3	71.9	71	< .001	73.7	74.0	72.8	73.1	74.1	< .001	71.4	73.6	< .001
Female	25.5%	23.6%	23.0%	< .001	18.3%	16.9%	15.4%	16.8%	17.0%	< .001	24.5%	17.7%	< .001
White race	90.4%	90.7%	91.0%	.051	91.5%	91.2%	92.2%	87.3%	78.7%	< .001	90.6%	91.2%	< .001
Teaching hospital	60.5%	30.7%	45.1%	< .001	63.9%	33.8%	48.4%	46.3%	41.0%	< .001	49.7%	56.2%	< .001
Urban location	95.5%	88.2%	93.6%	< .001	95.4%	92.8%	93.9%	100%	97.2%	< .001	93.2%	95.0%	< .001
Hospital Bedsize				< .001						< .001			< .001
Small	7.0%	8.2%	5.5%		8.6%	4.4%	8.2%	13.0%	0.0%		7.0%	7.9%	
Medium	17.9%	26.7%	23.0%		15.5%	22.1%	19.5%	9.4%	24.4%		21.2%	17.0%	
Large	75.1%	65.1%	71.5%		75.9%	73.5%	72.3%	77.6%	75.6%		71.8%	75.1%	
Emergent admission	13.6%	21.0%	11.5%	< .001	3.0%	2.6%	2.0%	1.4%	3.0%	< .001	15.1%	2.8%	< .001

EVAR, endovascular aneurysm repair; VS, vascular surgeons; GS, general surgeons; CS, cardiac surgeons; IC, interventional cardiologists; IR, interventional radiologists; P-values compare differences within the treatment groups

Figure 1. Proportion of all abdominal aortic aneurysm repairs (both open and endovascular) performed by each physician specialty from 2001-2009 in the Nationwide Inpatient Sample (totals sum to 100%)



Intact AAA Repair

With 55%, VS performed the majority of open AAA repairs (increasing from 52% to 65% from 2001 to 2009, P < .001). Over this same time period GS performed 24% of all intact open repairs (decreasing from 25% to 16%, P < .001), followed by CS with 22% of cases (24% to 19%, P <. 001, Figure 2a). VS also performed the majority of EVARs at 67%, (increasing from 60% to 67% from 2001 to 2009), followed by 16% performed by GS (19% to 17%, P < .001), 13% by CS (10.5% to 11.3%, P = .009) and 4% by IC and IR combined (10% to 6%, P = .015, Figure 2b). The absolute number of EVARs increased from 5,906 in 2001 (33% of the annual intact AAA repairs) to 16,252 in 2009 (78%). Over the same period, the number of open repairs decreased from 12,188 (67%) to 4,678 (22%). Consequently, EVAR has become the primary treatment method for intact AAA in all three surgical specialties (Figure 3). Since VS perform a greater proportion of endovascular procedures, the rise in EVAR utilization has in part led to VS performing an increasing majority of overall intact AAA repairs (54% in 2001 to 66% in 2009, P < .001).

Rupture AAA Repair

VS performed 49% of open ruptured AAA repairs (increasing from 37% to 53%, P < .001, Figure 4A), followed by GS with 35% (44% to 33%, P < .001) and 16% by CS (19% to 14%, P = .001). With 73%, VS also carried out the majority of ruptured EVAR (rEVAR) (28% to 73%, P < .001, Figure 4B), while GS performed

15% (54% to 16%, P < .001) and CS 9% (18% to 8%, P = .008). IC and IR together are responsible for 3% of rEVARs (0% to 3%, P = .095). A dramatic overall increase in the utilization of rEVAR was observed (5% to 38% of the annual ruptured volume). This was most pronounced for VS, where the utilization of rEVAR went from 4% in 2001 to 46% in 2009 (P < .001, Figure 5).

Figure 2a. Proportion of all open repairs for intact abdominal aortic aneurysms performed by physician specialty from 2001-2009 in the Nationwide Inpatient Sample (totals sum to 100%)

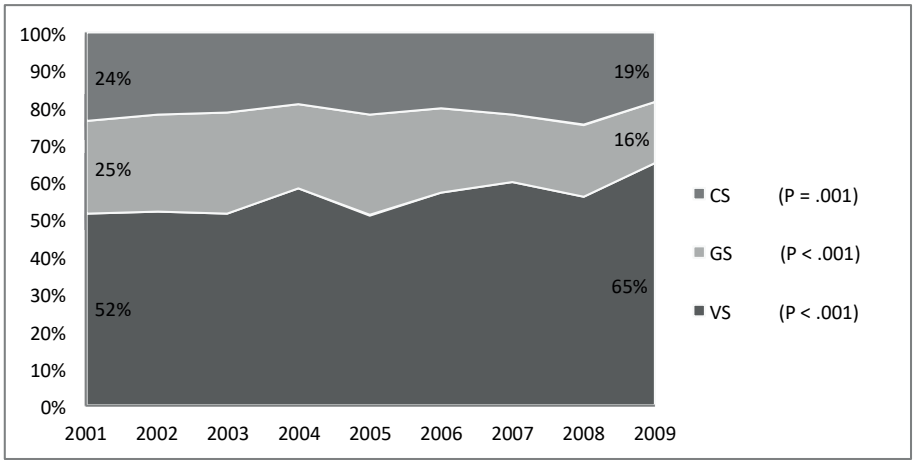


Figure 2b. Proportion of all endovascular repairs for intact abdominal aortic aneurysms performed by physician specialty from 2001-2009 in the Nationwide Inpatient Sample (totals sum to 100%)

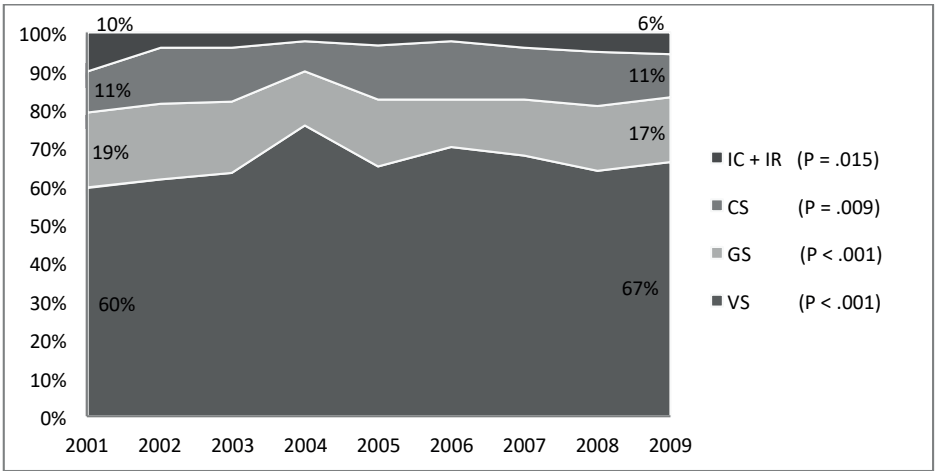
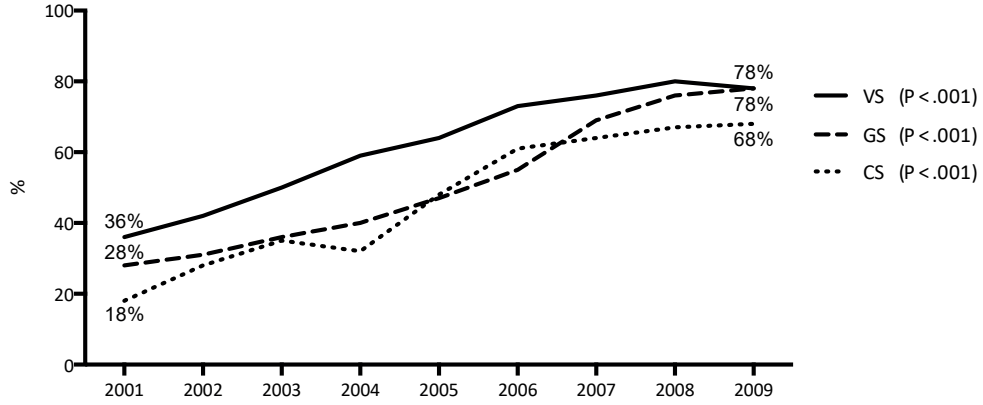


Figure 3. Proportion of intact abdominal aortic aneurysms treated by endovascular repair within each specialty from 2001-2009 in the Nationwide Inpatient Sample



Likelihood of receiving EVAR

Compared to treatment by VS, treatment by CS and GS was associated with a significantly lower likelihood of receiving EVAR (OR: 0.55, 95% CI: 0.53 – 0.56 for CS and OR: 0.66, 95% CI: 0.64 – 0.68 for GS, Table 2). Additionally, women (OR: 0.57, 95% CI: 0.55 – 0.58) those with non-white race (OR: 0.88 95% CI: 0.84 – 0.91), and emergency admission (OR: 0.14, 95% CI: 0.14 – 0.15) were significantly less likely to undergo EVAR. Advanced age (OR: 1.42, 95% CI: 1.40 – 1.44, per 10 years), treatment in a teaching hospital (OR: 1.27, 95% CI: 1.25 – 1.30) and urban designation of the hospital (OR: 1.33, 95% CI: 1.27 – 1.40) were predictive of EVAR. Over the study period, the probability for receiving EVAR increased annually (OR: 1.33, 95% CI: 1.32 – 1.34, per year).

DISCUSSION

The main finding of this study is that with the introduction of EVAR, the proportion of AAA repairs being performed by each physician specialty has changed. Vascular surgeons performed an increasing majority of both open and endovascular intact AAA repairs, while the proportion carried out by CS and GS has steadily declined. The distribution of specialties performing rAAA repair shifted from predominantly GS in the first years of the study towards VS in later years. Over the study period, EVAR has become the dominant treatment for intact AAA repair and is being utilized for an increasing number of ruptured AAA repairs as well. As EVAR is most likely performed by VS, the overall proportion of repairs done by VS –intact and ruptured– increased substantially with the widespread adoption of EVAR.

Figure 4a. Proportion of all open ruptured AAA repairs performed by physician specialty from 2001-2009 in the Nationwide Inpatient Sample (totals sum to 100%)

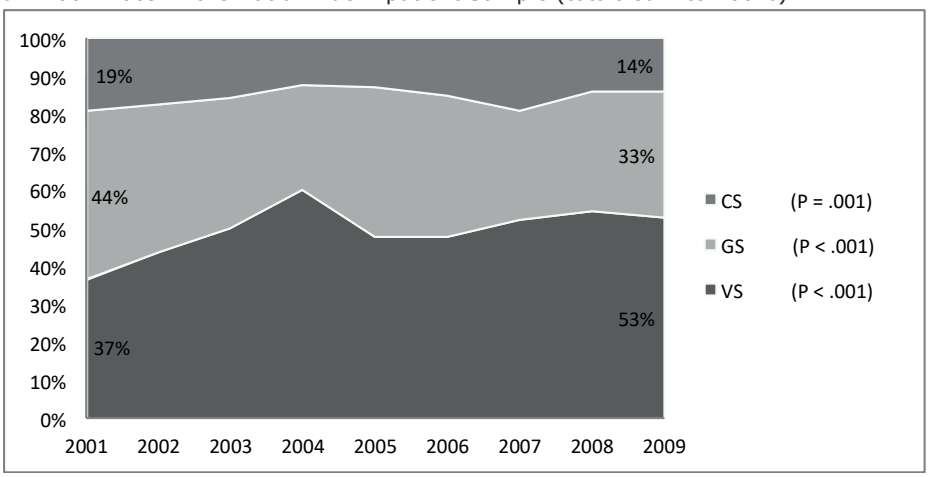
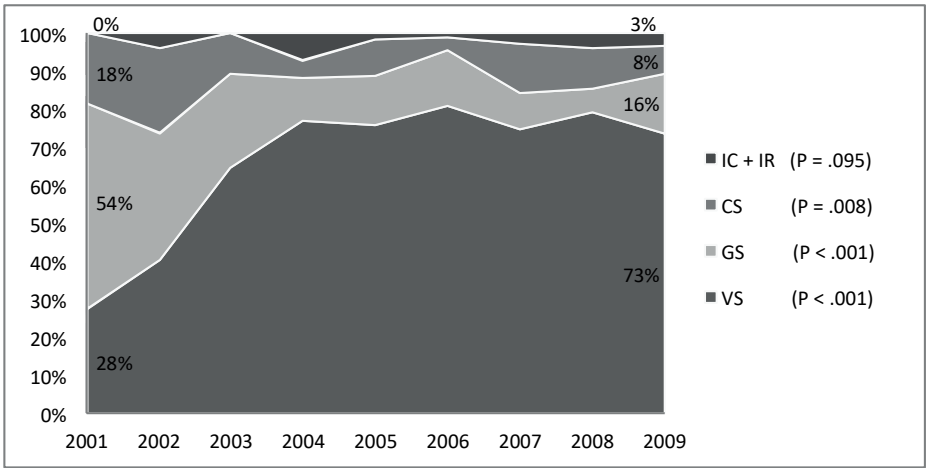


Figure 4b. Proportion of all EVARs for ruptured AAA repairs performed by physician specialty from 2001-2009 in the Nationwide Inpatient Sample (totals sum to 100%)



Regarding intact AAA repair, our results are in line with a study by Birkmeyer et al., showing that between 1998 and 1999 intact open repairs were predominantly performed by VS. However, Birkmeyer et al. found a relatively even distribution with 39% being done by VS, 33% by CS and 28% by GS, while our results showed that VS already performed a majority of the open repairs in the early years of the study and this difference continued to increase over time. Regionalization of open AAA repairs to high-volume centers during the turn of the century is likely

Figure 5. Proportion of ruptured abdominal aortic aneurysms treated by endovascular repair within each specialty from 2001-2009 in the Nationwide Inpatient Sample

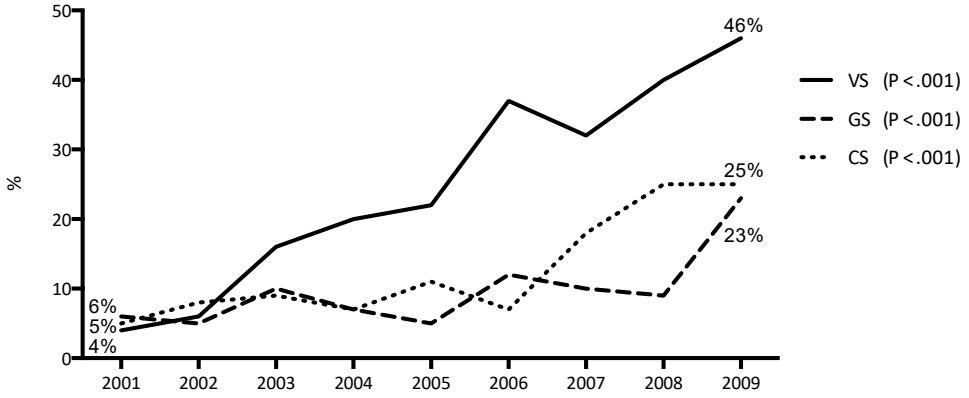


Table 2. Multivariable predictors for the likelihood of receiving EVAR (OR >1 predicts EVAR)

Variable	Odds ratio	95% CI	P-value
Surgeon Specialty			
Vascular surgeons	*Reference*	-	-
Cardiac surgeons	0.55	0.53 – 0.56	< .001
General surgeons	0.66	0.64 – 0.68	< .001
Emergent admission	0.14	0.14 – 0.15	< .001
Age (per 10 y)	1.42	1.40 – 1.44	< .001
Female sex	0.57	0.55 – 0.58	< .001
Non-white race	0.88	0.84 – 0.91	< .001
Year of surgery (per y)	1.33	1.32 – 1.34	< .001
Teaching hospital	1.27	1.25 – 1.30	< .001
Hospital location	1.33	1.27 – 1.40	< .001
Hospital Bed size			
Small	*Reference*	-	-
Medium	0.72	0.69 – 0.76	< .001
Large	0.98	0.94 – 1.02	< .319

to have contributed to VS being increasingly responsible for AAA surgery.[11] In addition, retirement of senior surgeons who were trained at a time when GS and CS customarily performed repair of abdominal aortic aneurysms and may have been less likely to obtain endovascular skills may have added to the shift towards VS. Similar to the early years of our study, previous reports show that GS performed the majority of ruptured AAA repairs at 39%, followed by VS at 33%, and CS at 29% before the introduction of EVAR.[12] As EVAR became

more widely used in the emergency setting, this distribution changed towards a growing proportion of emergency repairs being performed by VS. Since VS also performed an increasing proportion of open rAAA repairs separately from trends in endovascular repair, centralization of rAAA care is likely to have contributed to the shift from GS towards VS as well. Yet a persistent presence of GS treating open rAAA repair remained, which could be due to geographic location where the presence of VS may be lacking.[13] In these areas, the emergent nature of a ruptured AAA may preclude the transfer of the patient to a center with VS necessitating immediate treatment by an available GS.

The phenomenon of disruptive technologies in healthcare is not new. In coronary artery disease, the number of coronary revascularizations performed with coronary stenting rapidly increased after the first coronary stent was introduced in 1994, while the utilization of coronary bypass grafting declined.[2] As a result, interventional cardiologists rather than cardiac surgeons currently perform the majority of coronary revascularizations. A similar shift was seen in vascular surgery with the introduction of carotid stenting. Before its introduction, carotid revascularization through endarterectomy was predominantly done by VS and, to a lesser extent GS, CS and neurosurgeons.[14] We noted that GS and CS practice included a substantial percentage of carotid endarterectomies (8.6% and 10.0% of the selected procedures we identified, respectively) (Supplemental Table 2). However, we did not evaluate changes in carotid revascularization over time in this study. After FDA approval in 2004, carotid stenting is increasingly utilized with rapid adoption by not only surgeons, but also interventional radiologists and interventional cardiologists.[15, 16] Currently, carotid endarterectomy use is still declining, while some patients are being treated through stenting predominantly by interventional cardiologists.[17, 18] EVAR has certainly changed how AAA is being treated but contrary to the examples above, VS have only increased their role as the treating surgeon for intact and ruptured AAA.

Our study has several limitations that should be addressed. Since administrative databases were used, important clinical data such as anatomical information or hemodynamic status, which could influence the choice of procedure and subsequent outcomes, could not be assessed. Additionally, the difficulty of distinguishing a pre-existing comorbid condition from a post-operative complication in this dataset makes an adequate risk-adjustment model difficult. Therefore, we chose not to perform outcomes analysis using NIS. However, the NIS does afford national representation of all age groups thus making it an optimal source of epidemiologic data. Also, as the NIS database does not include the specialty of the attending physician, we employed an algorithm incorporating specialty specific procedures similar to what has been described before.[7, 19, 20] Our algorithm for

identifying vascular surgeons is arbitrary (75% vascular surgery cases), suggesting that some board certified VS may have been mistakenly classified as GS or vice versa. However, our methodology reflects what physicians were actually doing routinely in practice and focused on the change over time. Additionally, our algorithm generated similar distributions of physician's specialty performing open repair in the early years of the current studied period when compared to a previously published large study using physician self identification of specialty.[4] Further, procedures coded as open repairs performed by IC or IR (0.1%) were excluded from this study, as they are, most likely, miscoded endovascular procedures. Unfortunately, it is not possible to identify similar procedural coding errors for the remaining open repairs. Consequently, a very small proportion of miscoded procedures may have remained. Finally, the discontinuation of the surgeon-identifying variable after 2009 prevented the inclusion of more recent years. However, as is demonstrated in this study, the major shift from open repair to EVAR was already well established by 2009.[21]

CONCLUSIONS

Our results show that VS are performing an increasing majority of AAA repairs, in large part driven by the increased utilization of EVAR for both intact and ruptured AAA repair. However, GS and CS still perform AAA repair. Treatment by GS and CS, as well as emergent admission, female sex and non-white race are associated with a decreased likelihood of receiving EVAR. Advanced age, more recent year of surgery, treatment in a teaching hospital and urban designated area of the hospital increased the probability of receiving EVAR. Further studies should examine the implications of these national trends on the outcome of AAA repair.

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Supplemental Table 1. Procedures used to identify physician specialty

Vascular Surgeon	
ICD-9	**Description**
38.12	Carotid endarterectomy
39.29	Peripheral vascular bypass
84.15	Below knee amputation
84.17	Above knee amputation
General Surgeon	
ICD-9	**Description**
17.11-24; 53.00-9	Hernia repair
47.01-19	Appendectomy
51.21-24	Cholecystectomy
Cardiac Surgeon	
ICD-9	**Description**
36.10-19	Coronary artery bypass grafting
35.20-28	Heart valve replacement
39.61	Cardiopulmonary bypass
Interventional Cardiologist	
ICD-9	**Description**
00.66; 36.01-02; 36.05	Percutaneous transmural coronary angioplasty
36.04	Intracoronary thrombolysis
36.06-07	Intracoronary stenting
37.21-23	Heart catheterization
Interventional Radiologist	
ICD-9	**Description**
33.26	Closed lung biopsy
39.1	Transjugular intrahepatic portosystemic shunt
50.11	Closed liver biopsy
55.03-04	Percutaneous nephrostomy
78.49; 81.65	Percutaneous vertebroplasty
99.25	Chemoembolization

Supplemental Table 2. Top 15 procedures performed per physician specialty

Vascular Surgeon		
ICD-9	**%**	**Description**
38.12	17.6%	Carotid endarterectomy
39.29	10.0%	Peripheral vascular bypass
39.5	7.7%	Angioplasty or atherectomy of other non-coronary vessel(s)
39.71	5.2%	Endovascular implantation of graft in abdominal aorta
38.7	3.4%	Interruption of the vena cava
39.49	3.3%	Revision of anastomosis of blood vessel or vascular procedure
39.27	3.0%	Arteriovenostomy for renal dialysis
38.44	2.8%	Resection of vessel with replacement, aorta, abdominal
86.22	2.5%	Excisional debridement of wound, infection, or burn
39.25	2.4%	Aorta-iliac-femoral bypass
84.15	2.2%	Other amputation below knee
84.17	2.2%	Amputation above knee
38.95	2.1%	Venous catheterization for renal dialysis
38.18	1.8%	Endarterectomy, lower limb arteries
84.11	1.7%	Amputation of toe
General Surgeon		
ICD-9	**%**	**Description**
51.23	10.2%	Laparoscopic cholecystectomy
38.12	8.6%	Carotid endarterectomy
39.29	4.1%	Peripheral vascular bypass
47.09	3.8%	Other appendectomy
47.01	3.1%	Laparoscopic appendectomy
45.73	2.5%	Open and other right hemicolectomy
38.93	2.5%	Venous catheterization
86.22	2.4%	Excisional debridement of wound, infection, or burn
45.76	2.1%	Open and other sigmoidectomy
39.5	2.0%	Angioplasty or atherectomy of other non-coronary vessel(s)
51.22	1.9%	Cholecystectomy
39.27	1.8%	Arteriovenostomy for renal dialysis
38.7	1.7%	Interruption of vena cava
86.04	1.6%	Other incision with drainage of skin and subcutaneous tissue
54.59	1.6%	Other lysis of peritoneal adhesions
Cardiac Surgeon		
ICD-9	**%**	**Description**
38.12	10.0%	Carotid endarterectomy
36.12	9.1%	(Aorto)coronary bypass of two coronary arteries
36.13	8.9%	(Aorto)coronary bypass of three coronary arteries

Supplemental Table 2. (continued)

36.14	4.2%	(Aorto)coronary bypass of four or more coronary arteries
36.11	3.5%	(Aorto)coronary bypass of one coronary artery
36.15	3.2%	Single internal mammary-coronary artery bypass
39.29	3.1%	Peripheral vascular bypass
35.22	2.9%	Other replacement of aortic valve
35.21	2.9%	Replacement of aortic valve with tissue graft
38.44	1.7%	Resection of vessel with replacement, aorta, abdominal
32.4	1.7%	Lobectomy of lumg
39.71	1.5%	Endovascular implantation of graft in abdominal aorta
39.5	1.3%	Angioplasty or atherectomy of other non-coronary vessel(s)
32.29	1.3%	Other local excision or destruction of lesion
35.12	1.1%	Open heart valvuloplasty of mitral valve without replacement
Interventional Cardiologist		
ICD-9	**%**	**Description**
0.66	21.4%	Percutaneous transmural coronary angioplasty
37.22	13.7%	Left heart cardiac catheterization
39.5	11.7%	Angioplasty or atherectomy of other non-coronary vessel(s)
36.01	11.6%	Percutaneous transmural coronary angioplasty
39.71	2.5%	Endovascular implantation of graft in abdominal aorta
36.05	2.3%	Percutaneous transmural coronary angioplasty
0.61	2.1%	Percutaneous angioplasty or atherectomy of precerebral extracranial vessel(s)
37.23	2.1%	Combined right and left heart cardiac catheterization
37.72	1.9%	Initial insertion of transvenous leads [electrodes] into atrium and ventricle
37.61	1.2%	Implant of pulsation balloon
88.72	1.1%	Diagnostic ultrasound of heart
64	1.0%	Circumcision
57.94	0.9%	Insertion of indwelling catheter
35.52	0.9%	Repair of atrial septal defect with prosthesis, closed technique
88.56	0.7%	Coronary arteriography using two catheters
Interventional Radiologist		
ICD-9	**%**	**Description**
38.9	18.3%	Venous catheterization, not elsewhere classified
39.5	11.9%	Angioplasty or atherectomy of other non-coronary vessel(s)
38.7	7.0%	Interruption of the vena cava
54.91	6.8%	Percutaneous abdominal drainage
34.91	6.1%	Thoracentesis
38.95	2.9%	Venous catheterization for renal dialysis
55.03	2.4%	Percutaneous nephrostomy without fragmentation
50.11	2.1%	Closed (percutaneous) [needle] biopsy of liver

Supplemental Table 2. (continued)

88.41	2.1%	Arteriography of cerebral arteries
39.71	2.0%	Endovascular implantation of graft in abdominal aorta
33.26	2.0%	Closed (percutaneous) [needle] biopsy of lung
81.66	1.7%	Percutaneous vertebral augmentation
34.04	1.3%	Insertion of intercostal catheter for drainage
88.42	1.3%	Aortography
99.29	1.2%	Injection or infusion of other therapeutic or prophylactic substance

Supplemental Table 3. Proportion of the cohort per state

State	Proportion of cohort (%)
Arkansas	1.1%
Arizona	5.3%
Colorado	2.0%
Florida	17.6%
Georgia	0.4%
Iowa	2.1%
Kansas	0.7%
Kentucky	3.2%
Maryland	4.6%
Maine	0.1%
Michigan	4.2%
Minnesota	0.9%
Missouri	5.9%
Montana	0.1%
Nebraska	0.9%
New Hampshire	2.0%
New Jersey	5.8%
Nevada	0.8%
New York	14.4%
Oregon	0.6%
Pennsylvania	5.8%
Rhode Island	0.2%
South Carolina	1.4%
South Dakota	0.1%
Tennessee	5.4%
Texas	8.9%
Virginia	4.3%
Washington	1.4%
West Virginia	<0.1%
Wyoming	<0.1%

Supplemental Table 4. Annual proportions of AAA repairs performed per specialty

Overall	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**p-value**
Vascular surgeons	52.4%	54.3%	56.4%	67.1%	58.6%	65.2%	65.1%	62.2%	65.8%	< .001
General surgeons	25.2%	25.4%	24.1%	18.6%	22.5%	16.9%	16.1%	17.9%	17.2%	< .001
Cardiac surgeons	19.4%	18.9%	17.9%	13.2%	17.3%	16.2%	16.2%	16.1%	12.9%	< .001
IC + IR	3.1%	1.4%	1.7%	1.1%	1.6%	1.6%	2.6%	3.8%	4.0%	< .001
Intact Open										
Vascular surgeons	51.6%	51.9%	51.6%	58.2%	51.2%	56.9%	59.8%	56.3%	65.1%	< .001
General surgeons	24.7%	26.2%	26.9%	22.7%	27.0%	22.8%	18.2%	19.1%	16.0%	< .001
Cardiac surgeons	23.7%	21.9%	21.5%	19.1%	21.9%	20.4%	22.0%	24.7%	18.9%	.001
Intact EVAR										
Vascular surgeons	59.6%	61.6%	63.2%	75.9%	65.1%	70.0%	67.7%	63.9%	66.5%	< .001
General surgeons	19.4%	20.1%	18.8%	13.8%	17.2%	12.7%	14.6%	17.0%	16.7%	< .001
Cardiac surgeons	10.5%	14.2%	14.0%	8.2%	14.6%	14.7%	14.0%	14.0%	11.3%	.009
IC + IR	10.4%	4.1%	4.1%	2.1%	3.1%	2.5%	3.7%	5.1%	5.5%	.015
Ruptured Open										
Vascular surgeons	36.6%	43.6%	50.0%	59.9%	47.8%	47.9%	52.0%	54.3%	52.7%	< .001
General surgeons	44.1%	39.0%	34.0%	27.6%	39.0%	36.7%	28.6%	31.4%	33.3%	< .001
Cardiac surgeons	19.3%	17.4%	16.0%	12.5%	13.2%	15.4%	19.4%	14.3%	13.9%	.001
Ruptured EVAR										
Vascular surgeons	27.5%	40.2%	64.6%	77.0%	75.8%	81.2%	74.7%	79.2%	73.4%	< .001
General surgeon	54.1%	33.6%	24.9%	11.0%	12.7%	14.4%	9.9%	6.3%	15.8%	< .001
Cardiac surgeons	18.3%	22.4%	10.5%	4.9%	9.6%	3.3%	12.9%	10.4%	7.5%	.008
IC + IR	0%	3.8%	0%	7.1%	1.9%	1.2%	2.7%	4.1%	3.4%	.095

IC, interventional radiologists; IR, interventional radiologists

Chapter 11

Life Expectancy and Causes of Death after Repair of Intact and Ruptured Abdominal Aortic Aneurysms

Frederico Bastos Gonçalves[1, 2]
Klaas H.J. Ultee[1]
Sanne E. Hoeks[1]
Robert Jan Stolker[1]
Hence J.M. Verhagen[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, the Netherlands
2) Department of Angiology and Vascular Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

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ABSTRACT

Objective

Life expectancy and causes of death after abdominal aortic aneurysm (AAA) repair are not well characterized. Population aging and improved secondary prevention may have modified the prognosis of these patients. We designed a retrospective cohort study to determine the vital prognosis, causes of death, and differences in outcome after intact and ruptured AAA.

Methods

All patients with AAA treated from 2003 to 2011 at a single university institution in the Netherlands were analyzed. Survival status was derived from civil registry data. Causes of death were obtained from death certificates. The primary end point was overall mortality. Secondary end points were cardiovascular, cancer-related, and AAA-related mortality. Predictors for perioperative and late survival were obtained by logistic regression and Cox regression models, respectively.

Results

The study included 619 consecutive AAA patients (12% women; mean age, 72 years), of whom 152 (24.5%) had ruptured AAAs. Endovascular repair was performed in 390 (63%). Rupture (odds ratio [OR], 10.63; 95% confidence interval [CI], 4.80-23.5), open repair (OR, 3.59; 95% CI, 1.69-7.62), renal insufficiency (OR, 2.94; 95% CI, 1.51-3.46), and age (OR, 1.08 per year; 95% CI, 1.09-1.15) were predictors of 30-day mortality. Five-year survival expectancy was 65% for intact AAA and 41% for ruptured AAA ($P < .001$). Cardiovascular deaths unrelated to the AAA occurred in 35% and cancer-related deaths in 29% of deceased patients. Predictors for late mortality were history of prior malignant disease (hazard ratio, 2.83; 95% CI, 1.99-4.03) and age (hazard ratio, 1.08 per year; 95% CI, 1.05-1.10). After 30 days, only six deaths (1.1%) were AAA related.

Conclusions

Endovascular repair reduced perioperative mortality by threefold, but no survival benefit was observed at long term. After the perioperative period, survival of ruptured AAA and intact AAA patients was not different. Deaths were distributed in similar proportions between cardiovascular and cancer-related causes.

INTRODUCTION

The prognosis of patients with abdominal aortic aneurysm (AAA) undergoing repair is of major importance for decision-making, in both elective and acute situations. Whereas rupture contributes significantly to the mortality of untreated AAA patients,[1, 2] those undergoing successful repair are considered to have a worse life expectancy than the background population. This is thought to be mainly due to a high prevalence of occult or overt atherosclerotic disease (especially coronary artery disease).[3, 4] In addition, conflicting data have been published about the impact of rupture on survival expectancy beyond 30 days, with large studies suggesting worse prognosis for those surviving rupture and more recent data suggesting no difference.[5-7]

The evolution of AAA repair in the last decades has resulted in improved early outcomes for elective and ruptured situations alike. However, it is unclear if these improvements have been accompanied by a similar improvement in long-term prognosis for AAA patients. The effects of superior secondary prevention for atherosclerosis and modification of environmental and behavioral characteristics may have resulted in better survival and a shift away from cardiovascular deaths. On the other hand, changes in postoperative surveillance brought about by endovascular repair (frequently including repeated radiation exposure and nephrotoxic contrast agents) may have worsened the expected prognosis of this specific population.

The purpose of this study was to determine the contemporary prognosis of patients undergoing AAA repair, focusing on the possible differences between intact and ruptured AAAs and analyzing specific risk factors for overall, cardiovascular, and cancer-related mortality. In addition, we explore differences in prognosis after endovascular and open AAA repair.

METHODS

Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki Declaration on research ethics.

Study design

This was a retrospective, single-center cohort study.

Patients

The study sample was derived from the population of patients consecutively treated for AAA at the Erasmus University Medical Centre (EMC), Rotterdam, the Netherlands, from January 2003 to November 2011. These were included in a prospective AAA database, which was queried. The latest follow-up period considered was December 2011, therefore ensuring that all patients had at least an expected follow-up of 30 days. This limit to follow-up was determined by the latest available data sets for causes of death (see later). Patients with infectious aneurysms and patients with a prior history of abdominal aortic repair were excluded.

