Advancing Management of Aortic Aneurysm Disease

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(met een samenvatting in het Nederlands)

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Prof. dr. J.A. van Herwaarden
Prof. dr. M.L. Schermerhorn

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Chapter 1

General introduction and thesis outline

1.
General introduction

An abdominal aortic aneurysm (AAA) is an abnormal dilatation of the major abdominal arteries and comes from the greek ανεύρυσμα (aneurysma), which means "a widening".[1] If left untreated, AAAs risk rupturing, with high mortality and morbidity rates. The first description of aortic pathology data back to 1550 BC in the Ebers Papyrus which stated "Only magic can cure tumors of the major arteries".[2] While AAA has been described by Aristotle in the 4th century BC, treatment was only attempted in the 16th century and early interventions included ligation or banding.[2] Later the aneurysm would be wrapped in cellophane as was done for Albert Einstein in 1948, who would survive 6,5 more years after the intervention.[2] While until the 1990s open repair remained the only treatment for AAAs, the 1990s represented the start of a time of fundamental change in the treatment of AAAs. This all started when Juan C Parodi and Julio Palmaz described endovascular repair, the exclusions of the aneurysm sac by a stent graft, of an abdominal aortic aneurysm (EVAR) in 1991.[3] The dissemination of the technique rapidly expanded and since the introduction of EVAR, the annual number of deaths from intact and ruptured aneurysms has significantly decreased.[4]

The development of EVAR has caused an important paradigm shift in AAA management, especially for older patients and those with severe comorbidities. However, endoleaks, device migration and late rupture are potential complications after EVAR and therefore life-long follow-up is mandated.[5–7] Questions regarding the durability of EVAR continue to be made, especially in patients with complex anatomy such as hostile neck characteristics.[8] Therefore, ongoing examination of real world data remains essential to understand and transform AAA management. Registry and database studies have a unique position in the process of continuous quality improvement, especially so in the midst of a rapidly evolving technology.

This thesis consists of 3 parts. In part one, the value of outcome research in AAA management are discussed. Part two focusses on management of AAA in specific subpopulations. Part three discusses practice patterns and appropriate application of EVAR.

Thesis Outline

Part I focusses on the value of aortic aneurysm repair database research. As many administrative data and quality improvement registries are widely available and easily accessible, an understanding of the appropriate use is essential. The annual number of publications on Pubmed describing the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) increased from 78 in 2010 to 948 in 2020. The Vascular Quality Initiative publications was established in 2012 (1 publication) and increased to 178 publications in 2020. The claims-based NIS increased from 423 in 2010 to 1,021 in 2020 and Medicare database from 2,198 in 2010 to 4,094 in 2020. **Part I** contributes to the quality improvement of database research by increasing the understanding of the value, specific characteristics, strengths, and limitations of databases and database research.

Chapter 2 provides an overview of specific paradigm shift in AAA management driven by database outcomes research and describes challenges and opportunities. **Chapter 3** contains a comparison of the national insample (NIS) database, national surgical quality improvement program (NSQIP) registry, and vascular quality initiative (VQI) registry using AAA repair as a lens. Risk scores provide tools to patients and healthcare providers. In **chapter 4**, we utilized the NIS, VQI, and NSQIP, to compare the ability of the risk scores to assess in-hospital mortality based on available preoperative characteristics. Hereby rethinking quality metrics and emphasizing on the importance of understanding the characteristics of different databases.

In Part II "management of AAA in specific subpopulations" we focus on quality improvement in AAA management across diverse populations. Previous research shows differences in AAA prevalence, management, and outcomes across sex, racial, and ethnic groups. In most AAA studies the results are driven by white and male populations and these results might not be representative for female or non-white patients. By understanding these variations and identifying sex and race specific areas for quality improvement we can ensure that outcomes of AAA repair improve over time for all patients.

Chapter 5 evaluates the association of female sex and perioperative outcomes after endovascular and open complex AAA repair. Several studies have found that female patients have smaller aortic diameter at the time of repair for both intact and ruptured AAA compared with male patients.[9–12] Therefore, in **chapter 6** we propose sex-specific thresholds for AAA repair using aortic diameter, aortic size index, and aortic height index. In **chapter 7** we seek to describe racial differences in aortoiliac aneurysm repair and identify targeted areas of quality improvement to reduce these disparities.

In Part III "practice patterns and appropriate application of EVAR", challenges and opportunities of endovascular repair are discussed. The evolution of AAA management has been strongly tied to technological advancement. Therefore, continuously reassessing the current approach and areas for quality improvement is essential.

Long-term outcomes after large AAA repair are compared to smaller AAA repair in **chapter 8**, stratified by endovascular and open repair. **Chapter 9** focusses on long-term implication of compliance to the guideline recommended diameter threshold for elective EVAR. In **chapter 10** the adherence to device instruction for use and association with outcomes in elective AAA repair is examined.

Finally, **chapter 11** provides a summary of this thesis, a general discussion and future perspectives.

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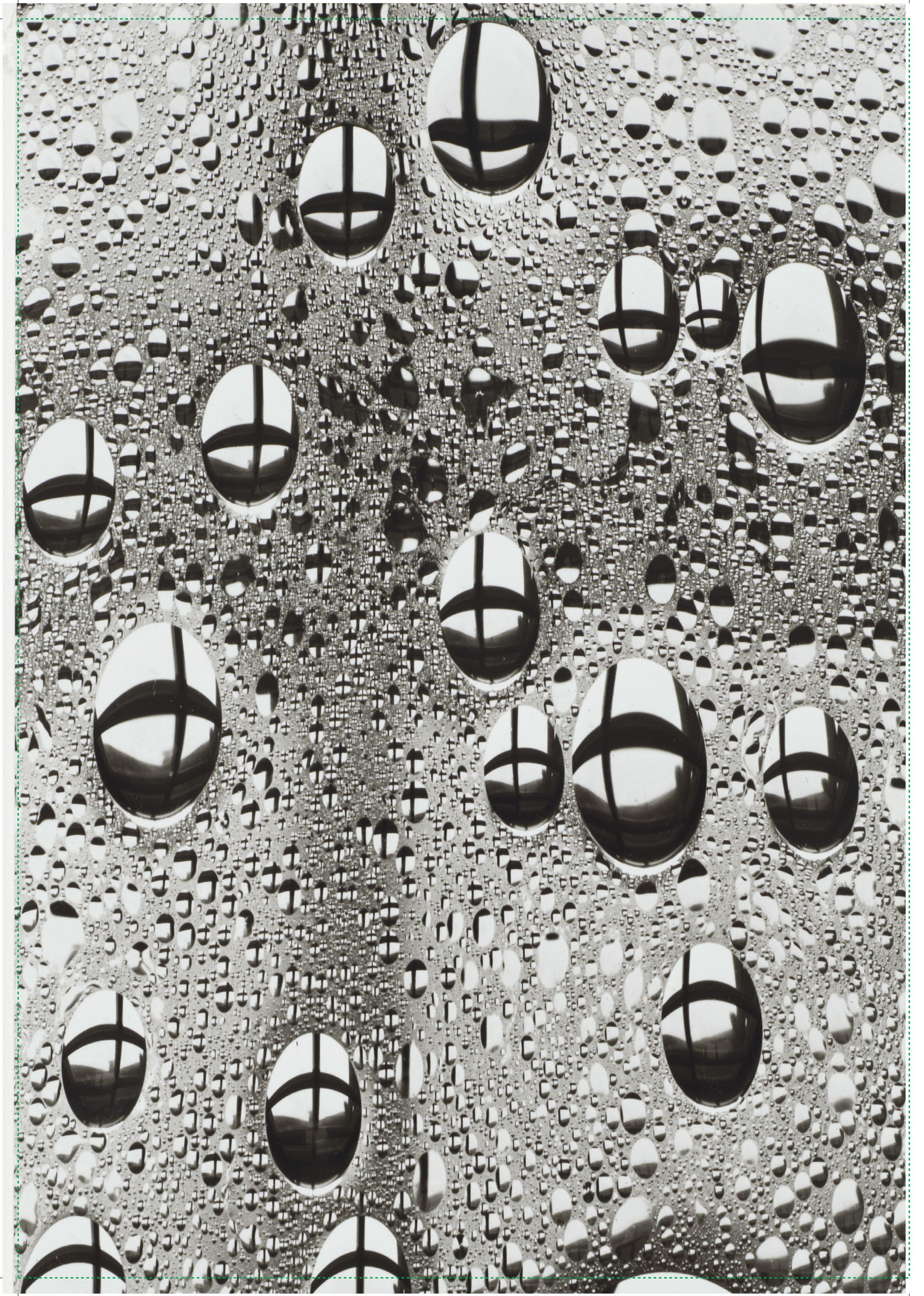

PART I

The value of outcome analyses in aortic aneurysm repair

Chapter 2

Paradigm shifts in abdominal aortic aneurysm management based on vascular registries

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Abstract

Abdominal aortic aneurysm (AAA) is a relatively common and potentially fatal disease. The management of AAA has undergone extensive changes in the last two decades. High quality vascular surgical registries were established early and have been found to be instrumental in the evaluation and monitoring of these changes, most notably the wide implementation of minimally invasive endovascular surgical technology. Trends over the years showed the increased use of endovascular aneurysm repair (EVAR) over open repair, the decreasing perioperative adverse outcomes and the early survival advantage of EVAR. Also, data from the early EVAR years changed the views on endoleak management and showed the importance of tracking the implementation of new techniques. Registry data complemented the randomized trials performed in aortic surgery by showing the high rate of laparotomy related reinterventions after open repair. Also, they are an essential tool for the understanding of outcomes in a broad patient population, evaluating the generalizability of findings from randomized trials and analyzing changes over time. By using large scale data over longer periods of time, the importance of centralization of care to high-volume centers was shown, particularly for open repair. Additionally, large-scale databases can offer an opportunity to assess practice and outcomes in patient subgroups (e.g. treatment of AAA in women and the elderly) as well as in rare aortic pathologies. In this review article, we point out the most important paradigm shifts in AAA management based on vascular registry data.

Introduction

Abdominal Aortic Aneurysm (AAA) is a major cause of mortality as a result of aneurysm rupture.[1] With an aortic aneurysms prevalence of 6% in males, the health burden of AAA is substantial.[2] However, a better understanding of aneurysmal disease, earlier detection, the introduction of minimally invasive endovascular aneurysm repair (EVAR) and increasing experience have improved outcomes for patients with AAA. Therefore, the management of AAA has changed radically over the years and is in constant evolution.

The management of AAA has been extensively studied and guidelines have been established by the European Society for Vascular Surgery (ESVS) and the Society for Vascular Surgery (SVS).[3,4] These recommendations are founded on Randomized Controlled Trials (RCT), prospective data and retrospective studies. Although RCTs are considered the gold standard in evaluating the effectiveness of a treatment, it is important to understand their inherent limitations.[5] Strict inclusion and exclusion criteria and high costs can limit the external validation and generalizability of the results. Also, the study setting and conditions, with specific surgeons and centers performing operations on selected patients might not relate to broader clinical practice. In times where technique, technology and experience improve rapidly, RCT results might no longer reflect contemporary practice by the time they get published. Furthermore, at the time of early RCTs, when the new technology was introduced, long-term behavior, complications and their treatment were largely unknown and may have affected the results. Thus, RCTs cannot be used to answer every clinical question. Also, existing RCTs may be underpowered to detect differences for outcomes with low event rates. Vascular registry data can complement RCTs and are an essential tool for the understanding of outcomes in a broad patient population, evaluating the generalizability of RCT findings, rapid assessment of new technology and procedures, and analyzing changes over time. Registries offer data for large-scale outcome analysis, over longer periods of time and in multiple regions, countries or continents, enabling continuous assessment and improvement of AAA management.

Registries are defined as an organized system that collects uniform data through observational study methods to evaluate outcomes for patients defined by a disease or exposure, for a predetermined purpose.[6] The first formal vascular registry was created by DeBakey and Simeone during the World War II with a subsequent review of more than 2000 vascular injuries.[7] Their observations on the treatment of vascular injuries with ligation showed high amputation rates. However, alternative management strategies were investigated and showed poor outcomes.[7] These data caused arterial ligation to become the United States (US) Army policy.[7] During the Korean War, Dr. Carl Hughes showed an important decline from the 49% amputation rates in World War II to 13% in the Korean War.[8] The outcomes in the Korean War registry emphasized that revascularization should only be attempted within eight hours of injury. With the implementation of Medicare in the US in 1965, collection of its administrative data started. Medicare is a federal health insurance program for individuals in the US who are aged ≥65 years and selected younger individuals with disabilities or end-stage renal disease, and in 2015 over 55 million beneficiaries were covered. These data have been essential for providing real-world evidence among older individuals in the US. In 1966, Dr. Norman Rich established the Vietnam Vascular Registry (VVR) which contains information from over 7500 patients. The long-term follow-up of this database provided insight in the long-term outcomes of these revascularizations.[9,10] Data collection by National Inpatient Sample (NIS) started in 1988 and includes a stratified 20% random sample of all nonfederal inpatient hospital admissions throughout the US.[11] When used with adequate weighting, this database represents nearly 95% of all inpatients admissions in the US. The Vascular Study Group of New England (VSGNE) database was created in 2001 by Jack Cronenwett in New England and was followed by the launch of the Vascular Quality Initiative (VQI) by the Society for Vascular Surgery (SVS) in 2011. The VQI was designed to improve the quality, safety, effectiveness, and cost of vascular surgery and reports quality measures to physicians and hospitals.13

In Europe, the predecessor of the Swedish Vascular registry (Swedvasc), the Vascular Registry in Southern Sweden (VRISS) was established in 1987 by Sven-Erik Bergentz, David Bergqvist, Thomas Troëng, Eibert Einarsson and Lars Norgren and gained national coverage in 1994. This first population-based registry in vascular surgery has been an essential data source for research and enabled important quality improvement projects. In England, the Hospital Episode Statistics (HES) database was established in 1989 and collects information about all patients admitted to National Health Service hospitals in England.[11] The European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) registry was established in 1996 and has tracked the implementation and evolution of EVAR. In 1997, as demand for a collaborative dataset to compare vascular surgical practice in different countries rose, Vascunet, a combination of European and Australasian national and regional vascular registries, was created. In 2014, a collaboration of Vascunet, the SVS VQI and manufacturers formed the International Consortium of Vascular Registries (ICVR), combining existing vascular quality improvement registries from in America, Europe and Australasia.[12] An overview of the administrative datasets and quality improvement registries employed in vascular surgical research is provided in Table 1.

Table 1. An overview of registries and national administrative datasets used in vascular surgical research and quality improvement initiatives included in the current review.

Name	**Coverage**
Administrative datasets	
Medicare	US population of Medicare beneficiaries (>65 years)
Hospital episode statistics	National Health Service (NHS) hospitals in England
National inpatient sample	20% of all discharges from US community hospitals
Quality improvement registries	
Swedvasc	National coverage for vascular surgery in Sweden
EUROSTAR	Participating centers in Europe
SVS-VQI*	Participating vascular centers in US
International registry collaborations	
Vascunet	European and Australasian national and regional vascular registries
ICVR#	Transatlantic collaboration of vascular registries (SVS-VQI and Vascunet)

**SVS-VQI: Society for vascular surgery quality improvement registry; ICVR: International consortium of vascular registries.*

Quality improvement, administrative, and combined databases have specific limitations due to their distinctive designs. While quality improvement databases, such as the Swedvasc and the VQI, have the advantage of clear variable definitions and granularity, the voluntary basis of these registries could cause potential bias and long-term follow-up is often limited. Administrative data, such as HES, Medicare or NIS, offer large patient numbers and often national coverage. However, inconsistency in coding systems and limited details are inherent limitations. Combination databases, such as Vascunet and ICVR, contain large patient numbers and geographic variation but are limited due to the heterogeneity of the databases they combine.