Definitions

Ruptured aneurysms were defined as either evidence of retroperitoneal blood on computed tomography angiography immediately before intervention or clear mention of periaortic hematoma in the operative report. AAAs were otherwise considered intact. Renal insufficiency at admission was considered present if the estimated glomerular filtration rate, calculated by the Modification of Diet in Renal Disease formula,[8] was <60. Anemia at admission was considered if the serum hemoglobin level was <13 mg/dL (12 mg/dL in a female patient), according to the World Health Organization definition.[9]

Institutional management of AAA

The Erasmus University Medical Centre is a tertiary teaching institution performing around 100 aortic procedures yearly. Elective AAA repair is routinely performed for AAAs with a maximum diameter >5.5 cm or growth >5 mm in 6 months or whenever symptoms are present. Selection for endovascular aneurysm repair (EVAR) is individualized, considering the patient's comorbidities, anatomic characteristics, and informed consent. In the latter half of the study, preference was generally given to EVAR for both intact and ruptured AAAs.

Survival status

Survival status was derived from inquiry of civil registry database information. Only deaths occurring within the study time frame (2003-2011) were considered to capture the cause of death for each event.

Causes of death

The causes of death were obtained by inquiry of the Dutch Central Bureau of Statistics (study ID: 7465). To obtain information on cause of death, a database with all patients deceased within the study interval was anonymized and matched to the official death certificate reports using International Classification

of Diseases, Tenth Revision codes. According to Dutch privacy legislation, data analysis was allowed only to authorized researchers (K.U., F.B.G.) inside a secure environment, and all output was checked by the Central Bureau of Statistics for privacy violation before it was allowed for publication purposes. Autopsy was not routinely performed, and the expected cause leading to health deterioration before death was considered the true cause of death, in parallel to the strategy used for the overall Dutch population. The causes of death were grouped according to the International Classification of Diseases, Tenth Revision. The following codes were used: for cardiovascular death, I10-I79; for cancer-related death, C00-C43, C45-C97, D00-D03, and D05-09; and for AAA-related death, I71.3, I71.4, I71.8, I71.9, and I72.3. The proportion of coding based on autopsy vs clinical evaluation could not be determined.

End points

The primary end points are overall early and late mortality. Secondary end points are AAA-related, cardiovascular, and cancer-related mortality.

Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables) or means and standard deviations (continuous variables). Differences at baseline were assessed using Pearson χ^2 or Student *t*-test, where appropriate. Estimates of survival were obtained using Kaplan-Meier plots and tabulated with the respective 95% confidence intervals (CIs) at yearly intervals. General population survival estimates were generated after age and gender matching. Independent risk factors for 30-day death after AAA repair were obtained by a logistic regression model using variables selected a priori on the basis of clinical relevance, which included age, gender, renal function at admittance, anemia at admittance, maximum preoperative AAA diameter, indication for treatment (rupture vs intact), type of anesthesia (general vs locoregional), and type of repair (open vs EVAR). For long-term outcome, a Cox regression model was constructed to determine risk factors for all-cause, cardiovascular, and cancer-related death. Similarly, variables were selected a priori and included age, gender, prior history of cardiovascular disease (cardiac, cerebrovascular, or peripheral ischemic disease), prior history of diabetes mellitus, prior history of cancer, renal insufficiency at admittance, anemia at admittance, indication for treatment, and type of repair. To determine the influence of radiation exposure resulting from postoperative surveillance strategies after endovascular repair, we performed a subanalysis of patients without a prior history of cancer and compared cancer-related mortality between endovascular and open surgery using a χ^2 test. All tests were two

sided, and significance was considered a *P* value < .05. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc, Chicago, Ill).

RESULTS

From January 2003 to November 2011, 619 patients underwent primary repair for noninfected AAA at our institution. Survival status was available for all but one patient (because of emigration), who was excluded from further analysis. Mean age was 71.9 ± 7.6 years, 74 (12%) were female, and 152 (25%) were ruptured AAAs. Endovascular repair was performed in 390 patients (63%).

Baseline characteristics

A greater proportion of patients undergoing repair for intact AAA had a prior history of ischemic heart disease (46% vs 35% for ruptured AAA) and diabetes (15% vs 8%;Table 1). Other demographics and past medical history were not different between these two groups. More patients in the ruptured AAA group had

Table 1. Baseline characteristics by surgical indication

	Intact AAA *N=466*	***Ruptured AAA*** *N=152*	***P-value***
Demographics			
Female gender – N (%)	56 (12)	18 (12)	0.954
Age (years, mean ± SD)	71.8 ± 7.5	72.3 ± 7.7	0.553
Prior medical history			
Ischemic heart disease – N (%)	216 (46)	50 (35)*	0.016
Cerebrovascular disease – N (%)	91 (19)	22 (15)*	0.279
Diabetes mellitus – N (%)	72 (15)	12 (8)*	0.036
History of cancer – N (%)	97 (21)	17 (12)*	0.023
PAD – N (%)	87 (19)	16 (11)*	0.040
Preoperative eGFR<60 – N (%)	142 (30)	75 (49)	<0.001
Preoperative anaemia– N (%)	116 (25)	113 (75)	<0.001
AAA characteristics			
Max AAA diameter, mm – mean ± SD	62 ± 12	77 ± 17 †	<0.001
Operative details			
Loco-regional anaesthesia – N (%)	97 (21)	25 (16)	0.198
Open surgical repair – N (%)	137 (29)	91 (60)	<0.001

Legend * 11 rAAA patients (2%) missing baseline data; † 20 patients missing baseline diameter; PAD – Peripheral arterial obstructive disease; eGFR – estimated glomerular filtration ratio

estimated glomerular filtration rate <60 (49% vs 30% for intact AAA; *P* < .001) and were anemic (75% vs 25%; *P* < .001) at admittance, as expected because of their acute presentation. Also, the maximum AAA diameter of ruptured cases was generally greater (77 ± 17 mm vs 62 ± 12 mm; *P* < .001). The choice of anesthetic technique did not differ for intact and ruptured AAA patients. Patients with intact AAA, however, were less likely to undergo open surgical repair (29% vs 60% for ruptured cases; *P* < .001). Baseline characteristics are detailed in Table 1.

Early postoperative mortality

Overall, there were 66 deaths within 30 days. As expected, patients with ruptured AAA had a higher early mortality rate (n = 50 [32.9%] vs n = 16 [3.4%] for intact aneurysms;*P* < .001). Age (odds ratio [OR], 1.08 per year increase; 95% CI, 1.09-1.15), renal insufficiency at admittance (OR, 2.94; 95% CI, 1.51-3.46), rupture as indication (OR, 10.63; 95% CI, 4.80-23.5), and open surgical repair (OR, 3.59; 95% CI, 1.69-7.62) were independent predictors of death within 30-days after surgery (Table 2).

Table 2. Risk factors for early mortality (logistic regression)

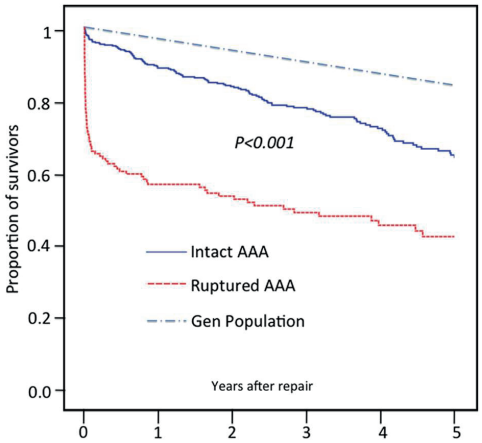
	Univariable	*Multivariable*
Risk factor	*OR (95% CI)*	*OR (95% CI)*
Age *	1.08 (1.04 to 1.12)	1.09 (1.04 to 1.15)
Female gender	0.93 (0.66 to 2.80)	1.01 (0.39 to 2.62)
Renal insufficiency	3.50 (2.06 to 5.94)	2.94 (1.5 to 5.71)
Anaemia	5.94 (3.33 to 10.61)	1.66 (0.79 to 3.46)
Baseline AAA †	1.02 (1.01 to 1.04)	0.99 (0.96 to 1.01)
Rupture	13.79 (7.55 to 25.2)	10.63 (4.80 to 23.5)
General anaesthesia	3.47 (1.36 to 8.83)	1.48 (0.47 to 4.60)
Open repair	4.68 (2.69 to 8.14)	3.59 (1.69 to 7.62)

Legend: * per unit (year) increase; † per unit (mm) increase. OR: Odds Ratio

Late overall mortality

During a median follow-up of 2.4 years (range, 8.9 years), there were 157 deaths after 30 days. The estimated survival after operation for intact AAA was 78% and 65% at 3 and 5 years, respectively. For ruptured AAA, the estimated survival was 48% and 41%, respectively (Fig 1). The independent predictors for late overall mortality after AAA repair were age (hazard ratio [HR], 1.08 per year increase; 95% CI, 1.05-1.10) and prior history of cancer (HR, 2.83; 95% CI, 1.99-4.03; Table 3). If 30-day deaths were not considered, there would be no difference in prognosis for intact and ruptured AAA patients during the first 5 years (Fig 2).

Figure 1. Kaplan-Meier survival estimates after abdominal aortic aneurysm (*AAA*) repair compared with an age- and gender-matched general population.

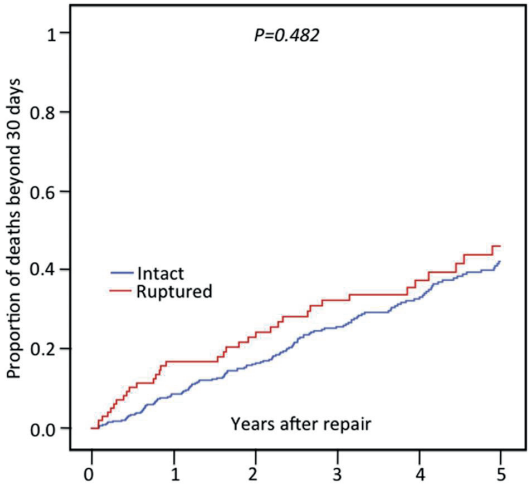


Intact AAA	466	376	296	218	148	107
	-	0.89	0.84	0.78	0.72	0.65
	(-)	(0.015)	(0.018)	(0.021)	(0.025)	(0.029)

N at risk, proportion of survivors, (Standard Error)

Ruptured AAA	152	76	62	49	34	25
	-	0.56	0.53	0.48	0.45	0.41
	(-)	(0.041)	(0.042)	(0.043)	(0.044)	(0.046)
General Population		0.97	0.94	.91	.88	.84

Figure 2. Estimated proportion of deaths beyond 30 days of abdominal aortic aneurysm (AAA) repair.



N at risk

Intact	450	376	296	218	148	107
Ruptured	102	76	62	49	34	25

Table 3. Risk factors for late mortality (Cox-regression)

	Overall		CV related		Cancer related	
Mortality	*Univariable*	*Multivariable*	*Univariable*	*Multivariable*	*Univariable*	*Multivariable*
Risk factor	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Age *	1.08 (1.04 to 1.12)	1.08 (1.05 to 1.10)	1.08 (1.04 to 1.12)	1.08 (1.04 to 1.13)	1.05 (1.01 to 1.10)	1.05 (1.01 to 1.09)
Female gender	0.93 (0.55 to 1.59)	0.90 (0.51 to 1.59)	1.06 (0.46 to 2.49)	1.14 (0.48 to 2.72)	1.33 (0.56 to 3.13)	1.50 (0.39 to 2.78)
Renal insufficiency	1.56 (1.13 to 2.15)	1.23 (0.88 to 1.72)	2.32 (1.37 to 3.94)	1.71 (0.98 to 2.96)	1.94 (1.49 to 1.78)	0.80 (0.41 to 1.56)
Anaemia	1.74 (1.26 to 2.39)	1.42 (0.99 to 2.02)	2.05 (1.20 to 3.49)	1.38 (0.76 to 2.47)	1.67 (0.93 to 3.01)	1.56 (0.79 to 3.05)
CV history	1.39 (1.00 to 1.92)	1.33 (0.94 to 1.89)	1.79 (1.01 to 3.18)	1.71 (0.94 to 3.11)	0.84 (0.47 to 1.50)	0.90 (0.48 to 1.67)
Cancer history	2.73 (1.96 to 3.83)	2.83 (1.99 to 4.03)	1.55 (0.82 to 2.94)	1.67 (0.86 to 3.24)	5.17 (2.89 to 9.24)	5.06 (2.73 to 9.38)
Diabetes history	0.87 (0.54 to 1.41)	0.85 (0.52 to 1.39)	1.22 (0.60 to 2.49)	1.24 (0.60 to 2.56)	0.75 (0.29 to 1.89)	0.70 (0.27 to 1.81)
Rupture	1.24 (0.85 to 1.83)	1.25 (0.80 to 1.98)	1.79 (0.99 to 3.24)	1.69 (0.86 to 3.34)	1.17 (0.56 to 2.43)	1.50 (0.64 to 3.54)
EVAR	0.88 (0.65 to 1.22)	0.81 (0.57 to 1.15)	0.81 (0.47 to 1.39)	0.78 (0.44 to 1.39)	1.18 (0.64 to 2.17)	1.05 (0.53 to 2.08)

Legend: * per unit (year) increase. HR – Odds Ratio; CV – Cardiovascular; EVAR – Endovascular Aneurysm Repair

Late cardiovascular and cancer-related mortality

During follow-up, there were 55 (35%) cardiovascular deaths. Only age (HR, 1.08 per year increase; 95% CI, 1.04-1.13) was identified as an independent predictor of cardiovascular death after AAA surgery. Cancer-related deaths occurred in 46 patients (29%). Lung cancer was the most common type (22 of 46), followed by neoplasms of the digestive tract (11 of 46). Age (HR, 1.05 per year increase; 95% CI, 1.01-1.09) and prior history of cancer (HR, 5.06; 95% CI, 2.73-9.38) were independent predictors of cancer-related death. When patients with a prior history of cancer were excluded, there was no difference in cancer-related mortality between endovascular and open surgery patients (4.6% vs 5.6%, respectively; *P* = .83)

AAA-related late mortality

After 30 days, six (1.1%) deaths were coded as being AAA related (Table 4). Three of these occurred in the intact AAA group (0.7%), and three occurred in the ruptured AAA group (3.0%; *P* = .042). Only one of these six events was coded as a direct consequence of rupture, which was a patient on postoperative day 34 after EVAR for ruptured AAA. One death in the intact AAA group and two deaths in the ruptured AAA group occurred within 3 months of operation, which suggests a possible association with the primary event. There was no difference in AAA-related late mortality in patients undergoing open repair (2 deaths of 182 30-day survivors [1.1%]) or EVAR (4 deaths of 370 [1.1%]; *P* = .951).

Other causes of death

For the remaining 32% of patients, causes of death were diverse and not easily grouped. The most common alternative causes were infection, respiratory failure, and dementia.

DISCUSSION

Determining the vital prognosis of patients after AAA repair is paramount for selection of patients and informed consent. In the presented results, it is clear that AAA patients undergoing repair have a worse vital prognosis compared with the age- and gender-matched population. Interestingly, the predominant causes of death beyond 30 days are cardiovascular and cancer related, in similar proportions. The results also suggest that life expectancy after ruptured AAA is similar to that of those treated electively, once a patient endures the critical perioperative period. Last, our findings confirm the early survival benefit of EVAR (in both ruptured and intact patients), which is lost at long term.

Table 4. AAA-related late mortality

Patient	*Gender*	*Age*	*Days after surgery*	*Associated causes (ICD-10 codes)*	*Type of repair*	*Indication for repair*	*Place of death*
1	Male	68	34	Sepsis (A41.9)	EVAR	Rupture	Hospital
2	Male	93	73	Postprocedural complications of the circulatory system, unspecified (I97.9) Dementia (F03.0), Renal insufficiency (N18.9)	EVAR	Intact	Nursing home
3	Male	73	90	Sequelae of complications of surgical and medical care (T98.3), Embolism or thrombosis of arteries of the lower extremities (I74.3)	Open	Rupture	Nursing home
4	Male	75	147	Sequelae of complications of surgical and medical care (T98.3), Atherosclerosis of the aorta (I70.0)	Open	Rupture	Nursing home
5	Male	62	223	Sequelae of complications of surgical and medical care (T98.3), Sepsis (A41.9)	EVAR	Intact	Nursing home
6	Male	71	772	Vascular graft infection (T82.7)	EVAR	Intact	Hospital

Comparison of overall survival to previous literature

The benchmark randomized studies and large observational studies comparing EVAR and open surgery have shown us that the survival of AAA patients after repair is worse than survival of the age- and gender-matched background population. In a recent meta-analysis including four large randomized trials and data from the Medicare and Swedvasc databases, Stather et al reported a 14% to 15% mortality at 2 years and 33% to 34% mortality at 4 years or more for elective AAA repair.[1] In a large Swedvasc-based publication on long-term survival after AAA repair spanning 1987 to 2005, Mani et al have reported a 69% and 42% crude 5-year survival after intact and ruptured AAA repair.[7] The estimated survival in our series was 65% at 5 years for intact AAAs and 41% for ruptured AAAs. Although these estimates appear relatively similar, they may not be entirely comparable populations; it is likely that before EVAR was generalized, patients with less physiologic reserve (elderly or higher risk patients) were not offered treatment. In our study, the proportion of EVAR patients is much greater.

Cardiovascular mortality shift

Contemporary epidemiologic studies have shown that life expectancy continues to increase and that there is a proportional trend toward a decrease in cardiovascular deaths in the overall population.[10] Although aortic aneurysmal disease typically

coexists with atherosclerosis,[4] the proportion of our patients dying of any cardiovascular cause was relatively low (35%). A historical study of 1112 AAA patients operated on between 1970 and 1975 reported cardiovascular-related deaths in more than two-thirds of patients, a proportion much greater than observed in this study.[11] In a more contemporary series, dating from 1999 to 2004, Brown et al reported 256 cardiovascular deaths of 524 deaths in patients randomized for the EVAR 1 trial during 5.5 years.[12] This corresponds to 49% cardiovascular mortality, a proportion much greater than we observed. The same group reported 46 (32%) fatal myocardial infarctions or strokes in 145 deaths of patients randomized to EVAR for the EVAR 2 trial and observed for 2 to 8 years.[13] These results suggest a greater contribution of cardiovascular causes for death in these trial populations compared with the cohort of our study. The Dutch Randomized Endovascular Aneurysm Management (DREAM) trial reported cardiovascular deaths in 32 of 106 (30.1%), a proportion closer to the one found in this study.[14] These disparities may be explained by geographic differences and recent evolution in secondary prevention for this population, particularly with the generalized use of antiplatelet and statin therapy. Although we could not obtain exact figures on the proportion of patients receiving appropriate secondary prevention, it is likely that most received lifelong antiplatelet and statin therapy as part of our local protocol. Naturally, both the DREAM and EVAR 1 trials included only patients considered fit for prophylactic open repair and do not reflect the real-life population of AAA patients included in the present study.

Cancer-related mortality in AAA patients

Cancer-related mortality is an important cause of mortality for AAA patients, responsible for almost one-third of deaths in our population and second only to cardiovascular disease. If coronary ischemic disease, stroke, and peripheral arterial disease were considered separately, malignant disease would be the most frequent cause of death by a large margin. Aside from age, only a prior history of cancer was a strong predictor of overall death, increasing the risk by nearly threefold, and of cancer-related death, increasing the risk by fivefold. This suggests that a prior history of cancer has a strong impact on the overall survival of AAA patients and may need to be considered in the decision process for elective treatment. Despite an apparent decrease in incidence of cancer in Western populations,[15] this pathologic process has a marked impact on the prognosis of patients with AAA.

Cancer-related mortality was similar between EVAR and open surgery patients. This remained true after exclusion of patients without a prior history of cancer, suggesting that the effect of cumulative radiation of a typical post-EVAR surveil-

lance protocol did not result in an increase in incidence of cancer during the study period. We cannot conclude that repeated radiation exposure resulting from postoperative surveillance has no impact on survival at long term because stochastic effects of exposure may become clinically evident only many years later. However, the relatively limited life expectancy of AAA patients is likely to obscure possible carcinogenic effects of ionizing radiation.

AAA-related deaths

Previous publications suggest a yearly risk of AAA-related death of 0.5% to 1%.[1] In a publication by Wyss et al,[16] the authors even suggest that these are responsible for the midterm survival catch-up effect of endovascular vs open repair, in a way canceling the early survival benefit of EVAR. The proportion of patients dying of an AAA-related cause is smaller in this study, however. This may be explained by selection of patients or by the time period involved (improved planning, procedural skills, and device technology). Interestingly, infection was the primary event in the majority of AAA-related deaths, a matter that deserves consideration in the future. We could not determine if patients suffering from graft infection could be at higher risk because of sterility breach or operation outside the operation theater (in an angiography suite), but this could be a possible explanation for late infections.

Because of the paucity of events and the chance of misinterpretation (potentially leading to both underestimation and overestimation), data on AAA-related deaths must be interpreted with special care and in light of the aforementioned intrinsic limitation.

Impact of rupture on outcome for AAA patients

The timing of surgery had a strong impact on early survival after AAA repair, with ruptured AAA patients having an expected 10-fold increase in mortality. More important, timing had no influence on *late* mortality, as illustrated by the parallel evolution of the survival curves beyond 30 days. This similarity in long-term prognosis may seem counterintuitive, especially considering that the intact AAA group had a higher incidence of coronary disease, diabetes, and peripheral arterial disease at baseline in our study. However, it confirms the similar long-term survival expectancy between intact and ruptured AAA patients observed by Mani et al.[7] This interesting finding suggests that an increment in perioperative survival for ruptured AAA patients is the most influential attitude for improving vital prognosis of AAA patients.

Impact of treatment alternatives on survival

The choice of treatment (endovascular vs open) had a strong impact on 30-day outcome, as already demonstrated extensively in the literature.[1] Specifically, open repair was associated with a 3.6-fold increased mortality risk irrespective of presentation. However, the type of repair had no influence on overall or AAA-related late mortality. Although endovascular patients are known to require a higher number of secondary interventions and to have a persistent (yet small) risk of late ruptures, these appear to have no important influence on survival expectancy. There were six AAA-related deaths in our series. Four of these were after endovascular repair, of which three had septic complications, suggesting endograft infection to be the predominant cause of AAA-related death after endovascular repair. These results challenge the suggestion by Wyss et al that postimplantation ruptures were mainly responsible for the convergence of survival expectancy between open repair and EVAR observed in the EVAR 1 trial.[16] Globally, however, our results show no long-term prognostic difference between open and endovascular repair, which supports a previous publication by Schermerhorn et al.[17]

Limitations

There are limitations to consider in this study. First, this is a retrospective study of a single institution and therefore subject to selection and reporting bias. Also, postmortem examinations are not routinely done in the Netherlands, limiting the diagnostic acuity of codification. This may be especially concerning in the case of AAA-related deaths because of the paucity of events and the chance of misinterpretation. We are unable to determine the proportion of patients in the study in whom autopsies were performed. The causes of death reported, however, were obtained through the Central Bureau of Statistics, had an availability of 100%, and represent the most accurate way available to acquire information on mortality. The Netherlands has a strict and sustained policy of rigor in reporting causes of death. Reliability of cause of death coding in the Netherlands for major causes of death including cancer and myocardial infarction has been investigated by Harteloh et al and was found to be higher than 90% for the period of this study.[18] These authors concluded that accuracy was especially high for cardiovascular causes. In light of this, overall survival data were used as primary end points (hard end points), and causes of death were considered secondary end points (soft end points). Careful interpretation of the cause of death data is required, taking into account the degree of uncertainty present.

Finally, the study's generalizability may be compromised by the predominantly western European origin of included patients, by the level of secondary prevention and incidence of cancer observed in the study setting, and by the local

expertise in aneurysm treatment. Genetic and environmental modifications may result in different outcome for AAA patients.

Conclusions

The results of this study suggest a trend toward improved overall and cardiovascular-related survival after AAA repair compared with historical series, with malignant disease assuming growing preponderance in the long term. Endovascular repair reduced 30-day mortality by threefold, but no survival benefit or increased mortality was observed in the long term. After the early postoperative period, the prognosis of patients after ruptured AAA is favorable and similar to that observed after intact AAA repair.

On the basis of these observations, an increased awareness for malignant disease in this specific population is necessary. Also, efforts should focus on improving perioperative mortality for ruptured AAA.

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Part III

chapter 12

Incidence of and Risk Factors for Bowel Ischemia following Abdominal Aortic Aneurysm Repair

Klaas H.J. Ultee[1,2]
Sara L. Zettervall[1]
Peter A. Soden[1]
Jeremy Darling[1]
Daniel J. Bertges[3]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]
on behalf of the Vascular Study Group of New England

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
3) Department of Surgery, Division of Vascular Surgery, University of Vermont Medical Center, Burlington, VT, USA

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ABSTRACT

Objective

Bowel ischemia is a rare but devastating complication following abdominal aortic aneurysm (AAA) repair. Its rarity has prohibited extensive risk factor analysis, particularly since the widespread adoption of endovascular repair (EVAR). Therefore, the purpose of this study was to assess the incidence of postoperative bowel ischemia following AAA repair in the endovascular era, and identify risk factors for its occurrence.

Methods

All patients undergoing AAA repair, either intact or ruptured, in the Vascular Study Group of New England between January 2003 and November 2014 were included. We compared patients with postoperative bowel ischemia to those without, and stratified by indication (intact and ruptured) and treatment approach (open repair and EVAR). Criteria for diagnosis were endoscopic or clinical evidence of ischemia, including bloody stools in patients who died before diagnostic procedures were performed. Independent predictors of postoperative bowel ischemia were established using multivariable logistic regression analysis.

Results

A total of 7312 patients were included, with 6668 intact (67.0% EVAR), and 644 ruptured AAA repairs (31.5% EVAR). The incidence of bowel ischemia following intact repair was 1.6% (open repair: 3.6%, EVAR: 0.6%), and 15.2% following ruptured repair (open repair: 19.3%, EVAR: 6.4%). Ruptured AAA was the most important determinant of postoperative bowel ischemia (OR:6.4, 95%CI:4.5 – 9.0), followed by open repair (OR:2.9, 95%CI:1.8 – 4.7). Additional predictive patient factors were advanced age (OR:1.4 per 10 years, 95%CI:1.1 – 1.7), female gender (OR:1.6, 95%CI:1.1 – 2.2), hypertension (OR:1.8, 95%CI:1.1 – 3.0), heart failure (OR:1.8, 95%CI:1.2 – 2.8), and current smoking (OR:1.5, 95%CI:1.1 – 2.1). Other risk factors included unilateral interruption of the hypogastric artery (OR:1.7, 95%CI:1.0 – 2.8), prolonged operative time (OR:1.2 per 60 min. increase, 95%CI:1.1 – 1.3), blood loss >1L (OR:2.0, 95%CI:1.3 – 3.0), and a distal anastomosis to the femoral artery (OR:1.7, 95%CI:1.1 – 2.7). Bowel ischemia patients had a significantly higher perioperative mortality after both intact (open repair: 20.5% vs. 1.9%, P<.001; EVAR: 34.6% vs. 0.9%, P<.001), as well ruptured AAA repair (open repair: 48.2% vs. 25.6%, P<.001; EVAR: 30.8% vs. 21.1%, P<.001).

Conclusion

This study underlines that although bowel ischemia following AAA repair is rare, the associated outcomes are very poor. The cause of postoperative bowel ischemia is multifactorial in nature, and can be attributed to patient factors, as well as operative characteristics. These data should be considered during pre-operative risk assessment, and optimization of both patient and procedure in an effort to reduce the risk of postoperative bowel ischemia.

INTRODUCTION

Bowel ischemia is a well-known complication following abdominal aortic aneurysm (AAA) repair. After elective AAA surgery the occurrence of bowel ischemia is rare, with a reported incidence of 1-3% for open repair and 0.5-3% for endovascular repair (EVAR).[1-9] Yet the importance of postoperative bowel ischemia should not be underestimated, as the associated perioperative mortality has been reported to be as high as 50%.[2, 9] Furthermore, the incidence of bowel ischemia is substantially higher in patients undergoing repair of a ruptured AAA, with similar increases in resulting mortality.[1, 9-11]

Previous studies have identified several risk factors, including rupture, age, renal insufficiency, operative time, (micro) embolizations in supplying vessels, and proximal clamp location during open repair.[2, 9, 12, 13] However, the rarity of postoperative bowel ischemia has prohibited extensive risk factor analysis, particularly among EVAR patients. Aside from limited evidence, the role of several other factors that have previously been implicated remains disputed. While some studies determined that hypogastric artery interruption –either through ligation/occlusion during open repair or embolization during EVAR– is an innocuous procedure,[4, 14-16] other studies determined that disruption of hypogastric blood flow is associated with ischemic complications, including bowel ischemia.[2, 5, 12, 17-19] There is also conflicting evidence on the benefits of EVAR compared to open repair. Perry et al. determined that EVAR was associated with significantly lower bowel ischemia rates.[13] Becquemin et al., however, reported no difference in the risk of bowel ischemia between open repair and EVAR patients, and concluded that other factors such as rupture and operative time are more important predictors.[9]

The primary aim of this study was to assess the incidence of postoperative bowel ischemia following AAA repair in the endovascular era, and identify overall and procedure-specific risk factors for its occurrence. As a secondary aim, we sought out to determine the impact of bowel ischemia on the perioperative prognosis.

METHODS

For this study, we used the Vascular Study Group of New England (VSGNE) database. The Vascular Study Group of New England is a voluntary, cooperative group of clinicians, hospital administrators, and research personnel from 30 academic and non-academic centers, who prospectively gather data for 12 commonly per-

formed vascular procedures, including AAA repair. The group strives to improve quality, safety, effectiveness, and costs of caring for patients with vascular disease through monitoring and evaluation of 140 detailed patient demographic, operative, and clinical outcome variables. Trained nurses or clinical data abstractors enter the data in the registry, and surgeons are responsible for the documentation of operative details and intraoperative complications. Researchers utilizing the VSGNE database are blinded to patient, surgeon, and hospital identifiers. The data are validated through audits of discharge claims from each of the participating institutions.[20] More details on this regional registry can be found at http://www.vsgne.org. The institutional review board of Beth Israel Deaconess Medical Center approved this study and patient consent was waived, due to the de-identified nature of the data.

All patients undergoing AAA repair, either intact or ruptured, between January 2003 and November 2014 were included. Criteria for the diagnosis of bowel ischemia were either colonoscopic evidence of ischemia, bloody stools in a patient who died before colonoscopy or laparotomy could be performed, or a clinical diagnosis of bowel ischemia treated with medical management only, as defined by the Vascular Quality Initiative.

Patients with and without postoperative bowel ischemia were compared on baseline and intraoperative characteristics, as well as postoperative outcomes. Baseline characteristics included demographics, comorbidities, and maximal aneurysm diameter. Heart failure was defined as any documented congestive heart failure. Intraoperative characteristics included operative time, blood loss, (un) intentional hypogastric artery coverage by the endograft, and interruption of a hypogastric artery, because of ligation/occlusion during open repair or embolization during EVAR. Additional procedure-specific variables were evaluated, which included concomitant procedures, proximal clamp location, type of graft (tube vs. bifurcation), and inferior mesenteric artery (IMA) management for open repair, and concomitant procedures, arterial injury, and endoleak at completion for EVAR.

Postoperative outcomes included 30-day mortality and in-hospital adverse outcomes, including renal deterioration, leg ischemia, wound complication, myocardial infarction, congestive heart failure, respiratory complications, >3 units of transfusion, return to the OR, (prolonged length of) stay in the intensive care unit (ICU), and prolonged length of postoperative hospital stay. Deterioration of renal function was defined as an increase in postoperative creatinine >0.5mg per dl and/or need for dialysis (peritoneal dialysis, hemodialysis, or hemofiltration). Leg ischemia was considered in case of loss of a previously palpable pulse, previously measurable Doppler signals, decrease in the ankle-brachial

index greater than .15, blue toe, or tissue loss. Wound complications ranged between a superficial wound separation or infection, and return to the operating room. Myocardial infarction was considered when one of the following was documented: isolated troponin elevation, electrocardiogram change, or clinical evidence of myocardial infarction. Congestive heart failure was defined as a new onset of pulmonary edema requiring transfer or treatment in an intensive care unit. Respiratory complications included pneumonia (lobar infiltrate on chest radiography and pure growth of recognized pathogen), or need for reintubation after initial weaning from the ventilator. Prolonged length of stay was defined as longer than 7 days postoperatively for open repair and 2 days for EVAR, in accordance with the Center for Medicare and Medicaid Services clinical benchmarks.[8] Prolonged ICU length of stay for open repair was considered when ICU stay was longer than 48 hours following open repair.

Statistical analysis

Comparisons between those with and those without postoperative bowel ischemia were performed using Pearson's χ^2 and Fisher's exact testing for categorical variables, and student t-testing and Mann-Whitney U test for continuous data, where appropriate. Analyses were stratified by indication for the procedure (intact and ruptured) and treatment approach (open repair and EVAR). Independent predictors of postoperative bowel ischemia were established using multivariable logistic regression analysis. Individual factors were first tested by univariate analysis. Variables with P-value ≤ .1 were subsequently entered into the multivariable model, after which the final model was obtained using stepwise backward elimination (exit P > .05). EVAR patients were assigned a separate category for open repair specific procedure characteristics, and vice versa, to avoid exclusion of patients when including procedure-specific variables into the multivariable model. All tests were two-sided and significance was considered when p-value <0.05. Statistical analysis was performed using SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 7389 patients were identified, of which 77 (1.0%) were excluded because of missing data on bowel ischemia occurrence. The remaining 7312 patients (intact 91.2%, rupture 8.8%) were included, with 4675 (63.9%) undergoing EVAR and 2637 (36.1%) undergoing open repair. Among open repairs, 441 (16.7%) were performed for ruptured AAA, and 203 (4.3%) patients underwent EVAR for rupture. Bowel ischemia was diagnosed in 202 (2.8%) patients, with 91 (1.2%)

requiring surgical treatment. The incidence of bowel ischemia was significantly higher following open repair compared to EVAR (6.2% vs. 0.8%, P<.001). After stratification by indication, this difference remained for both intact (3.6% vs. 0.6%, P<.001), and ruptured AAA repair (19.3% vs. 6.4%, P<.001).

Baseline characteristics

Baseline characteristics are detailed in Table 1. Among intact open repair patients, those with postoperative bowel ischemia were significantly older than those without (73.1 vs. 70.0 years, respectively, P<.001), while a trend was observed for intact EVAR (77.2 vs. 74.0, P=.054). Patients with bowel ischemia following intact AAA repair more often had hypertension (Open: 93.6% vs. 82.8%, P=.012; EVAR: 100% vs. 84.9%, P=.025), heart failure (Open: 16.7% vs. 5.8%, P<.001; EVAR: 26.9% vs. 10.9%, P=.009), and were more frequently on dialysis preoperatively (Open: 2.6% vs. 0.5%, P=.003; EVAR: 7.7% vs. 0.7%, P<.001). Patients with bowel ischemia treated with EVAR for intact aneurysms also had increased rates of coronary artery disease (61.5% vs. 33.4%, P=.002). Finally, among ruptured open repair patients, COPD was more frequently present in those with postoperative bowel ischemia (48.8% vs. 37.1%, P=.048).

Intraoperative characteristics

For both intact and ruptured open repair, operative time was significantly longer among patients with postoperative bowel ischemia (Intact: 261 vs. 220 minutes, P=.001; Rupture: 227 vs. 199 minutes, P=.011, respectively, Table 2a). Similarly, blood loss exceeding 1L (Intact: 67.9% vs. 53.5%, P=.012; Rupture: 96.4% vs. 83.9%, P=.001), and intraoperative blood transfusion (Intact: 49.4% vs. 29.3%, P<.001; Rupture 95.3% vs. 85.9%, P=.016) occurred more frequently among those with postoperative bowel ischemia. In addition, patients with bowel ischemia more frequently had the graft anastomosed to the femoral artery (Intact: 25.6% vs. 14.5%, P=.049; Rupture: 21.4% vs. 11.0%, P=.022). Among the intact open repair patients, those with postoperative bowel ischemia were more likely to have had the IMA reimplanted (10.3% vs. 3.6%, P=.012), and the proximal clamp placed above the renal arteries (45.5% vs. 32.2%, P<.001). Also, in patients undergoing open repair for ruptured AAA, bowel ischemia was associated with a higher rate of hypogastric artery ligation (12.0% vs. 5.2%, P=.036), although this relation could not be established for bilateral hypogastric ligation (1.2% vs. 4.0%).

Similar to open repair, intact EVAR patients with postoperative bowel ischemia had a longer operative time (255 min. vs. 158 min., P=.003, Table 2b), extensive blood loss (15.4% vs. 2.4%, P=.003), and intraoperative blood transfusion

Table 1. Baseline characteristics

	Intact AAA					
	Open Repair			EVAR		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=78	No N=2118	P-value	Yes N=26	No N=4446	P-value
Age – (mean ± sd)	73.1 (7.6)	70.0 (8.5)	<.001	77.2 (7.2)	74.0 (8.6)	.054
Female gender – N (%)	29 (37)	596 (28.1)	.082	12 (46)	877 (19.7)	.001
Hypertension – N (%)	73 (94)	1753 (82.8)	.012	26 (100)	3772 (84.9)	.025
Diabetes – N (%)	7 (9)	298 (14.1)	.20	7 (27)	864 (19.4)	.34
CAD – N (%)	23 (29)	662 (31.3)	.74	16 (62)	1484 (33.4)	.002
CHF – N (%)	13 (17)	122 (5.8)	<.001	7 (27)	483 (10.9)	.009
CABG/PCI – N (%)	20 (26)	610 (28.8)	.59	11 (42)	1371 (30.9)	.21
COPD – N (%)	35 (45)	730 (34.5)	.058	10 (38)	1505 (33.9)	.62
Renal insuf – N (%)	8 (11)	134 (6.4)	.16	4 (17)	262 (6.0)	.047
Dialysis – N (%)			.003			<.001
Working transplant	1 (1)	3 (0.1)		0 (0)	7 (0.2)	
On dialysis	2 (3)	10 (0.5)		2 (8)	32 (0.7)	
Smoking – N (%)			.29			.80
Never	9 (12)	179 (8.5)		4 (15)	608 (13.7)	
Past	31 (40)	1021 (48.3)		13 (50)	2512 (56.6)	
Current	38 (49)	916 (43.3)		9 (35)	1322 (29.8)	
Max Diameter (mm, ± sd)	60.8 (15.2)	60.3 (13.9)	.78	56.1 (20.5)	56.9 (18.5)	.84

Table 1. (continued)

	Ruptured AAA					
	Open Repair			EVAR		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=85	No N=356	P-value	Yes N=13	No N=190	P-value
Age – (mean ± sd)	74.0 (7.8)	72.7 (9.4)	.44	72.8 (10.0)	73.3 (9.7)	.86
Female gender – N (%)	22 (26)	69 (19.4)	.18	4 (31)	45 (23.7)	.52
Hypertension – N (%)	65 (79)	273 (77.6)	.74	12 (92)	160 (84.7)	.70
Diabetes – N (%)	13 (16)	45 (12.8)	.44	3 (23)	27 (14.4)	.42
CAD – N (%)	26 (33)	96 (27.9)	.38	3 (23)	53 (28.2)	>.99
CHF – N (%)	10 (12)	32 (9.2)	.39	0 (0)	24 (12.8)	.37
CABG/PCI – N (%)	17 (21)	76 (21.7)	.89	1 (8)	32 (17.0)	.70
COPD – N (%)	41 (49)	129 (37.1)	.048	7 (54)	53 (28.3)	.052
Renal insuf – N (%)	15 (20)	47 (14.0)	.19	0 (0)	29 (16.0)	.36
Dialysis – N (%)			.70			>.99
Working transplant	0 (0)	2 (0.6)		0 (0)	0 (0)	
On dialysis	0 (0)	1 (0.3)		0 (0)	3 (1.6)	
Smoking – N (%)			.45			.49
Never	11 (14)	49 (14.3)		1 (8)	43 (22.8)	
Past	28 (36)	148 (43.1)		5 (42)	71 (37.6)	
Current	39 (50)	146 (42.6)		6 (50)	75 (39.7)	
Max Diameter (mm, ± sd)	78.1 (20.1)	76.5 (19.6)	.53	83.6 (24.9)	73.0 (19.6)	.086

Table 2a. Intraoperative characteristics open repair

	Intact AAA			Ruptured AAA		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=78	No N=2118	P-value	Yes N=85	No N=356	P-value
Operative time – (min. ± sd)	261.4 (108.1)	220.4 (89.5)	.001	227.2 (91.3)	199.4 (89.0)	.011
Blood loss >1L	53 (68)	1126 (53.5)	.012	81 (96)	297 (83.9)	.001
Ren/visc ischemia time >30 min	11 (14)	228 (11.0)	.34	14 (17)	54 (15.9)	.76
Transfusions ≥1 unit	38 (49)	617 (29.3)	<.001	81 (95)	305 (85.9)	.016
Retroperitoneal access– N (%)	18 (23)	500 (23.7)	.90	5 (6)	26 (7.3)	.64
Proximal clamp location			<.001			.37
Infrarenal	42 (55)	1421 (67.8)		47 (57)	217 (62.5)	
Above one renal	7 (9)	225 (10.7)		5 (6)	27 (7.8)	
Above both renals	12 (16)	309 (14.7)		8 (10)	37 (10.7)	
Supracoeliac	16 (21)	142 (6.8)		23 (28)	66 (19.0)	
Distal anastomosis – N (%)			.049			.022
Aorta	37 (47)	1125 (53.5)		46 (55)	230 (66.3)	
CIA	18 (23)	536 (25.5)		15 (18)	70 (20.2)	
EIA	3 (4)	137 (6.5)		5 (6)	9 (2.6)	
CFA	20 (26)	304 (14.5)		18 (21)	38 (11.0)	
Hypogastric art. ligat./occl.– N (%)			.21			.036
Unilateral	9 (12)	136 (6.5)		10 (12)	18 (5.2)	
Bilateral	2 (3)	66 (3.1)		1 (1)	14 (4.0)	
IMA – N (%)			.012			.48
Occluded	32 (41)	914 (43.8)		45 (56)	204 (59.6)	

Table 2a. (continued)

	Intact AAA			Ruptured AAA		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=78	No N=2118	P-value	Yes N=85	No N=356	P-value
Ligated	28 (49)	1098 (52.6)		35 (43)	128 (37.4)	
Reimplanted	8 (10)	76 (3.6)		1 (1)	10 (2.9)	
Cold renal perfusion - N (%)	3 (4)	141 (6.7)	.48	0 (0)	6 (1.7)	.60
Any concomitant procedure - N (%)	13 (17)	325 (15.3)	.75	26 (31)	61 (17.1)	.005
Renal bypass	3 (4)	128 (6.0)	.62	0 (0)	3 (0.8)	>.99
Lower extremity bypass	2 (3)	35 (1.7)	.38	3 (4)	5 (1.4)	.19
Other abdominal procedure	4 (5)	120 (5.7)	>.99	8 (9)	20 (5.6)	.20
Thrombo-embolectomy	6 (8)	79 (3.7)	.075	19 (22)	39 (11.0)	.005
Delayed closure - N (%)	0 (0)	0 (0)	-	36 (46)	72 (21.0)	<.001

Table 2b. Intraoperative characteristics EVAR

		Intact AAA			Ruptured AAA		
		Bowel Ischemia			Bowel Ischemia		
		Yes N=26	No N=4446	P-value	Yes N=13	No N=190	P-value
Operative time – (min. ± sd)		254.8 (151.3)	158.4 (73.9)	.003	199.3 (98.6)	178.5 (86.4)	.41
Anesthesia				.81			.82
Local		0 (0)	55 (1.2)		2 (17)	29 (15.6)	
Locoregional		2 (8)	412 (9.3)		0 (0)	6 (3.2)	
General		24 (92)	3955 (89.4)		10 (83)	151 (81.2)	
Blood loss >1L		4 (15)	106 (2.4)	.003	4 (31)	25 (13.4)	.10
Transfusions ≥1 unit		8 (31)	264 (6.0)	<.001	11 (85)	118 (62.1)	.14
Arterial injury		5 (19)	108 (2.6)	<.001	0 (0)	9 (5.0)	>.99
Endoleak	*I*	1 (4)	116 (2.6)	.50	0 (0)	5 (2.7)	>.99
	II	4 (15)	938 (21.2)	.63	1 (8)	21 (11.4)	>.99
	III	2 (8)	15 (0.3)	.004	0 (0)	3 (1.6)	>.99
	IV	1 (4)	74 (1.7)	.36	1 (8)	4 (2.2)	.27
Overall hypogastric coverage				.67			.33
Unilateral		3 (12)	497 (11.3)		0 (0)	26 (14.1)	
Bilateral		1 (4)	71 (1.6)		0 (0)	3 (1.6)	
Unintentional hypogastric coverage				.80			.66
Unilateral		1 (4)	92 (2.1)		0 (0)	3 (0)	
Bilateral		0 (0)	12 (0.3)		0 (0)	0 (0)	
Hypogastric embolization preop				.89			-
Unilateral		1 (4)	113 (2.5)		0 (0)	0 (0)	

Table 2b. (continued)

	Intact AAA			Ruptured AAA		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=26	No N=4446	P-value	Yes N=13	No N=190	P-value
Bilateral	0 (0)	10 (0.2)		0 (0)	0 (0)	
Any concomitant procedure - N (%)	15 (58)	1282 (28.8)	.001	4 (31)	68 (35.8)	>.99
Hypogastric embolization			.39			.40
Unilateral	3 (12)	242 (5.4)		0 (0)	10 (5.3)	
Bilateral	0 (0)	10 (0.2)		0 (0)	0 (0)	
Graft Extension	4 (15)	392 (8.8)	.28	2 (15)	29 (15.3)	>.99
Femoral Endarterectomy	2 (8)	190 (4.3)	.31	0 (0)	13 (6.8)	>.99
Femoro-femoral bypass	1 (4)	127 (2.9)	.53	2 (15)	30 (15.8)	>.99
Iliac angioplasty or stent	7 (27)	440 (9.9)	.004	1 (8)	17 (8.9)	>.99
Ilio-femoral bypass	0 (0)	30 (0.7)	>.99	0 (0)	4 (2.1)	>.99
Renal angioplasty or stent	2 (8)	148 (3.3)	.22	1 (8)	3 (1.6)	.23
Other arterial reconstruction	2 (8)	104 (2.3)	.13	0 (0)	3 (1.6)	>.99
Thrombo-embolectomy	3 (12)	36 (0.8)	.001	1 (8)	10 (5.3)	.53
Repair arterial injury	0 (0)	48 (1.1)	>.99	0 (0)	2 (1.1)	>.99

(30.8% vs. 6.0%, P<.001) compared to those without bowel ischemia. In addition, arterial injury (19.2% vs. 2.6%), and type III endoleak at completion (7.7% vs. 0.3%P=.004) occurred more often among those with bowel ischemia. Further, an iliac angioplasty or stenting procedure, and a thrombo-embolectomy were also more often performed in patients with postoperative bowel ischemia (26.9% vs. 9.9%, P=.004; 11.5% vs. 0.8%, P=.001, respectively).

Postoperative outcomes

Postoperative outcomes are listed in Table 3. Considerably higher rates of 30-day mortality were found in patients with postoperative bowel ischemia after open repair for intact aneurysms (20.5% vs. 1.9%, P<.001), intact EVAR (34.6% vs. 0.9%, P<.001), as well as open repair for ruptured AAA (48.2% vs. 25.6%, P<.001). Following EVAR for ruptured aneurysms, mortality was increased among patients with bowel ischemia, although significance was not achieved (30.8% vs. 21.1%, P=.49). Bowel ischemia was also associated with various other complications, including wound-, cardiovascular-, and respiratory complications, acute kidney injury, leg ischemia, requirement for return to OR, and need for >3 postoperative transfusions.

Predictors of bowel ischemia

In adjusted analysis (Table 4), surgery for a ruptured AAA proved to the most important determinant of postoperative bowel ischemia (OR: 6.4, 95% CI: 4.5 – 9.0). Also, open repair was associated with a considerable higher risk of bowel ischemia compared to EVAR (OR 2.9, 95% CI: 1.8 – 4.7). Predictive demographic factors included advanced age (OR: 1.4 per 10 years, 95% CI: 1.1 – 1.7), as well as female gender (OR: 1.6, 95: CI: 1.1 – 2.2). Other patient factors associated with bowel ischemia included hypertension (OR: 1.8, 95% CI: 1.1 – 3.0), heart failure (OR: 1.8, 95% CI: 1.2 – 2.8), and current smoking (OR: 1.5, 95% CI: 1.1 – 2.1). Interruption of the hypogastric artery, because of ligation/occlusion during open repair or embolization during EVAR, was also associated with an increased risk of postoperative bowel ischemia (OR: 1.7, 95% CI: 1.0 – 2.8), although this association could not be established for bilateral occlusion. Additional operative risk factors for bowel ischemia were prolonged operative time (OR: 1.2 per 60 min. increase, 95% CI: 1.1 – 1.3), blood loss >1L (OR: 2.0, 95% CI: 1.3 – 3.0), and aorto-femoral artery anastomosis during open repair (OR: 1.7, 95% CI: 1.1 – 2.7).

Table 3. Postoperative outcomes

	Intact AAA					
	Open repair			EVAR		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=78	No N=2118	P-value	Yes N=26	No N=4446	P-value
30-day Mortality – N (%)	16 (21)	41 (1.9)	<.001	9 (35)	41 (0.9)	<.001
Renal deterioration – N (%)	36 (46)	252 (11.9)	<.001	15 (58)	144 (3.3)	<.001
Dialysis – N (%)	11 (14)	39 (1.8)	<.001	6 (23)	15 (0.3)	<.001
Leg Ischemia – N (%)	9 (12)	36 (1.7)	<.001	5 (19)	41 (0.9)	<.001
Wound complication – N (%)	14 (18)	71 (3.4)	<.001	2 (8)	30 (0.7)	.014
MI – N (%)	11 (14)	105 (5.0)	<.001	2 (8)	70 (1.6)	.065
CHF – N (%)	12 (15)	78 (3.7)	<.001	5 (19)	46 (1.0)	<.001
Respiratory complication - N (%)	38 (49)	222 (10.5)	<.001	15 (58)	83 (1.9)	<.001
>3 transfusions – N (%)	21 (34)	131 (6.8)	<.001	6 (24)	54 (1.2)	<.001
Return to OR – N (%)	37 (47)	118 (5.6)	<.001	14 (54)	70 (1.6)	<.001
Prolonged length of stay – N (%)[α]	56 (72)	845 (39.9)	<.001	25 (96)	1110 (25.0)	<.001
Prolonged ICU stay – N (%)[β]	70 (90)	959 (45.3)	<.001	19 (73)	286 (6.4)	<.001

Table 3. (continued)

	Ruptured AAA					
	Open repair			EVAR		
	Bowel Ischemia			Bowel Ischemia		
	Yes N=85	No N=356	P-value	Yes N=13	No N=190	P-value
30-day Mortality – N (%)	41 (48)	91 (25.6)	<.001	4 (31)	40 (21.1)	.49
Renal deterioration – N (%)	51 (65)	99 (28.0)	<.001	8 (67)	42 (22.2)	.002
Dialysis – N (%)	16 (20)	21 (5.9)	<.001	2 (17)	9 (4.8)	.13
Leg Ischemia – N (%)	22 (26)	16 (4.5)	<.001	1 (8)	6 (3.2)	.38
Wound complication – N (%)	17 (20)	39 (11.0)	.022	3 (23)	11 (5.8)	.050
MI – N (%)	29 (35)	52 (14.6)	<.001	2 (15)	24 (12.6)	.68
CHF – N (%)	15 (18)	35 (9.9)	.038	2 (15)	17 (8.9)	.35
Respiratory complication - N (%)	58 (69)	147 (41.4)	<.001	8 (67)	34 (17.9)	<.001
>3 transfusions – N (%)	45 (74)	134 (47.3)	<.001	9 (82)	82 (45.8)	.028
Return to OR – N (%)	50 (59)	86 (24.2)	<.001	9 (69)	32 (16.8)	<.001
Prolonged length of stay – N (%)[α]	49 (58)	229 (64.3)	.25	9 (69)	151 (79.5)	.48
(Prolonged) ICU stay – N (%)[β]	63 (74)	259 (73.2)	.86	13 (100)	121 (63.7)	.005

α defined as >7 days for open repair, and >2 days for EVAR
β defined as >48 hours following open repair, and any ICU stay following EVAR

Table 4. Independent predictors of bowel ischemia following AAA repair

Variable	OR	95% CI	P-value
Age (per 10 years)	1.4	1.1 – 1.7	.002
Female gender	1.6	1.1 – 2.2	.008
Hypertension	1.8	1.1 – 3.0	.015
Heart Failure	1.8	1.2 – 2.8	.008
Current smoking	1.5	1.1 – 2.1	.010
Open repair	2.9	1.8 – 4.7	<.001
Rupture	6.4	4.5 – 9.0	<.001
Hypogastric interruption			
Unilateral	1.7	1.0 – 2.8	.040
Bilateral	0.7	0.2 – 2.1	.55
Procedure time (per 60 min)	1.2	1.1 – 1.3	<.001
Blood loss >1L	2.0	1.3 – 3.0	.002
Distal anastomosis			
Femoral artery	1.7	1.1 – 2.7	.012

DISCUSSION

This study demonstrates that although the incidence of bowel ischemia following AAA repair is low, it is associated with very poor outcomes. In addition to various complications, 30-day mortality was much worse in those with postoperative bowel ischemia, ranging between a factor of two among patients undergoing open repair for ruptured AAA, and a factor of 38 among those undergoing EVAR for intact AAA. Adjusted analysis demonstrated that repair for a ruptured AAA and open repair were the most dominant predictors of bowel ischemia. Other factors included patient factors such as age, gender, hypertension, heart failure, and smoking, as well as operative factors, such as prolonged operative time, and increased blood loss. Further, interruption of the hypogastric artery, because of ligation/occlusion during open repair or embolization during EVAR, and using the femoral artery for the distal anastomosis during open repair were also independent predictors of bowel ischemia.

Since the risks of bowel ischemia differ according to the indication of the AAA repair (intact vs. ruptured), and the operative approach (open repair vs. EVAR), the reported incidence varies based on the composition of the studied cohort. The study by Becquemin et al. with similar proportions in terms of operative approach and ruptures as the present study found an overall bowel ischemia rate of 2.9%, which is comparable to the 2.8% in this study.[9] When comparing our results to studies conducted among open repair patients only, the incidence of

3.6% for intact AAA is on the higher end with previous studies showing occurrence rates between 1-3%.[1-3] This may be related to the fact that the diagnosis of bowel ischemia in our study could be established based on either clinical basis or colonoscopy, while other studies required confirmation through colonoscopy for all cases. For open repair of ruptured AAA, the rate of 19.3% falls well within the reported range of 7 – 36%.[1, 9, 10, 22] Furthermore, our results for EVAR are on the lower end of what has previously been reported for EVAR series, with 0.6% vs. 0.5 – 3% for intact, and 6.4% vs. 4 – 23% for ruptured EVAR.[4-8, 11]

While crude analysis in the study by Becquemin et al. demonstrated that open repair was followed by a higher rate of bowel ischemia compared to EVAR, no relation was established in adjusted analysis.[9] A study utilizing the Nationwide Inpatient Sample, however, did show that open repair was an independent risk factor for bowel ischemia.[13] In line with the latter report, open surgery was associated with a 2.7-fold increase risk of bowel ischemia in our study. Confirming previous studies,[9, 12] longer operative time and excessive blood loss were also established as predictive of bowel ischemia. As addressed previously, this risk should not be attributed to the duration of the procedure, but rather the technical difficulty it represents.[9] Apart from operative stress, our adjusted analysis demonstrated that women were at a higher risk of bowel ischemia than men. The relation between female gender and higher risks of bowel ischemia has been demonstrated before,[13] and is most likely due to the fact that women are more likely to encounter intraoperative difficulties as a result of their smaller vasculature.[23-25] These difficulties include embolic complications, which have been implicated as an important cause of postoperative bowel ischemia after both open repair and EVAR.[4, 6, 26]

The role of the hypogastric arteries and their management remains disputed. While some studies demonstrated that interruption the hypogastric arteries, either because of ligation/occlusion during open repair or embolization or coiling during EVAR, can safely be performed,[4, 14-16] others concluded that hypogastric artery interruption is associated with ischemic complications, including spinal, pelvic, and bowel ischemia.[2, 5, 7, 12, 17-19] In the present study, we found that disruption of one hypogastric artery was associated with increased risks of bowel ischemia postoperatively. Although the relation was demonstrated for unilateral interventions, the relation could not be confirmed for two-sided interruption. This is most likely the result of the limited number of patients receiving bilateral hypogastric artery interruption (N=98), the rarity of bowel ischemia (N=4), and consequent lack of statistical power, rather than a lack of association. These demonstrated risks emphasize the need to assess patency of the superior mesenteric artery and to evaluate any history of colonic surgery that could impact

collateral flow in the colon. Also, these data highlight the potential benefit of utilizing iliac branch graft systems in those with a high a priori risk of bowel ischemia. Of note, coverage of the hypogastric artery by the endograft during EVAR –uni- or bilateral– was not associated with an increased risk of bowel ischemia. This is likely related to the fact that this group included a large number of patients that did not undergo hypogastric embolization, indicating that their hypogastric artery may not have been patent at the time of surgery, or that with a short seal zone in the distal common iliac and no hypogastric aneurysm, embolization was not needed and collateral circulation was maintained. Notably, no distinction could be made between the use of coils and plugs in this database.

Similar to previous studies,[9, 12] we found that the femoral artery as the target for the distal anastomosis was also predictive of bowel ischemia. The choice for femoral anastomosis is often related to aneurysmal or occlusive disease in the common and/or external iliac arteries. Although the hypogastric artery is typically not ligated in case of aorto-femoral anastomosis, occlusive disease in the external iliac may limit retrograde flow into the hypogastric arteries. Patients with a femoral anastomosis also typically have a more advanced state of atherosclerosis generally, with the potential of (micro)embolization of dislodged atherothrombotic debris, atherosclerosis of the mesenteric vessels, and poor collateral flow through the marginal artery in case of IMA or hypogastric interruption. [4, 6, 26] Since smoking is a strong etiologic contributor to atherosclerosis, these factors may also explain the increased risks associated with current smoking. Interestingly, Brewster et al. found that IMA ligation was the most important predictor for bowel ischemia following open repair.[2] Yet in our study, not ligation, but rather reimplantation of the IMA was associated increased risks of bowel ischemia. Although this association was lost in multivariable analysis, our results indicate that IMA reimplantation is currently not standard practice, and that it is only performed in those at the highest risk of suffering from postoperative bowel ischemia.

This study has several limitations. First, as the VSGNE collects data through a registry, the potential exists for underreporting of data. Second, the severity of the bowel ischemia beyond need for surgery, and the extent of the bowel resection were unknown. Third, we were unable to distinguish patients with a clinical diagnosis of postoperative bowel ischemia from those who underwent endoscopic diagnostic procedures, which precluded sub- or sensitivity analysis between these patients. Also, the importance of prior abdominal surgery, particularly previous bowel resection, has been addressed in prior studies,[4, 6, 9] but remains unclear. Unfortunately, data on prior abdominal surgery were not documented, precluding its consideration in the multivariable model. In addition,

although many operative characteristics were evaluated on their association with postoperative bowel ischemia, other factors, including hypogastric artery revascularization and mesenteric vessel stenting, were unfortunately not documented in this data set. It should also be noted that the bowel ischemia was presumed to be in the colon, but the data set did not distinguish small bowel ischemia from colonic ischemia. Finally, due to the limited follow-up data, we were unable to determine the incidence of late laparotomy, and the impact of perioperative bowel ischemia on long-term survival.

In conclusion, this study underlines that although bowel ischemia following AAA repair is rare, the associated outcome is very poor. The cause of postoperative bowel ischemia is multifactorial. In contrast to some previous work, open repair proved to be an important predictor. Other risk factors included age, gender, hypertension, heart failure, and factors indicative of more operative stress, including longer operative time, and extensive blood loss. Interruption of the hypogastric artery and the distal anastomosis to the femoral artery were also established as risk factors for bowel ischemia. These data should be considered during operative planning in an effort to adequately assess patient risk for bowel ischemia, and undertake efforts to reduce it.

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chapter 13

Predictors of Renal Dysfunction following Endovascular and Open Repair of Abdominal Aortic Aneurysms

Sara L. Zettervall[1]
Klaas H.J. Ultee[1,2]
Peter A. Soden[1]
Sarah E. Deery[1]
Katie E. Shean[1]
Alexander B. Pothof[1]
Mark C. Wyers[1]
Marc L. Schermerhorn[1]

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Objectives

Renal complications following repair of abdominal aortic aneurysms (AAA) have been associated with increased morbidity and mortality. However, limited data have assessed risk factors for renal complications in the endovascular era. This study aims to identify predictors of renal complications following endovascular (EVAR) and open repair.

Methods

Patients who underwent EVAR or open repair of a non-ruptured infrarenal AAA between 2011 and 2013 were identified in the Targeted Vascular module of the National Surgical Quality Improvement Project. Patients on hemodialysis preoperatively were excluded. Renal complications were defined as new postoperative dialysis or creatinine increase greater than 2mg/dL. Patient demographics, comorbidities, glomerular filtration rate (GFR), operative details, and outcomes were compared using univariate analysis between those with and without renal complications. Multivariable logistic regression was utilized to identify independent predictors of renal complications.

Results

We identified 4503 patients who underwent elective repair of infrarenal AAA (EVAR: 3869, Open: 634). Renal complication occurred in 1% of patients following EVAR and 5% of patients following open repair. There were no differences in comorbidities between patients with and without renal complications. A preoperative GFR < 60 occurred more frequently among patients with renal complications (EVAR: 81% vs. 37%, P < .01; Open: 60% vs. 34%, P < .01). 30-day mortality was also significantly increased (EVAR: 55% vs. 1% P < .01; Open: 30% vs. 4% P < .01). After adjustment, renal complications were strongly associated with 30-day mortality (Odds Ratio (OR): 38.3 95% Confidence Interval (CI): 20.4-71.9). Independent predictors of renal complications included: GFR < 60 (OR: 4.6, 95% CI: 2.4-8.7), open repair (OR: 2.6, 95% CI: 1.3-5.3), transfusion (OR: 6.1, 95% CI: 3.0-12.6), and prolonged operative time (OR: 3.0, 95% CI: 1.6-5.6).

Conclusion

Predictors of renal complications include elevated baseline GFR, open approach, transfusion, and prolonged operative time. Given the dramatic increase in mortality associated with renal complications, care should be taken to employ renal

protective strategies, achieve meticulous hemostasis to limit transfusions, and to utilize an endovascular approach when technically feasible.

INTRODUCTION

Renal complications following surgery are associated with increased mortality, prolonged hospital length of stay, and higher healthcare costs.[1-3] Following open repair of abdominal aortic aneurysms (AAA), both 30-day and long-term mortality have been strongly associated with post-operative renal complications.[4] Prior work has shown predictors of renal complications after AAA repair include pre-operative kidney dysfunction and chronic obstructive pulmonary disease.[4] Additional operative factors such as urgency of presentation, supra-renal clamping, and operative time have also been associated with renal complications.[2, 4] Despite these findings, previous studies have included predominantly open aneurysm repairs with varying proximal extent of aneurysms and operative urgency. The effects of renal dysfunction on mortality in the endovascular era, and the predictors of such complications following endovascular repair (EVAR) remain unclear.

Therefore, this study aims to identify the rate of post-operative renal complications and subsequent mortality associated with this adverse event among patients undergoing EVAR and open repair of intact infrarenal aneurysms in the endovascular era. Additionally, we intend to identify predictors of renal dysfunction among patients.

METHODS

Patients

The Targeted Vascular Module of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) was utilized to identify all patients undergoing elective repairs for intact infrarenal AAAs from 2011-2014. Patients with juxtarenal, pararenal, and suprarenal AAAs were excluded to minimize the effect of clamp time. Additionally, those on dialysis pre-operatively were excluded from this analysis (n=88). The targeted NSQIP is a national clinical registry developed in 2011, which collects patient demographics, operative details, and 30-day outcomes from patients undergoing surgical procedures at more than 65 self-selected hospitals. Further information is available at www.facs.org/quality-programs/acs-nsqip.

Variables

Patient demographics, age, and comorbid conditions were compared between those with and without renal complications. Smoking was defined as current tobacco use. Glomerular filtration rate (GFR - mL/minute per 1.73m^2) was calculated

in accordance with the Modification of Diet in Renal Disease (MDRD) equation, and chronic kidney disease was identified according the Kidney Disease: Improving Global Outcomes (KDIGO) and Acute Kidney Injury Network (AKIN) Clinical Practice Guidelines.[5-7]

The operative variables compared are listed in Table 2 and include: aneurysm diameter, transfusion, renal revascularization, and lower extremity revascularization, as defined by NSQIP. Transfusion was defined as any transfusion within 72 hours of the initial operation. Prolonged operative time was defined as greater than 2 standard deviations from the mean (greater than 180 minutes for EVAR and greater than 360 minutes for open repair).

All outcomes measured occurred within 30-days of operation. A renal complication was defined as a creatinine increase greater than 2 mg/dL from baseline or new dialysis in the 30-day post-operative period, as defined by NSQIP. A pulmonary complication was defined as pneumonia, failure to wean from mechanical ventilation within 48 hours, re-intubation, or pulmonary embolism. Prolonged length of stay was defined as great than 2 days following EVAR and greater than 7 days following open repair.

Statistics

All statistical analyses were performed using the SPSS statistical package (version 21.0). Univariate analysis was stratified by EVAR or open repair, and patients with and without renal complications were compared using chi-square and Fisher's exact tests for categorical variables, as appropriate. The Student's t-test and Mann-Whitney U-test were utilized to assess continuous variables, as appropriate. All pre-operative variables and outcomes compared had less than 2% missing data, with the exception of lower extremity revascularization (10.9% missing data). Independent predictors of renal complications, mortality, and prolonged length of stay were established using multivariable logistic regression. Purposeful selection was utilized to select variables for inclusion.[8] This included all variables with $P < 0.1$ on univariate analysis as well as those variables shown to be predictive of the outcome of interest in previous studies. The Hosmer-Lemeshow goodness of fit test was used to evaluate each model. A P-value < 0.05 was considered significant. The institutional review board of Beth Israel Deaconess Medical Center approved this study and consent was waived due to the de-identified nature of the NSQIP database.

RESULTS

We identified 4503 patients, 3869 of whom underwent EVAR and 634 had open repair. Renal complications, as defined by NSQIP, occurred in 33 patients (1%) following EVAR and 30 patients (5%) after open repair. Dialysis was initiated in 22 (0.6%) patients following EVAR and 26 (4%) of patients following open repair.

Baseline Characteristics

Among those treated with EVAR, patients with renal complications were older (80 years vs. 75 years, P = 0.01), less commonly male (67% vs. 81%, P = 0.03), and more commonly had a GFR < 60 (81% vs. 37%, P < .01). Among patients undergoing open repair, only GFR < 60 differed between patients with and without renal complications (60% vs. 34%, P < .01, respectively) (Table 1).

Operative Characteristics

Following EVAR, patients with renal complications had longer operative times (183 minutes vs. 132 minutes, P < .01), more lower extremity revascularizations (13% vs. 4% P < .01) and transfusions (70% vs. 10%, P < .01). There were no significant differences in AAA diameter or proportion of patients undergoing renal revascularization.

Table 1 – Baseline Demographics and Comorbidities

Outcome	**EVAR**			**Open**		
	No Renal Complication N=3836	**Renal Complication** N=33	**P-Value**	**No Renal Complication** N=604	**Renal Complication** N=30	**P-Value**
Age: median (SD)	75 (8.6)	80 (9.3)	**0.01**	70 (9.3)	69 (10.3)	0.46
Male Gender	3121 (81%)	22 (67%)	**0.03**	451 (75%)	24 (80%)	0.51
White Race	3318 (87%)	27 (82%)	0.43	484 (80.1)	25 (83%)	0.67
GFR < 60	1435 (37%)	27 (81%)	**<.01**	203 (34%)	18 (60%)	**<.01**
Diabetes	616 (16%)	6 (18%)	0.74	693 (16%)	8 (13%)	0.53
COPD	106 (18%)	6 (20%)	0.81	796 (18%)	15 (24%)	0.23
CHF	9 (2%)	1 (3%)	0.39	67 (2%)	1 (2%)	0.96
Hypertension	493 (82%)	25 (83%)	0.81	3590 (81%)	55 (87%)	0.20
Smoking	259 (43%)	14 (47%)	0.71	1410 (32%)	26 (41%)	0.11

SD: Standard Deviation

Following open repair, patients with renal complications had longer operative times (374 minutes vs. 221 minutes, P <. 01), larger AAA diameters (6.6 cm vs. 5.8 cm, P < .01), and more lower extremity revascularizations (15% vs. 5%, P = 0.03). There were no differences in transfusions or proportion with concurrent renal revascularization (Table 2).