In this review we describe the most important paradigm shifts in abdominal aortic aneurysm management originating from vascular registry studies. We will also describe potential future breakthroughs. Eligible manuscripts were based on registry data including quality improvement, administrative and combined databases.

The shifting dominance and decreasing perioperative adverse outcomes of EVAR

The large patient samples and data collection over long periods of time make registry studies ideal sources for studying trends over time. Several registry studies spanning the previous four decades enabled the evaluation of the shift in utilization of EVAR and open surgery and showed the decreasing adverse outcomes over time. A study covering the last two decades of the 20th century showed no decrease in mortality after elective and ruptured AAA open repair (average operative mortality over the study period in elective repair: 5.6% and ruptured repair: 45.7%).[13] However, at the end of the 20th century, a shift in the treatment paradigm was observed as EVAR was increasingly utilized.[14] This trend was accelerated in the first decade of the 21st century, with EVAR use surpassing open repair in 2005 for elective surgery and the increasing dominance since (5.2% EVAR utilization in 2000; 74% EVAR in 2010).[15] Decreasing 30-day mortality rates were observed for endovascular repair despite the higher age and rates of comorbidities in the patients undergoing EVAR compared to open repair (Between 1994 – 1999: 3.4% 30-day mortality after EVAR and 1.1% between 2012 - 2016)(Table 2).[14,16,17] With the increasing expansion of EVAR use, overall operative mortality for elective AAA repair declined (4.9% in 1995 to 2.4% in 2008).[18] These findings proved that the results of randomized controlled trials were generalizable to the US population and justified the increased use of EVAR despite its higher costs, making it the preferred management for AAA repair with adequate aneurysm morphology.

Table 2. Surgical treatment and 30-day mortality for patients with abdominal aortic aneurysm in Sweden.

	1994-1999	2000-2005	2006-2011	2012-2016
Proportion of repairs with EVAR				
Intact AAA	6%	19%	47%	63%
Ruptured AAA	1%	5%	19%	37%
30-day mortality				
Intact EVAR	3.4%	3.9%	1.2%	1.1%
Intact open repair	6.2%	7.7%	3.1%	2.5%
Ruptured EVAR	68.8%	31.1%	20.6%	21.2%
Ruptured open repair	45.6%	47.3%	30.4%	28.1%

EVAR=Endovascular aneurysm repair. AAA=Abdominal aortic aneurysm. Source: Swedvasc reports and Bergqvist D, Mani K, Troëng T, Wanhainen A. Treatment of aortic aneurysms registered in Swedvasc. Gefasschirurgie. 2018;23(5):340–5.

EVAR survival advantage and the importance of late outcomes and follow-up

When looking at long-term survival in registry studies, the survival advantage after EVAR compared to open repair persisted for approximately three years, after which it was similar to survival after open repair.[17,19] In RCTs, with smaller patient populations, younger patients, and restricted inclusion criteria, this survival advantage with EVAR persisted for shorter periods of time.[20–22] Also, this study confirmed that late rupture rates are higher after EVAR compared to open repair (5.4% after EVAR and 1.4% after open repair, through eight years of follow-up).[17] These finding highlighted the importance of performing long-term follow-up after intervention. In terms of late reinterventions after AAA repair, analysis of Medicare data confirmed the RCT results showing higher aneurysm related reinterventions after EVAR compared to open repair (18.8% vs 3.7% at eight years), but for the first time also showed the higher rate of laparotomy related complications of hernia and bowel obstruction after open repair (8.2% after EVAR, 17.7% after open repair at eight years). This analysis prompted the RCT PIs to try to go back to find laparotomy related complications in the randomized patients as best as they could and these were reported subsequently.[19]

Registry studies using long-term follow up data also show the low annual imaging follow-up adherence after EVAR with less than half of the patients receiving follow-up five years after EVAR.[23,24] Also, loss to follow-up was highest in patients undergoing urgent repair (HR: 1.27 (95%CI 1.20-1.35).[23] Despite the low costs of ultrasound surveillance, follow-up imaging still primarily occurred through CT surveillance (with a decrease between 2002 and 2010 from 60.8% to 42.1%).[25] These studies showed alarming trends and important opportunities for quality improvement.

Centralization of open AAA surgery

The complexity of AAA repair procedures might warrant the centralization of these procedures to high-volume centers and by high-volume surgeons. In registry data from 2001-2003, the highest-volume centers used an endovascular approach 44% of the time compared to 18% EVAR use in the lowest-volume centers.[26] Also, ICVR data showed a clear increase in survival after open repair in higher-volume centers with 2.4% difference between the highest- and lowest-volume centers (Figure 1).[27] However this relationship was not evident in patients undergoing EVAR, where a decrease in mortality was seen between the first- and second-lowest volume quintiles (2.5% vs. 1.6%), but little effect of increasing volume on mortality in the following quintiles.[27,28,29] Surgeon volume had a similar association with perioperative mortality after EVAR and open repair.[30,31] After EVAR, VQI data showed no effect of surgeon volume on perioperative mortality (Q1: 1.8% vs Q5: 1.6%). However, perioperative mortality after open repair decreased with increasing surgeon volume (Q1: 6.4% vs. Q5: 3.8%). For the treatment of rupture repair, Vascunet data showed that centers with higher volume or with a primary EVAR approach were associated with decreased perioperative mortality (Figure 2).[32] The strong relationship between center and surgeon volume with perioperative mortality after open repair shown in these registry studies impacted the recommendation that open surgery should be centralized to high-volume centers and surgeons.

Although perioperative death is a highly relevant quality indicator for open AAA repair, it may not be as appropriate for EVAR. EVAR can be considered as a minimally invasive procedure, and consequently has a minimal perioperative risk. Instead, there is a concern with long-term durability for EVAR. Therefore, the need for late reoperation and the risk of late ruptures could be more relevant quality markers for EVAR. This aspect needs to be incorporated into future analyzes aimed at studying the potential need for centralization of EVAR operations as well.

Figure 1. Risk-adjusted analysis of volume impact on in-hospital mortality after EVAR and open repair of intact and ruptured abdominal aortic aneurysms using ICVR data. Reproduced from Scali et al.[27]

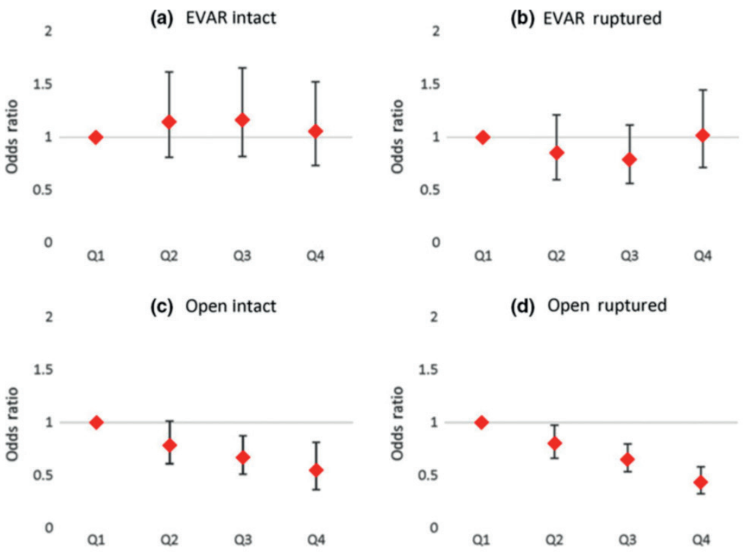
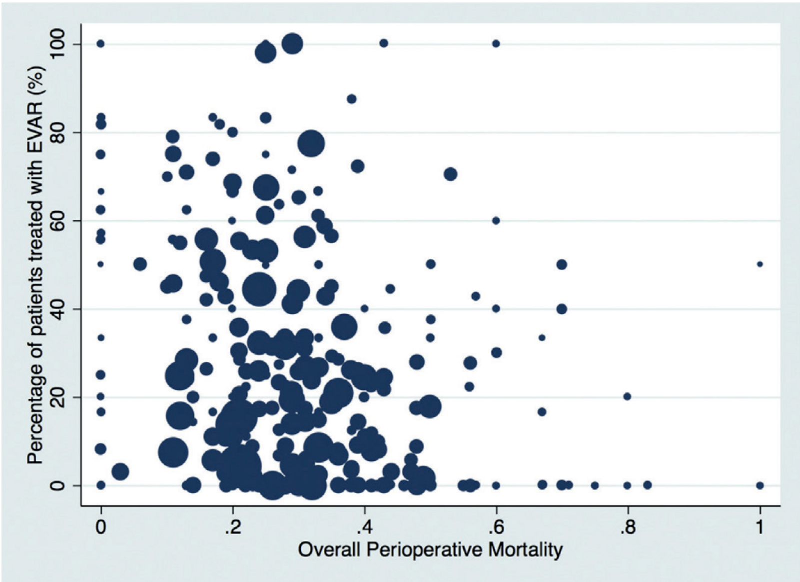


Figure 2. Ruptured AAA perioperative mortality and EVAR % per centre and volume in the Vascunet registry. Repro- duced from Budtz-Lilly et al.[32]



Understanding risk factors

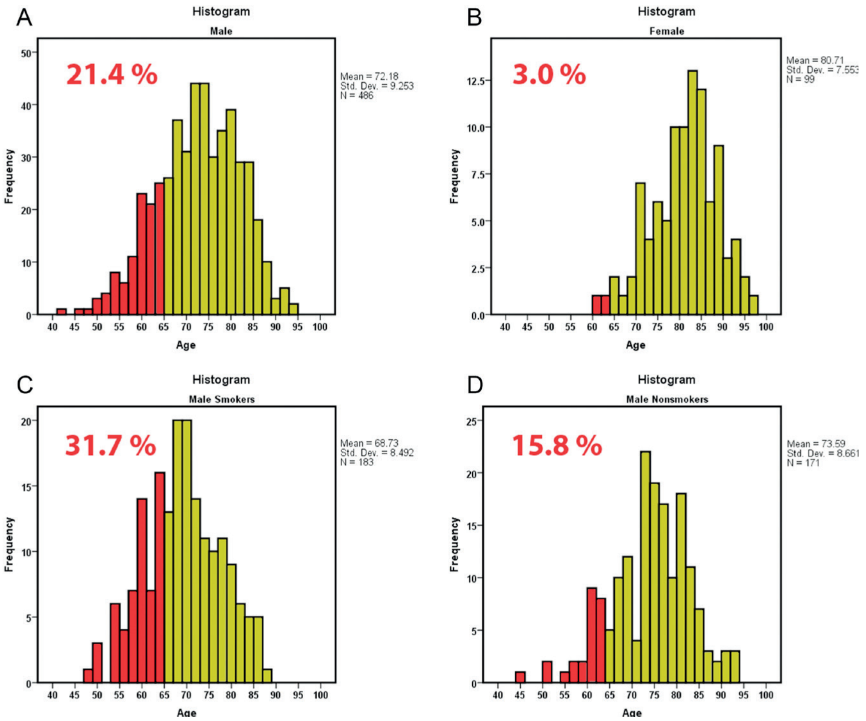
Registry data provide a unique tool for understanding risk factors as they contain a real-life population and can be used for better preoperative patient selection. Risk calculators predicting mortality after EVAR and open repair included comorbidities, sex and age (Figure 3).[33–35] This enables physicians to better identify high-risk patients and to guide clinical decision making. For specific subgroups, such as elderly patients, registry data can also help in the selection of treatment eligible patients. A study using the VQI data showed that elderly patients in the highest risk strata still had 50% survival at five years and only comprised 4% of the elderly population.[36] Also, scoring systems based on registry data can help identify risk factors for specific complications.[37,38] For example, Swedvasc data identified patient-related haemodynamic risk factors together with surgical skill and decision making as risk factors for intestinal ischaemia in 1997.[36] Also, VQI data showed that cold renal perfusion was associated with a decreased risk of acute kidney injury if clamp time exceeded 25 minutes during open juxtarenal AAA repair (OR: 0.4 [95%CI 0.2-0.97]).[35] Thirdly, understanding risk factors for AAA development has created better selection possibilities for screening. Screening data from the Lifeline registry showed that smoking cessation and a healthy lifestyle were associated with lower risk for AAA.[39] These screening data also showed that a large sample of the patients with AAA are not screening eligible under the current criteria.[39] In Finish data, over a fifth of male patients would experience an AAA rupture before reaching the screening eligible age of 65 years. In male smokers this proportion was even higher with 31.7% rupturing before age 65 (Figure 4).[40] Revisions to the current screening guidelines using up-to-date registry data may potentially reduce these rates of rupture. Also, in the light of a decreasing prevalence of the disease the target group for AAA screening may need to be modified and more selectively target high risk groups, in order to maintain the effectiveness of screening programs.[41]

Figure 3. Mortality Risk Score after EVAR or open repair using Medicare data. Reproduced from Giles et al.[34]

Risk Factor	Score
AGE	
> 80	+ 11
76–80	+ 6
71–75	+ 1
Female	+ 4
Renal failure	
Dialysis dependent	+ 9
No dialysis	+ 7
CHF	+ 6
PVD or CBVD	+ 3

	Total Score =	***Open***	***EVAR***
Risk	**Score Range**	**Predicted Mortality**	**Predicted Mortality**
High	> 11	> 6.3%	> 2%
Medium	3–11	2.8–6.3%	0.9–2.0%
Low	< 3	<2.8%	< 1%

Figure 4. Ruptured AAA frequency in relation to patients' age in Finland. Reproduced from Laine et al.[40]



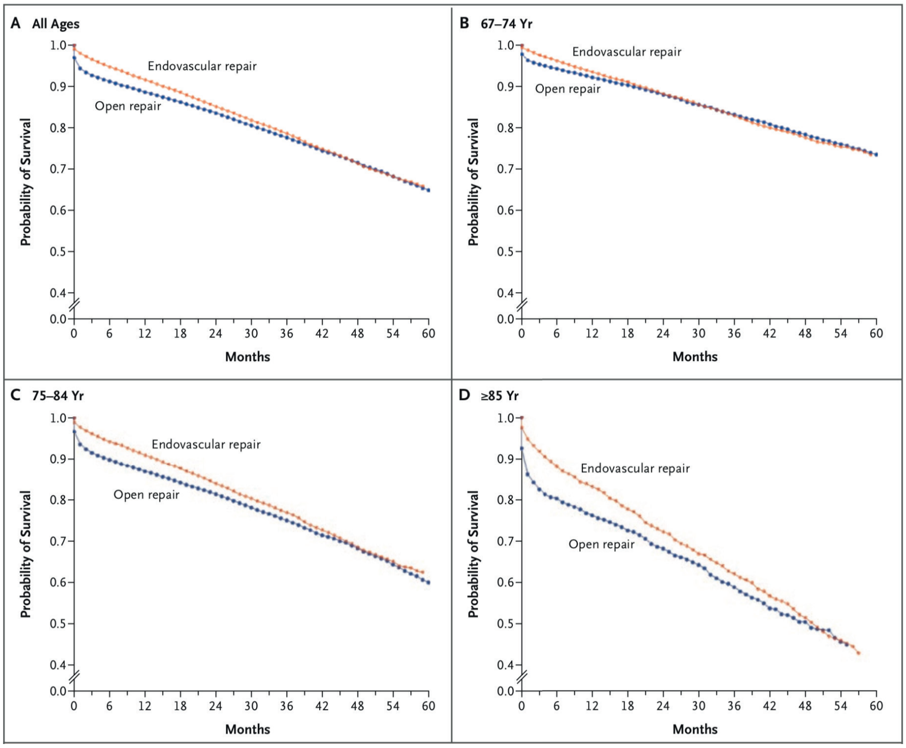
Endoleak management

After early aggressive treatment of endoleaks, EUROSTAR data showed that indication for reoperation should be dictated by aneurysm expansion.[42] The EUROSTAR registry was established in 1996 and collected data from patients undergoing infrarenal EVAR. The EUROSTAR data showed that persistent endoleaks, but not temporary endoleaks, were associated with sac expansion and late rupture.[43] These results highlighted the importance of screening for endoleaks after EVAR.[43] Eurostar data also showed that type I and III endoleaks had a significant negative impact on late rupture but not type II, [45] this latter fact was confirmed by others, although the true long-term significance of type II leaks is yet to be determined.[44,45] With these results, a better understanding of the natural history of endoleaks was achieved, hereby avoiding overtreatment by recommending routine follow-up for patients with type II endoleaks and reinterventions only in patients with sac increase. This showed the importance of following the implementation of new procedures with registry data and a decrease in re-intervention, primarily in coil embolization procedures (4.2% in 2001 – 2.5% in 2007), was subsequently noted after EVAR.