Outcomes

Both morbidity and mortality increased among patients with renal complications. Among EVAR patients, 30-day mortality was 55% in patients with renal complications compared to 1% without renal complications (P < .01). Major complications, including myocardial infarction (21% vs. 1%, P < .01), pulmonary complications (49% vs. 2%, P < .01), ischemic colitis (15% vs. 0.3%, P < .01), and lower extremity ischemia (15% vs. 1%, P < .01) were also more common among patients with renal complications. Median hospital stay was 8 days among patients with renal complications and 2 days among those without (P < .01).

Following open repair, 30-day mortality was 30% among those with renal complications and 4% among those without (P < .01). Similar to EVAR, pulmonary complications (80% vs. 13%, P < .01), ischemic colitis (23% vs. 2%, P < .01), and lower extremity ischemia (17% vs. 2%, P < .01) were increased among patients with renal complications. The median hospital stay was 19 days among patients with renal complications compared to 7 days among patients without (P < .01) (Table 3).

Table 2 – Operative Characteristics

Outcome	**EVAR**			**Open**		
	No Renal Complication N=3836	**Renal Complication** N=33	**P-Value**	**No Renal Complication** N=604	**Renal Complication** N=30	**P-Value**
Operative Time: min, median (IQR)	132 (103-171)	183 (130-275)	**< .01**	221 (168-285)	374 (220-457)	**<.01**
Diameter: cm, med. (IQR)	5.5 (5.1-6.0)	5.8 (5.1-7.7)	0.15	5.8 (5.2-6.7)	6.6 (5.8-8.6)	**<.01**
Transfusion	373 (10%)	24 (72%)	**<.01**	417 (69%)	23 (77%)	0.38
Renal Revascularization	170 (4%)	4 (12%)	0.06	25 (4%)	2 (7%)	0.50
LE Revascularization	138 (4%)	4 (13%)	**0.04**	39 (7%)	5 (17%)	**0.04**

IQR: Interquartile Range, cm: centimeters, LE: Lower Extremity

In multivariable analysis, adjusting for patient demographics, comorbidities, and operative approach, renal complications were predictive of both 30-day mortality (Odds Ratio (OR): 38.3 95% Confidence Interval (CI): 20.4-71.9) and prolonged length of stay (OR: 8.3, CI: 4.2-16.4).

Table 3 – Univariate Outcomes

Outcome Number (%)	**EVAR**			**Open**		
	No Renal Complication N=3836	**Renal Complication** N=33	**P-Value**	**No Renal Complication** N=604	**Renal Complication** N=30	**P-Value**
30-day Mortality	38 (1%)	18 (55%)	**<.01**	23 (4%)	9 (30%)	**<.01**
Pulmonary Complication	73 (2%)	16 (49%)	**<.01**	81 (13%)	24 (80%)	**<.01**
Ischemic Colitis	13 (0.3%)	5 (15%)	**<.01**	10 (2%)	7 (23%)	**<.01**
Lower Extremity Ischemia	45 (1%)	5 (15%)	**<.01**	11 (2%)	5 (17%)	**<.01**
Myocardial Infarction	46 (1%)	7 (21%)	**<.01**	12 (2%)	1 (3%)	0.47
Re-operation	22 (1%)	1 (3%)	0.18	12 (2%)	1 (3%)	0.47
Hospital Stay: median (IQR)	2 days (1-3)	8 days (4-20)	**<.01**	7 days (5-9)	19 days (12-29)	**<.01**

IQR: Interquartile Range

Table 4 – Multivariable Predictors of Renal Complications

	Odds Ratio	95% Confidence Interval	P-Value
Open Repair	2.6	1.3-5.3	**<.01**
GFR < 60	4.6	2.4-8.7	**<.01**
Transfusion	6.1	3.0-12.6	**<.01**
Prolonged Operative Time	3.0	1.6-5.6	**<.01**
Age (decade)	0.9	0.7-1.3	0.63
Female gender	1.0	0.5-1.9	0.93
CHF	0.7	0.1-5.3	0.71
COPD	1.4	0.7-2.7	0.33
Diabetes	0.9	0.4-2.0	0.73
Diameter	1.0	0.9-1.1	0.23
Renal Revascularization	1.4	0.5-3.9	0.48
Lower Extremity Revascularization	1.2	0.5-3.0	0.73

Predictors of Renal Complications

Following multivariable adjustment for only those characteristics available to surgeons pre-operatively, GFR < 60 (OR: 5.7, 95% CI: 3.0-10.6), AAA diameter (OR: 1.1, 95% CI: 1.02-1.2), and open repair (OR: 6.0, 95% CI: 3.5-10.3) were predictive of renal complications. When intraoperative characteristics were added to the same model, GFR < 60 (OR: 4.6, 95% CI: 2.4-8.7), open repair (OR: 2.6, 95% CI: 1.3-5.3), transfusion (OR: 6.1, 95% CI: 3.0-12.6), and prolonged operative time (OR: 3.0, 95% CI: 1.6-5.6) were independently predictive of renal complications (Table 4).

DISCUSSION

This study found that post-operative renal complications, defined as an increase in creatinine of 2.0mg/dL from baseline or new dialysis, occur in 1% of elective infrarenal EVARs and 5% of open repairs and are associated with a significant increase in mortality, morbidity, and prolonged length of stay compared to those patients without renal complications. Moreover, a baseline GFR < 60, open operative approach, transfusion, and prolonged operative time are independently predictive of renal complications.

The reported rates of renal complications vary in current literature. Following open repair, reported rates have ranged from 5-11%.[2, 4, 9] Lower rates have been reported following EVAR, occurring in 2-7% of patients. [9-11] Our study found a similar rate of renal complications following open repair to that reported by Grant et al., in a study of 2347 consecutive repairs, (6%) but was lower than other prior studies.[2] This variation was likely due to differences in study population and the definition of renal dysfunction. Our study evaluated infrarenal aneurysms only, with a renal complication defined by NSQIP as an increase in creatinine > 2.0mg/dL from baseline or new onset dialysis. This differs from previous work by both Patel and Ellenberg, who had a less stringent definition of renal complications, defined as all those with a creatinine increase > 0.5 mg/dL, and included all elective open repairs including those utilizing a suprarenal clamp, which is known to be independently associated with increased renal complications.[4, 12] Fewer studies have directly addressed renal function following EVAR, however Mehta reported rates of 3-7% following EVAR among patients treated in the first years of EVAR utilization (1996-2000) and also included physician-made grafts for patients with complex anatomy, both of which likely explain the increased renal complication rate compared to our study.[10] In a more recent study, Saratzis found a rate of renal complications of 19%. This rate was likely higher than

our work, and previous studies, due to their use of the highly sensitive KDIGO definition of renal dysfunction which included: increase in creatinine > 0.3mg/dL or well as low urine output.[13]

Given the infrequency of renal complications large databases are necessary to adequately power studies on acute kidney injury. However, a common definition of renal complications has not been widely utilized by any major databases including Vascular Quality Initiative, NSQIP, Medicare, or NIS leading to variable reports of such complications. The 2012 KDIGO and Acute Kidney Injury Network (AKIN) guidelines define acute kidney injury as an increase in creatinine > 0.3mg/dL, 50% increase in creatinine from baseline, or reduction in urine output to less than 0.5mL/kg per hour for more than 6 hours, are the most widely utilized guidelines for acute kidney injury.[7, 14] However, like many alternative definitions, the utility of this definition is challenged by the difficulty and reliability or urine collection at many institutions and the potential for fluid shifts among surgical patients. Nonetheless, NSQIP and other large databases would be improved by reporting of post-operative creatinine and GFR levels to more uniformly evaluate post-operative renal dysfunction.

Increased mortality among patients with renal complications following open AAA repair was also demonstrated in prior work.[2, 4, 13, 15, 16] Our study found 30-day mortality rates of 30% following open repair and 55% following EVAR amongst patients with renal complications. These rates are similar to those reported by Grant et al. who found a 30-day mortality rate of 35% in their study of 2378 open repairs. However, mortality rates among patients with renal complications vary tremendously in the literature and range from 9-58% following open repair. Much of this variation is likely due to differing definitions of renal dysfunction, with lower mortality rates seen in those studies that used the lower cutoff of 0.5 mg/dL increase from baseline as their definition of renal complication. Following EVAR, few studies have evaluated the mortality rates among patients with renal complications, and additional research is warranted to confirm our findings. Saratzis et al. found a mortality rate of 32% following EVAR; however this study utilized more sensitive definition of acute kidney injury including a significantly lower increase of serum creatinine.[5]

Despite differing rates of renal complications, we found similar predictors of this adverse outcome compared to prior work in patients undergoing open repair.[2, 4, 12, 16, 17] Only one previous study, from Wald et al., identified predictors following EVAR and open repair using the Nationwide Inpatient Sample (NIS) and found open repair, chronic kidney disease, and congestive heart failure to be associated with post-operative renal complications. However, due to limitations of the NIS database, the authors were unable to account for operative and

anatomic characteristics including transfusion, operative time, and aneurysm extent.[16] Additionally, the NIS is considered a suboptimal dataset for evaluation of post-operative morbidity, as it is an administrative dataset reliant on coding, rather than chart review, and cannot identify events occurring after discharge. Finally, previous work has shown administrative databases to be inferior to NSQIP and chart review in identifying perioperative complications.[18, 19] Following open repair, other authors have identified baseline kidney dysfunction, transfusion, urgency, clamp location, and renal ischemia as other predictors of renal complications; however such studies included suprarenal and ruptured aneurysms which have significantly different risks as compared to elective infrarenal aneurysms, and as such we elected to exclude them for this study.[2, 4, 12, 16, 17]

There are important clinical implications to the results in this study. Both chronic kidney disease and operative approach are characteristics known to the surgeon in the pre-operative period and should be utilized for patient education and risk assessment pre-operatively. Furthermore, given the risk of open repair in those with chronic kidney disease, surgeons should utilize an EVAR-first approach for patients with suitable anatomy. Additionally, in all patients, but particularly those with a GFR < 60, surgeons should take care to limit the volume of contrast used to avoid further renal deterioration and contrast nephropathy. Transfusion and operative time are characteristics reflective of challenging cases and may not be avoidable; however, given their strong association with renal complications, particular care to minimize blood loss and to ensure complete hemostasis at the closure of the case should be taken.

This study has multiple limitations, which must be noted. First, it is subject to generic limitations of a clinical registry including errors in coding, missing data, and limited variable definitions. Therefore, it is possible that other confounders including blood loss, clamp time, neck length, angulation, and thrombus may impact this study and cannot be accounted for. In the current era, open repairs are often more technically challenging due to poor anatomy for EVAR; however, in this analysis we excluded those patients with short necks (suprarenal, pararenal, and juxtarenal clamps). As a result the rates of renal dysfunction following open repair may not be reflective of all open AAA repairs. Additionally, this study was unable to assess the long-term effects of renal complications. This study was also unable to account for the volume of contrast used; however, contrast volume is often not known in the pre-operative period and as such does not assist with pre-operative risk stratification. Finally, in this study renal dysfunction is restricted to the VSGNE definition of renal dysfunction and characterized by a large increase in creatinine of > 2mg/dL, which neglects to include those

patients with less severe renal dysfunction; therefore, the effects of mild kidney injury and exact cause of dysfunction are unable to be evaluated.

Conclusions

Predictors of renal complications include elevated baseline GFR, open approach, transfusion, and prolonged operative time. Given the dramatic increase in mortality associated with renal complications, care should be taken to employ renal protective strategies, achieve meticulous hemostasis to limit transfusions, and to utilize an endovascular approach when technically feasible.

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Chapter 14

Conversion from EVAR to Open Abdominal Aortic Aneurysm Repair

Klaas H.J. Ultee[1,2]
Peter A. Soden[1]
Sara L. Zettervall[1]
Jeremy Darling[1]
Hence J.M. Verhagen[2]
Marc L. Schermerhorn[1]

1) Department of Surgery, Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
2) Department of Vascular Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Objective

Previous studies have found conflicting results regarding the operative risks associated with conversion to open abdominal aortic aneurysm (AAA) repair after failed endovascular treatment (EVAR). The purpose of this study was to assess the outcome of patients undergoing a conversion, and compare outcomes to standard open AAA repair and EVAR. Additionally, we sought out to identify factors associated with conversion.

Methods

All patients undergoing a conversion to open repair, and those undergoing standard EVAR and open repair between 2005 and 2013 were included from the National Surgical Quality Improvement Program (NSQIP). Multivariable logistic regression analysis was used to identify factors associated with conversion, and to assess independent perioperative risks associated with conversion compared to standard AAA repair. Subanalysis for factors associated with conversion was performed among patients additionally included in the more detailed Targeted Vascular Module of the NSQIP.

Results

A total of 32,164 patients were included, with 300 conversions, 7188 standard open repairs, and 24,676 EVARs. Conversion to open repair was associated with a significantly higher 30-day mortality than standard open repair (10.0% vs. 4.2%, P<.001, OR: 2.4, 95% CI: 1.6 – 3.6), and EVAR (10.0% vs. 1.7%, P<.001, OR: 7.2, 95% CI: 4.8 – 10.9). Conversion surgery was additionally followed by an increased occurrence of any complication (OR: 1.5, 95% CI: 1.2 – 1.9 (open); OR: 7.8, 95% CI: 6.1 – 9.9 (EVAR)). Factors associated with conversion were young age (OR: 1.2 per 10 years decrease, 95% CI: 1.1 – 1.4), female gender (OR: 1.5, 95% CI: 1.2 – 2.0), and non-white race (OR: 1.8, 95% CI: 1.3 – 2.6). Conversely, BMI > 30 was negatively associated with (OR: 0.7, 95% CI: 0.5 – 0.9). Among anatomic characteristics captured in the Targeted Vascular data set (N=4555), aneurysm large diameter demonstrated to be strongly associated with conversion (OR: 1.1 per 1 cm increase, 95% CI: 1.03 – 1.1).

Conclusion

Conversion to open repair after failed EVAR is associated with substantially increased perioperative morbidity and mortality compared to standard AAA repair. Factors associated with conversion are large diameter of the aneurysm, young

age, female gender, and non-white race, while obesity is inversely related to conversion surgery.

INTRODUCTION

Owing to the perioperative benefits over open repair,[1-4] the use of endovascular treatment modalities (EVAR) for abdominal aortic aneurysm (AAA) repair has rapidly increased since its introduction.[5-7] EVAR is currently the primary mode of treatment for AAA, with over 80% of elective cases being performed through endovascular repair.[8-10] Although rare, a conversion to open repair is sometimes required.[11, 12] A conversion can either be performed acutely, necessitated by intraoperative complications during EVAR, such as access-related problems and errors in endograft deployment,[13-16] or as a late reintervention following graft migration, persistent endoleak, graft thrombosis, or infection.[15-19]

Due to the rarity of the procedure, evidence on the frequency and prognostic implications of performing a conversion is largely limited to small retrospective series from mostly single-institution experiences.[13, 16, 20-24] These studies did show that conversion surgery was associated with substantial perioperative mortality, averaging 12% and 10% after acute and late conversion respectively.[11] Consequently, many of these studies concluded that having to convert from EVAR to open repair is associated with worse outcomes than either standard open AAA repair or EVAR. Yet in the largest study to date using the National Quality Improvement Program (NSQIP) from 2005 to 2008 with 72 conversion patients, Newton et al. found no differences in perioperative outcomes between patients undergoing a conversion and those undergoing standard open AAA repair.[25] The purpose of this study was to assess the outcome of patients undergoing conversion, and compare outcomes to standard open AAA repair and EVAR. Additionally, we aim to identify factors associated with conversion to open AAA repair using the regular NSQIP, as well as the newly available Targeted Vascular module.

METHODS

Data Source

For this study, we used the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. The NSQIP is a quality improvement initiative of the American College of Surgeons, and is designed to provide robust, reliable and risk-adjusted surgical outcomes intended to identify elements in current healthcare practice for quality improvement purposes. Dedicated surgical clinical nurse reviewers at each hospital prospectively collect preoperative and procedural risk factors, as well as 30-day postoperative outcomes according to

standardized definitions.[26, 27] The validity of the ACS NSQIP has been confirmed previously. The database contains de-identified data only without any protected health information. Therefore, Institutional Review Board approval and patient consent were waived. In order to identify anatomy-related factors associated with conversion, we performed a subanalysis among patients who are also captured in the Targeted Vascular data set of the ACS NSQIP. The Targeted Vascular data set is a newly available module, which includes additional disease and procedure specific characteristics, and procedure-related outcomes chosen by vascular surgeons. Additional information on the ACS NSQIP and the Targeted Vascular data set are available at www.acsnsqip.org.

Patients undergoing a conversion to open repair between January 2005 and December 2013 were included in the study. Procedures were identified using Current Procedural Terminology coding (CPT). CPT codes for conversion to open AAA repair are: 34830, 3481, and 34832, which respectively correspond to open AAA repair using tube, aortobiiliac, and aortobifemoral prostheses after unsuccessful EVAR. Since these same CPT codes are used for both acute and late conversions, we were unable to distinguish between conversions performed immediately after failed EVAR and those performed as late reinterventions.[28] Therefore, we considered our cohort to comprise of both acute and late conversions. The CPT codes for conversion also encompass the attempted EVAR in case of an acute conversion, which precluded us from determining whether the conversion was immediate or not based on the time between the EVAR and conversion. Standard EVAR (CPT: 34800, 34802, 34803, 34804, 34805), and non-ruptured open AAA repair (CPT: 35081, 35102) patients were also included for comparison. Cases with a postoperative diagnosis indicating the treatment of a ruptured aneurysm, as defined by the International Classification of Diseases – 9th revision (ICD-9), were excluded (ICD-9: 441.3).

Conversion patients were compared to open repair and EVAR patients on baseline and intraoperative characteristics, as well as 30-day postoperative outcomes. Age was considered both as a categorical variable, and as a continuous variable, with 90+ coded as 90 to prevent individual patient identification. Body mass index (BMI) was calculated using height and weight data (kg/m2). Postoperative outcomes included 30-day mortality and morbidity including acute kidney injury, respiratory complications, wound complications, myocardial infarction, sepsis, septic shock, and return to the operating room. Acute kidney injury was defined as a rise in creatinine of >2 mg/dl from preoperative value, and/or requirement of hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration, or ultrafiltra-

tion within 30 days of the operation. A respiratory complication was defined as prolonged ventilator dependence (>48 hours), reintubation, or a postoperative pneumonia. Wound complications included superficial, deep, and organ space infections. Patients with systemic inflammatory response syndrome (SIRS), sepsis, or septic shock prior to surgery were not considered for postoperative sepsis and septic shock analysis. Additional anatomical characteristics assessed in the subanalysis among patients captured in the Targeted Vascular data set were aneurysm diameter, and distal aneurysm extent. In order to identify differences in postoperative morbidity aside from death, 30-day mortality was not included in the any complication measure.

Statistical analyses

Categorical variables are presented as counts and percentages. Normally distributed continuous variables are presented as mean ± standard deviation and non-parametric distributions as median and interquartile range. Differences between treatment groups were assessed using χ^2 and Fisher's exact testing for categorical variables and Student's t-test, and Mann Whitney U test for continuous variables, where appropriate. Trend analyses were performed with the Cochran-Armitage test for trend. Independent associations between conversion and adverse postoperative outcomes were established using multivariable logistic regression analysis. Baseline characteristics were univariately tested, and variables with a P-value ≤ .1 were subsequently entered into the multivariable model. Separate models were constructed for 30-day mortality, acute kidney injury, and the occurrence of any complication. To identify factors associated with conversion, differences in demographics, comorbidities, and aneurysm diameter were assessed using logistic regression analysis. Similar to the outcomes analysis, variables with a P-value ≤ .1 were added to the multivariable model. To avoid over-fitting in the subanalysis among patients captured in the Targeted Vascular data set (N=4555), a separate model was constructed. All tests were two-sided and significance was considered when P-value <0.05. Statistical analysis was performed using the SPSS Statistics 21 (IBM Inc., Chicago, IL).

RESULTS

A total of 32,164 patients were included, with 300 patients who underwent a conversion to open repair, 7188 open repairs, and 24,676 EVARs. During the study period, the conversion rate was 1.2 per 100 EVAR cases (range: 0.8 – 1.5), with no apparent upward or downward trend over time (P=0.836).

Baseline characteristics

Baseline characteristics are listed in Table 1. Compared to open repair patients, those undergoing a conversion were older (72.6 vs. 70.5, P<.001), but were comparable in terms of gender (P=.801), and race (P=.072). Similarly, no differences were found in comorbidities. However, those undergoing a conversion were less frequently current smokers than standard open repair patients (32.7% vs. 43.8%, P<.001), and were more often classified as a class 4 or greater on the American Association of Anesthesiologists (ASA) physical status classification system (37.1% vs. 29.3%, P=.004).

When comparing the conversions to EVAR patients, we found that those undergoing conversion were younger (72.6 vs. 74.0 years, P=006), more often female (25.8% vs. 18.6%, P=.002), and more frequently of non-white race (12.0% vs. 6.8%%, P=.002). In addition, the conversion patients were less likely to have diabetes (11.0% vs. 15.7%, P=.026) or obesity (24.6% vs. 31.4%, P=.012). Also, conversion patients more often had a ASA class of 4 or greater (37.1% vs. 22.6%, P<.001).

Intraoperative differences

Operative details are listed in Table 2. Conversion was associated with a significantly longer operative time compared to standard open repair (275 min. vs. 232 min, P<.001). In addition, conversion cases were more often classified as emergent compared to standard open repairs (10.0% vs. 6.4%, P=.013), and EVARs (3.9%, P<.001). There was no difference in proportion of cases performed by vascular surgeons with the vast majority for conversions and standard open repairs (96.3% vs. 96.1%, P=.832), as well as EVARs (96.5%, P=.892) being performed by this specialty.

Table 1. Baseline characteristics

	Conversion	Open repair	EVAR	P-value	
	N=300	*N=7188*	*N=24,676*	*Conversion vs. OR*	*Conversion vs. EVAR*
Age – years (sd)	72.6 (9.3)	70.5 (9.1)	74.0 (8.8)	<.001	.006
Categories – N (%)				<.001	.003
<59 years	30 (10.0)	795 (11.1)	1363 (5.5)		
60-69	75 (25.0)	2333 (32.5)	6126 (24.8)		
70-79	118 (39.3)	2888 (40.2)	9986 (40.5)		
80-89	76 (25.3)	1133 (15.8)	6618 (26.8)		
90+	1 (0.3)	39 (0.5)	583 (2.4)		
Female gender – N (%)	77 (25.8)	1896 (26.4)	4587 (18.6)	.801	.002
Race				.001	.001
White	239 (79.7)	5957 (82.9)	20920 (84.8)	.072	.002
Non-white	36 (12.0)	593 (8.2)	1683 (6.8)		
Unknown	25 (8.3)	638 (8.9)	2073 (8.4)		
Comorbidities					
Hypertension – N (%)	250 (83.3)	5865 (81.6)	19752 (80.0)	.446	.156
Diabetes – N (%)	33 (11.0)	910 (12.7)	3872 (15.7)	.396	.026
Insulin dependent diabetes – N (%)	4 (1.3)	179 (2.5)	785 (3.2)	.204	.068
COPD – N (%)	49 (16.3)	1386 (19.3)	4707 (19.1)	.204	.229
eGFR - ml/min/1.73m2	69.9 (25.8)	72.0 (26.6)	71.7 (27.2)	.179	.255
Heart failure – N (%)	2 (0.7)	79 (1.1)	392 (1.6)	.478	.343
Dialysis– N (%)	5 (1.7)	63 (0.9)	292 (1.2)	.157	.443
BMI >30 – N (%)	72 (24.6)	1942 (27.6)	7622 (31.4)	.260	.012
Current smoking – N (%)	98 (32.7)	3146 (43.8)	7498 (30.4)	<.001	.393
ASA class > III – N (%)	111 (37.1)	2103 (29.3)	5567 (22.6)	.004	<.001

Table 2. Intraoperative characteristics

	Conversion	Open repair	EVAR	P-value	
	N=300	*N=7188*	*N=24,676*	*Conversion vs. OR*	*Conversion vs. EVAR*
Operative time – min (± sd)	275 (124)	232 (99)	152 (75)	<.001	<.001
Anesthesia type – N (%)				.814	<.001
General	296 (98.7)	7100 (98.8)	21493 (87.1)		
Regional, other	4 (1.3)	85 (1.2)	3181 (12.9)		
Emergency procedure – N (%)	30 (10.0)	459 (6.4)	964 (3.9)	.013	<.001
Surgeon specialty – N (%)				.832	.892
Vascular surgeon	289 (96.3)	6907 (96.1)	23807 (96.5)		
Other	11 (3.7)	281 (3.9)	869 (3.5)		

Table 3. Postoperative outcomes

	Conversion	Open repair	EVAR	P-value	
	N=300	*N=7188*	*N=24,676*	*Conversion vs. OR*	*Conversion vs. EVAR*
30-day mortality – N (%)[α]	30 (10.0)	299 (4.2)	415 (1.7)	<.001	<.001
Creat rise >2 mg/dl – N (%)[β]	*22 (7.3)*	400 (5.6)	334 (1.4)	.194	<.001
Requiring dialysis – N (%)	*18 (6.0)*	253 (3.5)	215 (0.9)	.024	<.001
Respiratory complication	49 (16.3)	1018 (14.2)	549 (2.2)	.292	<.001
Pneumonia – N (%)	*29 (9.7)*	559 (7.8)	342 (1.4)	.233	<.001
>48 hour on ventilator	*41 (13.7)*	772 (10.7)	338 (1.4)	.110	<.001
Reintubation – N (%)	*22 (7.3)*	500 (7.0)	384 (1.6)	.801	<.001
Cardiac complication	*26 (8.7)*	271 (3.8)	340 (1.4)	<.001	<.001
Myocardial infarction – N (%)	*15 (5.0)*	156 (2.2)	232 (0.9)	.001	<.001
CPR – N (%)	*16 (5.3)*	133 (1.9)	128 (0.5)	<.001	<.001
Wound complication	*14 (4.7)*	319 (4.4)	577 (2.3)	.851	.008
Wound infection – N (%)	*11 (3.7)*	239 (3.3)	530 (2.1)	.747	.072
Wound dehiscence – N (%)	*3 (1.0)*	103 (1.4)	64 (0.3)	.801	.047
Return to OR – N (%)	*28 (9.3)*	639 (8.9)	1114 (4.5)	.792	<.001
Pulmonary embolism – N (%)	2 (0.7)	39 (0.5)	53 (0.2)	.680	.141
Stroke – N (%)	*3 (1.0)*	55 (0.8)	106 (0.4)	.505	.144
Sepsis – N (%)	*13 (4.3)*	263 (3.7)	195 (0.8)	.544	<.001
Septic shock – N (%)	*11 (3.7)*	258 (3.6)	152 (0.6)	.944	<.001
Graft failure – N (%)	*3 (1.0)*	39 (0.5)	132 (0.5)	.236	.221
≥1 postoperative transfusion	127 (42.3)	2270 (31.6)	1795 (7.3)	<.001	<.001
Any complication – N (%)[γ]	174 (58.0)	3375 (47.0)	3756 (15.2)	<.001	<.001
Any complication – N (%)[δ]	95 (31.7)	1912 (26.6)	2485 (10.1)	.052	<.001
Mean length of stay – days (sd)	10.7 (11.2)	9.8 (9.3)	3.3 (5.4)	.165	<.001
Median length of stay – days (IQR)	8 (5-11)	7 (5-11)	2 (1-3)`	.371	<.001

α Odds ratio conversion vs. open repair: 2.4 (95% CI: 1.6 – 3.6); Odds ratio conversion vs. EVAR: 7.2 (95% CI: 4.8 – 10.9) (adjusted for: age, gender, race, hypertension, insulin dependent diabetes, obstructive pulmonary disease, heart failure, estimated GFR <30 ml/min/1.73m2, preoperative dialysis, and obesity (BMI>30), emergency procedure)
β Odds ratio conversion vs. open repair: 1.3 (95% CI: 0.8 – 2.0), Odds ratio conversion vs. EVAR: 5.6 (95% CI: 3.5 – 8.9) (adjusted for: age, gender, race, hypertension, insulin dependent diabetes, obstructive pulmonary disease, heart failure, estimated GFR <30 ml/min/1.73m2, and current smoking, emergency procedure)
γ Odds ratio conversion vs. open repair: 1.5 (95% CI: 1.2 – 1.9), Odds ratio conversion vs. EVAR: 7.8 (95% CI: 6.1 – 9.9) (adjusted for: age, gender, race, hypertension, insulin dependent diabetes, obstructive pulmonary disease, heart failure, estimated GFR <30 ml/min/1.73m2, preoperative dialysis, obesity (BMI>30), and current smoking, emergency procedure)
δ incidence of any complication excluding postoperative blood transfusion

Postoperative outcomes

Compared to standard open repair, 30-day mortality following a conversion was significantly higher (10.0% vs. 4.2%, P<.001, Table 3). In addition, conversion patients were more likely to undergo new dialysis (6.0% vs. 3.5%, P=.024), cardiopulmonary resuscitation (5.3% vs. 1.9%, P<.001), postoperative blood transfusion (42.3% vs. 31.6%, P<.001), and have a myocardial infarction (5.0% vs. 2.2%, P=.001).

When comparing conversion patients to those undergoing EVAR, we found that 30-day mortality after a conversion was substantially higher (10.0% vs. 1.7%, P<.001). Similarly, conversion to open repair was associated with a higher rate of various adverse events, including acute kidney injury (7.3% vs. 1.4%, P<.001), respiratory complications (16.3% vs. 2.2%, P<.001), cardiac complications (8.7% vs. 1.4%, P<.001), wound complications (4.7% vs. 2.3%, P=.008), return to the operating room (9.3% vs. 4.5%, P<.001), and postoperative septic shock (3.7% vs. 0.6%, P<.001).

After adjustment for potential confounders, conversion to open repair proved to be associated with almost two-and-a-half times higher mortality risk compared to standard open repair (OR: 2.4, 95% CI: 1.6 – 3.6). Conversion surgery was additionally associated with increased risks for the occurrence of any complication (OR: 1.5, 95% CI: 1.2 – 1.9). Compared to EVAR, conversion to open repair was an independent predictor of 30-day mortality (OR: 7.2, 95% CI: 4.8 – 10.9), acute kidney injury (OR: 5.6, 95% CI: 3.5 – 8.9), and any complication (OR: 7.8, 95% CI: 6.1 – 9.9).

Factors associated with conversion

For multivariable analysis, demographics, comorbidities, and aneurysm diameter were considered. In the overall cohort, young age (OR: 1.2 per 10 years decrease,

95% CI: 1.1 – 1.4, Table 4), female gender (OR: 1.5, 95% CI: 1.2 – 2.0), and non-white race (OR: 1.8, 95% CI: 1.3 – 2.6) were associated with conversion. Conversely, BMI over 30 had a negative association with conversion (OR: 0.7, 95% CI: 0.5 – 0.9). For patients captured in the more detailed Targeted Vascular module (N=50 and N=4505, respectively for conversion and EVAR cases), additional subanalysis was performed. Among these patients, large diameter was strongly associated with conversion (mean diameter: 6.8cm vs. 5.7cm, P=.001; OR: 1.1 per 1 cm increase, 95% CI: 1.03 – 1.1).

Table 4. Factors associated with conversion

Overall cohort	***OR***	***95% CI***	***P-value***
Age (per 10 year decrease)	1.2	1.1 – 1.4	.001
Female gender	1.5	1.2 – 2.0	.002
Race			
non-white	1.8	1.3 – 2.6	.001
unknown	1.1	0.8 – 1.7	.531
Diabetes	0.7	0.5 – 1.0	.074
BMI >30	0.7	0.5 – 0.9	.008
Targeted Variables[α]			
Aneurysm diameter	1.1	1.0 – 1.1	0.002

α subanalysis of patients captured in the Targeted NSQIP (N=50 and N=4505, respectively for conversion and EVAR cases)

DISCUSSION

This study demonstrates that conversion to open repair is independently associated with an increased risk of mortality and other adverse outcomes during the postoperative period compared to standard open repair. In addition to almost a two-and-a-half fold increase in perioperative mortality, patients undergoing a conversion more often suffered adverse events, such as myocardial infarction, acute kidney injury requiring dialysis, need for CPR, and postoperative blood transfusion. Multivariable analysis showed that younger age, female gender, and non-white race were associated with conversion surgery, while obesity was inversely related to conversion. Inclusion of targeted module variables established that aneurysm diameter is also an important determinant of conversion.

The first study assessing the outcome following a conversion from endovascular to open repair was published in 1997.[20] With an incidence of almost 16% (11.5% acute, 4.5% late), the conversion rate was substantially higher than the 1.2% in the present study. The reduction is most likely the result of improved

patient selection and surgeon experience, as well as technical advances in endovascular repair allowing for patients with more challenging anatomy to be successfully treated using endovascular treatment modalities. This is supported by a decline in conversion rates in more recent reports.[12, 13] In the 1997 study by Jacobowitz et al., the perioperative mortality following conversion –acute or chronic– was 17%. Mortality rates in subsequent studies have ranged between 0% and 28.5%. This variability is likely the result of the small sample sizes of these single-center studies.[13, 16, 24, 29] A pooled data-analysis by Moulakakis et al. determined the perioperative mortality to be 12% and 10%, respectively for acute and late conversion. This is comparable to the 10% found in our study. Considering that this is over twice the norm for standard open AAA repair, our results –not surprisingly– showed that conversion surgery was associated with a significantly increased perioperative mortality risk compared to open repair, as well as EVAR. However, in the largest reported conversion cohort to date, which was obtained from the same database as the present study and included the same patients for the years 2005 to 2008, Newton et al. found no difference in mortality between conversion patients and those undergoing standard open AAA repair (4.2% vs. 3.2%, respectively). This difference in outcome appears to be result of a higher perioperative mortality following conversion to open repair in the later years of the past decade in this database. In the study by Newton et al., the mortality rate of 4.2% in a cohort of 72 patients corresponds to only 3 deaths in the perioperative period. Considering the consequent susceptibility to sample variability, the discrepancy with the present study may simply be the result of an increase in sample size. This highlights the value of reexamination when more data are available. An actual increase in mortality over time may be caused by an increase in the proportion of suprarenal bare-metal stents being explanted due to the rise in utilization of these stents in more recent years.