Treatment of elderly

Elderly patients are often excluded in RCT studies. However, this subgroup has been studied in registry data, showing that treatment of AAA is often performed in elderly patients, and that patients over 80 years with reasonable life expectancy and quality of life can undergo elective AAA repair with excellent outcomes. Also, the survival benefit of EVAR over open repair, which was shown using Medicare data, was most pronounced in older patients (67 to 69 years old: 2.1% absolute perioperative mortality difference; 85 years and older: 8.5% difference) (Figure 5).[19] Also, the increasing adoption of EVAR over the years was most dramatic in patients over age 80 and this age group also had the most dramatic reduction in deaths due to rupture.[18]

Figure 5. Survival after EVAR and open repair, per age group in Medicare data. Reproduced from Schermerhorn and Cotterill.[19]

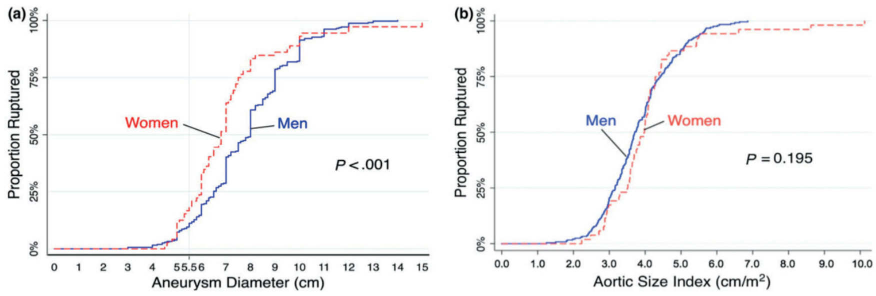


From the Swedvasc registry, it was found that the importance of age for short-term outcome after AAA repair has diminished,[46] and that octogenarians selected for AAA repair in fact had a superior long-term survival compared to the general population.[47] VQI data showed excellent survival in the majority of elderly patients after contemporary EVAR with only 4% of the elderly population in the highest risk strata.[36] These observations suggests that the observed change in indication that has occurred with the introduction of EVAR, with a dramatic increase in older patients being offered AAA repair in recent times, is so far a reasonable development.

Treatment of female patients

There are concerning sex discrepancies in AAA presentation, management, and outcomes that disadvantage female patients. As female patients are underrepresented in clinical trials, the natural history of AAA in female patients is not clearly defined. Analysis of vascular registry data showed that female patients are treated at older age (median age 75 vs. 72 years, P<.001) and at smaller diameters (57 vs. 59mm, P<.001).[48] Also, female patients undergo repair of rupture at smaller average diameters (71 vs. 79mm, P<.001) than men.[48] More female patients have hostile neck characteristics such as shorter and more angulated necks.[49] After intact repair, female patients have worse 30-day outcomes when undergoing EVAR (3.2% vs. 1.2%, P < .001) and open repair (8.0% vs. 4.0%, P = .04).[48,50,51] However, this early discrepancy in survival outcome diminished over time, and survival after EVAR was similar in female and male patients after approximately two years.[48] A vascunet-study has shown that the biggest difference in 30-day mortality between open surgery and EVAR is seen in females over 80 years of age, so elderly females benefit the most from EVAR compared to open surgery(1.3% vs. 9.7%).[51] As a specific aneurysm diameter generally represents a relative greater increase in aortic diameter in women than in men, diameter might not have the same predictive value in female patients as in males. Registry data were therefore used to study the impact of aortic size index, a measure indexing aneurysm diameter to body size. In female patients, the aortic size index was the most important determinant of aneurysm rupture, while aneurysm diameter alone was the most predictive determinant of rupture in male patients (Figure 6).[52] Also, in patients with a ruptured AAA in Sweden, female patients less often received surgery than males (58.6% vs. 78.7%, *P* < 0.001).[53] These registry studies added to the understanding of sex differences in treatment of AAA and outcomes after repair, and showed that more well-designed sex-specific research is essential.

Figure 6. Distribution of ruptured repair as a function of aortic diameter (a) and aortic size index (b) using VQI data. Reproduced from Lo et al.[52]



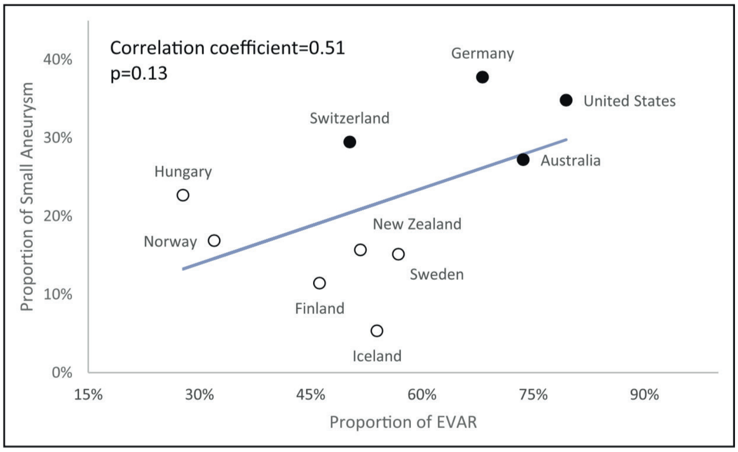
Use outside of IFU

Patients treated with EVAR outside the Instructions For Use (IFU) criteria for the available stent grafts are not included in RCTs. This highlights the importance of registry data to analyze the performance of endografts in the general population, as they are being used currently. Registry studies showed that a high proportion of patients undergo EVAR outside of the IFU. When using a conservative definition of device IFU, 42% of patients met the criteria and even when using the most liberal definition of device IFU, only 69% met the criteria and suggested they may be more prone to sac enlargement.[54] However, long-term all-cause mortality and aneurysm related mortality were unaffected by IFU adherence in another study.[55] More data with more granular details of specific IFU criteria are clearly needed to define the appropriate role of EVAR outside of the manufacturers IFU

Geographic variation

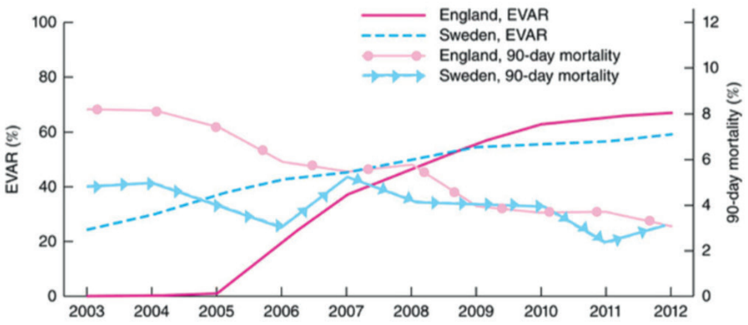
Registries combining data from different countries such as Vascunet and the ICVR, or registries differentiating between regions such as the VQI, can provide essential information for identifying best practices or regions where quality improvement is needed. Large variation in patient selection for elective EVAR, including aneurysm size and patient risk profile is seen.[56] Use of EVAR as compared to open repair (Range: 28% in Hungary - 79% in the US ($P<0.01$)) and treatment of patients over age 80 (Range: 12% of all patients in Hungary to 29% in Australia ($P<0.01$)) also significantly vary between countries.[12] A potential contributor to this variation is the different healthcare reimbursement models, such that countries with a fee-for-service system more commonly operate at a smaller aneurysm size and on older patients (Figure 7).[12]

Figure 7. Correlation of aneurysm size at time of intact AAA repair, use of endovascular technique (EVAR) for repair, and healthcare reimbursement model in eleven countries. Reproduced from Beck et al.[12]



Analysis of variation between regions or countries can also show geographical discrepancies and potential areas for quality improvement. In a study comparing outcomes in several European countries, mortality after EVAR was initially significantly worse in the United Kingdom compared to Sweden. However, with increasing uptake of EVAR combined with centralization of care in England, mortality rates decreased, and after 2007, no difference could be found between the two countries (Figure 8).[57] Also, a Vascunet comparison of outcomes after ruptured AAA showed lower perioperative mortality in centers with a primary EVAR approach and those with higher case volume for open repair.[32]

Figure 8. Use of endovascular aneurysm repair (EVAR) and 90 day mortality in England and Sweden using HES & Swedvasc data. Reproduced and adapted from Karthikesalingam et al.[57]



Even within a country, patient selection and outcomes can vary widely between regions. VQI data from the US showed significant variations in patient selection between regions.[58] When looking at outcomes after AAA repair, several regions did not meet in-hospital mortality benchmarks from the SVS guidelines (range, 0%-7%; P=.55).[59] Awareness of these discrepancies is essential and should prompt changes in management and potentially regionalization of care for open AAA.

Treatment of ruptured AAA

Registry data of Malmö (Sweden) from 1993 highlighted the poor outcomes for ruptured AAA, with 50% operative mortality and 85% overall mortality.[60] While early RCT results did not show any advantage in the treatment of ruptured AAA using EVAR over open repair, Medicare research showed increasing utilization of EVAR over time with decreased EVAR and overall mortality. No increase in mortality with open repair over time was seen, suggesting the trend was most likely due to the utilization of EVAR with its lower operative mortality.[61] A recent study using NIS data showed that EVAR became the dominant treatment module for ruptures AAA repair in 2014.[62] When comparing ruptured AAA management between countries, it was observed that when aneurysm repair was offered to a greater proportion of patients with ruptured AAA, in-hospital mortality was significantly lower.[63] Also, centers with an EVAR-first approach or high open repair case volumes showed lower perioperative adverse outcomes.[32] Overall rupture rates with and without repair declined over time and is likely due to a combination of declining AAA prevalence; treatment of elderly patients with elective EVAR who previously would have been deemed unfit for repair when open surgery was the only option; and improved medical management.[18,64,65] However, ruptured AAA rates in female patients declined in Finland but did not decline over time in Sweden.[53,64]

Rare diseases

The research on uncommon vascular conditions such as endograft infection, internal iliac aneurysms or mycotic aneurysms primarily consists of case reports and small patient series. However, the large patient numbers of registries enable analysis of these rare diseases. The Vascular Low Frequency Disease Consortium (VLFDC) allows centers world-wide to contribute de-identified patient data and study rare vascular diseases. This provides a platform to improve the quality and enables studies of rare diseases. For example, a rare but highly morbid complication of EVAR is aortic endograft infection. A study using data from the VLFDC showed the high morbidity (35%) and mortality (11%) of this complication and enabled the comparison of treatment strategies. Results suggested that the recommended management was surgical excision and that autogenous reconstruction was preferred over prosthetic graft replacement when possible.[66]

Similarly, even though internal iliac aneurysms are rare, the high rupture and mortality rates of internal iliac aneurysms make the understanding of their natural history and the adequate patient selection for surgical treatment essential. Through an international collaboration of vascular registries, Laine et al could study a large series of ruptured internal iliac aneurysms and showed that it was probably safe to increase the repair threshold from 3cm to 4cm.[67] Another international registry study looking at mycotic aneurysm treatment showed that EVAR is feasible with good results in the near term,[68] and in a Swedish nationwide study using propensity score matching it was shown that EVAR for mycotic AAA was associated with a significantly higher short-term survival in comparison with open repair, with similar incidence of late serious infection-related complications and reoperations.[69] However, in young and fit patients with mycotic aneurysm, in situ reconstruction with autologous graft seems to be the best solution as in yet another multicenter registry-based study, which collected data from 56 patients with mycotic aneurysms from 6 countries, showed that after reconstruction of mycotic aneurysms with biological grafts, mortality was low (3/56) and reinfection rate at 26 months was zero.[70]

Future challenges and breakthroughs

Although several registry-based studies have improved the quality of care among patients with AAA, registry-based studies can be improved significantly by specific maneuvers which will improve data validity and expand the data crucial to AAA research.

Future breakthroughs in registry research will come from improving registry participations, partnerships with different stakeholders and linkage of data.

The incorporation of registry data as elements in the electronic health records will be an essential breakthrough in registry research. Directly using electronic medical records data will improve the accuracy of the data and standardization of data collection.

An important challenge will be to diminish financial obstacles associated with participating in a vascular registry and therefore potential for bias. Also, harmonization of variable definitions across registries will be essential to advance collaborations and currently presents a challenge for established registries to update data elements.

Through partnerships with different stakeholders and linkage of data, registry data can reach its full potential. An ongoing project linking data from the VQI and Medicare databases (The Vascular Implant Surveillance and Interventional Outcomes Network (VISION) database) combines the clinical, anatomical and procedural granularity from a prospective vascular-specific database with long-term administrative follow-up data to detect re-admissions, re-interventions, and ruptures after AAA repair.

An important shift in the interpretation of vascular registry research will come from the way quality is measured. Although mortality is the most common outcome measure in current studies and is likely appropriate for measuring quality after open AAA repair, it does not adequately discriminate high from low quality EVAR. Other important quality indicators such as rate of conversion from EVAR to open repair, late rupture, adherence to IFU, follow-up compliance, endoleak rates, or reinterventions should be considered when evaluating EVAR but the appropriate metrics are yet to be defined. Therefore, collection of these outcomes by registries and determination of the appropriate quality indicators will be essential.

Conclusion

The continuous and rapid technological progress in aortic surgery and the exponential growth in knowledge has caused dramatic changes in the management of patients with AAA. Furthermore, registries provide data to study the changes in epidemiology, treatments and outcomes over time. By understanding the strengths and limitations of vascular registries, researchers can use them to improve quality, to develop management guidelines, and to compliment outcomes from RCTs.