In regards to factors associated with conversion, some studies found no relation between patient factors and conversion to open repair.[14, 25] However, in the Lifeline registry, which described both acute and late conversions, it was found that female gender was strongly associated with conversion, in addition to large aneurysm diameter.[7] Both of these factors were also associated with conversion in the present study. The relation between gender and conversion in the Lifeline registry was in large part driven by acute conversion rates, which fits with studies showing higher intraoperative complication rates among woman during EVAR –particularly access-related– due to complex anatomy and smaller artery diameters.[30-32] However, subsequent studies have also determined female gender to be a predictor of late conversion,[29] which may also be the result of more complex aneurysm anatomy in females, as well as more late complications

requiring reintervention, such as graft thrombosis.[33, 34] The positive correlation between diameter and conversion risk may also be different for acute and late conversions. For acute conversions the correlation is likely to represent the technical difficulty of establishing adequate seal in patients with large diameter aneurysms, while the larger diameter observed in late conversion patients is more likely the result of sac growth, which has prompted the decision for conversion to open repair. Cuypers et al. reported that low body weight was associated with higher conversion rates in a cohort consisting of both acute and late conversions.[35] In the present study, we also found an inverse association between BMI and conversion. This may be related to a greater comorbidity burden and technical difficulty in obese patients with consequent higher complication rates. Cuypers et al. additionally showed that advanced age was a risk factor for conversion. In our study, however, young age was associated with an increased likelihood of conversion. The correlation with young age could suggest that our cohort consisted more of patients undergoing late conversions, as younger patients will live long enough to benefit from conversion surgery. The difference with the study by Cuypers et al. may therefore be related to the proportion of acute versus late conversions in each cohort. Similar to the explanation for the correlation between BMI and conversion, the association with young age may also be mediated by the fact that younger patients are more often deemed healthy enough to undergo conversion surgery compared to older patients.

This study has several limitations that should be addressed. First, since the data for this study were gathered through a prospective data registry, the potential exists for underreporting of events. Second, as the American Medical Association recommends the CPT coding for conversion to be used for acute and late conversions,[28] we assumed our cohort to consist of both. Unfortunately, we were unable to differentiate between conversions performed immediately and those performed as a late reintervention. However, multicenter studies, as well as meta-analysis have shown the perioperative outcomes to be similar between these two groups.[11, 15] Third, previous studies have demonstrated that some older stent grafts are associated with graft migration, and other untoward events during follow-up. Since these grafts are no longer used, it should be noted that the possible inclusion of these grafts in the present study may have affected our results on the current conversion rate, as well as the factors associated with conversion. Also, baseline characteristics of conversion patients were obtained at the time of the conversion procedure. A more appropriate comparison would have included age and comorbidity at the time of the original EVAR. Unfortunately, these data were not available. Additionally, conversion to open repair may be an indicator of complex anatomy and more severe comorbid-

ity. Despite adjustment for potential confounders in multivariable analysis, these factors may also have contributed to the poor outcome of conversion patients. In addition, the ACS NSQIP does not include long-term follow-up data, which precludes analysis on reintervention rates, late ruptures, and long-term survival. Finally, the anatomic-characteristics provided by the Targeted Vascular module were only available for a subset of our cohort. Consequently, we were unable to adjust for all the initially identified predictive factors in the subanalysis to avoid over-fitting the model. However, sensitivity analysis demonstrated that aneurysm diameter remained significant when adjusting for factors that were most predictive in the overall cohort (i.e. age, gender, non-white race, obesity).

In conclusion, this study demonstrated that conversion to open repair after failed EVAR is associated with substantially increased perioperative mortality, as well as a higher rate of complications such as myocardial infarction and need for dialysis. Multivariable analysis showed that in addition to large diameter of the aneurysm, young age, female gender, and non-white race are associated with conversion surgery, while obesity is inversely related to conversion.

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LONG-TERM PROGNOSIS AFTER VASCULAR SURGERY

Part IV

Chapter 15

Low Socioeconomic Status is an Independent Risk Factor for Survival after Abdominal Aortic Aneurysm Repair and Open Surgery for Peripheral Artery Disease

Klaas H.J. Ultee[1]
Frederico Bastos Gonçalves[1,2]
Sanne E. Hoeks[3]
Ellen V. Rouwet[1]
Eric Boersma[4]
Robert Jan Stolker[3]
Hence J.M. Verhagen[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, the Netherlands
2) Department of Angiology and Vascular Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
3) Department of Anaesthesiology, Erasmus University Medical Center, the Netherlands
4) Department of Cardiology, Thorax center, Erasmus University Medical Center, the Netherlands

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ABSTRACT

Objective

The association between socioeconomic status (SES), presentation and outcome after vascular surgery is largely unknown. This study aims to determine the influence of SES on postoperative survival and severity of disease at presentation among vascular surgery patients in the Dutch setting of equal access to and provision of care.

Methods

Patients undergoing surgical treatment for peripheral artery disease (PAD), abdominal aortic aneurysm (AAA) or carotid artery stenosis (CS) between January 2003 and December 2011 were retrospectively included. The association between SES, quantified by household income, disease severity at presentation and survival was studied using logistic and Cox regression analysis adjusted for demographics, medical and behavioral risk factors.

Results

A total of 1178 patients were included. Low income was associated with worse postoperative survival in the PAD cohort (n=324, HR: 1.05, 95% CI: 1.00 – 1.10, per 5,000 euro decrease) and AAA cohort (n=440, quadratic relation, p = .006). AAA patients in the lowest income quartile were more likely to present with a ruptured aneurysm (OR: 2.12 95% CI: 1.08 – 4.17). Lowest income quartile PAD patients presented more frequently with symptoms of critical limb ischemia, although no significant association could be established (OR: 2.02, 95% CI: 0.96 – 4.26).

Conclusions

The increased health hazards observed in this study are caused by patient related factors rather than differences in medical care, considering the equality of care provided by the study setting. Although the exact mechanism driving the association between SES and worse outcome remains elusive, consideration of SES as a risk factor in preoperative decision-making and focus on treatment of known SES-related behavioral and psychosocial risk factors may improve the outcome of patients with vascular disease.

INTRODUCTION

The association between socioeconomic deprivation and poor health in the general population is well documented. Low socioeconomic status (SES) also negatively impacts the prognosis of a variety of diseases, such as colon carcinoma and pulmonary disease, and treatment outcomes.[1, 2] A limited number of studies have demonstrated a similar association between low SES and poor outcome for vascular diseases, including stroke and critical limb ischemia, as well as for vascular surgery.[2-5]

Many of these studies have been performed in the United States, where SES-related disparity in access to and provision of healthcare exists and is extensively affected by income.[2, 6, 7] Consequently, the relationship between low SES and poor outcome is often ascribed to healthcare disparities.[5, 7, 8] Alternatively, since the prevalence of conventional cardiovascular risk factors and poor lifestyle is higher in socially deprived regions, the association between SES and outcome may be mediated through patient factors as well.[9] Due to healthcare inequality, the impact of SES-related patient factors on outcome remains largely undetermined.

Healthcare in the Netherlands is publicly provided and has been credited the most equally accessible healthcare system in the world.[10, 11] Therefore, minimal differences could be expected in access to and provision of care, including screening and access to medication, both in hospital and in primary care settings. Hence, as opposed to the US system, the Dutch healthcare system provides the opportunity to study the association between SES and outcome irrespective of healthcare disparities.

The objective of this study is to determine SES as a predictor for survival following surgical treatment for peripheral artery disease, abdominal aortic aneurysm and carotid artery stenosis. Additionally, we aim to assess whether SES is associated with severity of disease at presentation.

METHODS

Patients undergoing elective open or endovascular surgery under general or locoregional anesthesia for peripheral artery disease (PAD), abdominal aortic aneurysm (AAA) or carotid artery stenosis (CS) in the Erasmus University Medical Center between January 2003 and December 2011 were retrospectively included. Patients undergoing completely percutaneous procedures under local infiltration analgesia (i.e., carotid artery stenting, lower extremity angioplasty and/or stenting, or percutaneous EVAR) or open surgical procedures performed under local

infiltration analgesia were not included in this study. Identification was done using operation codes and surgical reports. When a patient underwent multiple vascular procedures within the study period, the first operation in this period was defined as the index operation and survival was assessed from that moment onward. Baseline characteristics were obtained from the medical records and included age at index operation, gender, comorbidities, prior vascular interventions, smoking status (current, former or never), and body mass index (BMI). Patients without registered and/or obtainable household income (e.g. due to illegal residency) were excluded. Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

Definitions

Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral anti-diabetics. Hypertension was defined as blood pressure >140/90 mmHg or use of anti-hypertensive medication, and a history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Further, severity of PAD at presentation was classified as claudication or critical limb ischemia (Fontaine stages III and IV), and smoking alludes to all active and former smokers. Cerebrovascular disease was defined as mentioning of symptomatic cerebrovascular disease (i.e., transient ischemic attack (TIA) or stroke) and/or a carotid endarterectomy or stenting procedure in the medical history. Ischemic heart disease was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention or evidence of myocardial ischemia in provocative pre-operative tests (dobutamine stress echocardiography or myocardial scintigraphy). Finally, prior vascular interventions were defined as either surgical or percutaneous vascular treatment prior to the index operation, not including coronary revascularization.

Follow-up

Survival status was obtained by inquiry of the civil registry. The latest date of follow up was considered December 31st 2012.

Socioeconomic status

Income is one of the most widely accepted and used methods to quantify SES and was found to provide a superior reflection of SES-related health disparities compared to other approaches such as educational status.[12-14] The income data used for this study was the gross household income earned in 2003, which included

every form of income of all people sharing a household or place of residence combined. The household income was not adjusted for household size. However, it has been demonstrated that adjustment for number of members in a household does not improve predictability of the associated health disparities.[13] Incomes were assigned percentiles and quartiles in accordance with the national income distributions, with the first quartile being the lowest income group and the fourth quartile including households with the highest incomes. The annual earnings were obtained by inquiry of the Dutch Central Bureau of Statistics (CBS) – study ID: 7465. To obtain information on SES, a database consisting of medical data on all study participants was anonymized by authorized data managers employed by CBS and matched to the household income dataset maintained by this entity. Income data is documented on an individual and household basis. According to Dutch privacy legislation, data analysis was only allowed to authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for publication purposes.

Endpoints

The primary endpoint was overall postoperative mortality. Secondary endpoints were severity of disease at presentation for AAA patients (i.e. rupture vs. non-rupture) and PAD patients (i.e. critical limb ischemia vs. claudication). Severity of disease at presentation was not studied among CS patients, because carotid revascularization in asymptomatic patients is only rarely performed in our hospital in accordance with clinical guidelines.[15]

Statistical methods

Income percentiles corresponding to the national gross income distribution were separated in quartiles. To clarify, first income quartile patients included members of a household with an annual salary that corresponds to 0-25% gross household incomes of the Dutch population. Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Income is presented as median and interquartile ranges, because of the skewness of the data distribution. Differences between quartiles at baseline were determined using Pearson's chi-square analysis and ANOVA, where appropriate.

Cox regression analyses were used to assess the predictive value of income for survival following treatment. The multivariate analyses were performed in two stages: in the first stage the model was adjusted for demographics only (age and gender), whereas in the second stage the full model included comorbidities and

behavioral risk factors (diabetes, cancer, ischemic heart disease, hypertension, smoking status, and BMI). In order to determine the type of association between income and postoperative survival, analyses were done both continuously, by hazard ratio per 5,000 euro decrease in gross household income, and categorical, by hazard ratio of the individual income quartiles compared to the fourth quartile (75-100%). Exponential properties in the relation between annual earnings and outcome were tested by including the quadratic term of household income in the regression model.

To investigate the relationship between income and severity of disease, odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression analyses. Similar to the primary endpoint, multivariate analyses for the secondary objective were done using a two-stage method. Covariates included in the multivariable model were identical to the Cox proportional hazards model. Ruptured AAA cases were only included in univariate and step 1 multivariate analyses for severity of disease at presentation, due to the number of missing values at baseline. Both regression models were tested for interactions. All tests were two-sided and significance was considered when p-value < .05. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL, USA).

RESULTS

A total number of 1260 patients underwent surgical treatment for AAA, CS or PAD between January 2003 and December 2011. The inquiry yielded the income of 1178 patients (93.5%): 577 with AAA, 277 with CS, and 324 with PAD. The cohort consisted of 915 men (78%) and 263 women (22%). The median gross household income was 30 889 euro annually (IQR: 21 779 – 51 620). The overall 5-year survival was 69% with a median follow-up time of 3.84 years (excluding patients treated for rAAA).

Baseline characteristics

Patients in the first and second income quartiles were older compared to the higher two quartiles ($p \leq .001$, Table 1a, b, c). Additionally, BMI differed across the income quartiles in the PAD cohort ($p = .014$), although no clear pattern was observed. In the AAA cohort, patients in the first quartile were more frequently female as compared to the higher three quartiles (22% vs. 11%, 9%, 9%, $p = .020$, Table 1b). Further, the third income quartile AAA patients more often suffered from PAD (28% vs. 15%, 14, 16%, $p = .030$). No additional differences were found in the PAD and CS cohorts at baseline (Tables 1a and 1c).

Table 1a. Descriptive statistics PAD cohort (N=324)

Variable	***Baseline Characteristics***				
Quartiles	**1** (n=95)	**2** (n=99)	**3** (n=75)	**4** (n=55)	**P-value**
Socioeconomic Status					
Median gross household income (median, €)	15 873	28 286	50 243	79 746	-
Demographics					
Female gender – N (%)	42 (44.2)	28 (28.3)	24 (32.0)	16 (29.1)	.086
Age (years, mean ± SD)	67.0 ± 11.2	63.9 ± 12.3	60.8 ± 9.9	61.2 ± 8.0	.001
Cardiovascular risk factors					
Diabetes mellitus – N (%)	35 (36.8)	27 (27.3)	27 (36.0)	11 (20.0)	.104
Hypertension – N (%)	65 (69.1)	64 (64.6)	55 (74.3)	37 (67.3)	.593
Smoking – N (%)	85 (90.4)	86 (86.9)	66 (88.0)	48 (87.3)	.881
Body Mass Index– (kg/length^2, mean ± SD)	25.4 ± 5.4	25.0 ± 3.8	27.2 ± 4.1	25.9 ± 4.9	.014
Comorbidities					
History of cancer – N (%)	18 (19.1)	15 (15.2)	14 (18.7)	2 (3.7)	.061
Ischemic heart disease– N (%)	47 (49.5)	47 (47.5)	29 (38.7)	22 (40.0)	.427
Peripheral artery disease – N (%)	95 (100)	99 (100)	75 (100)	55 (100)	-
Cerebrovascular disease – N (%)	19 (20.0)	16 (16.2)	10 (13.3)	5 (9.1)	.320
History of vascular interventions – N (%)	43 (45.7)	48 (48.5)	34 (45.3)	30 (54.5)	.715
Severity of symptoms at presentation					
Critical limb ischemia – N (%)*	61 (67.0)	51 (53.1)	40 (54.8)	26 (47.3)	.088

* 9 patients (3%) with missing disease severity data

Table 1b. Descriptive statistics intact AAA cohort (N=440)

Variable	***Baseline Characteristics***				
Quartiles	**1** (n=86)	**2** (n=188)	**3** (n=92)	**4** (n=74)	**P-value**
Socioeconomic Status					
Median gross household income (median, €)	17 452	28 041	46 201	82 765	-
Demographics					
Female gender – N (%)	19 (22.1)	20 (10.6)	8 (8.7)	7 (9.5)	.020
Age (years, mean ± SD)	74.4 ± 6.7	74.3 ± 5.9	67.5 ± 7.9	68.2 ± 7.0	< .001
Cardiovascular risk factors					
Diabetes mellitus – N (%)	16 (18.8)	26 (13.8)	20 (21.7)	10 (13.5)	.304
Hypertension – N (%)	53 (61.6)	133 (70.7)	66 (71.7)	50 (67.5)	.423
Smoking – N (%)	69 (80.2)	150 (81.5)	76 (83.5)	59 (79.7)	.922
Body Mass Index– (kg/length^2, mean ± SD)	25.3 ± 4.4	26.2 ± 4.1	26.5 ± 4.2	26.3 ± 3.8	.266
Comorbidities					
History of cancer – N (%)	17 (19.8)	49 (26.1)	13 (14.1)	15 (20.3)	.137
Ischemic heart disease– N (%)	41 (47.7)	92 (48.9)	34 (37.0)	38 (51.4)	.207
Peripheral artery disease – N (%)	13 (15.1)	27 (14.4)	26 (28.3)	12 (16.2)	.030
Cerebrovascular disease – N (%)	21 (24.4)	37 (19.7)	18 (19.6)	10 (13.5)	.390
History of vascular interventions – N (%)	9 (10.5)	24 (12.8)	10 (10.9)	8 (10.8)	.930

Table 1c. Descriptive statistics CS cohort (N=277)

Variable	***Baseline Characteristics***				
Quartiles	**1** (n=63)	**2** (n=96)	**3** (n=71)	**4** (n=47)	**P-value**
Socioeconomic Status					
Median gross household income (median, €)	17 886	26 116	46 371	83 308	-
Demographics					
Female gender – N (%)	23 (36.5)	32 (33.3)	20 (28.2)	9 (19.1)	.214
Age (years, mean ± SD)	71.8 ± 9.3	72.2 ± 8.5	64.9 ± 9.5	63.7 ± 8.2	< .001
Cardiovascular risk factors					
Diabetes mellitus – N (%)	13 (20.6)	21 (21.9)	16 (22.5)	11 (23.4)	.987
Hypertension – N (%)	42 (66.7)	67 (69.8)	46 (64.8)	35 (74.5)	.705
Smoking – N (%)	50 (80.6)	73 (76.0)	59 (84.3)	44 (93.6)	.073
Body Mass Index– (kg/length^2, mean ± SD)	26.6 ± 4.1	26.4 ± 4.1	26.2 ± 3.6	26.2 ± 2.8	.935
Comorbidities					
History of cancer – N (%)	11 (17.7)	11 (11.7)	8 (11.3)	6 (12.8)	.672
Ischemic heart disease– N (%)	26 (41.3)	44 (45.8)	22 (31.0)	15 (31.9)	.177
Peripheral artery disease – N (%)	5 (7.9)	17 (17.7)	15 (21.1)	6 (12.8)	.166
Cerebrovascular disease – N (%)	63 (100)	96 (100)	71 (100)	47 (100)	-
History of vascular interventions – N (%)	6 (9.5)	10 (10.4)	10 (14.1)	6 (12.8)	.828

Peripheral artery disease

Surgical revascularization for limb ischemia was performed in 324 patients. During a median follow-up of 3.60 years, 96 deaths occurred with a 5-year survival rate of 69% (Table 2). The median income among the PAD patients was 33 248 euro (IQR: 19 802 – 55 353). With income as a continuous variable, adjusted analysis proved that low income was significantly associated with worse survival (step 2 HR: 1.05, 95% CI: 1.00 – 1.10, per 5,000 euro decrease, Table 3). Regarding the hazard expressed per income quartile, a similar linear relation with increasing hazard as income decreased was observed in the first two quartiles compared to the fourth quartile (step 2 HR: 3.05, 95% CI: 1.25 – 7.44 and HR: 2.50, 95% CI: 1.03 – 6.07, for the first and second quartiles, respectively), while no significant association was found for the third quartile (HR: 2.47, 95% CI: .98 – 6.24, p = .056).

In terms of disease severity, patients in the first income quartile presented more often with critical limb ischemia, although no significant association could be established in step 2 multivariable analysis (OR: 2.02, 95% CI: .96 – 4.26, p = .064, Table 4).

Table 2. Follow-up of the study cohort (N=1041, excluding rAAA patients)

Indication	*Death (%)*	*5-year survival (*±SE)	*Median follow-up (years, IQR)*
PAD	96 (27.2)	69.2% (± 3.0)	3.60 (1.90 – 5.60)
AAA	159 (36.1)	62.1% (± 2.8)	3.17 (1.75 – 5.17)
CS	64 (23.1)	78.8% (± 2.7)	4.77 (3.39 – 6.04)

Abdominal aortic aneurysm

Of the 577 included AAA patients, 440 (76%) received treatment for non-ruptured AAA. During a median follow-up of 3.17 years, 159 patients died, which resulted in a 5-year survival of 62% among elective AAA patients. The median income was 31 232 euro (IQR: 22 653 – 51 230). In multivariate quartile analyses, low income was not significantly associated with worse survival following AAA repair. With income as a continuous variable, however, there was an exponential increase in mortality hazard associated with a decrease in income (p = .006). The quadratic relation implies that the negative effect on survival for which low SES is responsible, is more severe in the lowest percentiles and diminishes exponentially as income increases. This indicates that only survival of non-ruptured AAA patients in the lowest income regions within the first quartile is affected by low SES.

Table 3. The association between income and survival (hazard ratio per quartile, relative to the fourth quartile [75-100%])

	Continuous	*Quartile 1*	*Quartile 2*	*Quartile 3*	*Quartile 4*
PAD					
Deaths – N (%)		38 (40)	32 (32)	20 (27)	6 (11)
Univariate	1.08 (1.03 – 1.13)	4.74 (2.00 – 11.22)	3.29 (1.38 – 7.87)	3.01 (1.21 – 7.50)	-
Multivariate step 1	1.06 (1.01 – 1.11)	3.89 (1.62 – 9.33)	3.05 (1.27 – 7.32)	3.23 (1.30 – 8.07)	-
Multivariate step 2	1.05 (1.00 – 1.10)	3.05 (1.25 – 7.44)	2.50 (1.03 – 6.07)	2.47 (0.98 – 6.24)	-
AAA					
Deaths – N (%)		41 (48)	76 (40)	26 (28)	16 (22)
Univariate	Quadratic (P<0.001)	2.07 (1.16 – 3.69)	1.76 (1.03 – 3.02)	1.14 (0.61 – 2.12)	-
Multivariate step 1	Quadratic (P=0.001)	1.56 (0.86 – 2.85)	1.32 (0.76 – 2.29)	1.15 (0.62 – 2.14)	-
Multivariate step 2	Quadratic (P=0.006)	1.50 (0.80 – 2.81)	1.33 (0.75 – 2.38)	1.34 (0.71 – 2.55)	-
CS					
Deaths – N (%)		17 (27)	24 (25)	15 (21)	8 (17)
Univariate	1.03 (0.98 – 1.09)	1.39 (0.60 – 3.23)	1.31 (0.59 – 2.91)	1.03 (0.44 – 2.43)	-
Multivariate step 1	1.02 (0.96 – 1.07)	1.06 (0.44 – 2.58)	0.97 (0.42 – 2.25)	0.97 (0.41 – 2.30)	-
Multivariate step 2	1.02 (0.96 – 1.07)	1.02 (0.41 – 2.50)	1.00 (0.43 – 2.33)	1.05 (0.44 – 2.49)	-

Regarding the relationship between income and severity of disease at presentation, low household income was associated with more severe presentation. After adjusting for demographics, patients in the first quartile were more likely to present with a ruptured aneurysm as compared to those in the fourth quartile (OR: 2.12 95% CI: 1.08 – 4.17). The second step multivariate analysis was not performed because of the missing baseline characteristics in the rAAA group.

Carotid artery stenosis

The median follow-up period of the 277 patients who underwent a carotid endarterectomy was 4.77 years, during which 64 patients died, resulting in a 5-year survival of 79%. The median income was 31 796 euro (IQR: 22 054 – 51 604). Low income was not associated with worse survival. Severity of disease at presentation was not studied, since carotid revascularization is only rarely performed in asymptomatic patients in the Netherlands, according to clinical guidelines.[15]

Table 4. The association between income and the severity of symptoms at presentation (Odds ratio per quartile, relative to the fourth quartile [75-100%])

	Quartile 1	*Quartile 2*	*Quartile 3*	*Quartile 4*
PAD				
CLI – N (%)	61 (67)	51 (53)	40 (55)	26 (47)
Univariate	2.27 (1.14 – 4.51)	1.26 (0.65 – 2.46)	1.35 (.67 – 2.73)	-
Multivariate step 1	2.00 (0.99 – 4.02)	1.18 (0.60 – 2.31)	1.38 (0.68 – 2.79)	-
Multivariate step 2	2.02 (0.96 – 4.26)	1.16 (0.58 – 2.34)	1.28 (0.61 – 2.70)	-
AAA				Reference
Ruptures – N (%)	40 (32)	55 (23)	25 (21)	17 (19)
Univariate	2.03 (1.06 – 3.87)	1.27 (0.69 – 2.34)	1.18 (0.60 – 2.35)	-
Multivariate step 1	2.12 (1.08 – 4.17)	1.30 (0.69 – 2.47)	1.18 (0.59 – 2.35)	-

Legend: CLI: critical limb ischemia (Fontaine stage III, IV)

DISCUSSION

Previous reports of socioeconomic deprivation and its association with cardiovascular disease (CVD) have demonstrated increased lifetime cumulative risks of acute myocardial infarction, stroke, heart failure, coronary death, and PAD in deprived subjects.[16] The current study demonstrates that, in addition to increased risk of a range of CVD presentations, socioeconomic status –as determined by income– also negatively impacts survival after vascular surgery.

The different income quartiles, as defined by the national income distribution, were –by approximation– equally represented in our cohort, indicating that this patient group is a good reflection of the national socioeconomic situation. Low SES was associated with worse postoperative survival among PAD and AAA patients, even after adjusting for demographics, conventional cardiovascular risk factors, and comorbidities. The relation between low SES and poor outcome was strongest in patients who underwent surgical revascularization for PAD. Patients in the lowest income quartile were 3 times more likely to die after surgery as compared to those in the highest income group. Although the exact reasons are unclear, the importance of SES for especially PAD patients has been demonstrated in previous studies.[16] In AAA patients a similar relation was present, albeit only in patients with the lowest income. Although it has been reported that SES affects mortality after stroke,[17] we found no association between mortality

hazard and gross household income in patients undergoing carotid endarterectomy for symptomatic CS.

The present data underlines the importance of socioeconomic deprivation as a risk factor for the prognosis of people with established cardiovascular disease (CVD). But which factors drive the relationship between low SES and poor health? Studies conducted in the US showed a clear link between income, insurance status and outcome. For example, uninsured patients were 4 times more likely to die following AAA repair.[8, 18, 19] Discrepancies in mortality hazards associated with insurance status and low SES are generally attributed to poor access to and/or low quality of healthcare. However, the present study was conducted in the Dutch setting with equal access to and quality of healthcare, irrespective of income.[10] Hence, the association between income and postoperative survival that was demonstrated in our study cannot be attributed to inequality in healthcare resources. In addition, low income as a predictor of poor outcome was found to be independent of conventional cardiovascular risk factors, such as age, smoking status, diabetes, and obesity, as well as common comorbidities, including cancer and ischemic heart disease, since we corrected for these factors in multivariate analyses.

Several alternative factors may mediate the association between SES and poor survival. Psychosocial risk factors implicated in the etiology of cardiovascular disease, such as psychological stress, depression and social isolation, are more often observed in low SES individuals.[20-23] In addition, socioeconomic disadvantage has been established as a risk factor for poor compliance with medication, diet, and lifestyle restrictions.[24-28] Also, SES has been shown to be an important determinant of physical activity and exercise,[29] which –in turn– is associated with health status and life-expectancy.[29, 30] Fourth, even in developed countries, material deprivation in people from disadvantaged backgrounds is increasingly associated with poorer dietary quality.[31-34] Fifth, lower SES patients more often live in disadvantaged neighborhoods with higher concentrations of harmful air pollutants and worse housing conditions, which are associated with worse health outcomes.[35-37] Additionally, physical demand, low decision latitude and high job strain, which are more common in lower employment grades, may explain some of the excess risk among disadvantaged groups.[38] Finally, a recent study suggests that perhaps even epigenetical factors among lower socioeconomic classes may play a role in SES-related health disparities.[39] Although the interaction between SES and poor prognosis is complex, a better understanding of these acquired health hazards may attenuate the health inequalities. In addition, increased physician awareness and consideration of SES in clinical practice, for example by incorporating a number of –voluntary– questions to existing questionnaires (e.g.

employment of the patient and his or her partner, residential area and household income category), and focus on treatment of these established SES-related risk factors may help to improve outcome of low SES vascular patients. Although this study shows the relation of SES with outcome and the potential benefit of its consideration, further study is needed on how to integrate SES with current decision-models for risks of restenosis, amputation, and survival.

In line with previous reports,[4, 5, 19, 40] AAA patients with low income were more likely to present with a ruptured aneurysm, while PAD patients with lower annual earnings more often presented with symptoms of critical limb ischemia. These results indicate that the severity of disease at presentation is affected by SES as well. Since patients with lower SES tend to postpone seeking healthcare even in the absence of financial barriers, a lack of disease awareness and knowledge in lower socioeconomic classes is likely to be responsible for delayed presentation.[41] Regarding PAD patients, it is well recognized that the prognosis for patients presenting with critical limb ischemia is worse than for those with claudication. Therefore, additional analyses to determine the relative influence of SES and disease severity were performed. These analyses showed that both income and disease severity at presentation independently influenced survival in our cohort (data not shown). Considering that delayed presentation appeared to be associated with SES as well, a lack of awareness and knowledge may also partially account for SES-related disparities in the outcome of vascular surgery patients.

This study has several limitations that must be considered. First, the study was performed retrospectively, which comes with its inherent disadvantages. Second, local law prohibits the documentation of ethnicity, unless explicit approval is provided. Although we assume most patients to be of Western European origin, the ethnicity was not obtainable for this study, making racial differences in our analyses inaccessible. Another limitation was the missing data among the ruptured AAA patients. Due to a high number of missing baseline data, we could not include these patients in multivariable analysis beyond step one (age and gender adjusted). Also, it should be considered that only patients who underwent surgery were identified. Patients who were treated conservatively, or patients with prohibitive surgical risks due to severe comorbidity were not included in this study. As a result, a selection bias towards patients suited for surgery may be present. Further, patients undergoing endovascular procedures under local infiltration analgesia were not included in this study. Since endovascular treatment approaches are increasingly utilized, further study is warranted to assess the importance of SES for outcome of patients undergoing less invasive endovascular procedures. In addition, treatment indication for carotid revascularization

(i.e. TIA or stroke) was not graded in this study. Some studies have noticed different perioperative complication rates for different treatment indications.[42, 43] However, for long-term survival, which was the primary endpoint in the present study, the impact of treatment indication is not well-established.[44-46] Finally, gross household income was acquired for all patients in 2003, suggesting that the income used for analyses may be the income earned several years prior to surgery. However, the mean age in the cohort was 69 years, meaning that major differences between the income used in the analyses and the actual income at the time of surgery are not very likely.

In conclusion, this study demonstrates that socioeconomic deprivation is a predictor of adverse outcome after vascular surgery independent from conventional risk factors, in particular for peripheral artery disease. For AAA patients, the association was of an exponential nature, indicating that the mortality hazards rapidly decrease as income rises, while for PAD patients the relation followed a linear path. Although the precise mechanisms accounting for this risk remain elusive, the increased health hazards observed in this study are caused by patient related factors rather than differences in medical care, considering the equality of care provided by the study setting. Consideration of SES, for example assessed by household income, as a risk factor in preoperative decision-making and focus on treatment of the associated behavioral and psychosocial risk factors may improve the outcome of patients with vascular disease.

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Chapter 16

The Relation between Socioeconomic Status and Surgical Outcome in the Dutch Setting of Equal Access to and Provision of Healthcare

Klaas H.J.Ultee[1*]
Elke K.M. Tjeertes[2*]
Frederico Bastos Gonçalves[1,3]
Ellen V. Rouwet[1]
Anton G.M. Hoofwijk[4]
Robert Jan Stolker, MD[2]
Hence J.M. Verhagen[1]
Sanne E. Hoeks[2]
[*] the authors have contributed equally to this work.

1) Department of Surgery, Erasmus University Medical Center, the Netherlands
2) Department of Anaesthesiology, Erasmus University Medical Center, the Netherlands
3) Department of Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
4) Department of Surgery, Orbis Medical Centre, Sittard, the Netherlands

Submitted

ABSTRACT

Objective

The impact of socioeconomic disparities on surgical outcome in the absence of healthcare inequality remains unclear. Therefore, we set out to determine the association between socioeconomic status (SES) and overall survival after surgery in the Dutch setting of equal access and provision of care. Additionally, we aim to assess whether SES is associated with cause-specific survival and major 30-day complications.

Methods

Patients undergoing surgery between March 2005 and December 2006 in a general teaching hospital in the Netherlands were prospectively included. Adjusted logistic and cox regression analyses were used to assess the independent association of SES –quantified by gross household income– with major 30-day complications and long-term postoperative survival.

Results

A total of 3929 patients were included, with a median follow-up of 6.3 years. Low SES was associated with worse survival in continuous analysis (HR: 1.05 per 10.000 euro decrease in income, 95% CI: 1.01 – 1.10) and in income quartile analysis (HR: 1.58, 95% CI: 1.08 – 2.31, first [i.e. lowest] quartile relative to the fourth quartile). Similarly, low SES patients were at higher risk of cardiovascular death (HR: 1.26 per 10.000 decrease in income, 95% CI: 1.07 – 1.48, first income quartile: HR: 3.10, 95% CI: 1.04 – 9.22). SES was not independently associated with cancer-related mortality and major 30-day complications.

Conclusions

Low SES is associated with increased overall and cardiovascular mortality risks among surgical patients. Considering the equality of care provided by this study setting, the associated survival hazards can be attributed to patient factors, rather than disparities in healthcare. Increased physician awareness of SES as a risk factor in preoperative decision-making and focus on improving established SES-related risk factors may improve surgical outcome of low SES patients.

INTRODUCTION

The relation between socioeconomic status (SES) and outcome of medical treatment has been the subject of many studies over the past years, and SES-related risks of poor outcome have been demonstrated previously.[1-9] However, these studies were predominantly performed in the United States, where health care is not publicly provided. Differences in outcome between socioeconomic classes were therefore predominantly attributed to differences in accessibility and provision of care, rather than patient factors.[1, 6, 9, 10] Hence, the role of SES on surgical outcome in the absence of healthcare disparities remains unclear.