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Chapter 3

Not All Databases are Created Equal, A Comparison of Administrative Data and Quality Improvement Registries for Abdominal Aortic Aneurysm Repair

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Abstract

Objective: Databases are essential in evaluating surgical outcomes and gauging the implementation of new techniques. However, there are important differences in how data from administrative databases and surgical quality improvement (QI) registries are collected and interpreted. Therefore, we aim to compare trends, demographics, and outcomes of open and endovascular aortic abdominal aneurysm (AAA) repair in an administrative database and two QI registries.

Methods: We identified patients undergoing open and endovascular repair of intact and ruptured AAAs between 2012 and 2015 within the National Inpatient Sample (NIS), The National Surgical Quality Improvement Program (NSQIP), and the Vascular Quality Initiative (VQI). We described the differences and trends in overall AAA repairs for each dataset. Moreover, patient demographics, comorbidities, mortality and complications were compared among the datasets using Pearson's χ^2 test.

Results: A total of 140,240 NIS patients, 10,898 NSQIP patients and 26,794 VQI patients were included. Rupture repairs comprised 8.7% of NIS, 11% of NSQIP, and 7.9% of VQI. EVAR rates for intact repair (range: 83-84%) and ruptured repair (range: 51-59%) were similar in the three databases. In general, rates of comorbidities were lower in NIS than in the QI registries. Following intact EVAR, in-hospital mortality rates were similar in all three databases (NIS: 0.8%, NSQIP: 1.0%, and VQI: 0.8%, P=.06). However, after intact open repair and ruptured repair, in-hospital mortality was highest in NIS and lowest in VQI (Intact open: NIS: 5.4%, NSQIP: 4.7%, and VQI: 3.5%, P<.001; Ruptured EVAR: NIS: 24%, NSQIP: 20%, and VQI: 16%, P<.001; Ruptured Open: NIS: 36%, NSQIP: 31%, and VQI: 26%, P<.001). After stratifying by intact and ruptured presentation and repair strategy, several discrepancies in morbidity rates remained among the databases. Overall, the number of cases in NSQIP represent 7-8% of the repairs in NIS and the number of cases in VQI grew from 12% in 2012 to represent 23% of the national sample in 2015.

Conclusion: NIS had the largest number of patients as it represents the nationwide experience and is an essential tool to evaluate trends over time. The lower in-hospital mortality seen in NSQIP and VQI questions the generalizability of the studies that use these QI registries. However, with a growing number of hospitals engaging in granular quality improvement initiatives, these QI registries provide a valuable resource to potentially improve the quality of care provided to all patients.

Introduction

Comparison studies supported by large databases have emerged as an essential tool for evaluating the effectiveness of vascular surgery procedures as traditional randomized controlled trials (RCT) are limited by significant sponsor costs, lengthy timelines to data read-outs, and limited translatability beyond the enrolled patient population. As a result, studies supported by large databases have emerged as an essential tool for establishing standards of care in vascular surgery. These studies are being used to supplement the RCTs with administrative and Quality Improvement (QI) registry data to ensure the generalizability of RCT data and to analyze questions that cannot be answered using RCTs, particularly with respect to the management of abdominal aortic aneurysms (AAA).[1] In order to optimize the quality of database research, it is necessary to understand the differences between the various databases and the relative limitations of each.

Administrative databases utilize the International Classification of Disease (ICD) diagnosis and procedure codes to collect data. These codes are collected on discharge and are used for insurance reimbursement purposes. Examples of administrative databases include: the National (Nationwide) Inpatient Sample (NIS), Medicare Database, State Inpatient Database, and the National Readmission Database. The validity of using administrative databases for clinical research has been challenged because these databases use insurance claims with limited accuracy in recording post-operative complications.[3, 4] These critiques have been countered by using specific codes to capture post-operative outcomes and compare the frequency of these outcomes to national QI registries, with subsequent chart review to better understand the discrepancy (Table 1).[5, 6]

QI registries use pre-determined metrics to analyze the quality of patient care received at each participating center. The most well-known surgical QI registry in the United States is the National Surgical Quality Improvement Program (NSQIP) which collects a standardized set of 30-day outcomes in patients undergoing any surgical procedure. Targeted NSQIP databases for vascular surgical procedures were designed by vascular surgeons to capture more granular, procedure-specific variables. The Vascular Quality Initiative (VQI) is a QI registry focused on vascular surgical procedures and outcomes. In both these QI registries, trained reviewers collect pre-defined data elements through chart review. These data elements were selected by vascular surgeons with the intent to improve patient care and are specific to each individual vascular procedure.[7] With data entry by trained clinical staff, QI registries distinguish themselves by granular data. Because of the detailed nature of these data, QI registries can support a broad array of risk adjusted analyses and QI projects. Critiques of the QI registries note the significant financial and administrative barriers associated with hospital participation in these registries. As a result, participating hospitals usually have a dedicated focus for QI and therefore the collected data may not be generalizable (Table 1).

Table 1. A comparison of the National Surgical Quality Improvement Program (NSQIP), Vascular Quality Initiative (VQI), National Inpatient Sample (NIS), and Medicare Coverage Database

	Quality Improvement Registries				**Administrative Databases**			
	Targeted NSQIP 2011 - current		**VQI 2001 - current**		**NIS 1988 - current**		**Medicare 1965 - current**	
	+	-	+	-	+	-	+	-
Patients Included:	Vascular specific operations. Up to case maximum dependent upon hospital volume/ number of data abstractors.	Center participation elective.	Vascular specific operations. Includes USA, Canada and Singapore. Allows for international compar-isons.	Center and specific module participation elective.	Includes representative sample of all inpatient encounters. Uses census data to create a population estimate.	Excludes long-term care facilities and veteran hospitals. Each state can elect to participate.	Includes all encounters for Medicare patients.	Excludes non-Medicare. Limited information on patients enrolled in Medicare HMO's.
How data are collected:	Trained reviewers collect pre-defined data from chart review and telephone calls.	Only includes variables that can be obtained by reviewers in the patient medical record including the operative note.	Trained reviewers collect pre-defined data with input from surgical team. Enables cost analyses.	Reliant on the surgical team accurately measuring and inputting data such as neck length, angulation, etc.	Hospital coders using only ICD diagnosis and procedure codes. Enables cost analyses.	No clinician reviewing data input. Not vascular specific. Influenced by coding changes (change from ICD9 - ICD10 in 2015).	Hospital coders using ICD diagnosis and procedure codes. Physicians using CPT procedural codes allow improved specificity and accuracy. Enables cost analyses.	No clinician reviewing ICD data input. Not vascular specific. Influenced by coding changes (change from ICD9 - ICD10 in 2015).

	Quality Improvement Registries				Administrative Databases			
	Targeted NSQIP 2011 - current		VQI 2001 - current		NIS 1988 - current		Medicare 1965 - current	
	+	-	+	-	+	-	+	-
Costs and administrative time	Dedicated clinical abstractors for data entry and review.	Annual fee (independent of number of modules) and salary for clinical nurses (depen-dent on number of modules and volume).	Dedicated clinical staff to maintain the registry.	Annual fee (per module) and salary for clinical staff.	No additional staff required or participation cost for data submission.	Cost to obtain the data ($160-750 depending on the year of data requested). Strict Data Use Agreement.	No additional staff required or participation cost for data submission.	Expensive database to obtain. Strict Data Use Agreement and cumbersome data management.
Comorbid Conditions	Identification of pre-existing conditions and disease severity.	Binary comorbid condition variables with strict inclusion criteria. Disease severity not consistently defined or comparable to other databases.	Identification of pre-existing conditions with specificity for disease severity (e.g. mild - moderate - severe instead of yes/no).	Disease severity not consistently comparable to other databases.	Comor-bidities captured by diagnoses billed for during hospita-lization.	Limitations in distinguishing pre-existing condition from procedural complications (e.g. stroke, mi, renal failure etc.). Limited interpretation of disease severity. Inconsistent conversion from ICD 9 to ICD 10.	Improved accuracy for comorbidity identification by abstracting from diagnoses prior to index admission (outpatient and inpatient).	Limited inter-pretation of disease severity. Inconsistent conversion from ICD 9 to ICD 10.
Operative details	Data reviewers abstract details from operative reports. Not reliant on CPT codes and data abstraction is independent of billing records.	Only includes operative variables that nurses can abstract from the operative report (limited anatomical variables).	Operative details included as dictated or entered manually by the surgeon. Not reliant on CPT codes and data abstraction is independent of billing records.	Operative details are not consistently entered for each center.	Presence or absence of operations as determined by ICD9/10 procedure codes.	Operative details limited by ICD procedure codes. Unknown timing or order of multiple procedures. Laterality not specified.	Presence or absence of operations as defined by CPT codes - more specific than ICD procedure codes.	Operative details limited by CPT codes. Unknown timing of multiple procedures (simultaneous vs. staged).

	Quality Improvement Registries				Administrative Databases			
	Targeted NSQIP 2011 - current		VQI 2001 - current		NIS 1988 - current		Medicare 1965 - current	
	+	-	+	-	+	-	+	-
Outcomes and Long-term follow-up	Chart review supplemented with nurse phone calls as needed for complete in-hospital and 30-day data.	Limited to 30-day outcomes. No unique identifier to link with other procedures. No center and surgeon identifiers which prohibits volume analyses.	Granular in-hospital outcomes. 1-year outcomes available. Database linked to Medicare for complete granular long-term follow-up in the subset of Medicare (non-HMO) patients.	1-year follow-up is suboptimal and varies by procedure. Only Medicare patients have long-term follow-up. Medicare Advantage (HMO) patients have survival but not reintervention follow-up.	Only certain outcomes can be analyzed accurately: (e.g. in-hospital mortality, length of stay and discharge disposition).	Includes only in-hospital outcomes. Unable to distinguish postoperative complication from pre-existing condition (e.g. stroke with CEA, renal failure, MI) Long-term follow-up data are not available.	Improved ability to determine complications when compared with NIS. Long-term mortality is accurate and many long- term reinterventions and complications are captured.	Difficulties to determine additional complication in patients with preexisting conditions (e.g. MI). Only includes follow-up for patients who stay in non-HMO Medicare.
Recommended use	Research requiring discrete variable definitions and granularity; outcome tracking and benchmarking; quality assurance/ improvement projects Studies are limited to in-hospital and 30-day outcomes. Inherent selection bias introduced as hospitals elect to participate.		Research requiring discrete variable definitions and granularity; outcome tracking and benchmarking; quality assurance/ improvement, cost analyses projects. Medicare-linkage provides long-term follow-up and reintervention data. Inherent selection bias introduced as hospitals elect to participate.		Large epidemiological studies and temporal trends over time. Research scope limited to no patient and operative characteristics except if sex, age, race, and specific non-acute comorbidities are needed. No accurate risk adjustment possible for other variables. Appropriate study outcomes limited to performance of an operation, in-hospital mortality, LOS, and discharge disposition.		Large epidemiological studies and temporal trends in care including costs and outcomes research. Ability to study procedures that are not included in VQI (e.g. open thoracoabdominal repair) or procedures for which larger numbers are essential. Studies for which long-term outcomes are essential (including outcomes documented at outpatient/ ED visits)	

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative
Medicare was included for comparison purposes. However, Medicare was not included in this analysis

We aim to elucidate the inherent characteristics of administrative databases and QI registries, and describe their relative value for research purposes. By using management of AAA as a lens, we will describe the differences in demographics, treatment strategies and outcomes among NIS, NSQIP, and VQI.

Methods

Data source

The NIS is maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project.[2] It has collected data since 1988 and contains a 20% random sample of all non-federal inpatient hospital admissions throughout the US. The discharge information is weighted using data from the United States (U.S.) Census Bureau to create a cohort that represents approximately 95% of all inpatient admissions in the U.S. More information is available at https://www.hcup-us.ahrq.gov/nisoverview.jsp. NIS captures 25 diagnosis and 15 procedure codes upon patient discharge.

The NSQIP was created in 2004 by the American College of Surgeons and procedure specific targeted NSQIP databases was established in 2011. NSQIP is a validated nationwide QI registry that collects data from over 700 participating centers in the U.S, for general surgery procedures. Over 270 variables are collected by trained and certified surgical clinical reviewers, including patient demographics, anatomic and operative details, as well as predefined outcomes up to 30 days after the index procedure. Additional information is available at www.facs.org/quality-programs/acs-nsqip.

The VQI, the successor of the Vascular Study Group of New England (VSGNE) founded in 2001, was established in 2011. With over 550 participating centers, VQI captures over 350 pre-defined variables including patient demographics, procedural and anatomical characteristics, as well as in-hospital outcomes. Additionally, VQI established a link with the Social Security Death Index, which allows analysis of long-term mortality data. More information about VQI is available at http://www.vascularqualityinitiative.org.

NSQIP subsequently designed the targeted modules. One senior author was involved with the conception of both the targeted NSQIP modules and the VQI. While both the NSQIP targeted modules and the VQI were designed by vascular surgeons, NSQIP was created so the information could be abstracted from reports by nurses while the VQI variables require input from the surgical team. Therefore, the VQI has greater anatomic and procedure specificity including, for example, the alpha and beta angle when describing proximal sealing zone characteristics. The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and considering the retrospective and de-identified nature of the study, waived the requirement for patient consent.

Patient Population

We included all patients undergoing open and endovascular repair of intact and ruptured AAA between 2012 and 2015 within all three databases. To reduce coding variability, we did not include admissions after 2015 as the diagnosis codes changed from ICD-9 to ICD-10 at the end of 2015. For NIS, we identified admissions with both an ICD-9 diagnosis code of AAA (441.3-Abdominal Aneurysm Rupture, 441.4-Abdominal Aneurysm Without Rupture) and ICD-9 procedure codes for AAA repair (38.34-Aorta resection and Anastomosis, 38.44-Replacement of Abdominal Aorta, 38.64-Excision of Aorta, 39.52-Other repair of Aneurysm, 39.71-Endovascular Abdominal Aorta Repair). The ICD coding system changed from ICD-9 to ICD-10 at the end of 2015. Therefore, we used the first three quarters of 2015 to extrapolate an estimated patient population for the fourth quarter. For NSQIP we used the targeted vascular open AAA and endovascular aortic repair (EVAR) modules and for VQI we used the endovascular and open aneurysm repair datasets. In NSQIP and VQI, infrarenal, juxtarenal and suprarenal aneurysms were included. However, NIS does not specify the proximal extent of the AAA and therefore it is unknown if the aneurysms in the NIS cohort are infrarenal, juxtarenal or suprarenal pathologies.

For all patients, we collected demographics, comorbidities and outcomes. There are several differences with how the databases define covariates. For the NIS, we used the pre-defined Elixhauser covariates to identify comorbidities and used further modification to optimize inclusion of relevant comorbidities (Table 2).[8] All variables collected in NSQIP are binary variables. However, VQI categorizes the comorbidity and complication variables to reflect different levels of severity. To improve ease of comparison, we recoded these into binary variables. After adjusting the variables, some discrepancies remained. Age above 90 is coded as 90 years old in the QI registries. In the QI registries, only diabetes requiring medical therapy was included whereas in NIS it was not specified if treatment was given for diabetes. NSQIP defines a current smoker as a smoker in the 12 months prior to surgery while VQI considers any patient smoking in the month prior to surgery as a current smoker. NSQIP only includes hypertension treated with medication, while in NIS and VQI, any preoperative history of hypertension was included. Concerning congestive heart failure (CHF), NIS records any CHF history, while NSQIP included CHF with current signs and symptoms, whereas VQI tabulates any CHF including asymptomatic and mild CHF presentations.