As a result of governmental regulation, medical care in the Netherlands is equal among all layers of society, and has even been credited the most equally accessible healthcare system in the world.[11, 12] This characteristic of the present study setting provides a new and unique opportunity to assess the role of SES on outcome of care. Due to the healthcare equality, differences in outcome associated with SES can under these circumstances be attributed to patient factors, rather than healthcare disparities. We have previously demonstrated in a vascular surgery population that SES implicated significant postoperative survival risks, independent from conventional medical and environmental risk factors.[13] These findings suggest that SES encompasses a wide variety of risk factors and behaviors that are not adequately captured by conventionally considered risk factors.

The association between SES and prognosis in a non-vascular general surgical population remains unexplored. Moreover, it is well known that vascular disease and vascular patients are relatively more susceptive to environmental risk factors, which limits the generalizability of the previous study to non-vascular patients.

The primary objective of this study is to determine the association between SES and survival after surgery in a general surgical population. Additionally, we aim to establish whether SES is associated with cause-specific survival and major 30-day complications.

METHODS

Study population

Patients undergoing elective or acute surgery between March 2005 and December 2006 in a medium-sized general teaching hospital in the Netherlands were prospectively included.[14] Procedures are detailed in Supplemental Table 1. Since

the association between low SES and worse outcome among vascular surgery patients has been established in the previous study,[13] vascular procedures were excluded. Additional exclusion criteria were surgical interventions performed under local anesthesia, and patients younger than 14 years at the time of the procedure. Bariatric surgery was not performed in this hospital. When a patient underwent multiple surgical procedures within the study period, the first operation was included for analysis and survival was assessed from that moment onward. The institutional review board of Zuyderland Medical Center approved this study, and patient consent was waived due to the de-identified nature of the data. The study complies with the Helsinki declaration on research ethics.

Baseline characteristics

Medical characteristics were obtained by a surgeon or a surgical resident during a routine visit prior to surgery. Pulmonary disease was defined as an illness of the lung or respiratory system (i.e. asthma, lung cancer, chronic infections, previous pulmonary embolisms, chronic obstructive pulmonary disease (COPD)). Cardiac disease was considered when the medical history included coronary artery disease (with or without coronary revascularization), heart failure, arrhythmias, valvular heart disease or cardiomyopathy. Cerebrovascular disease was defined as either a Transient Ischemic Attack (TIA) or ischemic stroke in the medical history. A patient was considered diabetic when diabetes mellitus was mentioned in the prior history or medical records show use of insulin or oral anti-diabetics. Hypertension was considered when hypertensive disease was mentioned in the medical history or the patient received anti-hypertensive medication. A history of cancer was defined as malignant neoplastic disease in the prior medical history.

Gathered surgery-related data included the type of anesthesia (locoregional or general) and the surgical setting (inpatient or outpatient). The risk of the performed procedure was defined as low, intermediate or high risk conform the surgical risk classification system by Boersma et al. (Supplemental Table 1).[15] High-risk surgical procedures solely consist of major vascular procedures and were not included in this study for previously mentioned reasons. Finally, all events following surgery were documented. A surgical resident as well as a member of the surgical staff independently scored all complications. To ensure complications were interpreted objectively and systematically, a classification proposed by Clavien et al. was used as guidance.[16] A major complication was defined as a complication requiring surgical, endoscopic or radiological intervention with or without residual organ dysfunction. Validation of the database using a random sampling audit procedure confirmed a high level of accuracy and completeness of the data.

Endpoints: The primary endpoint was overall mortality. Secondary endpoints were major 30-day complications, cardiovascular and cancer-related mortality.

Socioeconomic status

In this study, SES was defined as gross household income. Household income is one of the most widely accepted and used methods to quantify SES, and was found to provide a superior reflection of SES-related health disparities compared to other approaches such as educational status.[17-19] To avoid missing income data due to a patients' death in the year of surgery, gross household income in the year prior to the year of surgery was used to quantify SES. Annual earnings were obtained at the Dutch Central Bureau of Statistics (CBS), and encompassed all types of income of people sharing a household or place of residence combined, including salary, (state) pension, social compensation, and investment revenues. Patients were assigned income percentiles and quartiles in accordance with the national income distribution. To clarify, first income quartile patients included members of a household with an annual salary that corresponds to 0-25% gross household incomes of the Dutch population.

Cause of death

Causes of death obtained through national death registries, which are also maintained by the CBS. The high accuracy of Dutch cause-of-death registration has been demonstrated previously.[20] The cause of death was defined as the cause for the initial health deterioration, which subsequently resulted in death. This approach is similar to the strategy employed for the overall Dutch population death registrations and reports. Autopsy was not routinely performed. The causes of death were coded in accordance with *International Classification of Diseases, 10th Revision* (ICD-10). Cardiovascular death was defined as I10-I79, and cancer-related death as C00-C43, C45-C97.

To obtain information on SES and causes of death, a database consisting of medical data on all study participants was anonymised and matched to the household income and death registry data sets maintained by the CBS. Dutch privacy legislation stipulates that data analysis with national data is only allowed by authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for publication purposes.

Statistical methods: Baseline characteristics are presented as counts and percentages (dichotomous variables), means and standard deviations (continuous variables), or medians and interquartile ranges. Patients were grouped in quartiles in correspondence with the national gross household income distribution. Differences at baseline between income quartiles were tested using Pearson's chi-square analysis and ANOVA, where appropriate. The predictive value of SES for long-term survival was assessed using Cox-regression analysis. In order to determine both the type (i.e. linear or exponential) and the clinical significance of the relation between income and survival, analyses were performed with income as a continuous variable as well as categorical per income quartile. Exponential properties were tested by including higher-order terms of income in the regression model in continuous analysis. In income quartile analysis, the highest income quartile was designated reference category. The multivariable model included surgery risk, demographics (age, gender), medical characteristics (diabetes, hypertension, cerebrovascular disease, cardiac disease, malignant disease, pulmonary disease) and behavioral risk factors (smoking and BMI). Cause specific mortality hazards (i.e. cardiovascular and cancer-related) associated with SES were established with the same Cox model. The association between SES and major 30-day complications and death following surgery was studied using logistic regression analysis. The multivariable model consisted the same covariates as the long-term survival models. Sensitivity analyses were performed to assess whether the association between SES and postoperative survival existed among all patients, including vascular patients. All tests were two-sided and significance was considered when P-value <0.05. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL).

RESULTS

A total of 4153 patients were suitable for analysis. The gross household income could be retrieved for 3929 patients (94.6%).

Baseline characteristics

Baseline characteristics are detailed in Table 1. Low SES patients were younger (P<0.001) and were more frequently female (P<0.001). All medical conditions were more common among lower income quartile patients (P<0.001 for all medical conditions). Similarly, higher income patients were less often current or former smokers (P<0.001). BMI also significantly differed between the income quartiles (P<0.001).

Table 1. Baseline characteristics

	Quartile 1 (n=708)	Quartile 2 (n=1122)	Quartile 3 (n=1083)	Quartile 4 (n=1016)	P-value
Demographics					
Age – mean (± SD)	61.8 (19.4)	59.3 (16.5)	48.6 (15.6)	46.9 (14.5)	<0.001
Female gender – n (%)	435 (61)	538 (48)	525 (48)	446 (44)	<0.001
Comorbid conditions					
Diabetes mellitus – n (%)	91 (13)	96 (9)	68 (6)	45 (4)	<0.001
Hypertension – n (%)	189 (27)	242 (22)	160 (15)	119 (12)	<0.001
Cerebrovascular disease – n (%)	67 (10)	87 (8)	39 (4)	10 (<1)	<0.001
Cardiac disease – n (%)	184 (26)	239 (21)	131 (12)	76 (8)	<0.001
Malignant disease – n (%)	218 (31)	321 (29)	223 (21)	184 (18)	<0.001
Pulmonary disease – n (%)	128 (18)	197 (18)	124 (12)	79 (8)	<0.001
Surgery risk					
Low – n (%)	363 (51)	653 (58)	681 (63)	671 (66)	<0.001
Intermediate – n (%)	345 (49)	469 (42)	402 (37)	345 (34)	<0.001
Behavioral risk factors					
*Smoking * – n (%)*	236 (46)	431 (51)	428 (52)	284 (39)	<0.001
BMI – mean (± SD)	26.1 (4.7)	26.2 (4.4)	26.5 (4.8)	25.7 (4.3)	0.004
Type of anesthesia					
General – n (%)	618 (87)	936 (84)	920 (85)	855 (84)	0.135
Socioeconomic status					
Median income – € (IQR)	16 620.50 (13 914.25 – 19 280.75)	29 375.50 (25 119.50 – 34 474.75)	50 971.00 (44 961.00 – 57 645.00)	83 490.50 (72 924.50 – 101 192.75)	-

** approximately 25% missing values*

Major 30-day complications

In the first 30 days following surgery, 206 patients suffered a major complication requiring additional interventions (either surgical, endoscopic or radiological) (Table 2). Within this group, 37 patients (18%) were left with residual organ dysfunction. Income was associated with the occurrence of major complications in univariate continuous analysis (OR: 1.05, 95% CI: 1.004 – 1.11), as well as in income quartile analysis for the first quartile (OR: 1.99, 95% CI: 1.30 – 3.04) compared to the fourth quartile (Table 3). However, no association could be established in adjusted analysis.

Overall mortality

During a median follow-up of 6.3 years 570 deaths occurred (Table 2). Regarding the relation between SES and overall survival, a significant association was found

Table 2. Survival and short- and long-term event characteristics in accordance with household income quartiles

	Quartile 1 (n=708)	Quartile 2 (n=1122)	Quartile 3 (n=1083)	Quartile 4 (n=1016)	Total (n=3929)	P-value
5-year survival estimate (± se)	77% (1.6)	84% (1.1)	91% (0.9)	96% (0.6)	88% (0.5)	<0.001
Median follow-up – years (IQR)	6.2 (5.2 – 6.7)	6.3 (5.8 – 6.7)	6.4 (5.9 – 6.8)	6.4 (5.9 – 6.8)	6.3 (5.8 – 6.8)	-
Endpoints						
Severe complications – n (%)	52 (7)	61 (5)	54 (5)	39 (4)	206 (5)	0.014
Overall death – n (%)	189 (27)	222 (20)	107 (10)	52 (5)	570 (15)	<0.001
Cardiovascular death – n (%)	54 (8)	38 (3)	11 (1)	5 (<1)	108 (3)	<0.001
Cancer-related death – n (%)	71 (10)	117 (10)	60 (6)	33 (3)	281 (7)	<0.001

Table 3. The association between SES and major 30-day complications following surgery

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Major complications					
Univariate	1.05 (1.004 – 1.11)	1.99 (1.30 – 3.04)	1.44 (0.96 – 2.17)	1.32 (0.86 – 2.00)	-
Multivariate step 1	0.99 (0.95 – 1.03)	1.07 (0.66 – 1.73)	0.89 (0.57 – 1.39)	1.18 (0.76 – 1.81)	-
Multivariate step 2	1.01 (0.95 – 1.06)	1.09 (0.62 – 1.92)	1.02 (0.61 – 1.70)	1.41 (0.86 – 2.31)	-

Odds ratios in continuous analyses are determined per 10.000 euro decrease in household income. In quartile analyses, the fourth quartile serves as reference category

in continuous analysis (Table 4). In multivariable step 1, as well as adjusted for behavioral risk factors in step 2, mortality hazards proved to increase as income diminished (HR: 1.05 per 10.000 euro decrease in household income, 95% CI: 1.01 – 1.10,). A similar relation was found in income quartile analysis. In step 2 multivariable analysis, patients in the first quartile (i.e. the lowest income quartile) had significantly higher mortality risks (HR: 1.58, 95% CI: 1.08 – 2.31). The association lost significance in the second and third quartile, although a trend remained (HR: 1.41, 95% CI: 0.99 – 2.02, HR: 1.32, 95% CI: 0.90 – 1.93, respectively for the second and third quartile).

Cause specific mortality

Of the 570 deaths, 108 (19%) were due to cardiovascular causes. In both step 1 and step 2 continuous analysis, low SES was significantly associated with increased cardiovascular mortality risks (HR: 1.26 per 10.000 euro decrease in household income, 95% CI: 1.07 – 1.48, Table 5). In income quartile analysis, a significant independent SES-related cardiovascular survival hazard was observed in the first quartile (HR: 3.10, 95% CI: 1.04 – 9.22). No relation could be established for the higher two quartiles.

Cancer-related death was ascertained in 281 (49%) cases. In continuous analysis, a significant relation was found between SES and cancer-related survival in univariate analysis (HR: 1.19, 95% CI: 1.13 – 1.24). The relation was lost after adjusting for conventional risk estimators in multivariable analysis. Similarly, lower quartile patients were not burdened by additional cancer-related mortality in multivariable income quartile analysis.

Sensitivity analyses

Sensitivity analyses with vascular surgery patients included showed that SES was associated with worse overall survival in continuous step 2 multivariable analysis (HR: 1.05 per 10.000 euro decrease in household income, 95% CI: 1.01 – 1.09,), as well as cardiovascular survival (HR: 1.21, 95% CI: 1.02 – 1.41), while no increased risk was found for cancer-related survival (HR: 1.01, 95% CI: 0.96 – 1.07). Income quartile analyses showed similar results for overall and cancer-related mortality as well. For cardiovascular mortality, a non-significant trend towards increased cardiovascular survival hazards was observed among first quartile patients (P=0.055).

Table 4. The association between SES and overall mortality

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Overall mortality					
Univariate	1.25 (1.21 – 1.30)	5.89 (4.33 – 8.00)	4.17 (3.08 – 5.64)	1.97 (1.41 – 2.74)	-
Multivariate step 1	1.06 (1.01 – 1.10)	1.49 (1.06 – 2.09)	1.40 (1.02 – 1.93)	1.30 (0.93 – 1.83)	-
Multivariate step 2	1.05 (1.01 – 1.10)	1.58 (1.08 – 2.31)	1.41 (0.99 – 2.02)	1.32 (0.90 – 1.93)	-

Hazard ratios in continuous analyses are determined per 10.000 euro decrease in household income. In categorical analyses, the fourth quartile serves as reference category

Table 5. The association between SES and cause-specific mortality

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cardiovascular					
Univariate	1.41 (1.33 – 1.51)	17.99 (7.20 – 44.97)	7.59 (2.99 – 19.29)	2.11 (0.73 – 6.08)	-
Multivariate step 1	1.22 (1.09 – 1.37)	2.84 (1.08 – 7.50)	1.79 (0.69 – 4.65)	1.19 (0.41 – 3.46)	-
Multivariate step 2	1.26 (1.07 – 1.48)	3.10 (1.04 – 9.22)	1.40 (0.47 – 4.20)	1.17 (0.36 – 3.86)	-
Cancer-related					
Univariate	1.19 (1.13 – 1.24)	3.46 (2.29 – 5.23)	3.43 (2.33 – 5.05)	1.74 (1.14 – 2.66)	-
Multivariate step 1	1.04 (0.99 – 1.10)	1.28 (0.81- 2.02)	1.42 (0.95 – 2.14)	1.30 (0.85 – 2.01)	-
Multivariate step 2	1.01 (0.96 – 1.06)	1.04 (0.63 – 1.72)	1.40 (0.90 – 2.18)	1.36 (0.86 – 2.15)	-

Hazard ratios in continuous analyses are determined per 10.000 euro decrease in household income. In categorical analyses, the fourth quartile serves as reference category

DISCUSSION

The principal finding of this study is that SES is a significant predictor of long-term survival in an overall surgical population. Cause specific mortality analysis indicated that the mortality hazards associated with low SES were not caused by increased risks of death due to cancer-related causes, but rather a higher risk of cardiovascular death. Since the association maintained after adjusting for demographics, comorbidities and behavioral risk factors, the mortality risks add to conventionally considered risk estimators. Secondly, this study showed that SES is not related to short-term postoperative outcome, as demonstrated by the lack of association with major 30-day complications.

Differences in outcome after surgery between socioeconomic classes have previously been attributed to disparities in quality and provision of care.[1, 6, 9, 21, 22] However, the equality in access to and provision of care provided by this study setting suggests that not healthcare inequalities, but rather patient-related factors play a causal role in SES-related outcome differences. Hence, even in countries where healthcare is not publicly provided, differences in healthcare utilization are unlikely to fully account for divergences in outcome.[23, 24]

Although the relation between SES and outcome has not been described for a general surgical population, population-based studies have been conducted. In a study among Finnish men, it was shown that known behavioral risk factor pathways mediated much of the inverse relation between SES and survival, which is in line with our observation that smoking was more common in lower income quartiles.[25] However, as in the Finnish study, a residual association was established which was not fully captured by the wide variety of other risk factors also included in the analysis. Moreover, previous studies have reported that less than 50% of socioeconomic differences in disease occurrence and prognosis are explained by combined common behavioral risk factors, such as smoking.[18, 25-27]

Several factors may mediate the independent relation between low SES and worse surgical outcome. First, socioeconomic disadvantage is a known risk factor for poor compliance to medication, diet, and lifestyle restrictions.[28-32] Second, psychosocial risk factors implicated in the etiology of cardiovascular disease, such as psychological stress, depression and social isolation, are more often observed in low SES populations.[33-36] Also, material deprivation in individuals from disadvantaged backgrounds is associated with worse dietary quality.[37-40] In addition, SES has been has been established as an important determinant of physical activity and exercise,[41] which –in turn– is associated with health status and life-expectancy.[41, 42] Fifth, low SES patients tend to reside in more disadvantaged neighborhoods with higher concentrations of harmful air pollutants and

worse housing conditions, which are associated with worse health outcomes.[43-45] Physical demand, low decision latitude and high job strain, which are more common in lower employment grades, may also explain some of the excess risk among disadvantaged groups.[46]

These factors have been linked to especially increased risks of cardiovascular disease and mortality.[25, 45, 47-49] Moreover, literature based models suggest that perhaps even epigenetical factors among lower socioeconomic classes may be responsible for the higher prevalence of cardiovascular disease among lower socioeconomic classes.[50] This provides a valid explanation as to why low SES predominantly implied cardiovascular survival hazards in our study.[51, 52] Although no relation between SES and cancer-related death was found in the full model, studies have proven such relation to exist.[53, 54] Our results showed an association between SES and cancer-related mortality in univariate analysis, but no relation could be established when adjusting for conventional risk factors.[54] This is in line with previous studies showing that that much of the SES-related risk of cancer occurrence and mortality are through conventional risk factors, most importantly smoking.[51, 55-57] Although the association between low SES and worse outcome is multifactorial and complex, a better understanding of this relation may help to attenuate health disparities. Increased physician awareness and focus on bettering these established SES-related risk factors may help to improve outcome of low SES surgical patients.

In regards to the association between SES and major complications following surgery, a relation was found in univariate analysis, but point estimates decreased to 1 and significance was lost in the multivariable model. The fact that the relation did not maintain significance after adjusting for commonly considered health hazards suggests that SES is merely a proxy measure in this association and that it provides no additional value over conventional risk factors for the prediction of the short-term postoperative course.

This study has some limitations that should be considered. First of all, it should be noted that only patients who underwent surgery were included. Patients who were conservatively treated and those with prohibitive surgical risks due to severe comorbidity were consequently excluded. In addition, smoking status was unobtainable for a considerable amount of patients, and resulted in the exclusion of approximately 25% of cases in the full model. Finally, American studies that have reported on SES-related outcome and healthcare disparities often describe divergences between racial groups as well. Due to Dutch legislation, documentation of ethnicity in patient records is only allowed when medically relevant. Consequently, racial disparities could unfortunately not be investigated.

In conclusion, this study demonstrates that low SES is a risk factor for overall and cardiovascular mortality following surgery. Considering the equality in access to and provision of healthcare provided by this study setting, we can conclude that the observed health hazards accompanying low socioeconomic status are caused by patient factors, rather than differences in medical care. Although the exact mechanism mediating the postoperative SES-related survival risk remains unclear, increased physician awareness and improvement of known SES-related risk factors and behaviors may help to improve surgical outcome among low SES patients.

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Supplemental Table 1. Risk classification of included surgical procedures

Low risk surgery	**Procedure**
	Hernia surgery (except incisional hernia surgery)
	Varicose vein surgery
	Perianal surgery
	Minor trauma surgery
	Minor surgery of soft tissue
Intermediate risk surgery	**Procedure**
	Appendectomy
	Cholecystectomy
	Major abdominal surgery (i.e. liver, gastric, bowel, spleen esophagus, incisional hernia surgery)
	Head and neck surgery
	Thoracic surgery
	Major trauma surgery (i.e. multitrauma or trauma involving the femur or hip)

Chapter 17

Peripheral Artery Disease Patients May Benefit More from Aggressive Secondary Prevention than Aneurysm Patients to Improve Survival

Klaas H.J. Ultee[1]
Sanne E. Hoeks[2]
Frederico Bastos Gonçalves[1,3]
Eric Boersma[4]
Robert Jan Stolker[2]
Hence J.M. Verhagen[1]
Ellen V. Rouwet[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, the Netherlands
2) Department of Anaesthesiology, Erasmus University Medical Center, the Netherlands
3) Department of Angiology and Vascular Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
4) Department of Cardiology, Erasmus University Medical Center, the Netherlands

Atherosclerosis (in press)

ABSTRACT

Objective

Although it has become clear that aneurysmal and occlusive arterial disease are two distinct etiologic entities, it is still unknown whether the two vascular pathologies are prognostically different. We aim to assess the long-term vital prognosis of patients with abdominal aortic aneurysmal disease (AAA) or peripheral artery disease (PAD), focusing on possible differences in survival, prognostic risk profiles and causes of death.

Methods

Patients undergoing elective surgery for isolated AAA or PAD between 2003 and 2011 were retrospectively included. Differences in postoperative survival were determined using Kaplan-Meier and Cox regression analysis. Prognostic risk profiles were also established with Cox regression analysis.

Results

429 and 338 patients were included in the AAA and PAD groups, respectively. AAA patients were older (71.7 vs. 63.3 years, $p < 0.001$), yet overall survival following surgery did not differ (HR: 1.16, 95% CI: 0.87–1.54). Neither was type of vascular disease associated with postoperative cardiovascular or cancer-related death. However, in comparison with age- and gender-matched general populations, cardiovascular mortality was higher in PAD than AAA patients (48.3% vs. 17.3%). Survival of AAA and PAD patients was negatively affected by age, history of cancer and renal insufficiency. Additional determinants in the PAD group were diabetes and ischemic heart disease.

Conclusions

Long-term survival after surgery for PAD and AAA is similar. However, overall life expectancy is significantly worse among PAD patients. The contribution of cardiovascular disease towards mortality in PAD patients warrants more aggressive secondary prevention to reduce cardiovascular mortality and improve longevity.

INTRODUCTION

Traditionally, dilatation and occlusion were considered to represent two extremes on the same spectrum of arterial disease. As such, it was presumed that both entities were the result of extensive atherosclerosis.[1] This assumption was largely based on the fact that the two vascular diseases share a number of risk factors, such as smoking, hypertension, and older age.[2-6]

However, over the years, disparities in etiologic cardiovascular risk profiles were demonstrated, [7-11] as well as differences in the severity of atherosclerotic burden between patients suffering from aneurysmal and occlusive disease.[7, 12-16] In addition, differences in cytokine levels, inflammation, and enzyme activity were found in the arterial walls affected by aneurysmal or occlusive disease.[9, 17, 18] Also, recent studies show that genetic susceptibility, rather than environmental risk factors, plays a particularly important role in the pathogenesis of aneurysmal disease.[19-21] Although it is becoming clear that aneurysm formation and atherosclerosis are two separate clinical entities, it remains unclear whether this also translates into long-term prognostic differences between the two patient categories. Differences in long-term outcome, particularly of cardiovascular nature, would warrant more aggressive secondary prevention regimens for those at the highest risk.

With surgical treatment as a uniform indicator of severe disease, we aim to determine the long-term vital prognosis for abdominal aneurysmal and peripheral occlusive disease patients, focusing on possible differences in survival, risk profiles, and causes of death.

METHODS

Patients undergoing elective surgery for AAA or PAD at the Erasmus University Medical Centre in Rotterdam between January 2003 and December 2011 were retrospectively identified using operation codes and surgical reports. Long-term survival was assessed from the day of surgery onward. In order to improve homogeneity in terms of operative stress and severity of disease, all percutaneous endovascular procedures, i.e. percutaneous endovascular aneurysm repair (EVAR) and percutaneous lower limb PTA or stenting procedures, were excluded. AAA patients who underwent prior endovascular or open surgical revascularization for lower limb ischemia were excluded from this study. PAD patients who underwent prior treatment of an abdominal or thoracic aortic aneurysm were also excluded. Treatment indications for AAA and PAD were both in accordance with the Euro-

pean Society for Vascular Surgery guidelines.[22, 23] Similarly, all vascular surgery patients were treated in accordance with these guidelines regarding secondary cardiovascular prevention. As a result, all patients followed a lifelong regimen of anti-platelets and statins, as well as anti-hypertensive and anti-diabetes medication on indication. Baseline characteristics were obtained from hospital charts and included age, gender, comorbidity, prior vascular interventions, smoking status (current/former or non-smoker), and body mass index (BMI). Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

Definitions: Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral anti-diabetics. Hypertension was defined as blood pressure >140/90 mmHg or use of anti-hypertensive medication. A history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min as calculated from preoperative serum creatinine levels using the MDRD formula. Smoking status and BMI were derived from the medical records. Cerebrovascular disease was defined as mentioning of symptomatic carotid artery disease (i.e., transient ischemic attack or stroke) and/or a carotid endarterectomy or stenting procedure in the medical history. Ischemic heart disease was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention or evidence of myocardial ischemia in provocative pre-operative tests (dobutamine stress echocardiography or myocardial scintigraphy). Prior vascular interventions were defined as either surgical or percutaneous vascular treatment prior to the index operation, not including coronary revascularization.

Endpoints: The primary endpoint was overall mortality. Secondary endpoints were cardiovascular and cancer-related death.

Cause of death: Causes of death were obtained from the Dutch Central Bureau of Statistics (CBS). A database consisting of medical data on the study participants was anonymized by authorized data managers employed by CBS. This dataset was subsequently imported and linked to the Dutch death registry, which is maintained by the CBS. According to Dutch privacy legislation, data analysis was only allowed to authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for

publication purposes. Autopsy was not routinely performed. The cause of death was defined as the initial cause of health deterioration, consequently resulting in death. This approach is similar to the strategy used for the overall Dutch population. The causes of death were grouped according to the *International Classification of Diseases, 10th Revision* (ICD-10). For cardiovascular death, the following codes were used: I10-I79; for cancer-related death: C00-C43, C45-C97, D00-D03, and D05–09; for death due to obstructive pulmonary disease: J40-J47; and for digestive system-related causes: K00-K93.

For survival estimation in the general population, a comparative age and gender matched control group was derived from civil registries of the Dutch population –also maintained by the CBS– for both the AAA and PAD group separately. To assess differences in causes of death compared to the general population, deaths in the respective study groups were individually matched on demographic properties to cause of death distributions in the general population. For example, if deaths in the AAA group consisted for 5% of males between the aged between 80-85 at the time of death, the AAA matched cohort corresponds proportionally to the death distribution for males with the same age and gender characteristics from the general population.

Statistical methods: Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were determined using Pearson's chi-square analysis and student t-test, where appropriate. Survival for the aneurysmal and occlusive disease cohorts was initially assessed using Kaplan-Meier and log-rank analyses. Differences in the vital prognosis were subsequently investigated using adjusted Cox proportional hazards regression. Multivariable analyses adjusted for demographics, comorbidities, and other risk factors (age, gender, diabetes mellitus, ischemic heart disease [IHD], a history of cancer, renal insufficiency, BMI, and current smoking). The AAA group was designated as the reference category in these analyses. Prognostic risk profiles for the two study groups were established by determining hazard ratios for potential risk factors separately for the AAA and PAD group using Cox proportional hazards model. Univariately significant covariates were included in the multivariable model. All tests were two-sided and significance was considered when P-value < 0.05. Statistical analysis was performed using the SPSS Statistics 20 (IBM Inc., Chicago, IL).

RESULTS

A total of 470 patients undergoing elective surgery for AAA and 353 patients for PAD were identified. In the AAA group, 40 patients were excluded because of prior treatment for PAD, while 14 patients were excluded in the PAD group for prior aneurysm treatment. Two patients, one in each treatment group, were excluded due to unavailable follow-up data as a result of emigration. The remaining 429 AAA and 338 PAD patients were considered suited for analysis.

Baseline characteristics

Baseline characteristics are detailed in Table 1. Compared to the PAD group, AAA patients were older at the time of surgery (71.7 vs. 63.3 years, $p < 0.001$), and more often male (88% vs. 66%, $p < 0.001$). In addition, patients in de AAA group were more commonly affected by cancer (21% vs. 14%, $p = 0.025$) and renal insufficiency (29% vs. 20%, $p = 0.006$). Conversely, diabetes and current smoking were less common among AAA patients (16% vs. 30%, $p < 0.001$ and 38% vs. 49%, $p = 0.003$, respectively). AAA patients also less frequently underwent vascular interventions prior to the index operation (4% vs. 46%, $p < 0.001$).

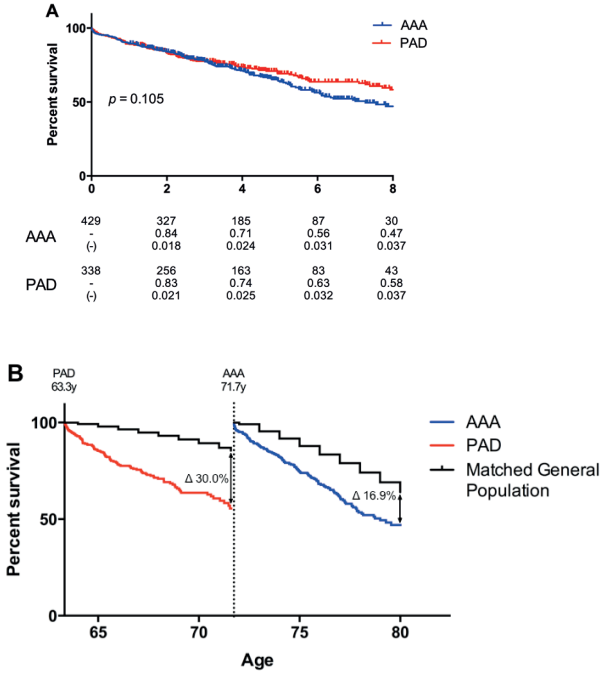
Table 1. Baseline characteristics per study group.

Variable	***AAA*** *(n=429)*	***PAD*** *(n=338)*	***P-value***
Demographics			
Female gender – n (%)	51 (12)	114 (34)	< 0.001
Age – (years, mean ± SD)	71.7 ± 7.5	63.3 ± 11.1	< 0.001
Cardiovascular risk factors			
Diabetes– n (%)	67 (16)	102 (30)	< 0.001
Hypertension – n (%)	291 (68)	231 (69)	0.782
Current smoking – n (%)	161 (38)	164 (49)	0.003
Body mass index – (mean ± SD)	26.2 ± 4.1	25.8 ± 4.6	0.217
Peripheral artery disease – n (%)	40 (9.3%)	338 (100%)	-
Comorbidities			
History of cancer – n (%)	88 (21)	48 (14)	0.025
Ischemic heart disease – n (%)	203 (47)	152 (45)	0.512
Coronary revascularization – n (%)	92 (21)	80 (24)	0.613
Cerebrovascular disease – n (%)	73 (17)	52 (15)	0.544
Renal insufficiency – n (%)	125 (29)	69 (20)	0.006
History of vascular interventions – n (%)	19 (4)	157 (46)	< 0.001

Overall survival

During a median follow-up of 3.6 years after surgery (IQR: 2.1 – 5.4 years) 154 patients died in the AAA group. For PAD patients, median follow-up time was 3.8 years (IQR: 2.0 – 5.9 years), during which 107 patients died. Postoperative survival proved to be similar for the two groups, in both unadjusted analysis, as determined by log-rank testing (p = 0.105; Figure 1a), as well as adjusted Cox-regression analysis (HR: 1.16, 95% CI: 0.87 – 1.54, Table 2). However, since AAA patients were substantially older at the time of intervention (71.7 vs. 63.3 years), postoperative survival did not adequately reflect life expectancy of the respective groups. Figure 1b represents the postoperative life expectancies for the two groups with the average age at the time of treatment as the starting point. A direct comparison with a Dutch general population with similar age and gender properties shows that in particular survival in the PAD cohort more strongly deviates from its matched general population (30.0% vs. 16.9%, respectively), indicating more life years lost as compared to the AAA cohort.

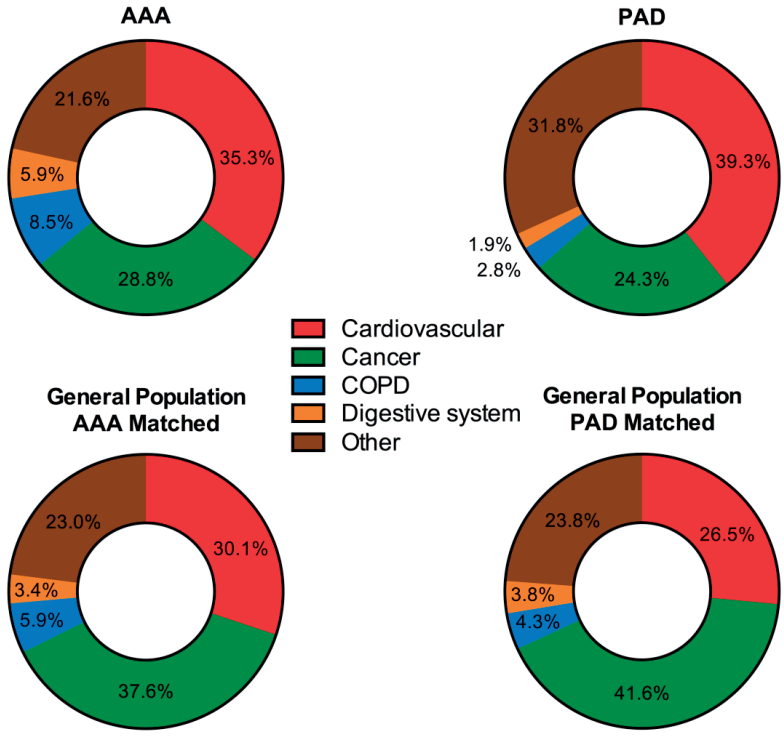
Figure 1. Long-term survival analysis for postoperative survival after AAA and PAD. (A) Kaplan-Meier analysis comparing survival after surgical intervention for AAA and PAD. (B) Postoperative life expectancy for patients treated for AAA and PAD. The starting points of the survival curves correspond to the average age at intervention in the study groups (i.e. 63.3 and 71.7 years, respectively in the PAD and AAA groups). Survival estimates of the general population are age- and gender-adjusted in accordance with the respective cohorts.



Cause of death

Causes of death could be obtained for 153 out of 154 patients (99.4%) in the AAA group and for all 107 deceased patients in the PAD group. Deaths were classified in five categories: cardiovascular, cancer-related, chronic obstructive pulmonary disease (COPD), intestinal disease, and other causes (Figure 2). Cardiovascular mortality was the leading cause of death in both AAA and PAD patients (35.3% vs. 39.3%, p = 0.944), followed by cancer-related death (28.8% vs. 24.3%, respectively, p = 0.220). However, cardiovascular mortality encompasses a much larger proportion in the PAD group as compared to the age- and gender-matched general population (39.3% vs. 26.5%) than in the AAA group (35.3% vs. 30.1%). Death due to intestinal disease or other causes was similar in the AAA and the PAD group (5.9% vs. 1.9%, p = 0.124; 21.6% vs. 31.8%, p = 0.249, respectively). Mortality resulting from COPD, however, was significantly more common among AAA patients compared to PAD patients (8.5 vs. 2.8%, p = 0.043).

Figure 2. Cause of death distribution in the AAA and PAD groups and an age- and gender-matched general Dutch population.



Risk adjusted survival analyses was additionally performed to assess whether cause-specific mortality risks differed between AAA and PAD patients. These analyses showed that no difference exists in risks of cardiovascular and cancer-related death between treatment groups (HR: 1.47, 95% CI: 0.93 – 2.31; HR: 1.14, 95% CI: 0.64 – 2.03, respectively, Table 2). For causes of death with smaller proportions, adjusted survival analysis was not possible due to limited number of events.

Table 2. Adjusted survival analysis for overall and cause-specific mortality. The AAA group served as the reference category.

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Overall death	0.82	0.64 – 1.04	1.16	0.87 – 1.54
Cardiovascular death	0.91	0.61 – 1.37	1.47	0.93 – 2.31
Cancer-related death	0.70	0.43 – 1.14	1.14	0.64 – 2.03

Risk profile all-cause mortality

Risk profile analysis was performed for the two study groups separately (Table 3). In the AAA group, univariately significant risk factors that proved to be independently associated with increased mortality were age (HR: 1.70, 95% CI: 1.34 – 2.15, per 10 year increase), history of cancer (HR: 2.44, 95% CI: 1.72 – 3.46) and renal insufficiency (HR: 1.78, 95% CI: 1.27 – 2.51). Higher BMI was protective against mortality (HR: 0.93, 95% CI: 0.89 – 0.97, per BMI unit increase). Ischemic heart disease appeared to negatively affect survival of AAA patients in univariable analysis, but this effect was lost in the multivariable model (HR: 1.33, 95% CI: 0.95 – 1.85).

Similar risk factors found in the PAD cohort were age (HR: 1.30, 95% CI: 1.08 – 1.57, per 10 year increase), a history of cancer (2.26, 95% CI: 1.45 – 3.54) and renal insufficiency (HR: 1.57, 95% CI: 1.02 – 2.42). Additionally, diabetes (HR: 1.69, 95% CI: 1.14 – 2.50) and ischemic heart disease (HR: 1.76, 95% CI: 1.18 – 2.60) worsened survival of PAD patients. Hypertension was a significant predictor of mortality in univariable analysis in the PAD group, but could not be established as an independent risk factor in the adjusted model (HR: 1.18, 95% CI: 0.75 – 1.85).

Table 3. Risk profiles for all-cause mortality for the AAA and PAD group.

	AAA				PAD			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age per 10 year incr.	1.83	1.47 – 2.30	1.70	1.34 – 2.15	1.47	1.22 – 1.76	1.30	1.08 – 1.57
Gender	1.06	0.64 – 1.76	-	-	1.15	0.77 – 1.70	-	-
Diabetes	0.91	0.58 – 1.45	-	-	2.03	1.38 – 2.99	1.69	1.14 – 2.50
IHD	1.41	1.03 – 1.94	1.33	0.95 – 1.85	2.01	1.36 – 2.96	1.76	1.18 – 2.60
Cancer	2.57	1.84 – 3.59	2.44	1.72 – 3.46	3.14	2.04 – 4.82	2.26	1.45 – 3.54
Renal insufficiency	1.96	1.42 – 2.71	1.78	1.27 – 2.51	2.46	1.64 – 3.69	1.57	1.02 – 2.42
Hypertension	1.39	0.98 – 1.97	-	-	1.62	1.04 – 2.52	1.18	0.75 – 1.85
BMI per unit incr.	0.93	0.89 – 0.97	0.93	0.89 – 0.97	1.03	0.98 – 1.07	-	-
Current smoking	0.90	0.65 – 1.25	-	-	0.93	0.64 – 1.37	-	-

DISCUSSION

This study demonstrates that postoperative survival is similar for patients undergoing surgery for aneurysmal or atherosclerotic occlusive arterial disease, despite the fact that PAD patients were almost 10 years younger at the time of surgery. The mortality rate of PAD patients was much higher than that of AAA patients as compared to their respective age- and gender-matched general populations. These data indicate a relatively greater loss of life years in PAD patients as compared to AAA patients.

What causes this difference in life expectancy between PAD and AAA patients? The leading causes of death, i.e. cardiovascular disease and cancer, were similar in the two patient groups in unadjusted as well as adjusted analyses. This is in agreement with a study from the REACH registry, showing no difference in 1-year cardiovascular death between the two patient groups.[8] Interestingly, however, the proportion of cardiovascular mortality in PAD patients was almost 50% higher than in the age- and gender-matched general population, whereas in the AAA group the difference with the general population was rather small. This suggests that cardiovascular disease is a relatively more important determinant of life expectancy in PAD when compared to AAA patients in spite of their younger age. These findings are in line with previous studies showing more severe systemic atherosclerosis – reflected by increased carotid intima-

media thickness – in patients with occlusive arterial disease as compared to those with AAA.[7, 12-16] Interestingly, it has been demonstrated that as little as a tenth of a millimeter increase in arterial wall thickness is already associated with considerable increases in risk of myocardial infarction, stroke, and even death.[24-27] In PAD patients, a relatively severe progression of atherosclerotic disease is therefore likely to be responsible for the similar survival compared to the much older AAA patients, and the poor prognosis compared to the matched general population. Of note, COPD-related death was more frequent among AAA patients, which may be due to a common -genetically determined- defect in the extracellular matrix.[28, 29] This further supports the divergence in pathophysiology between aneurysmal and occlusive vascular disease.

In order to identify what drives mortality in the respective groups, we compared their mortality risk profiles. These analyses showed that age was more than twice as important for AAA patients as compared to PAD patients (HR: 1.70 vs. 1.30, per 10 year increase). Conversely, a history of ischemic heart disease and the presence of diabetes were more important for the prediction of death in PAD patients. Besides hazardous risk estimators, we found that higher BMI was associated with prolonged survival in the AAA group. This phenomenon, known as the obesity paradox, has been described multiple times in many different study populations. Although the exact mechanism for this phenomenon remains unknown, the association between chronic disease and malnutrition is believed to play a role.[30, 31] The hazard ratios of 0.9 for current smoking and diabetes in univariate analysis appear to represent a protective effect of these factors for mortality. However, the wide confidence intervals indicate that rather no association existed between these factors and mortality.

Since cardiovascular risk factors, as opposed to age, are potentially modifiable, this provides the opportunity to improve life expectancy in PAD patients. Regrettably, in spite of widespread guidelines for cardiovascular risk management and the undeniable benefits of secondary prevention, studies such as the REACH registry show that PAD patients do not achieve adequate risk factor control as frequently as individuals with coronary or cerebrovascular disease,[32] despite comparable risks of future cardiovascular events. Pande et al. found that only 27% of primary PAD patients were on antiplatelet therapy, and a mere 19% received statins.[33] Thus, there is still a large gap between therapeutic goals and current secondary preventive care for PAD patients.[34, 35] Furthermore, tight control of blood pressure (i.e. ≤ 130-135 mmHg), as opposed to relaxed control (i.e. ≤140 mmHg), is associated with a further reduction in cardiovascular morbidity and mortality.[36, 37] The recent SPRINT trial even determined that blood pressure control with a target of <120 mmHg resulted in a 43% reduction in

cardiovascular mortality.[38] Similarly, tight regulation of blood glucose and lipids has been reported to improve the overall and cardiovascular prognosis.[39-41] In light of these benefits, narrowing of the tolerable margins of these classical cardiovascular risk factors should be considered, particularly in PAD patients.

This study has limitations that should be addressed. First, this study is of retrospective nature, which has inherent limitations with regard to data collection. Also, it should be considered that only patients who underwent surgery were identified. Patients treated conservatively, or by less invasive -percutaneous- techniques, and those with prohibitive surgical risks were not included in this study. Although this approach provided more uniformity in terms of severity of disease and operative risks, a selection bias towards patients suited for surgery may have resulted. Also, Dutch law prohibits the documentation of ethnicity in medical records, which precluded its consideration in this study. For reference, a review of the ethnical proportions in the Dutch general population showed that 77.8% is of Dutch descent, 6.2% African descent, and 7.0% Mediterranean descent. In addition, it is virtually impossible to determine the onset of aneurysmal or atherosclerotic disease. As surgical treatment is a uniform indicator of severe disease, long-term survival was assessed from the day of surgery onward. PAD patients more often underwent some kind of revascularization prior to the index operation in this study, which indicates that the age difference demonstrated for timing of the index operation between occlusive and aneurysmal disease may even underestimate the difference in the age at onset between the two respective diseases. This adds support to the argument that AAA and PAD are two distinct entities. Finally, the increasing utilization of endovascular treatment approaches warrants evaluation and comparative assessment of the postoperative prognosis following minimally invasive AAA and PAD treatment under local anesthesia.

In conclusion, this study shows that aneurysmal and occlusive vascular disease do not only differ in terms of etiology and pathophysiology, but are also distinct entities in terms of prognosis. Life expectancy in PAD patients is shorter and is predominantly reduced by cardiovascular morbidity, as opposed to age in AAA patients. This warrants emphasis on aggressive cardiovascular risk factor modification particularly for PAD patients in order to maximize longevity.

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Chapter 18

Coronary Revascularization Induces a Shift from Cardiac towards Non-Cardiac Mortality Without Improving Survival in Vascular Surgery Patients

Klaas H.J. Ultee[1]
Ellen V. Rouwet[1]
Sanne E. Hoeks[2]
Felix van Lier[2]
Frederico Bastos Gonçalves[1,3]
Eric Boersma[4]
Robert Jan Stolker[2]
Hence J.M. Verhagen[1]

1) Department of Vascular Surgery, Erasmus University Medical Center, the Netherlands
2) Department of Anaesthesiology, Erasmus University Medical Center, the Netherlands
3) Department of Angiology and Vascular Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
4) Department of Cardiology, Thorax center, Erasmus University Medical Center, the Netherlands

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ABSTRACT

Objective

While evidence has shown that ischemic heart disease (IHD) in vascular surgery patients has a negative impact on the prognosis after surgery, it is unclear whether directed treatment of IHD may influence cause-specific and overall mortality. The objective of this study is to determine the prognostic implication of coronary revascularization (CR) on overall and cause-specific mortality in vascular surgery patients.

Methods

Patients undergoing surgery for abdominal aortic aneurysm (AAA), carotid artery stenosis (CAS) or peripheral artery disease (PAD) in a university hospital in the Netherlands between January 2003 and December 2011 were retrospectively included. Survival estimates were obtained using Kaplan-Meier and Cox regression analysis.

Results

A total of 1104 patients were included. Adjusted survival analyses showed that IHD significantly increased the risk of overall and cardiovascular death (HR: 1.50, 95% CI: 1.21 – 1.87 and HR: 1.93, 95% CI: 1.35 – 2.76, respectively). Patients previously undergoing CR had similar overall and cardiovascular mortality compared to those without CR (HR: 1.38 vs. 1.62, P = .274; HR: 1.83 vs. 2.02, P = .656, respectively). Non-revascularized IHD patients were more likely to die of IHD (6.9% vs. 35.7%), whereas revascularized IHD patients more frequently died of cardiovascular causes unrelated to IHD (39.1% vs. 64.3%, P = .018).

Conclusion

This study confirms the significance of IHD for postoperative survival of vascular surgery patients. Coronary revascularization was associated with lower IHD-related death rates. However, it failed to provide an overall survival benefit due to an increased rate of cardiovascular mortality unrelated to IHD. Intensification of secondary prevention regimens may be required to prevent this shift towards non-IHD-related death and thereby improving life expectancy.

INTRODUCTION

A number of reports have shown that long-term survival in patients undergoing vascular surgery procedures is as low as 25% after 10 years.[1] Cardiovascular causes account for the majority of early and late mortality following vascular surgery, surpassing 60%.[2] It is well known that patients undergoing vascular surgery are frequently affected by coronary artery disease, symptomatic or not.[3] Since the presence of ischemic heart disease (IHD) is associated with postoperative morbidity and mortality after non-cardiac vascular surgery, IHD has been the subject of numerous studies regarding survival, preoperative evaluation, as well as perioperative management. While evidence has shown that IHD in vascular surgery patients has a negative impact on the prognosis after surgery, it is unclear whether this is solely due to IHD-related death or due to non-IHD-related mortality risks as well.[4, 5]

In an attempt to improve postoperative survival, several studies have investigated the effectiveness of coronary revascularization on the prognosis of patients undergoing non-cardiac interventions. [6-14] The interpretation of these studies in terms of survival benefits is hampered by either relatively short follow up periods, small sample sizes, or heterogeneity within the studied population regarding patient and procedural risks. Retrospective data suggested that prior coronary bypass surgery was associated with a reduction of 30-day myocardial infarction and death rates.[6] However, subsequent randomized trials demonstrated that coronary revascularization prior to vascular surgery does not improve survival. [7, 8]

In light of these results and the systemic nature of atherosclerotic disease, we hypothesize that long-term survival will be similar between IHD patient with or without coronary revascularization due to a shift from IHD-related towards non-IHD-related mortality. [15-17] The objective of this study is to determine the prognostic implication of ischemic heart disease and coronary revascularization on long-term overall and cardiovascular mortality in patients undergoing vascular surgery.

METHODS

Patients undergoing elective open or endovascular surgery under general or locoregional anesthesia for abdominal aortic aneurysm (AAA), carotid artery stenosis (CAS) or peripheral artery disease (PAD) in the Erasmus University Medical Center between January 2003 and December 2011 were retrospectively included.

Identification was done with the use of operation codes and surgical reports. Since we were interested in the effect of IHD and prior coronary revascularization (CR) on procedures that are accompanied by severe cardiac stress, patients undergoing percutaneous procedures (i.e. percutaneous EVAR, carotid artery stenting and lower extremity revascularization) or procedures performed under local anesthesia were not included in this study. When a patient underwent multiple vascular procedures within the study period, the first operation in this period was defined as the index operation and survival was assessed from that moment onward. Baseline characteristics were obtained from hospital records and included age, gender, cardiac history, other comorbidities, smoking status (current, former or never) and body mass index (BMI). Patients were grouped according to their cardiac status prior to the index operation. Ischemic heart disease was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention or evidence of myocardial ischemia in provocative pre-operative tests (dobutamine stress echocardiography or myocardial scintigraphy). CR was defined as coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) at any time prior to the index vascular operation. Treatment indications for coronary revascularization were in accordance with the AHA guidelines (Appropriateness Criteria for Coronary Revascularization). Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

Definitions: Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral anti-diabetics. Hypertension was defined as blood pressure >140/90 mmHg or use of anti-hypertensive medication. A history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min as calculated from preoperative serum creatinine levels using the MDRD formula. Smoking status and BMI were derived from the medical records.

Follow up: Survival status was obtained by inquiry of the civil registry. The latest date of follow up was considered December 31st 2012.

Cause of death: Data regarding the causes of death were obtained from the Dutch Central Bureau of Statistics (CBS). A database containing all relevant patient characteristics from the hospital records was anonymised and imported into the CBS and was subsequently linked to the Dutch death registries. Because of CBS

regulation, data analysis was only performed by authorized researchers (KU, FBG) in a secure environment at the CBS head office. Before data was approved to be used for publication purposes, all output was independently checked for privacy violations by two separate reviewers. The cause of death was defined as the cause for the initial health deterioration, which subsequently resulted in death. This approach is similar to the strategy employed for the overall Dutch population death registrations and reports. Autopsy was not regularly performed. The causes of death were grouped according to the *International Classification of Diseases, 10th Revision* (ICD-10). For cardiovascular death, the following codes were used: I10-I79; for IHD-related death: I20-I25, I50; and for non-IHD cardiovascular death: I10-I19, I26-I49, I51-I79 (Supplemental Table 1). Since ischemic heart disease is the principal etiology of heart failure, death due to heart failure-related causes was classified as IHD-related death.[18, 19]

Endpoints: The primary endpoints were long-term overall and cardiovascular mortality. Secondary endpoints were IHD-related and non-IHD-related cardiovascular mortality.

Statistical methods: Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were determined using Pearson's chi-square analysis and one-way ANOVA-testing, where appropriate. For survival analyses, patients were grouped according to their cardiac medical history. Patients overall survival was initially assessed using Kaplan-Meier analyses. Cox proportional hazards models were constructed to study the impact of IHD and the influence of invasive treatment on overall and cardiovascular survival in an adjusted manner. Multivariate analyses included demographics (i.e. age and gender), comorbidities (i.e. diabetes, hypertension, a history of cancer, renal insufficiency and body mass index) and behavioural risk factors (i.e. smoking). To determine the prognostic implications of invasive and non-invasive treatment strategies for IHD (i.e. CABG or PCI), the overall IHD group was subdivided into a non-coronary revascularization group (non-CR) and a coronary revascularization group (CR). The non-IHD group was designated the reference category for the Cox regression analyses. Differences in cardiovascular death distribution, i.e. different proportions of IHD-related and non-IHD-related death, were tested with the use of chi-square analyses. All tests were two-sided and significance was considered when P-value $< .05$. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL).

RESULTS

Between January 2003 and December 2011, a total of 1107 patients received surgical treatment for AAA, CS or PAD. Three patients (0.3%) were excluded because of unobtainable follow up due to emigration. Among the resulting 1104 patients, 499 (45.2%) had a history of IHD. Within the IHD group, coronary revascularization was performed preoperatively in 245 cases (22.2%).

Baseline characteristics

Baseline characteristics per study group (i.e. non-IHD, non-CR IHD and CR IHD) are listed in Table 1. Vascular surgical patients with IHD were older, were more frequently of male gender, and had a higher BMI as compared to those without IHD. Furthermore, diabetes, renal insufficiency, and hypertension were more

Table 1. Baseline characteristics.

Variable	***non-IHD*** *(n=605)*	***non-CR IHD*** *(n=254)*	***CR IHD*** *(n=245)*	***P-value***
Demographics				
Female gender – N (%)	174 (29)	47 (19)	36 (15)	< .001
Age (years, mean ± SD)	67.4 (± 10.2)	70.0 (± 9.6)	69.4 (±9.3)	.001
Prior medical history				
Diabetes mellitus – N (%)	112 (19)	65 (26)	67 (27)	.006
History of cancer – N (%)	98 (16)	45 (18)	41 (17)	.868
Peripheral arterial occlusive disease – N (%)	251 (41)	108 (43)	123 (50)	.062
Renal insufficiency – N (%)	126 (21)	76 (30)	82 (33)	< .001
Cerebrovascular disease – N (%)	238 (39)	100 (39)	94 (38)	.962
Hypertension – N (%)	375 (62)	190 (75)	190 (78)	< .001
History of vascular interventions – N (%)	133 (22)	64 (25)	63 (26)	.406
IHD Characteristics				
Myocardial infarction – N (%)	0	186 (73)	189 (77)	-
Angina – N (%)	0	91 (36)	202 (83)	-
CABG/PTCA – N (%)	0	0	245 (100)	-
Environmental Risk Factors				
Smoking – N (%)	257 (43)	97 (38)	75 (31)	.005
Body Mass Index – (kg/length^2, mean ± SD)	25.7 (±4.1)	26.2 (±4.3)	26.9 (4.1)	.001

IHD: Ischemic Heart Disease.
CR: Coronary Revascularization (i.e. CABG or PTCA).

common among patients with IHD. Finally, current smoking was more frequently observed among non-IHD patients.

Overall mortality

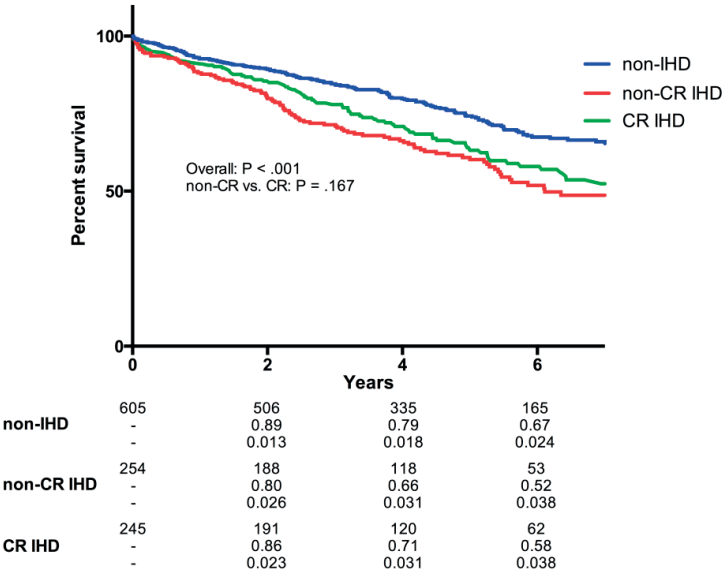
During a median follow up of 4.1 years (IQR: 2.3 – 5.9), 164 (27.1%), 108 (42.5%) and 91 (37.1%) deaths occurred in the non-IHD, non-CR IHD, and CR IHD groups, respectively (Table 2). Kaplan-Meier analyses showed a significant difference in the postoperative prognosis between non-IHD and IHD patients, with an expected survival at 5 years of 74% and 62%, respectively (P < .001; Figure 1). There was no significant difference in survival between IHD patients without or with coronary revascularization (60% and 62% at 5 years for non-CR and CR IHD groups, respectively, P = .167). Ischemic heart disease was confirmed as an independent risk factor for all cause mortality in Cox-regression analysis as compared to vascular surgical patients without a history of IHD (HR: 1.50, 95% CI: 1.21 – 1.87, Table 3). Regarding survival for the non-CR IHD and CR IHD separately, both groups were burdened by additional survival hazards compared with the non-IHD group (HR: 1.62, 95% CI: 1.26 – 2.08, HR: 1.38, 95% CI: 1.05 – 1.80, respectively, for the non-CR IHD and the CR IHD groups.). However,

Table 2. Mortality and the causes of death for the study groups separately. Percentages are relative to the total obtained deaths per study group.

Cause of Death	***non-IHD*** *(n=605)*	***non-CR IHD*** *(n=254)*	***CR IHD*** (n=245)
All cause	164[a]	108	91
Cancer	54 (33.1)	23 (21.3)	20 (22.0)
Cardiovascular	53 (32.5)	46 (42.6)	42 (46.2)
IHD-related	13 (8.0)	28 (25.9)	15 (16.5)
Non-IHD cardiovascular	40 (24.5)	18 (16.7)	27 (29.7)
Cerebrovascular disease	14 (8.6)	<5 (<4.6)[c]	<5 (<5.5)
Other arterial disease	17 (10.4)	13 (12.0)	17 (18.7)
Non-ischemic heart disease[b]	6 (3.7)	<5 (<4.6)	6 (6.6)
Other[d]	<5 (<3.1)	<5 (<4.6)	<5 (<5.5)
COPD	10 (6.1)	<5 (<4.6)	5 (5.5)
Digestive system	10 (6.1)	<5 (<4.6)	<5 (<5.5)
Other causes	36 (22.1)	32 (29.6)	22 (24.2)

[a] 163/164 deaths (99.3%) were obtained.
[b] e.g. valvular heart disease, cardiomyopathy
[c] Numbers smaller than 5 were not provided to protect privacy
[d] i.e. hypertensive and pulmonary circulatory disease

Figure 1. Kaplan-Meier analyses for overall survival.



there was no significant difference in overall survival between the revascularized and the non-revascularized IHD groups (P = .274).

Cardiovascular mortality

Causes of death could be obtained for all but one patient (99.7%). Cardiovascular disease was reported as the cause of death in 53 (32.5%) cases in the non-IHD group, and in 46 (42.6%) and 42 (46.2%) cases in the non-CR and CR IHD groups, respectively (Table 2). Adjusted analysis showed that patients with IHD were at higher risk of cardiovascular death compared to patients without IHD (HR: 1.93, 95% CI: 1.35 – 2.76, Table 3). Both the non-revascularized and the revascularized groups had an increased risk of cardiovascular death compared to the non-IHD group (HR: 2.02, 95% CI: 1.34 – 3.04, HR: 1.83, 95% CI: 1.19 – 2.81). Equivalently to overall survival, cardiovascular survival between the non-CR and CR groups was similar (P = .656).

Ischemic heart disease-related and non-ischemic heart disease related cardiovascular mortality

IHD-related death occurred 13 times (8.0%) in the non-IHD group during the follow-up period. In the non-revascularized and revascularized IHD groups, IHD-related death was determined in 28 (25.9%) and 15 (16.5%) cases, respectively (Table 2, Figure 2). Death due to cardiovascular causes other than IHD was ascer-

Figure 2. Proportions of specific cardiovascular death causes among the different study groups. Percentages are relative to the total cardiovascular deaths per study group.

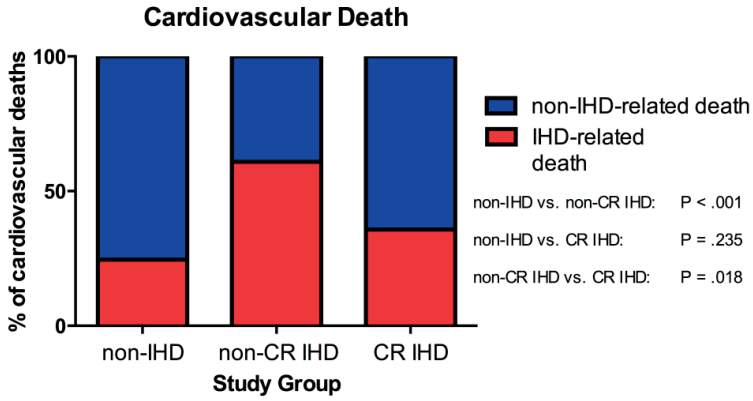


Table 3. Cox regression analyses for overall and cardiovascular mortality. Hazard ratio's for the two IHD groups separately were established in a model with the non-IHD group as reference category.

	Univariate			***Multivariate***		
Overall death	*HR*	*95% CI*	*P-value*	*HR*	*95%CI*	*P-value*
Overall IHD	1.64	1.33 – 2.01	< .001	1.50	1.21 – 1.87	< .001
non-CR	1.80	1.41 – 2.29	< .001	1.62[a]	1.26 – 2.08	< .001
CR	1.48	1.15 – 1.92	.003	1.38[a]	1.05 – 1.80	.019
Cardiovascular death	*HR*	*95% CI*	*P-value*	*HR*	*95%CI*	*P-value*
Overall IHD	2.24	1.59 – 3.15	< .001	1.93	1.35 – 2.76	< .001
non-CR	2.36	1.59 – 3.50	< .001	2.02[b]	1.34 – 3.04	.001
CR	2.12	1.41– 3.18	< .001	1.83[b]	1.19 – 2.81	.006

[a] Overall survival between the non-CR and the CR IHD did not differ (P = .274).
[b] Cardiovascular survival between the non-CR and the CR IHD did not differ (P = .656).

tained in 40 (24.5%), 18 (16.7%) and 27 (29.7%) cases. The distribution of the cardiovascular cause of death subgroups, IHD-related and non-IHD related, was significantly different between the non-IHD and the non-CR IHD groups. Patients with a history of IHD were more likely to die of IHD-related causes, whereas the majority of cardiovascular death among non-IHD patients was unrelated to coronary artery disease (P < .001). No significant divergences were found in the cardiovascular death distributions between the non-IHD and the CR-IHD groups (P = .235). The distribution between non-revascularized and revascularized IHD patients, however, differed significantly. Cardiovascular death in the non-CR IHD

group was predominantly due to IHD-related causes, whereas the majority of cardiovascular death among revascularized patients was due to non-IHD-related disease (P = .018).

DISCUSSION

The results of the present study confirm that prior ischemic heart disease is a significant prognostic factor for long-term overall and cardiovascular survival after vascular surgery. Interestingly, patients with previous coronary revascularization had similar total cardiovascular mortality but proportionally less ischemic cardiac related deaths compared to patients with a history of IHD but no prior revascularization. However, prior coronary revascularization did not provide a survival benefit for patients with IHD. This indicates that coronary intervention had an impact on the occurrence of subsequent cardiac events, but failed to provide protection for cardiovascular death in general.

Our findings are in line with the study by Back et al., who showed that although perioperative cardiac factors are the primary determinants of life expectancy, patients with a history of coronary revascularization did not have a better survival following major arterial reconstruction.[12] In addition, the CARP and DECREASE-V trials demonstrated that even preoperative coronary revascularization in patients with extensive myocardial ischemia on preoperative cardiac testing failed to improve postoperative survival compared to best medical treatment alone in patients undergoing elective vascular surgery.[7-9, 20] These studies formed the basis for the current standpoint that coronary revascularization prior to major non-cardiac surgery should not routinely be performed.[21]

As hypothesized, overall mortality and the death rate distribution among the main categories, including cardiovascular and cancer-related death, were similar in the non-CR and CR IHD group. Further, we found that cardiovascular death in patients with established IHD who had not been treated for coronary stenosis by CABG or PCI was most frequently due to ischemic cardiac events. However, those who underwent prior coronary treatment more often died of non-cardiac ischemic events, the majority of which were related to peripheral arterial rather than cerebrovascular disease. Thus, in spite of the impact on cardiac events, treatment of IHD induces a shift in the cause, rather than providing protection against cardiovascular death. Such a shift in mortality from IHD-related towards non-IHD-related death implicates that a history of IHD in vascular surgery pa-

tients should be regarded as a sign of advanced atherosclerotic disease. This is in agreement with several previous studies showing that vascular patients are often burdened by advanced atherosclerotic disease, whether or not symptomatic, in multiple vascular beds.[22, 23] Also, it has been shown that the rates of ischemic events in other vascular beds are higher in vascular patients with a history of IHD as compared to those without.[24-26]

In view of the risks conferred by advanced atherosclerotic disease, intensification of cardiovascular risk management may be a potential means to reduce non-cardiac cardiovascular health hazards and improve postoperative outcome in these high-risk individuals. Although the effectiveness of secondary prevention measures for reducing overall and cardiovascular death is well established, studies have demonstrated that adherence to the guidelines is less than 60%.[27] A lack of knowledge and attitude of both patients and physicians have been implicated to play a causal role.[28, 29] Therefore, improving patient and physician attitude regarding the importance of atherothrombotic risk and secondary prevention is worthwhile. In addition to stimulating guideline adherence, stricter management of the cardiovascular risk factors should be considered. For example, tight control of blood pressure (i.e. ≤ 130-135mmHg), as opposed to relaxed control (i.e. ≤140mmHg), might be associated with a reduction in cardiovascular morbidity and mortality.[30, 31] Moreover, lowering blood pressure by as little as 10mmHg has been reported to reduce the lifetime risk for cardiovascular and stroke-related death by 25% to 40%.[32] Similar associations have been found for both blood glucose and lipid levels.[33-35]

The limitations of this study are inherent to its retrospective nature. Since all symptomatic IHD patients were grouped into a single ischemic heart disease group, we could not differentiate between prognostic differences in relation to severity of ischemic heart disease. Previous studies have questioned whether survival benefits from coronary revascularization are generalizable.[36] Evidence suggests that survival benefits from coronary revascularization before vascular surgery are most significant among severely affected coronary patients.[6] Additionally, no difference was made based on the time between CR and the index operation. Prior research has shown that the protective effect of coronary revascularization for adverse cardiac events diminishes as time progresses.[11, 37] This suggests that the demonstrated shift from IHD towards non-IHD-related cardiovascular mortality will be more apparent in vascular patients who have undergone recent coronary revascularization. Our study could not discriminate between CABG and PCI in survival benefit analysis. Finally, stratified analyses for each surgical indication

separately was not performed due to the limited event rates in the subgroups and the consequent lack of statistical power.

CONCLUSION

In conclusion, this study adds new insights in the implications of IHD on long-term survival in vascular surgery patients. Our data confirms the significance of IHD for postoperative survival of these patients as well as the effectiveness of coronary revascularization in the reduction of cardiac ischemic events. However, we also show that treatment of IHD alone is insufficient to improve life expectancy in these high-risk patients. Patients with prior revascularization for IHD indeed have reduced risks of fatal cardiac ischemic events, but this does not translate into an overall survival benefit since they have a greater risk to die of cardiovascular causes unrelated to ischemic heart disease. Further research is warranted to determine whether more aggressive secondary prevention regimens are justified to prevent the shift towards non-IHD-related health hazards and thus improve postoperative survival in patients with advanced atherosclerotic disease.