Table 2. A comparison of variable definitions in the National Surgical Quality Improvement Program (NSQIP), Vascular Quality Initiative (VQI), and National Inpatient Sample (NIS)

Variable	Database	Definition
AGE, median (IQR)	NIS	Age in years at admission
	NSQIP	Patient age at procedure, (>90 reported as 90)
	VQI	Patient age at procedure, (>90 reported as 90)
Sex	NIS	Indicator of sex
	NSQIP	Patient's gender as per the medical record
	VQI	Use gender at birth
Race	NIS	White Black Other: Hispanic, American Indian, Alaska Native, Native Hawaiian or Other Pacific Islander, Asian
	NSQIP	1 - American Indian or Alaskan Native 2 - Asian 3 - Black or African American: A person having origins in any of the black racial groups of Africa. 4 - Native Hawaiian or Other Pacific Islander 5 - White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa. 6 - More than one race 7 - Unknown/other: If documentation does not state patient's race, report as Unknown.
	VQI	1 - American Indian or Alaskan Native 2 - Asian 3 - Black or African American 4 - Native Hawaiian or other Pacific Islander 5 - White 6 - More than 1 race 7 - Unknown / Other
Underweight x	NIS	783.22 Underweight
978-94-6416-840-2	NSQIP	BMI<18.5
	VQI	BMI<18.5
Obese (BMI>30)	NIS	278.00, 278.01, 278.03-Obesity including Morbid Obesity
	NSQIP	BMI>=30
	VQI	BMI>=30

Variable	Database	Definition
Diabetes	NIS	249.X-Secondary Diabetes, 250.X-Diabetes, 648.00-648.04-Diabetes of Mother with Delivery
	NSQIP	Diabetes requiring therapy
	VQI	0 - None 1 - Diet 2 - Non-insulin medication 3 - Insulin
Current smoker	NIS	-
	NSQIP	Smoked within the 12 months prior to surgery. Excludes: cigars, pipes, chewing tobacco, or marijuana.
	VQI	1 - Prior Smoker = quit over a month ago 2 - Current = Smoking within a month of surgery, includes cigarettes, pipe or cigar.
Hypertension	NIS	401.x-405.x, Benign essential HTN, HTN related to heart and kidney disease, 642.0-642.2, 642.7, 642.9-HTN related to pregnancy
	NSQIP	Hypertension requiring medication or medication should be prescribed.
	VQI	History of hypertension or recorded blood pressure >=140/90 on 3 or more occasions
CHF	NIS	398.9-Rheumatic HF 402.01, 402.11, 402.91-Hypertensive HF 404.01, 404.03, 404.11, 404.13, 404.91, 404.93-HF relating to CKD 428.x-Congestive Heart Failure
	NSQIP	Newly diagnosed CHF or active CHF with current signs or symptoms, in the 30 days prior to surgery
	VQI	1 - Asymptomatic, hx CHF, No limitation of physical activity. 2 - Mild, Slight limitation of physical activity. 3 - Moderate, Marked limitation of physical activity. 4 - Severe, Unable to carry out any physical activity without discomfort
COPD	NIS	490.x-491.x-Chronic Bronchitis 492.x-Emphysema 493.x-Asthma , 494.x-Bronchiectasis 496-Chronic Airway Obstruction, Not Elsewhere Specified
	NSQIP	Medicated or functional disabababled from COPD or hospitalized at any time for COPD or An FEV1 of <75% of predicted on a prior pulmonary function test
	VQI	1 - Not treated, COPD documented in record but not treated with medication 2 - On Medication 3 - On Home Oxygen

Variable	Database	Definition
End-stage renal disease	NIS	403, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93-Hypertensive Chronic Kidney Disease Stage V or ESRD 585.6, 585.5-Chronic renal failure, stage 5, ESRD V45.1 Postsurgical Renal Dialysis Status
	NSQIP	Renal failure requiring dialysis 2 weeks prior to surgery
	VQI	1 - Functioning Transplant 2 - On Dialysis
Chronic kidney disease (stage I-IV)	NIS	404, 404.1, 404.90, 404.91-Hypertensive Heart And Chronic Kidney Disease, Stage I Through Stage Iv, Or Unspecified 585.9-Chronic Kidney Disease, Unspecified
	NSQIP	eGFR <90 without dialysis (CKD-EPI formula using most recent creatinine measurement taken before procedure)
	VQI	eGFR<90 without dialysis (CKD-EPI formula using most recent creatinine measurement taken before procedure)
Transfer from other hospital	NIS	Transferred in from a different acute care hospital, or another facility
	NSQIP	Transfer from acute care hospital inpatient, outside emerggency department or other (e.g., Spinal Cord Injury Unit or other facility not listed)
	VQI	1 - Hospital, transferred in from another hospital (any other acute care hospital or emergency room) 2 - Rehab unit (i.e. units where a patient qualifies for rehab).
Maximum AAA Diameter, median (IQR)	NIS	-
	NSQIP	Aneurysm Diameter
	VQI	Max diameter measured at right angle to centerline or use max AP diameter.

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative

Table 3. A comparison of outcome definitions in the National Surgical Quality Improvement Program (NSQIP), Vascular Quality Initiative (VQI), and National Inpatient Sample (NIS)

Outcome Variable	Database	Definition
Wound	NIS	998.32, 998.31-Dehiscence 998.30-Disruption of wound, unspecified convert
	NSQIP	Wound disruption-The spontaneous reopening of a previously surgically closed wound.
	VQI	-
Pneumonia	NIS	003.22-Salmonella Pneumonia 011.6-TB Pneumonia 055.1-Post measeles Pneumonia 073.0-Ornithosis With Pneumonia 115.05-115.95-Histoplasma Pneumonia 480.0-Viral Pneumonia 488.11-Influenza Due To Identified 2009 H1N1 Influenza Virus W/ Pneumonia 516.30-Idiopathic Interstitial Pneumonia, Not Otherwise Specified 516.35-Idiopathic Lymphoid Interstitial Pneumonia 516.36-Cryptogenic Organizing Pneumonia 516.37-Desquamative Interstitial Pneumonia 517.1-Rheumatic Pneumonia 997.31-Ventilator Associated Pneumonia 997.32-Postprocedural Aspiration Pneumonia
	NSQIP	Diagnosis of pneumonia
	VQI	Treatment with antibiotics and a chart diagnosis of pneumonia
Urinary Tract Infection	NIS	595 Cystitis, Acute cystitis 599.0 UTI, site not specified 996.64 CAUTI 646.63 Infections of genitourinary tract in pregnancy, antepartum condition or complication 646.60 Infections of genitourinary tract in pregnancy, unspecified as to episode of care or not applicable 041.04 Streptococcus infection in conditions classified elsewhere and of unspecified site, streptococcus, group D [Enterococcus]
	NSQIP	An infection in the urinary tract (kidneys, ureters, bladder, and urethra).
	VQI	-
Acute Renal Failure	NIS	584.5-584.9- Acute kidney failure
	NSQIP	Creatinine Increase (>2 mg/dl) or new postoperative dialysis requirment
	VQI	Creatinine Increase (>0.5 mg/dl) or postoperative dialysis requirment

Outcome Variable	Database	Definition
Deep Vein Thrombosis	NIS	453.4x-Acute Venous Embolism And Thrombosis Of Deep Vessels Of Lower Extremity 453.8x-Acute Venous Thrombosis Of Deep Vessels Of Upper Extremity
	NSQIP	New diagnosis of blood clot or thrombus within the venous system (superficial or deep) and requires treatment.
	VQI	-
Cerebrovascular Accident	NIS	431-Intracerebral Hemorrhage 433.x-Occlusion or Stenosis of an artery with Cerebral Infarction
	NSQIP	An interruption or severe reduction of blood supply to the brain resulting in severe dysfunction.
	VQI	1 - Minor deficit from stroke = Ability to carry out all activities despite some symptoms 2 - Major stroke = More severe deficit causing some disability
Myocardial Infarction	NIS	410.x-Acute Myocardial Infarction
	NSQIP	Blockage of blood flow to the heart causing damage or death to part of the heart muscle. (ECG, troponin or clinical)
	VQI	1 - Postoperative Myocardial Infarction - troponin only 2 - Posotoperative MI - EKG or clinical
Cardiac Arrest	NIS	427.5-Cardiac Arrest
	NSQIP	The absence of cardiac rhythm or presence of a chaotic cardiac rhythm requiring the initiation of cardiopulmonary resuscitation.
	VQI	-

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative

In all three databases, any severity of chronic obstructive pulmonary disease (COPD) was included. For end-stage renal disease, we included chronic kidney disease stage V and/or dialysis-dependence for NIS subjects, while only designating this comorbidity to patients currently on dialysis in both the NSQIP and VQI data sources. The assignment of *any* chronic kidney disease (CKD) was included as all codes for CKD stage I to IV in NIS but was defined as a preoperative eGFR<90 without being on dialysis in the QI registries. Patients were further stratified in NSQIP and VQI to calculate the proportion with eGFR<60 (Stage III CKD) and eGFR<30 (Stage IV CKD).

For postoperative complications in the NIS, we used ICD-9 codes that most closely described complications that are included in either of the QI registries. Even though NSQIP contains 30-day outcomes, we only included the in-hospital events. While the occurrence of pneumonia was included in all three databases, only VQI specified that the pneumonia was medically treated. Although NIS included any acute renal failure (ARF), NSQIP included patients with a creatine increase above 2mg/dL while VQI included patients with a creatinine increase above 0.5mg/dL. Any cerebrovascular accident (CVA) and myocardial infarction (MI) were similarly defined in all three databases. Some outcomes were not available in VQI and only analyzed in NIS and NSQIP. This includes wound disruption, urinary tract infections (UTI), deep vein thrombosis (DVT), and cardiac arrest. A specific description of post-operative outcome definitions for each database can be found in the Table 3.

Analysis

Our primary outcome was the proportion of open and EVAR and post-operative mortality in each database. Our secondary outcomes included demographics and postoperative complications. The patient demographics were compared among the three databases for intact and rupture repairs separately. For post-operative mortality and complications we further stratified the intact and rupture repairs into EVAR and open repair as the anticipated perioperative complications of EVAR and open repair are different.[9] Additionally, we evaluated aneurysm repair captured by each of the datasets annually. We presented categorical variables as counts and percentages and continuous variables as median (interquartile range). We compared demographics and outcomes and performed a Pearson's χ^2 tests for statistical significance. All variables had less than 5% missing data, except the race variable in NSQIP for which a dummy variable was introduced.

Results

We identified a total of 140,240 NIS patients, 10,989 NSQIP patients and 26,794 VQI patients who underwent open or endovascular repair of intact or ruptured AAA. The proportion of repairs performed for rupture was 8.7% in NIS, 11% in NSQIP, and 7.9% in VQI. The proportion of endovascular repair was 84% in NIS, 83% in NSQIP, and 83% in VQI for intact repair and 51% in NIS, 51% in NSQIP, and 59% in VQI for ruptured repairs.

Intact Aneurysm repair

For patients undergoing an intact repair, all three databases reported similar ages for patients. The proportion of female patients was slightly lower in NSQIP and the proportion of patients of white race was highest in VQI. Overall, the proportion of patients with captured comorbidities was lower in NIS. Patients in NIS were less likely to be obese (NIS: 11%, NSQIP: 32%, and VQI: 30%, P<.001), have hypertension, CHF (NIS: 0.4%, NSQIP: 1.7%, and VQI: 11%, P<.001), and CKD (NIS: 14%, NSQIP: 85%, and VQI: 84%, P<.001). Also, patients within NIS were less likely to have been transferred from another facility. However, the rates were highest in NIS for diabetes and end-stage renal disease. For COPD rates were lower in NSQIP (Table 4).

When evaluating variables only available in NSQIP and VQI, current smoking rates were similar and AAA diameter was similar. Patients in VQI were more likely to undergo infrarenal repair compared with juxtarenal and suprarenal/type IV repairs (infrarenal repair: NSQIP: 84% and VQI: 88%; juxtarenal repair: NSQIP: 11% and VQI: 8.8%; and suprarenal: NSQIP: 5.4% and VQI: 2.7%) (Table 4).

With respect to in-hospital outcomes, we stratified results by intact and ruptured indications, as well as by EVAR and open repair strategies. After intact EVAR, in-hospital mortality rates were similar in all three databases (NIS: 0.8%, NSQIP: 1%, and VQI: 0.8%, P=.06). In contrast, in-hospital mortality after intact, open repair was highest in NIS and lowest in VQI (Intact, open: NIS: 5.4%, NSQIP: 4.7%, and VQI: 3.5%, P<.001). A more proximal aneurysm extent was associated with a higher mortality in both NSQIP and VQI. For intact aneurysm repair stratified by EVAR and open repair, there was no significant difference in mortality between the three data sources; however, open suprarenal/type IV thoracoabdominal repair mortality was significantly lower in VQI (NSQIP: 9.7% and VQI: 6.8%, P=.05) (Table 5).

Table 4. Demographics of intact abdominal aortic aneurysm (AAA) repairs, by database

	NIS	NSQIP	VQI	P-Value
N	127,305	9,645	24,679	
Proximal extent				
Infrarenal	-	7,645 (84%)	21,827 (88%)	**<.001**
Juxtarenal	-	1,008 (11%)	2,176 (8.8%)	**<.001**
Suprarenal/Type IV	-	492 (5.4%)	676 (2.7%)	**<.001**
Age	73 (67, 79)	74 (68, 80)	73 (67, 79)	
Female Sex	26680 (21%)	1898 (20%)	5198 (21%)	**0.02**
Race				
White	104565 (87%)	7806 (81%)	22270 (93%)	**<.001**
Black	6285 (5.2%)	484 (5.0%)	1298 (5.4%)	0.12
Other Race	9420 (7.8%)	207 (2.1%)	444 (1.8%)	**<.001**
Unknown Race		1148 (12%)		
Underweight (BMI<18.5)	85 (0.1%)	204 (2.2%)	647 (2.6%)	**<.001**
Obese (BMI>30)	13520 (11%)	3020 (32%)	7397 (30%)	**<.001**
Diabetes	25185 (20%)	1497 (16%)	3796 (15%)	**<.001**
Current Smoker	-	3209 (33%)	8362 (34%)	0.38
Hypertension	97970 (77%)	7765 (81%)	20757 (84%)	**<.001**
CHF	545 (0.4%)	167 (1.7%)	2797 (11%)	**<.001**
COPD	42325 (33%)	1803 (19%)	8030 (33%)	**<.001**
End-stage renal disease	1950 (1.5%)	126 (1.3%)	281 (1.1%)	**<.001**
Chronic kidney disease (stage I-IV)	18180 (14%)	7836 (85%)	20314 (84%)	**<.001**
eGFR < 60 but not on dialysis	-	3234 (35%)	8289 (34%)	0.93
eGFR < 30 but not on dialysis	-	320 (3.5%)	865 (3.6%)	0.4
Transferred from other hospital	4925 (3.9%)	632 (6.6%)	1461 (5.9%)	**<.001**
Maximum AAA Diameter	-	5.5 (5.1, 6.2)	5.5 (5.1, 6.1)	

AAA: abdominal aortic aneurysm; NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; Age (years); IQR: Interquartile range; BMI: Body Mass Index (kg/m2); CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate.
Values are median (inter quartile range) or total events (percentages)
Boldface P values represent significance (P<.05)

Table 5. Postoperative mortality and complications after intact abdominal aortic aneurysm (AAA) repair

	EVAR				Open			
	NIS 106415	**NSQIP 7998**	**VQI 20516**	**P-value**	**NIS 21800**	**NSQIP 1647**	**VQI 4163**	**P-value**
In hospital morality	805 (0.8%)	79 (1.0%)	168 (0.8%)	0.06	1165 (5.4%)	77 (4.7%)	147 (3.5%)	**<.001**
Infrarenal	-	61 (0.9%)	139 (0.7%)	0.44	-	29 (3.6%)	65 (3%)	0.59
Juxtarenal	-	9 (2.2%)	19 (3.4%)	0.63	-	29 (4.9%)	59 (3.6%)	0.34
Suprarenal	-	4 (1.3%)	10 (3%)	0.97	-	17 (9.7%)	23 (6.8%)	**0.05**
LOS	2 (1,3)	1 (1, 3)	1 (1, 3)	-	7 (5,10)	7 (6, 10)	7 (6, 9)	-
Wound dehiscence	140 (0.1%)	-	-	0.001	240 (1.1%)	12 (0.7%)	-	0.15
Pneumonia	1700 (1.6%)	56 (0.7%)	125 (0.6%)	<.001	1635 (7.6%)	93 (5.6%)	136 (3.3%)	**<.001**
UTI	3445 (3.2%)	42 (0.5%)	-	<.001	1540 (7.1%)	33 (2.0%)	-	**<.001**
ARF	6240 (5.9%)	76 (1.0%)	779 (4.0%)	<.001	5380 (25%)	110 (6.7%)	792 (19%)	**<.001**
DVT	365 (0.3%)	17 (0.2%)	-	0.05	265 (1.2%)	27 (1.6%)	-	0.15
CVA	345 (0.3%)	17 (0.2%)	44 (0.2%)	0.01	235 (1.0%)	8 (0.5%)	32 (0.8%)	**0.02**
MI	1040 (1%)	66 (0.8%)	225 (1.1%)	0.09	650 (3.0%)	53 (3.2%)	205 (4.9%)	**<.001**
Cardiac Arrest	365 (0.3%)	36 (0.5%)	-	0.12	435 (2.0%)	42 (2.6%)	-	0.14

AAA: abdominal aortic aneurysm; NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; LOS: length of stay; UTI: urinary tract infection; ARF: acute renal failure; DVT: deep vein thrombosis; CVA: cerebrovascular accident; MI: myocardial infarction.
Values are median (inter quartile range) or total events (percentages)
Boldface P values represent significance (P<.05)

Ruptured Aneurysm repair

In patients undergoing ruptured repair, age was similar among the databases as was the proportion of females. Patients were most likely to be of white race in VQI. As with intact repair, the rate of coexisting conditions was most commonly lower in NIS. NIS had the lowest rates of underweight patients, obesity, CHF (NIS: 1.7%, NSQIP: 2.9%, and VQI: 11%, P<.001), and CKD (NIS: 18%, NSQIP: 89%, and VQI: 89%, P<.001). Again, patients in NIS were less likely to be transferred in when compared with the QI registries. However, rates were highest in NIS for diabetes and end-stage renal disease, hypertension rates were highest in VQI, and COPD rates were lowest in NSQIP.

Table 6. Demographics of ruptured abdominal aortic aneurysm (AAA) repairs, by database

	NIS	NSQIP	VQI	P-Value
N	12,195	1253	2115	
Extent				
Infrarenal	-	830 (74%)	1667 (79%)	**<.001**
Juxtarenal	-	217 (19%)	251 (12%)	**<.001**
Suprarenal/Type IV	-	81 (7.2%)	197 (9.3%)	0.005
AGE, median (IQR)	73 (66, 81)	73 (66, 81)	73 (66, 80)	
Female Sex	2,670 (22%)	267 (21%)	490 (23%)	0.44
Race				
White	9,670 (86%)	975 (78%)	1859 (92%)	**<.001**
Black	645 (5.7%)	57 (4.5%)	143 (7.0%)	**0.01**
Other Race	915 (8.2%)	28 (2.2%)	27 (1.3%)	**<.001**
Unknown Race		193 (15%)		
Underweight (BMI<18.5)	15 (0.1%)	33 (3.3%)	75 (3.8%)	**<.001**
Obese (BMI>30)	1,460 (12%)	330 (33%)	684 (34%)	**<.001**
Diabetes	1975 (16%)	152 (12%)	238 (11%)	**<.001**
Current Smoker	-	477 (38%)	923 (45%)	**<.001**
Hypertension	8580 (70%)	849 (68%)	1672 (80%)	**<.001**
CHF	210 (1.7%)	36 (2.9%)	227 (11%)	**<.001**
COPD	3840 (31%)	246 (20%)	637 (31%)	**<.001**
End-stage renal disease	490 (4.0%)	32 (2.6%)	31 (1.5%)	**<.001**
Chronic kidney disease (stage I-IV)	2175 (18%)	998 (89%)	1795 (89%)	**<.001**
eGFR < 60 but not on dialysis	-	634 (56%)	1114 (55%)	0.42
eGFR < 30 but not on dialysis	-	148 (13%)	251 (12%)	0.96
Transfered from other hospital	3565 (29%)	739 (59%)	1280 (61%)	**<.001**
Maximum AAA Diameter, median (IQR)	-	7.5 (6.1, 9)	7.5 (6.1, 9.0)	

AAA: abdominal aortic aneurysm; NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; Age (years); IQR: Interquartile range; BMI: Body Mass Index (kg/m2); CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate.
Values are median (inter quartile range) or total events (percentages)
Boldface P values represent significance (P<.05)

Among the variables only recorded in the QI registries, patients were more commonly current smokers in VQI compared with NSQIP (NSQIP: 38% and VQI: 45%, P<.001) and diameter was similar in the QI registries. The proximal extent was also more likely to be infrarenal in VQI (Infrarenal repair: 74% in NSQIP and 79% in VQI, juxtarenal repair: 19% in NSQIP and 12% in VQI, and suprarenal: 7.2% in NSQIP and 9.3% in VQI) (Table 6).

Table 7. Postoperative mortality and complications after ruptured abdominal aortic aneurysm (AAA) repair

	EVAR				Open			
	NIS	**NSQIP**	**VQI**	**P-value**	**NIS**	**NSQIP**	**VQI**	**P-value**
	6265	*639*	*1238*		*6090*	*614*	*877*	
In hospital morality	1480 (24%)	125 (20%)	197 (16%)	**<.001**	2180 (36%)	189 (31%)	230 (26%)	**<.001**
Infrarenal	-	102 (19%)	192 (16%)	0.81	-	91 (30%)	111 (25%)	0.26
Juxtarenal	-	9 (25%)	2 (22%)	**<.001**	-	48 (27%)	61 (25%)	0.12
Suprarenal	-	3 (19%)	3 (30%)	0.41	-	16 (25%)	58 (31%)	**<.001**
LOS	5 (3, 11)	6 (3, 11)	5 (2, 10)		9 (3,17)	9 (4, 17)	10 (5, 19)	
Wound	40 (0.6%)	1 (0.2%)	-	0.13	135 (2.2%)	13 (2.1%)	-	0.68
Pneumonia	754 (12%)	62 (9.7%)	67 (5.6%)	**<.001**	1145 (19%)	90 (15%)	77 (9.2%)	**<.001**
UTI	530 (8.5%)	9 (1.4%)	-	**<.001**	695 (11%)	13 (2.1%)	-	**<.001**
ARF	2520 (40%)	70 (11%)	280 (24%)	**<.001**	3195 (52%)	114 (19%)	363 (44%)	**<.001**
DVT	120 (1.9%)	18 (2.8%)	-	0.12	195 (3.2%)	25 (4.1%)	-	0.26
CVA	135 (2.2%)	11 (1.7%)	24 (2.1%)	0.71	185 (3.0%)	10 (1.6%)	39 (4.7%)	**0.009**
MI	460 (7.3%)	40 (6.3%)	127 (11%)	**0.001**	600 (9.9%)	43 (7.0%)	123 (15%)	**<.001**
Cardiac Arrest	430 (6.9%)	58 (9.1%)	-	**0.05**	700 (11%)	75 (12%)	-	0.62

AAA: abdominal aortic aneurysm; NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; LOS: length of stay; UTI: urinary tract infection; ARF: acute renal failure; DVT: deep vein thrombosis; CVA: cerebrovascular accident; MI: myocardial infarction.
Values are median (inter quartile range) or total events (percentages)
Boldface P values represent significance (P<.05)

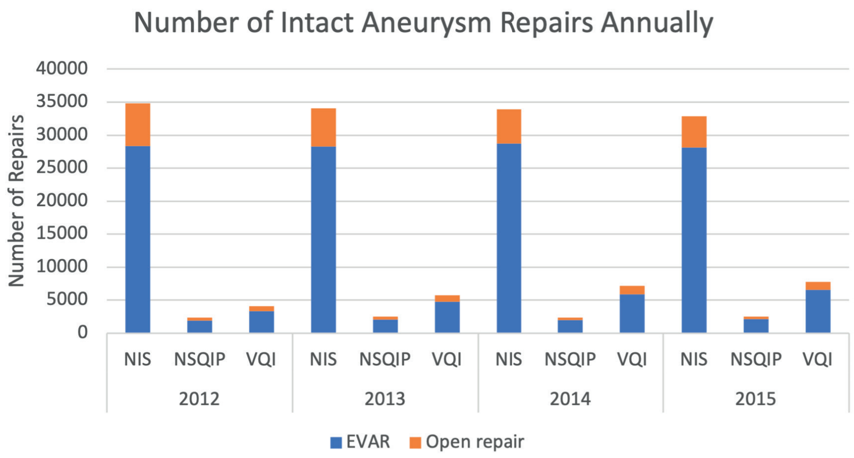
For a ruptured indication, in-hospital mortality was again highest in NIS and lowest in VQI for both EVAR and open repairs (Ruptured, EVAR: NIS: 24%, NSQIP 20%, and VQI: 16%, P<.001; Ruptured, open: NIS: 36%, NSQIP: 31%, and VQI: 26%, P<.001). Similar to elective repair, more proximal aneurysm extent was associated with a higher mortality. For juxtarenal, ruptured repair using EVAR, there was a higher mortality in NSQIP (NSQIP: 25% and VQI: 22%, P<.001) while for suprarenal/ Type IV indications, mortality was greatest in VQI (NSQIP: 25% and VQI: 33%, P<.001) (Table 7).

Several differences in rates of specific in-hospital complications were observed between the databases. For example, the incidence of pneumonia, UTI and ARF were all higher in NIS. CVA and ARF rates were lowest in NSQIP while POMI rates were highest in VQI. In contrast, length of stay, wound dehiscence and rate of DVT were similar among the databases. (Table 7).

Trends over time

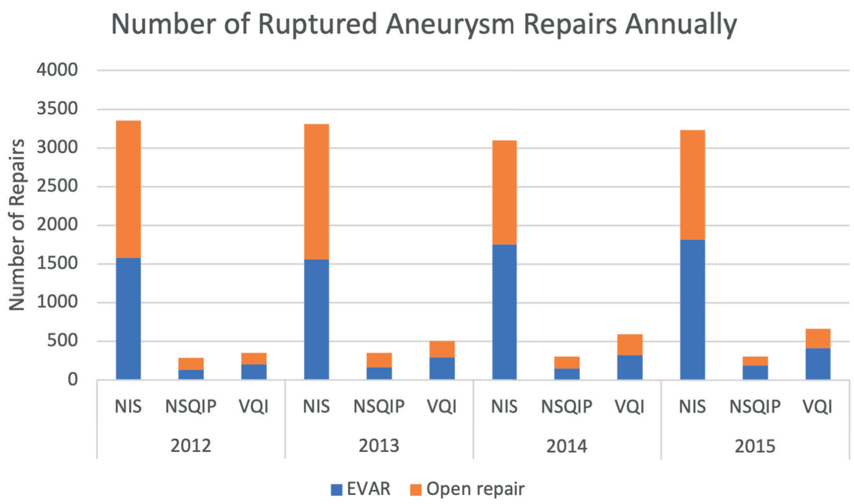
From 2012 to 2015, the total number of intact repairs that were captured declined slightly in NIS, while it remained constant in NSQIP but increased in VQI due to the increasing number of centers participating in VQI over time (Figure 1). Based on NIS estimates of total US case numbers, the number of cases in NSQIP represented 7-8% of the intact repairs in NIS annually and the number of cases in VQI increased from 12% in 2012 to 24% in 2015. NSQIP case numbers represented 9-11% of rupture repairs annually and the number of cases in VQI increased from 10% to 21%. The proportion of intact and rupture repairs being performed with EVAR increased over the years in all three databases (Figure 1-2).

Figure 1: Number of annual intact aneurysm repairs per database, stratified by total and endovascular repairs.



NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative

Figure 2: Number of annual ruptured aneurysm repairs per database, stratified by total and endovascular repairs.



NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative

Discussion

This study described the demographics and rates of complications after AAA repair, using NIS, NSQIP, and VQI from 2012 to 2015. We found that overall, NIS reported a lower frequency of comorbid conditions and a higher in-hospital mortality rate when compared with NSQIP and VQI. Complication rates were inconsistent between the databases and the NIS lacked the granularity to determine if an acute event during that hospital admission occurred post-operatively. The number of aneurysm repairs in the VQI is increasing and represented 23% of the NIS in 2015. The proportion of EVARs performed over the study period, for each year, were similar and increasing in all three datasets.

The demographics of the patients who underwent repair for both intact and ruptured AAA were different among the three databases. Both intact and ruptured repairs followed a similar pattern with the largest difference in proportion of patients diagnosed with obesity, CHF and CKD. This is likely due to differences in how these covariates are defined in different databases. For example, in NIS, CHF is captured if there is a diagnosis code for CHF. In VQI, CHF is captured with any prior diagnoses and specifies the symptoms of CHF. In NSQIP, CHF is only captured if a patient has exhibited symptoms in the last 30 days. These findings are consistent with a prior study, where the discrepancy in these variables were also seen in a comparison of VQI and NSQIP for lower extremity bypass.[11] In NIS, the CKD covariate includes anyone with stage 1 kidney disease, even though these patients have an eGFR>90 mL/min/1.73m^2. The QI registries include a preoperative creatinine which allows for calculation of eGFR. Differences in these comorbidities are important to note as previous research showed that CHF and CKD are two of strongest predictors when evaluating post-operative mortality in AAA repair.[10] This fundamental understanding of how databases define variables, and therefore capture the true risk associated with each comorbidity, is critical for QI efforts and health outcomes research. Therefore, it stands to reason that databases would benefit from more harmonization of comorbidity and end-point definitions. Further, the severity of the comorbidity will affect the beta-coefficient and the impact for a final risk prediction model. Therefore, all models should clearly describe the type of data used and outline the definition of their covariates.