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Supplemental Table 1. Causes of death definitions in accordance with ICD-10 classification

Cancer-related death	
ICD-10	**Description**
C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue
C76-C80	Malignant neoplasms of ill-defined, secondary and unspecified sites
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue
C97-C97	Malignant neoplasms of independent (primary) multiple sites
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms
D37-D48	Neoplasms of uncertain or unknown behavior
Cardiovascular death	
Ischemic heart disease-related cardiovascular death	
ICD-10	**Description**
I20-I25	Ischemic heart disease
I50-I50	Heart failure
Non-ischemic heart disease-related cardiovascular death	
ICD-10	**Description**
I10-I15	Hypertensive disease
I26-I28	Pulmonary heart disease and diseases of the circulatory system
I30-I49	Other forms of heart disease
I51-I52	Other forms of heart disease
I60-I69	Cerebrovascular disease
I70-I79	Diseases of arteries, arterioles and capillaries
Chronic obstructive pulmonary disease-related death	
ICD-10	**Description**
J40-J47	Chronic lower respiratory diseases
Digestive system-related death	
ICD-10	**Description**
K00-K14	Diseases of oral cavity, salivary glands and jaws
K20-K31	Diseases of oesophagus, stomach and duodenum
K35-K38	Diseases of appendix
K40-K46	Hernia
K50-K52	Noninfective enteritis and colitis
K55-K64	Other disease of intestines
K65-K67	Diseases of peritoneum
K70-K77	Diseases of liver
K80-K87	Disorders of gallbladder, biliary tract and pancreas
K90-K93	Other diseases of the digestive system

Summary

SUMMARY

In *Part I,* the current position of endovascular repair for the treatment of acute thoracic and abdominal aortic pathologies was assessed. Chapter 1 demonstrates that thoracic endovascular aortic repair (TEVAR) is now the dominant surgical approach for traumatic thoracic aortic injuries, with substantial perioperative morbidity and mortality benefits over open repair. Overall mortality following admission for traumatic aortic injuries has declined, which appears to be the result of both the replacement of open repair by TEVAR, as well as the broadened eligibility for surgical repair. In line with these findings, Chapter 2 showed that TEVAR is now the primary surgical treatment for ruptured thoracic aortic aneurysms as well. The introduction of endovascular treatment appears to have broadened the proportion of patients undergoing surgical repair, particularly among the elderly. Also, overall mortality has declined significantly since the introduction of TEVAR. For ruptured abdominal aortic aneurysms, the compiled evidence in Chapter 3 suggests that endovascular repair (EVAR) is an effective and safe strategy as a primary treatment modality for ruptured abdominal aortic aneurysms (AAA). Although the survival advantage for EVAR persisted during the first five years after repair, no difference in survival was observed thereafter. The institutional series in Chapter 4 supports this conclusion, demonstrating that endovascular repair is associated with superior perioperative mortality over open repair, which was maintained for three years. Additionally, these data suggest that elderly patients, and those presenting with haemodynamic instability may particularly benefit from minimally invasive treatment. Chapter 5 focuses on early outcomes of symptomatic AAA repair. It was observed that patients with symptomatic AAAs have a two-fold increased risk of perioperative mortality, compared to asymptomatic aneurysms undergoing repair. Endovascular repair proved to be favorable to open repair for this acute indication as well.

Part II was dedicated to clarify, and assess risks associated with technical aspects of performing AAA repair. Chapter 6 and Chapter 7 focused on the risks of performing concomitant procedures at the time of elective AAA repair. This analysis revealed that performing concomitant procedures is not risk free, with simultaneous femoral endarterectomy and renal angioplasty or stenting during endovascular aneurysm repair (EVAR) established as independent risk factors for 30-day mortality. For open repair, performing concomitant renal bypass surgery, a thrombo-embolectomy, and other abdominal procedures is predictive of early mortality. These and other procedures during endovascular and open repair are additionally risk factors for the occurrence of various other adverse perioperative outcomes. Chapter 8 assessed the relative performance of endovascular repair

for abdominal aneurysms with complex proximal anatomy. This study revealed that EVAR for anatomically complex AAA is associated with significantly reduced perioperative morbidity and mortality compared to complex open repair, but –in turn– does carry a higher risk of adverse outcomes than standard infrarenal EVAR. In Chapter 9, differences between patients undergoing transperitoneal vs. retroperitoneal AAA repair were assessed. The data showed that retroperitoneal surgery is more commonly used for proximally located aneurysms, and aneurysms during which concomitant renal, visceral, and lower extremity revascularization procedures were performed. Although crude analysis indicated a more complicated postoperative period following retroperitoneal surgery, no significant differences were established after adjustment for confounding factors. Chapter 10 shows that vascular surgeons are performing an increasing majority of AAA repairs, in large part driven by the increased utilization of EVAR for both intact and ruptured AAA repair. However, cardiac surgeons and general surgeons still perform AAA repair, in particular ruptured AAAs treated through open repair. Chapter 11 was dedicated to assess long-term outcome after AAA repair, focusing on the implications of surgical techniques and timing of the procedure. While rupture was associated with more than a tenfold increase in early mortality, patients with a ruptured AAA surviving the first 30 days proved to have a similar vital prognosis as those undergoing elective repair. A trend towards improved overall and cardiovascular survival was observed following EVAR, with an increasing importance of cancer-related mortality.

In *Part III*, various complications encountered after AAA repair are analyzed in detail to clarify their incidence, significance, and risk factors for occurrence. Chapter 12 reveals that the incidence of bowel ischemia following intact AAA repair was 1.6%, and 15.2% following ruptured repair. The cause of postoperative bowel ischemia is multifactorial in nature, and can be attributed to patient factors, including age, gender, comorbid conditions, and smoking, as well as operative characteristics such as operative time, treatment approach, and hypogastric interruption. The most important risk factors, however, are open repair and rupture, which were associated with a three-fold and six-fold increase, respectively. Chapter 13 demonstrates that early renal complications occur in 1% of patients undergoing EVAR and 5% of those undergoing open repair. Early mortality is significantly greater among patients with renal complications, and preoperative creatinine, perioperative transfusion, and open technique are the major predictors of its occurrence. Chapter 14 shows that conversion surgery to open repair is performed in 1.2 per 100 EVAR cases. Conversion surgery is hazardous, with perioperative mortality rates more than twice as high as standard open AAA repair. Factors associated with conversion are large diameter

of the aneurysm, young age, female gender, and non-white race, while obesity is inversely related to conversion surgery.

In *Part IV*, the authors shed light on underexposed characteristics affecting the long-term performance after surgery. Chapter 15 demonstrated that socioeconomic deprivation is a predictor of adverse outcome after vascular surgery independent of healthcare disparities and conventional risk factors. For AAA patients, the association was of an exponential nature, while for peripheral artery disease (PAD) patients the relation followed a linear path. In Chapter 16, we attempted to extrapolate this association beyond vascular surgery. The relation between socioeconomic status and long-term postoperative survival was confirmed to exist in a general surgical population. Additionally, this study showed that the predictive value of socioeconomic deprivation was particularly apparent for cardiovascular mortality, while for cancer-related mortality it was not. Chapter 17 confirms the significance of ischemic heart disease (IHD) for postoperative survival of vascular surgery patients. More importantly, the data show that coronary revascularization is associated with lower IHD-related death rates, but fails to provide an overall survival benefit due to an increased rate of cardiovascular mortality unrelated to IHD. Chapter 18 demonstrates that aneurysmal and occlusive vascular disease do not only differ in terms of etiology and pathophysiology, but are also distinct entities in terms of prognosis. Life expectancy in PAD patients is shorter and is predominantly reduced by cardiovascular morbidity, as opposed to age in AAA patients.

General Discussion

GENERAL DISCUSSION

Endovascular repair for acute aortic pathologies

As an alternative to open repair, endovascular surgery (TEVAR) was first reported for acute thoracic aortic surgery in 1997.[1-3] Although single institution series showed promising results favoring TEVAR, an absolute survival benefit of TEVAR over open repair could not be confirmed for traumatic thoracic aortic injuries, nor for ruptured descending thoracic aortic injuries on a large scale.[17, 18] **Chapter 1 and 2** confirmed that for thoracic traumatic aortic injuries as well as ruptured aneurysms, TEVAR has replaced open repair as the primary mode of treatment and showed that the use of TEVAR has led to an increase in the proportion of patients treated surgically, particularly among patients older than 80. More importantly, TEVAR provided favorable perioperative outcome in terms of in-hospital mortality and adverse perioperative events compared to open repair, despite a worse preoperative condition of patients selected for endovascular repair. Although consistent with institutional-based studies,[4-16] the favorability of TEVAR over open repair in the perioperative period was yet to be established on this scale. The conflicting results with prior national studies is most likely due to a combination of improved outcome of TEVAR in more recent years, as well an increase in TEVAR volume in the present study. The present findings support the Society for Vascular Surgery Practice Guideline (2011) to preferentially perform TEVAR over open surgical repair and nonoperative management.[19] In **Chapter 3**, the controversial subject of utilizing endovascular repair (EVAR) for acute abdominal aortic surgery is handled. A literature review was conducted to compare open surgery to EVAR in the setting of ruptured AAA repair. It was demonstrated that concurrent with the widespread adoption of EVAR since the turn of the century, perioperative mortality declined from 53% to 39%. Moreover, 30-day mortality was less than half of that following open repair. Yet so far, the completed randomized-controlled trials failed to establish a benefit of endovascular repair (EVAR) over open repair for ruptured abdominal aortic aneurysms.[20, 21] This apparent contradiction stresses the need for future studies investigating the use of EVAR in the acute setting. It is important to realize that endpoints in these trials may not have been the most clinically relevant. Furthermore, these trials were analyzed on an intention-to-treat basis, which may have precluded clarification of the most important clinical questions. As a result, the use of an endovascular-first strategy has remained controversial. In the institutional series of ruptured AAA patients described in **Chapter 4**, crude mortality for EVAR was very similar to the mortality rate presented in in the IMPROVE trial (approximately 24%),[21] and much lower than the reported mortality after open repair which did not notably change during the last decades. Consistent

with the findings for thoracic aortic surgery in this thesis and the IMPROVE trial, older patients and those in worse preoperative condition benefitted most from the introduction of endovascular repair.[21] Additionally, the present results indicate that variability exists in the role of preoperative risk factors for each of the treatment strategies, which suggests that different patient factors affect outcome depending on the type of repair. Although less life-threatening than ruptured aneurysms, symptomatic disease is also considered to require (semi-)acute repair. Prior to the introduction of EVAR, many studies have demonstrated symptomatic AAA repair to be associated with substantially worse perioperative prognosis compared to elective surgery.[22-27] In a more recent study, which showed no difference between elective and symptomatic patients, it was suggested that increased utilization of endovascular repair, as well as improved perioperative care have reduced adverse outcomes of symptomatic AAA patients.[28] The largest series of symptomatic AAAs to date presented in **Chapter 5** demonstrates that symptomatic AAA repair remains associated with twice the perioperative mortality compared with asymptomatic patients in the endovascular era. Nevertheless, perioperative mortality among patients with symptomatic aneurysms was substantially lower in comparison with prior reports in which the majority were treated with open repair. Therefore, these data support an EVAR-first approach for symptomatic aneurysms with suitable anatomy.

Clarifying procedural risk factors for AAA repair

Although numerous technical aspects of both open and endovascular AAA repair have been studied over the years, the safety and effectiveness of many other facets of AAA surgery remain elusive. AAA repair may be performed in conjunction with additional procedures. These concomitant procedures are done for various reasons, such as gaining adequate access to aorto-iliac vessels, establishing adequate endograft seal, but also to resolve intraoperative pitfalls, or to treat unrelated conditions. With 29% of patients undergoing one or more additional procedure, **Chapter 6** demonstrates that concomitant procedures are commonly performed during elective endovascular AAA repair.[29] Renal artery angioplasty or stenting and femoral endarterectomy were independent risk factors for perioperative mortality, with various other interventions, including iliac angioplasty or stenting, hypogastric embolization, femoro-femoral bypass, being predictors of 30-day complications and prolonged length of stay. This is somewhat in contrast to the largest report on this subject by Hobo et al., which showed that only open surgical interventions for peripheral vascular disease significantly worsened outcome, while concomitant endovascular procedures were associated with low to zero additional risks.[29] Although some concomitant procedure are a necessitated

by their facilitating role to the endograft delivery, the present findings highlight the importance of careful deliberation of the operative risks and the necessity of additional procedures during operative planning. The poor outcome of thrombo-embolectomy stresses the importance of adequate intraoperative anticoagulation. Similar conclusions may be drawn for concomitant procedures during open repair, as **Chapter 7** showed that concomitant renal artery bypass surgery, other abdominal interventions, and performing a thrombo-embolectomy were predictive of substantially increased 30-day mortality. Moreover, for concomitant renal bypass it has even been demonstrated that normotension is less often achieved after combined aortorenal reconstruction as compared to a staged approach.[30, 31] Through advancements in endovascular treatment techniques, including chimney, fenestrated and branched stent grafts, EVAR can now be offered to patients with complex proximal neck anatomy.[32] **Chapter 8** demonstrates that endovascular repair for juxta- and suprarenal aneurysms has favorable outcome compared to open repair, but –in turn– is associated with increased perioperative risks compared to infrarenal EVAR. This is in agreement with a large national series from the United Kingdom, which demonstrated that fenestrated endovascular repair can be performed with a high degree of technical and clinical success,[33] even though systematic reviews showed conflicting results.[34-36] Nevertheless, this study demonstrates that as a result of advancements in endovascular treatment techniques, EVAR has become a good alternative to conventional open repair for treatment of anatomically juxta- and suprarenal aneurysms. Further research is warranted to determine whether the favorable outcome of EVAR for juxta- and suprarenal AAA is maintained during long-term follow-up. In spite of these technical advancements and the consequent increasing eligibility for EVAR, open surgical repair remains necessary to treat patients anatomically unsuitable for endovascular repair and those unable to comply with long-term surveillance.[37-40] Some studies comparing perioperative outcomes of transperitoneal and retroperitoneal approach for AAA repair suggest that the retroperitoneal approach may result in lower rates of ileus, shortened hospital length of stay, and improved respiratory function than transperitoneal procedures.[41-47] Randomized data, however, indicated that such trends were independent of transperitoneal versus retroperitoneal approach.[48, 49] In **Chapter 9**, we confirmed the findings from the randomized study in a larger cohort, as multivariable analysis showed that the associations with worse outcome were mostly mediated by concomitant procedures, and that neither of the two operative approaches showed clear benefits over the other in adjusted analysis. In light of these findings, the operative approach may be motivated by anatomy and surgeon preference. **Chapter 10** reveals that as the utilization of EVAR increases, vascular surgeons are performing an increasing majority of AAA repairs. In addi-

tion to the widespread adoption of EVAR, regionalization of open AAA repairs to high-volume centers since the turn of the century is likely to have contributed.[50] The rise in responsibility of vascular surgeons for AAA care is endorsed by the fact that patient outcomes of EVAR were found to be better when procedures were performed by surgeons instead of interventionalists.[51] Nevertheless, general surgeons and cardiac surgeons still participate in the care for AAA patients, particularly emergent AAA repair, which is likely due to rural geographic locations where the presence of specialized vascular surgeons is lacking.[52] Operating these patients with ruptured AAA can only be truly beneficial if they have a reasonable life expectancy afterwards. Previous studies have shown that the long-term prognosis of patients surviving the perioperative period after ruptured AAA repair is similar to that of electively treated patients.[53] **Chapter 11** confirms this in a more recent cohort, and additionally reveals a shift towards cancer as a dominant cause of late mortality. The reason for this substantial contribution is unknown, and is in contrast to current mortality trends showing a decrease in the incidence of malignant disease in the Western world.[54] Nevertheless, the marked impact of cancer on the prognosis of AAA patients suggests that the focus of care should not only be on secondary cardiovascular prevention, but also on early detection and treatment of malignancies.

Complications following AAA repair

Aside from generic complications such as pneumonia and wound infections, the postoperative period after AAA repair may be troubled by adverse outcomes specific to AAA repair. A better understanding of their etiology may aid in prevention and adequate allocation of the necessary care. **Chapter 12** confirms that although the incidence of bowel ischemia following AAA repair is low, it is associated with very poor outcomes. The increase in perioperative mortality ranged from of a factor of two among patients undergoing open repair for ruptured AAA, and a factor of 38 among those undergoing EVAR for intact AAA. The cause of postoperative bowel ischemia is multifactorial in nature, and can be attributed to patient factors, as well as operative characteristics. In contrast to some previous work, open repair proved to be an important predictor.[55] In addition to bowel ischemia, open AAA surgery is also a well-established risk factor for renal dysfunction. **Chapter 13** revealed that postoperative renal complications occur in 1% of elective infrarenal EVARs and 5% of open repairs, and are associated with a detrimental prognosis, with perioperative mortality ranging between 30-55%. Elevated baseline creatinine, open surgical approach, transfusion, and operative time were most predictive of renal complications. Given the dramatic increase in mortality in those affected, care should be taken to utilize an endovascular approach when techni-

cally feasible, to achieve meticulous hemostasis, and to employ renal protective strategies, including adequate perioperative volume expansion and minimization of exposure to nephrotoxic drugs and contrast agents.

Recently, it has become apparent that endovascular treatment is associated with more early and late graft-related complications compared to open repair, and that endovascular patients more commonly undergo reinterventions.[56-58] As an ultimate failure of endovascular treatment, some patients require conversion to open repair. This subject was studied in **Chapter 14**. Our data showed an occurrence rate for conversion of 1.2 per 100 EVARs in a cohort of almost 25,000 EVAR cases from 2005 onward. This is substantially lower than the first conversion series from 1997 showing a rate of nearly 16% (11.5% acute, 4.5% late).[59] The difference is most likely the result of improved patient selection and surgeon experience, as well as technical advances in endovascular repair allowing for patients with more challenging anatomy to be successfully treated using endovascular treatment modalities. This is supported by a decline in conversion rates in more recent reports.[57, 60] In contrast to the largest conversion cohort to date, the data presented in Chapter 14 revealed that conversion surgery is associated with more than double the 30-day mortality compared to standard open repair (10.0% vs. 4.2%).[61] However, since conversion to open repair is a rare occurrence, we believe that open surgery should not regularly be considered as a first line treatment with future risks of conversion in mind.

Long-term prognosis after vascular surgery

Many studies have been dedicated to assessing risk factors for long-term survival after vascular surgery, among which socioeconomic status (SES). These studies were often performed in the United States, where SES-related disparity in access to and provision of healthcare exists and is extensively affected by income. As a result, the relationship between low SES and poor outcome is often attributed to healthcare disparities.[62-66] Healthcare in the Netherlands is publicly provided and has been credited the most equally accessible healthcare system in the world.[67, 68] Hence, as opposed to the US system, the Dutch healthcare system provides the unique opportunity to study the association between SES and outcome irrespective of healthcare disparities. In **Chapter 15** we were able to demonstrate that socioeconomic deprivation is a predictor of adverse outcome after vascular surgery independent from conventional risk factors, in particular for peripheral artery disease patients. Considering the equality of care provided by the study setting, the increased health hazards observed in this study should be attributed to patient related factors rather than differences in medical care. The SES-related mortality hazard most likely comprises of various established health risks associated with

low socioeconomic status, including poor dietary habits, limited physical activity, psychosocial stress, and perhaps even epigenetical factors.[69-88] **Chapter 16** showed that the survival risks associated with low SES not only affect vascular patients, whom are considered to be relatively more susceptive to environmental risk factors, but rather all surgical patients. Furthermore, it was shown that low SES particularly worsens cardiovascular survival, and was not predictive of cancer-related mortality after adjusting conventional risk factors. Although the association between low SES and worse outcome is multifactorial and complex, a better understanding of this relation may help to attenuate health disparities. In addition, increased physician awareness, perhaps through the consideration of SES in preoperative risk scores, and focus on improving these established SES-related risk factors may help to improve outcome of low SES surgical patients. In **Chapter 17** we investigated the subject of heterogeneity within vascular disease, and the possible long-term differences between aneurysmal and occlusive vascular disease. The results showed that aneurysmal and occlusive vascular disease not only differ in terms of etiology and pathophysiology, but are also distinct entities in terms of prognosis. The relative high contribution of cardiovascular disease towards mortality in PAD patients suggests that emphasis on aggressive cardiovascular risk factor modification in particularly these patients may be beneficial in order to maximize longevity. Therefore, increased attention to medication compliance,[89] and implementation of intensified secondary prevention strategies, such as tightened control of blood pressure, lipids, and glucose margins in diabetics, should be considered in these patients.[90-95] Due to the systemic nature of atherosclerosis, vascular surgery patients are frequently affected by ischemic heart disease (IHD), symptomatic or not.[96] While evidence has shown that IHD in vascular surgery patients has a negative impact on the postoperative prognosis, it is unclear whether this is solely due to IHD-related death or due to non-IHD-related mortality risks as well.[97, 98] In an attempt to improve postoperative survival, several studies have investigated the effectiveness of coronary revascularization on the prognosis of patients undergoing non-cardiac interventions.[99-107] **Chapter 18** revealed that coronary revascularization was associated with lower IHD-related death rates compared to conservatively treated IHD, but failed to provide an overall survival benefit due to an increased rate of cardiovascular mortality unrelated to ischemic heart disease. Therefore, these data suggests that vascular surgery patients who have undergone a coronary revascularization may also benefit from intensification of cardiovascular risk management.

In conclusion, this thesis demonstrates that endovascular repair for aortic surgery has become a widely implemented and good alternative to open repair not only

in an elective setting, but also for those requiring acute aortic repair. Through an assessment of various procedural aspects of aortic repair, as well as a critical review of the perioperative and long-term prognosis after aortic and peripheral vascular surgery, this thesis has contributed to a better understanding of patient performance following vascular surgery. Although continued research remains necessary in this ever-evolving field, these new findings may provide clinical guidance and serve as potential leads for improvement of patient care, and thereby patient outcome.

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Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

In *deel I* wordt de huidige positie van endovasculaire behandeling voor acute thoracale en abdominale aortapathologie bestudeerd. Hoofdstuk 1 laat zien dat endovasculaire behandeling van de thoracale aorta (TEVAR) tegenwoordig de dominante chirurgische aanpak is voor traumatische thoracaal aortaletsel. Bovendien was TEVAR geassocieerd met aanzienlijke verbeteringen in perioperatieve morbiditeit en mortaliteit in vergelijking met open chirurgie. De algehele mortaliteit na opname voor traumatisch thoracaal aortaletsel is afgenomen, wat het gevolg is van zowel de vervanging van open chirurgie door TEVAR, als een toename in het aantal patiënten dat door de introductie van TEVAR in aanmerking komt voor chirurgische reparatie. In lijn met deze bevindingen blijkt uit hoofdstuk 2 dat TEVAR tevens de primaire chirurgische behandeling van geruptureerde thoracale aorta-aneurysmata is. Ook hier lijkt de hoeveelheid patiënten die in aanmerking komt voor chirurgische behandeling te zijn toegenomen door de introductie van TEVAR, met name onder ouderen. De literatuurbespreking in hoofdstuk 3 concludeert dat endovasculaire behandeling (EVAR) als primaire behandelingsmodaliteit een effectieve en veilige strategie is voor geruptureerde aneurysmata van de abdominale aorta (AAA). Alhoewel het perioperatieve overlevingsvoordeel na EVAR in vergelijking met open chirurgie gedurende de eerste vijf jaar blijft bestaan, wordt er op een langere termijn geen verschil in mortaliteit geconstateerd. Het institutionele cohort in hoofdstuk 4 ondersteunt deze conclusie gezien de bevinding dat endovasculaire behandeling geassocieerd is met een lagere perioperatieve sterfte in vergelijking met open reparatie, welke op middellange termijn gehandhaafd blijft. Daarnaast toont de data dat oudere patiënten en patiënten die zich presenteren met hemodynamische instabiliteit met name kunnen profiteren van deze minimaal invasieve behandeling. Hoofdstuk 5 richt zich op de vroege uitkomsten na de behandeling van het symptomatische AAA. Patiënten met een symptomatisch AAA hebben een tweemaal verhoogd risico op perioperatieve mortaliteit in vergelijking met patiënten die behandeld worden voor een asymptomatische aneurysma. Naast geruptureerde aneurysmata blijkt endovasculair herstel eveneens voor deze indicatie gunstigere resultaten op te leveren dan open chirurgie.

Deel II is gewijd aan het ophelderen van de risico's verbonden aan verscheidene operatieve aspecten van AAA zorg. Hoofdstuk 6 en hoofdstuk 7 zijn gericht op het in kaart brengen van de risico's die gekoppeld zijn aan het uitvoeren van gelijktijdige procedures tijdens electieve AAA chirurgie. Deze onderzoeken laten zien dat het uitvoeren van gelijktijdige procedures niet geheel zonder risico's is. Ge-

lijktijdige endarteriëctomie van het femoraaltraject en renale angioplastiek tijdens EVAR blijken onafhankelijke risicofactoren voor dertigdagenmortaliteit te zijn. Bij open AAA chirurgie zijn het gelijktijdig uitvoeren van een renale bypassoperatie, een trombo-embolectomie en andere abdominale procedures risicofactoren voor perioperatieve mortaliteit. Deze en andere behandelingen tijdens endovasculaire en open AAA chirurgie zijn bovendien geassocieerd met het optreden van verscheidene andere perioperatieve complicaties. In hoofdstuk 8 zijn de prestaties van EVAR in vergelijking met open chirurgie voor AAA's met complexe anatomie van de aneurysmahals onderzocht. Deze studie toonde dat EVAR voor anatomisch complexe AAA geassocieerd is met significant lagere perioperatieve morbiditeit en mortaliteit vergeleken met open chirurgie. Op zijn beurt draagt complexe EVAR wel een hoger risico op complicaties met zich mee in vergelijking met standaard infrarenale EVAR. In hoofdstuk 9 zijn de verschillen tussen de transperitoneale en retroperitoneale benadering van open AAA chirurgie beoordeeld. Een retroperitoneale benadering werd vaker toegepast voor relatief proximaal gelegen aneurysmata en bij patiënten die gelijktijdig een revascularisatie van de viscerale arteriën, nier en onderste extremiteit ondergingen. Alhoewel de retroperitoneale benadering bij initiële analyse geassocieerd leek met een meer gecompliceerd postoperatief beloop, werden na correctie geen significante verschillen gevonden. Uit hoofdstuk 10 blijkt dat vaatchirurgen verantwoordelijk zijn voor een groeiende meerderheid van AAA chirurgie. Dit is grotendeels het gevolg van de toename van het gebruik van EVAR voor zowel intacte als geruptureerde AAA's. Echter, hartchirurgen en algemeen chirurgen voeren nog steeds AAA operaties uit, voornamelijk de behandeling van geruptureerde AAA's middels open chirurgie. Hoofdstuk 11 is gewijd aan de langetermijnresultaten na AAA reparatie en richt zich op de invloed van de verschillende chirurgische technieken en de timing van de procedure. De behandeling van een geruptureerd aneurysma was geassocieerd met een meer dan tienvoudig risico op perioperatieve mortaliteit in vergelijking met electieve chirurgie. Echter, na de eerste dertig dagen was de overleving vrijwel identiek voor patiënten met een geruptureerde en intact AAA. Daarnaast werd een trend in de richting van een verbeterde algehele en cardiovasculaire overleving gevonden in patiënten behandeld middels EVAR, met een toenemend aandeel van kankergerelateerde sterfte.

In *deel III* zijn verscheidene complicaties na AAA reparatie in detail geanalyseerd om hun incidentie, klinische betekenis en risicofactoren op te helderen. Hoofdstuk 12 laat zien dat de incidentie van darmischemie na intacte AAA chirurgie 1,6% is en 15,2% na een operatie voor geruptureerde aneurysmata. De oorzaak van postoperatieve darmischemie is multifactorieel en kan worden toegeschreven aan

patiëntfactoren zoals leeftijd, geslacht, comorbiditeit en roken, maar ook aan operatieve parameters als operatieduur, type chirurgie en onderbreking van de arteria hypogastrica. De belangrijkste risicofactoren zijn echter open chirurgie en ruptuur van het aneurysma, welke respectievelijk geassocieerd zijn met een drie- en zesvoudig verhoogd perioperatief sterfterisico. Uit hoofdstuk 13 blijkt dat nierfunctiestoornissen optreden bij één procent van de patiënten na EVAR en bij vijf procent na open chirurgie. Perioperatieve mortaliteit was aanzienlijk hoger in deze patiëntengroep. Risicofactoren voor het ontstaan van nierfunctiestoornissen zijn preoperatieve creatinine, perioperatieve transfusie en open chirurgie. In hoofdstuk 14 werden de incidentie en risico's van converteren van endovasculaire naar open AAA herstel onderzocht. Hieruit is gebleken dat conversiechirurgie 1,2 keer per honderd EVAR's voorkomt. Met een relatieve perioperatieve sterftekans van meer dan twee in vergelijking met standaard open AAA chirurgie is conversiechirurgie zeer risicovol. Factoren geassocieerd met converteren naar open chirurgische behandeling zijn grote diameter van het aneurysma, jonge leeftijd, vrouwelijk geslacht en niet-blanke afkomst, terwijl obesitas een invers verband heeft met conversiechirurgie.

In *deel IV* wordt aandacht besteed aan de onderbelichte kenmerken die van invloed zijn op de lange termijn uitkomsten na (vaat)chirurgie. Hoofdstuk 15 toont aan dat sociaaleconomische achterstelling een voorspeller is voor een slechte prognose na vaatchirurgische interventie onafhankelijk van verschillen in de kwaliteit en toegankelijkheid van gezondheidszorg en andere conventionele risicofactoren. Voor AAA patiënten liet deze relatie een exponentieel verband zien, terwijl voor patiënten met perifeer vaatlijden (PAV) deze relatie van een lineaire aard was. In hoofdstuk 16 hebben we geprobeerd om deze associatie te extrapoleren naar vakgebieden buiten de vaatchirurgie. De relatie tussen sociaaleconomische status en postoperatieve overleving werd bevestigd voor een algemeen chirurgische populatie. Bovendien werd aangetoond dat de voorspellende waarde van de sociaaleconomische achterstelling voornamelijk van toepassing is op cardiovasculaire mortaliteit, terwijl het voor kanker-gerelateerde mortaliteit geen predictieve waarde heeft. Hoofdstuk 17 bevestigt het klinische belang van ischemische hartziekten (IHZ) voor de postoperatieve overleving van vaatchirurgische patiënten. Belangrijker is dat coronaire revascularisatie geassocieerd was met lagere IHZ-gerelateerde sterftecijfers, maar er niet in slaagt om een totaal overlevingsvoordeel te bewerkstelligen als gevolg van een verhoogde cardiovasculaire mortaliteit die niet verwant is aan IHZ. Uit hoofdstuk 18 blijkt dat aneurysmatische en occlusieve vaatziekten niet alleen verschillen ten aanzien van etiologie en pathofysiologie, maar ook afzonderlijke entiteiten zijn voor wat

betreft prognose. De levensverwachting van PAV patiënten is korter en wordt hoofdzakelijk beperkt door cardiovasculaire morbiditeit, terwijl een hoge leeftijd voor AAA patiënten op de voorgrond staat.

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List of Publications

LIST OF PUBLICATIONS

1. Eefting D, **Ultee KH**, Von Meijenfeldt GC, Hoeks SE, ten Raa S, Hendriks JM, Bastos Goncalves F, Verhagen HJ. Ruptured AAA: state of the art management. J Cardiovasc Surg (Torino). 2013;54(1 Suppl 1):47-53.
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31. Bastos Gonçalves F, Oliveira NF, van Rijn MJ, **Ultee KH**, Hoeks SE, ten Raa S, Stolker RJ, Verhagen HJ. Iliac seal zone dynamics and clinical consequences after endovascular aneurysm repair. (Submitted for publication Eur J Vasc Endovasc Surg)

PhD Portfolio

PHD PORTFOLIO

Name PhD student: Klaas H.J. Ultee	PhD period: 2013 – 2016
Erasmus MC Department: Surgery	Promotors: Prof.dr. H.J.M. Verhagen & Prof.dr. R.J. Stolker
Research School: COEUR	Copromotor: Dr. M.L. Schermerhorn

1. PhD training

Courses and academic skills	**Year**	**ECTS**
- Biomedical English writing course	2013	2.0
- Research Integrity course	2013	0.3
- Study Design (CC01, NIHES)	2013	4.7
- Basic introduction course on SPSS	2014	0.3
- Introduction in GraphPad Prism	2014	0.3
- Excel course (Basic)	2014	0.3
- Survival analysis course	2014	0.5
Presentations	**Year**	**ECTS**
- Research Conference Department of Anesthesiology. Erasmus MC Rotterdam, the Netherlands (oral)	2014	1.0
- NVvH Chirurgendagen. Veldhoven, the Netherlands (oral)	2014	1.0
- Vaatdagen. Noordwijkerhout, the Netherlands (oral)	2015	1.0
- Vascular Study Group of New England Semi-Annual Meeting. Boston, MA, USA (oral)	2015	1.0
- Harvard Surgery Research Day Symposium. Boston, MA, USA (poster)	2015	1.0
- Society for Vascular Surgery Annual Meeting. Chicago, IL, USA (3 posters)	2015	3.0
- European Society for Vascular Surgery Annual Meeting. Porto, Portugal (oral)	2015	1.0
- Society for Clinical Vascular Surgery Annual Symposium. Las Vegas, NV, USA (3 orals, 3 posters)	2016	6.0
- Society for Vascular Surgery Annual Meeting. Washington, DC, USA (poster)	2016	1.0
Symposia & Meetings	**Year**	**ECTS**
- National conferences	2013-2016	4.2
- International conferences	2013-2016	8.4

2. Teaching

Lecturing	**Year**	**ECTS**
- Erasmus Anatomy Research Project (EARP, anatomy masterclass) thoracic anatomy	2012-2013	3.0
- Erasmus Anatomy Research Project (EARP, anatomy masterclass) abdominal anatomy	2013-2014	3.0

Curriculum Vitae

CURRICULUM VITAE

Klaas Hendrik Jan Ultee was born on March 12th, 1992 in The Hague, the Netherlands. After graduating high school in 2010, he spent a year studying Economics at Erasmus University Rotterdam. After finishing his first year, Klaas enrolled in Medical School at the same university. Early on, he developed an interest in the field of vascular surgery and started teaching anatomy courses. Participation in several research projects at the Department of Vascular Surgery eventually evolved into plans for a PhD program under the supervision of Professors Hence J.M. Verhagen and Robert Jan Stolker. Within this framework, Klaas moved to Boston, USA, for 15 months after finishing his bachelor's degree to work with Dr. Marc L. Schermerhorn as a research fellow at the Department Vascular and Endovascular Surgery at Beth Israel Deaconess Medical Center, Harvard Medical School.
Klaas will graduate Medical School in the spring of 2018.