Constrained by the definitions of ICD-9 codes, we were unable to confirm if an acute event occurred post-operatively or was an admission diagnosis that occurred pre-operatively. Efforts to remedy this problem include a present-on-admission (POA) variable used to distinguish a pre-existing condition from a new condition that arises during a hospitalization. However, other studies demonstrated that this indicator variable may not be reliable.[4] After evaluating the carotid revascularization procedures, authors found that between 40-60% of diagnoses that are more common post operatively than pre operatively were labeled with the POA indicator. These nuances have an important influence. If the patients' preoperative coexisting conditions are indistinguishable from postoperative complications, then it is impossible to accurately risk adjust. However, with certain administrative databases such as Medicare, the long-term follow-up data allows us to distinguish preoperative from postoperative diagnoses.[12, 13] Since the switch to ICD-10 in 2015, coding has become more specific given the ICD-10 complex taxonomy; however, distinguishing between a preoperative coexisting condition and a postoperative complication continues to be a challenge.

The difference in complications between administrative databases and QI registries are multifactorial, including differences in variable definitions, variation in coding, coding errors and uncertainty in distinguishing between a complication or pre-existing condition.[14-16] However, a blanket statement reporting that all complications are not accurately reported in administrative data is not necessarily correct. In 2018, a study was performed that evaluated postoperative MI, from 8 different hospitals, comparing NSQIP to Medicare, and subsequently validated each MI with chart review. The study found that QI registry data were not more accurate than administrative data.[6] Furthermore, a study performed evaluating the accuracy of ARF as defined in NIS, by comparing coding of each patient to chart review, found that coding for dialysis had a 94% positive predictive value.[17] While the sensitivity was not as high for ARF without dialysis, administrative coding was found to be an accurate way of evaluating patients receiving dialysis.

NIS was designed for reimbursement purposes and therefore certain limitations are inherent to its design. As a limited number of fields is available to record diagnoses and procedures, choices for diagnoses codes might be influenced by reimbursement value. The Medicare Severity Diagnosis Related Groups (MS-DRG) system classifies acute care inpatients and measures case mix. Correct ICD-9 diagnoses and procedure codes are essential to determine the MS-DRG and subsequent reimbursement. The Major Complication/Comorbidity (MCC) is the highest level of severity of the MS-DRG system and therefore incites a higher payment rate. The secondary diagnoses codes on which the MCC level is based include CHF, end-stage renal disease, CVA, MI and cardiac arrest. As our results show lower rates of CHF, MI and cardiac arrest in NIS compared with the QI registries, this could indicate an underestimation of the complexity coding and subsequent lost billing opportunities. [18]

The issues regarding definition discrepancies and coding limitations do not apply to all variables. Patient demographics, age and sex, type of operation, mortality and length of stay are unlikely to be influenced by the differences between administrative and QI registries and therefore we believe these variables to be accurate.

Regarding in-hospital mortality, the results gave insight into the differences between NIS centers and centers participating in QI registries. The patients who were treated in VQI and NSQIP had lower mortality, despite being potentially higher risk. Particularly when evaluating open intact AAA repair there was a 2% in-hospital mortality difference between NIS and VQI. Rupture repair mortality was significantly higher in NIS, approximately 8% higher than in VQI for EVAR and 10% higher for open AAA repair. While this study cannot determine the cause of the mortality difference, it is unlikely that a higher proportion of complex repairs are performed in the NIS. The QI registries include large volume, tertiary referral centers, that have a higher concentration of complex cases. Furthermore, hospitals that participate in NSQIP and VQI have improved reported post-operative outcomes and higher-volume hospitals are associated with improved survival.[19-22] Also, previous research showed that in the NIS in 2009, vascular surgeons performed 66% of all AAA repair.[23] Increased specialization in vascular surgery could be associated with improved outcomes this could have influenced the improved mortality rates in the QI registries compared to the NIS.[23,24] NIS represents the national experience, whereas the QI registries represent hospitals that have elected to participate in quality improvement. This suggests that hospitals dedicated to improving quality are associated with lower in-hospital mortality. However, the question persists of how to extend the benefits of quality improvement to nonparticipating centers.

The identified differences in postoperative mortality raise important questions about the generalizability of NSQIP and/or VQI to the U.S. population. While both QI databases have significant investment and support from participating hospitals, the results of this analysis appear to highlight that these two QI registries have limited ability to capture a national outlook on postoperative AAA mortality. In contrast, the NIS is a large administrative claims data source with greater representation of national outcomes for AAA repair. Importantly, the NIS has poor comorbidity and procedure level variable granularity making risk-adjusted comparisons much more difficult than the QI registries. Therefore, we recommend that administrative data should be used for large epidemiological or trend studies which demonstrate broadly the national perspective and provide complementary information to the QI experience. Preexisting conditions can not be accurately and completely identified in the NIS, precluding adjusted analyses for variables except sex, age, race and possibly non-acute conditions such as diabetes. Similarly, concerning outcomes in NIS, we would recommend only using in-hospital death, length of stay and discharge disposition. Other administrative databases such as Medicare have improved accuracy for comorbidity, complication and long-term outcome identification. Registry data can support adjusted analyses which demand granular patient characteristic, operative details and outcome data. However, studies for which long-term outcomes are essential are limited by the lack of adequate long-term follow-up in most registries (Table 1).

The results of this study should be interpreted in the context of the design. We were limited in the selection of our patient cohorts by the available AAA coding, and as NIS does not differentiate between infrarenal and complex AAA repair in their coding we cannot assess the rates and potential influence on the outcomes of complex repairs in NIS. Also, NIS does not capture symptomatic status and hospital or surgeon volume. As we have seen, in QI registries that complex repair, symptomatic aneurysms and low volume centers and surgeons are associated with a higher mortality, the lack of granularity in the NIS limits the interpretation of the data. Secondly, we know that the most accurate perioperative outcomes include in-hospital and 30-day outcomes and that the elevated "perioperative" mortality risk actually persists for at least 90 days after AAA repair.[25] In the VQI, 30-day and 1-year follow up is accurately recorded and with the linkage to Medicare long-term reinterventions and readmissions can be evaluated. However, as NIS only reports in-hospital outcomes, we only analyzed the in-hospital outcomes from VQI and NSQIP.

Conclusion

In this study we compared patients treated for AAAs as captured by the administrative NIS database, as well as both NSQIP and VQI, QI registries. Overall, 7-23% of AAA repairs performed nationally are captured by these QI registries and VQI continues to grow. While reported rates of comorbidities are higher in NSQIP and VQI, the mortality was lower in the QI registries. This suggests that the hospitals participating in the QI projects are associated with a lower mortality and also questions the generalizability of QI registry outcomes to all US hospitals. However, the QI registries have more granular data regarding pre-operative coexisting conditions and post-operative complications which are essential for accurate risk adjustment. Understanding these differences is crucial when interpreting the results of large database studies.

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Chapter 4

Not All Risk Scores are Created Equal, A Comparison of Risk Scores for Abdominal Aortic Aneurysm Repair in Administrative Data and Quality Improvement Registries

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Abstract

Objective: Accurate and contemporary prognostic risk prediction is essential to inform clinical decision-making surrounding abdominal aortic aneurysm (AAA) care. Therefore, we validated and compared three different in-hospital mortality risk scores in one administrative and two quality improvement registries.

Methods: We included patients undergoing elective AAA repair from 2012-2015 in the national inpatient sample (NIS), the vascular quality initiative (VQI) (excluding the VSGNE region), and the national surgical quality improvement program (NSQIP) datasets to validate three risk scores: Medicare, vascular study group of New England (VSGNE) and Glasgow Aneurysm Score (GAS). The receiver operating characteristic (ROC) area under the curve (AUC) of all risk scores was calculated and, their discrimination was compared within a dataset using the Delong test and between datasets using a Z-test. We constructed graphical calibration curves for the Medicare and VSGNE risk score and compared calibration using an Integrated Calibration Index (ICI), the weighted average of the absolute difference between the calibration curve and the diagonal line of perfect calibration.

Results: We identified a total of 25,461 NIS, 18,588 VQI, and 8,051 NSQIP patients who underwent elective open or endovascular AAA repair (EVAR). Overall, the Medicare risk score was more likely to overestimate mortality in the quality improvement registries while the VSGNE risk score underestimated mortality in all databases. After EVAR, the Medicare risk score had a higher AUC in the NIS compared to GAS ($P<.001$) but not compared to the VSGNE risk score ($P=.54$). The VSGNE risk score was associated with a significantly higher ROC AUC compared to the Medicare ($P<.001$) and GAS risk score ($P<.001$) in the VQI registry. Also, the VSGNE risk score showed improved calibration compared with the Medicare risk score across all three databases (All $P<.001$). After open repair, the Medicare risk score showed improved calibration compared with the VSGNE risk score in the NIS ($P<.001$). However, in the VQI registry, the VSGNE risk score compared to the Medicare risk score had significantly better discrimination ($P=.008$) and calibration ($P<.001$).

Conclusion: Overall, the VSGNE risk score performed best in the quality improvement registries but underestimated mortality. However, the Medicare risk score demonstrated better calibration in the administrative dataset after open

repair. Although the VSGNE risk score appeared to perform better in the quality improvement registries, its overly optimistic mortality estimates and its reliance on detailed anatomic and clinical variables reduces broader applicability to other databases.

Introduction

The decision for elective repair of an abdominal aortic aneurysm (AAA) is informed by weighing the risks and benefits of surgery. Current Society of Vascular Surgery (SVS) practice guidelines suggest repair after the AAA reaches a diameter of 5.5cm for male and 5.0cm for female patients.[1] However, while surgeons can use diameter to estimate annualized rupture rates, many other factors including comorbid conditions and patient anatomy affect the surgical risk. Accordingly, multiple different preoperative risk scores have been created to provide guidance to physicians, patients, and researchers to facilitate understanding of the predicted risk of in-hospital mortality after elective AAA repair.

These risk prediction scores are used as prognostic instruments to help inform patients and support clinical decision-making. The accuracy of a risk prediction model can be assessed by its ability to discriminate and to calibrate.[2,3] A model with adequate discrimination will allow reliable discernment between high and low-risk patient populations. A prediction model is well calibrated if the estimated risks correspond to the observed proportion of the event. For example, a model that consistently predicts which patients have higher risk of death has good discrimination. However, if that model can predict which patients are at higher risk, but consistently underestimates their risk, then the model has good discrimination but poor calibration. These data allow for accurate translation of a reliable average risk to individual patients. Therefore, both strong discrimination and calibration are essential for valid clinical decision-making and for understanding the value of a risk score, which is crucial for patients, clinicians and researchers.

Our aim was to assess the performance of risk scores in databases with different characteristics. Herein, we validated and compared three different risk scores in one administrative and two quality improvement (QI) registries in an effort to find the most accurate model for application in real-world practice. We analyzed three commonly used risk scores evaluating in-hospital mortality: the Medicare risk score developed by Giles et al.[4]; the Vascular Study Group of New England (VSGNE) risk score developed by Eslami et al.[5]; and the Glasgow Aneurysm Score (GAS) developed by Samy et al.[6] These risk scores were applied to data from the National Inpatient Sample (NIS), the Vascular Quality Initiative (VQI), and the National Surgical Quality Improvement Program (NSQIP) registry.

Methods

Data source

We included all patients undergoing elective AAA repair from years 2012-2015 from three large databases. We chose this time interval as the NIS underwent a change in coding in 2012 and implemented ICD-10 coding in 2016 which would have affected the comparability of the data. Further details and comparison of each dataset were previously published.[7]

The NIS is an administrative dataset that collects patient data with international classification of disease codes (ICD) from 20% of all non-federal hospital discharges. It is maintained by the Healthcare Utilization Project as part of the Agency for Healthcare Research and Quality. Further information can be found at https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp

The VQI is a QI patient-safety organization which is the parent entity for the regional VSGNE registry and uses identical methodology and variables for data collection. The VQI currently includes over 550 centers in the United States, Canada and Singapore. Trained reviewers collect pre-defined data with input from the surgical team for operative details. Further information can be found at https://www.vqi.org/. We excluded the VSGNE region in our analysis.

NSQIP is a QI registry maintained by the American College of Surgeons. For hospitals that elect to participate in NSQIP, a clinical nurse is hired to enter patient data and complete in-hospital and 30-day outcomes. We used the targeted AAA NSQIP registry which includes detailed AAA specific variables. Additional information can be found at https://www.facs.org/quality-programs/acs-nsqip

The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the requirement for patient consent due to the retrospective and de-identified nature of the study.

Risk scores

The Medicare risk prediction model was based on data from a population of Medicare beneficiaries undergoing elective open or endovascular AAA repair from 2001-2004.[4] The outcome was in-hospital mortality. The equation was{-5.02+0.42(Female)+0.15(Age(71-75years))+0.63(Age(76-80years))+1.14(Age(>80 years))+0.71(Chronic renal insufficiency)+ 0.95(Dialysis)+0.55(Congestive heart failure(CHF))+0.30(Prior vascular disease)+1.17(Open repair)}. The comorbidities were identified using the Elixhauser algorithm.[8]

The VSGNE risk prediction model was constructed using a cohort of patients that underwent elective infrarenal open and endovascular repair in >30 VSGNE centers between 2003 and 2013.[5] The risk model outcome was in-hospital mortality. The equation was{-6.76+1.08(Open repair with infrarenal aortic clamp)+1.905(Open repair with suprarenal aortic clamp)+0.78(Age≥75 years)+0.69(Female)+0.56(History of myocardial disease)+0.71(History of cerebrovascular disease)+0.95(History of chronic obstructive pulmonary disease(COPD))+0.89(1.5≤Creatinine<2mg/dL)+1.31(Creatine≥2mg/dL)+ 0.91(AAA diameter >6.5 cm)}.

The GAS used 500 randomly selected patients treated with open repair in Glasgow from 1980 to 1990.[6] The risk model outcome was in-hospital mortality. The equation was{0.074(Age)+ 1.289(Shock)+0.54(Myocardial disease)+0.736(Cerebrovascular disease)+1.055(Renal disease)}. As the baseline hazard was not published in the manuscript we could not calculate calibration using the GAS.

Variable definitions

For the Medicare risk score, the Elixhauser index was used to identify all variables in the NIS database.[8] Chronic renal insufficiency was defined as a preoperative eGFR<90 without being on dialysis in the QI registries. CHF was defined as any asymptomatic or symptomatic CHF presentations in VQI and as symptomatic CHF in NSQIP. Prior vascular disease was defined as history of arterial bypass, arterial peripheral vascular intervention, major amputation, carotid endarterectomy, carotid artery stenting in VQI; this variable was not captured in NSQIP (Table 1a).

Table 1a: Definitions Medicare Risk Score

Female Sex	
Medicare Risk Score	Not defined
NIS	Patient Sex
NSQIP	Gender as per the medical record
VQI	Use gender at birth
Age	
Medicare Risk Score	Age was categorized as 67-70, 71-75, 76-80, or >80 years. (Medicare beneficiaries age 67 or older)
NIS	Age at years of admission
NSQIP	Procedure Date - Date of Birth
VQI	Patient age at procedure (90 and above reported as 90)
Chronic Renal Insufficiency	
Medicare Risk Score	Identified using a version of the Elixhauser algorithm that was adapted to also include diagnoses that occurred only in the outpatient setting
NIS	ICD-9 codes 404, 404.1, 404.90, 404.91, 585.9
NSQIP	preoperative eGFR<90 without being on dialysis
VQI	preoperative eGFR<90 without being on dialysis
Dialysis	
Medicare Risk Score	Dialysis-dependent endstage renal disease
NIS	ICD-9 codes 403.01, 404.02, 404.03, 403.11, 404.12, 404.13, 403.91, 404.92, 404.93, 585, 585.5, 585.6
NSQIP	Acute or chronic renal failure requiring treatment with peritoneal dialysis, hemodialysis, hemofiltration, hemodiafiltration, or ultrafiltration, within two weeks prior to the principal operative procedure
VQI	Currently on hemo- or peritoneal dialysis.
CHF	
Medicare Risk Score	Identified using a version of the Elixhauser algorithm that was adapted to also include diagnoses that occurred only in the outpatient setting
NIS	ICD-9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x
NSQIP	CHF with current signs and symptoms
VQI	any CHF including asymptomatic and mild CHF presentations
Vascular Disease	
Medicare Risk Score	Prior vascular disease was defined as either a prior history of cerebrovascular disease or peripheral vascular disease.
NIS	ICD-9 codes 440.x, 441.x, 442.x, 443.1- 443.9, 447.1, 557.1, 557.9, V43.4
NSQIP	Not captured
VQI	history of arterial bypass, arterial peripheral vascular intervention, major amputation, carotid endarterectomy, carotid artery stenting
Open repair	
Medicare Risk Score	Not defined in the manuscript.
NIS	Identified using procedure codes (ICD-9 codes) and CPT codes
NSQIP	Based on database module
VQI	Based on database module

For the VSGNE risk score, the Elixhauser index was used to identify all variables in the NIS database.[8] NIS does not have information about clamp location for patients who underwent open repair and therefore all patients were categorized as infrarenal. History of myocardial disease was defined as a history of percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, or CHF in VQI; and as NSQIP does not collect other variables relating to history of myocardial disease, only current CHF was included in NSQIP. History of cerebrovascular disease as prior carotid endarterectomy, or carotid artery stenting in VQI; and was not captured in NSQIP. History of COPD was defined as history or any COPD, treated or untreated, in VQI and as current severe COPD in NSQIP. For the VSGNE risk score, patients with a creatinine above 2mg/dL accrue additional risk than those with a creatinine 1.5-2mg/dL (Table 1b).

Table 1b: Definitions VSGNE Risk Score

Open Aortic Surgery with infrarenal clamp	
VSGNE Risk Score	
NIS	Clamp location not captured; all patients included as infrarenal
NSQIP	Proximal clamp location
VQI	Proximal clamp location
Open Aortic Surgery with suprarenal clamp	
VSGNE Risk Score	Proximal clamp location
NIS	Clamp location not captured; all patients included as infrarenal
NSQIP	Proximal clamp location
VQI	Proximal clamp location
Female sex	
Risk Score	Not defined in manuscript
NIS	Patient Sex
NSQIP	Gender as per the medical record
VQI	Use gender at birth
History of myocardial disease	
VSGNE Risk Score	Not defined in manuscript
NIS	ICD-9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x
NSQIP	Current CHF
VQI	History of percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, or CHF
History of cerebrovascular disease	
VSGNE Risk Score	Not defined in manuscript.
NIS	ICD-9 codes 997.02, 436, 431, 433.x, 434.01, 434.11, 434.91
NSQIP	Not captured
VQI	Prior carotid endarterectomy, or carotid artery stenting

Open Aortic Surgery with infrarenal clamp	
History of COPD	
VSGNE Risk Score	Not defined in manuscript.
NIS	ICD-9 codes 490x-492.x, 493.x, 494x505.x, 506.4
NSQIP	Current severe COPD
VQI	History or any COPD, treated or untreated
1.5 ≤Creatinine<2mg/dL	
VSGNE Risk Score	Not defined in manuscript.
NIS	ICD-9 code 404.92
NSQIP	Pre-operative serum creatinine
VQI	Most recent creatinine measurement taken before procedure.
Creatine ≥ 2mg/dL	
VSGNE Risk Score	Not defined in manuscript.
NIS	ICD-9 codes 403.01, 404.02, 404.03, 403.11, 40412, 404.13, 403.91, 404.92, 404.93, 585, 585.5, 585.6
NSQIP	Pre-operative serum creatinine
VQI	Most recent creatinine measurement taken before procedure.
Diameter > 6.5cm	
VSGNE Risk Score	Not defined in manuscript.
NIS	Not captured
NSQIP	Use max diameter measured at right angle to centerline. If not possible, use max AP diameter. If multiple imaging modalities, use most accurate in following hierarchy: CT>MRI>Ultrasound>arteriogram.
VQI	Maximum AP AAA diameter

For the GAS, the Elixhauser index was used to identify all variables in the NIS database.[8] Since we only included elective repair, no patient had an increased risk because of shock. Renal disease was defined as a preoperative eGFR<60 or being on dialysis in both QI registries (Table 1c).

When variables were not included in a database, that parameter was excluded from the risk model. All variables included in the model had <4% missing.

Table 1c: Definitions Glascow Aneurysm Risk Score

Age	
GAS Risk Score	Not defined
NIS	Age at years of admission
NSQIP	Procedure Date - Date of Birth
VQI	Patient age at procedure (90 and above reported as 90)
Shock	
Risk Score	Based on clinical information of tachycardia, hypotension, pallor and sweating as stated in the patient's notes.
NIS	Not applicable as we only included elective AAA surgery in our cohort
NSQIP	Not applicable as we only included elective AAA surgery in our cohort
VQI	Not applicable as we only included elective AAA surgery in our cohort
Myocardial disease	
Risk Score	Comprises previous myocardial infarction and/or ongoing angina.
NIS	ICD-9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x
NSQIP	Current CHF
VQI	History of percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, or CHF
Cerebrovascular disease	
Risk Score	Refer to all grades of stroke including transient ischemic attack.
NIS	ICD-9 codes 997.02, 436, 431, 433.x, 434.01, 434.11, 434.91
NSQIP	Not captured
VQI	Prior carotid endarterectomy, or carotid artery stenting
Renal Disease	
Risk Score	Includes chronic and acute renal failure
NIS	ICD-9 codes 403.01, 404.02, 404.03, 403.11, 40412, 404.13, 403.91, 404.92, 404.93, 585, 585.5, 585.6, 404.92
NSQIP	Preoperative eGFR<60 or being on dialysis
VQI	Preoperative eGFR<60 or being on dialysis

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score; ICD-9: International Classification of Diseases, 9th Revision; CPT: Current Procedural Terminology.

Statistical analysis

To assess discrimination we constructed Receiver Operating Characteristics (ROC) curves which plot the sensitivity (true positive rate) against[1–(false positive rate)] for the probability of the outcomes. We calculated the ROC area under the curve

(AUC) and compared discrimination of the risk scores within a dataset using the Delong test and between datasets using a Z-test.

To measure the calibration, we constructed graphical calibration curves by disaggregating the patient population into ten quantiles. We then plotted their predicted mortality risk against the observed proportion of mortality (perfect predictions should be on the 45° line). In order to permit a numerical comparison between the risk scores and dataset, we used the Integrated Calibration Index(ICI) to assess calibration.[9] The ICI is a weighted average of the absolute difference between the calibration curve and the diagonal line of perfect calibration, where the absolute differences are weighted by the density function of the weights. The ICI standard error was compared within a dataset using the Delong test and between datasets using a Z-test. Also, the graphical representation indicates overprediction or underprediction.

Results

We identified a total of 25,461 NIS, 8,051 NSQIP, and 18,588 VQI patients who underwent elective open or endovascular AAA repair (EVAR). The proportion of EVAR was 83.6% in NIS, 83.9% in NSQIP and 84.8% in VQI.

Discrimination - EVAR

In the NIS, the Medicare risk score had a ROC AUC of 0.70, the VSGNE risk score had an AUC of 0.69 while the GAS had an AUC of 0.66 (Table 2, Figure 1). In the NIS, the ROC AUC was significantly higher using the Medicare risk score compared to GAS (Medicare vs. GAS: $P<.001$; VSGNE vs. GAS: $P=.10$; Medicare vs. VSGNE: $P=0.54$)

In the VQI registry, the Medicare risk score had a ROC AUC of 0.64, the VSGNE risk score had an AUC of 0.76, and the GAS has an AUC of 0.64(Table 2, Figure 1). In the VQI registry, the VSGNE risk score was associated with a significantly higher ROC AUC compared to the Medicare and GAS risk scores (Medicare vs. GAS: $P=.88$; VSGNE vs. GAS: $P<.001$; Medicare vs. VSGNE: $P<.001$).

In the NSQIP registry, the Medicare, VSGNE, and GAS risk scores had similar ROC AUCs of 0.68, 0.70, and 0.69, respectively (Medicare vs. GAS: $P=.68$; VSGNE vs. GAS: $P=.53$; Medicare vs. VSGNE: $P=.65$) (Table 2, Figure 1).

Table 2. C-statistic of the Area Under the Receiving Operating Curve of each Risk Score per dataset.

	NIS	VQI	NSQIP
Medicare	**EVAR**: AUC: 0.70 (SE: 0.02; 95%CI: 0.66-0.74) **Open**: AUC: 0.64 (SE: 0.02; 95%CI: 0.61-0.68)	**EVAR**: AUC: 0.64 (SE: 0.03; 95%CI: 0.59-0.69) **Open**: AUC: 0.66 (SE: 0.03; 95%CI: 0.60-0.72)	**EVAR**: AUC: 0.68 (SE: 0.04; 95%CI: 0.60-0.76) **Open**: AUC: 0.67 (SE: 0.04; 95%CI: 0.60-0.75)
VSGNE	**EVAR**: AUC: 0.69 (SE: 0.02; 95%CI: 0.65-0.74) **Open**: AUC: 0.61 (SE: 0.02; 95% CI: 0.58-0.65)	**EVAR**: AUC: 0.76 (SE: 0.03; 95%CI: 0.71-0.81) **Open**: AUC: 0.73 (SE: 0.02; 95%CI: 0.68-0.78)	**EVAR**: AUC: 0.70 (SE: 0.04; 95%CI: 0.62-0.79) **Open**: AUC: 0.74 (SE: 0.04; 95%CI: 0.67-0.80),
GAS	**EVAR**: AUC: 0.66 (SE: 0.02; 95%CI: 0.62-0.71) **Open**: AUC: 0.63 (SE: 0.02; 95%CI: 0.59-0.67)	**EVAR**: AUC: 0.64 (SE: 0.03, 95%CI: 0.59 - 0.69) **Open**: AUC: 0.69 (SE: 0.03, 95%CI: 0.63 - 0.74)	**EVAR**: AUC: 0.69 (SE: 0.04; 95%CI: 0.61-0.76) **Open**: AUC: 0.73 (SE: 0.73; 95%CI: 0.67-0.80)

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score

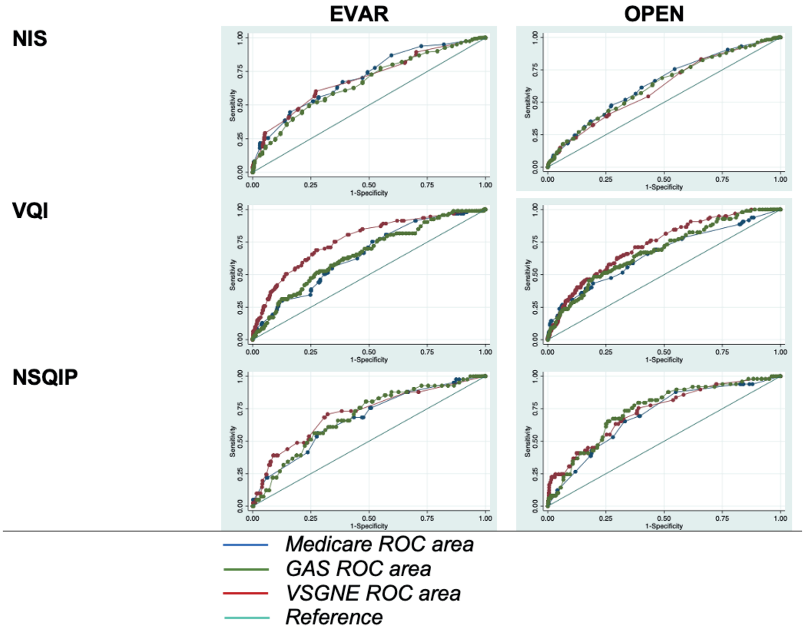
The Medicare risk score was associated with a higher AUC in the NIS compared to the VQI registry(P=0.005) but not compared to NSQIP(P=0.27). The VSGNE and GAS were not associated with better discrimination in any database compared to the other.

Calibration - EVAR

In the NIS, observed in-hospital mortality was 0.80% and expected mortality was 1.0% using the Medicare risk score and 0.25% using the VSGNE risk score. In the VQI, the observed mortality was 0.65% and the expected mortality was 2.1% using the Medicare risk score and 0.44% using the VSGNE risk score. Finally, in the NSQIP registry, observed in-hospital mortality was 0.61% and expected mortality was 1.9% using the Medicare risk score and 0.25% using the VSGNE risk score (Figure 2).

In all three databases, the VSGNE risk score showed improved calibration compared with the Medicare risk score (Table 3, NIS: P<.001; VQI: P<.001; NSQIP: P<.001).

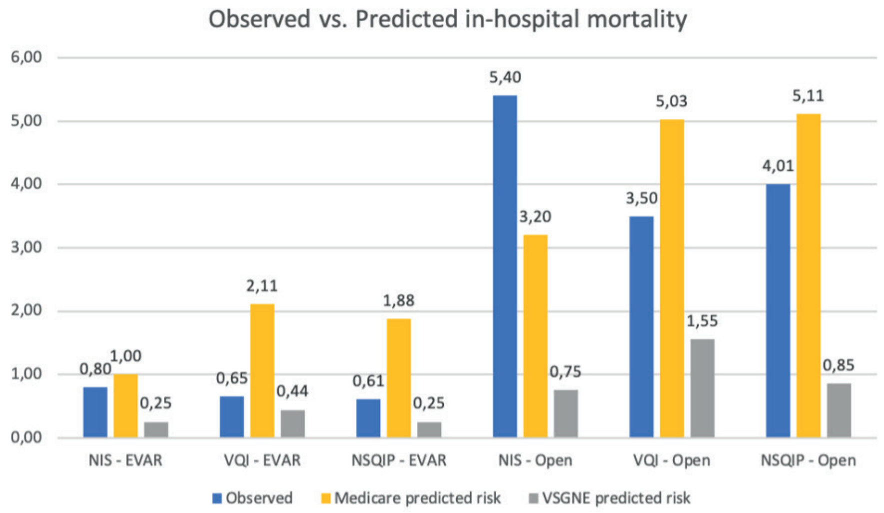
Figure 1. Receiver Operating Characteristics showing the discrimination of each risk score in the three databases, stratified by repair type.



ROC: Receiver Operating Characteristics; *NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score*

The Medicare risk score had improved calibration in the NIS compared to both the NSQIP(P<.001) and VQI scores(P<.001). The VSGNE risk score showed improved calibration in the VQI database compared to NIS(P<.001) and NSQIP scores(P<.001). Similarly, VSGNE score demonstrated superior calibration to the NIS score in the NSQIP AAA targeted registry(P=.02) (Table 3, Figure 3).

Figure 2: Observed and median predicted mortality, stratified by database and repair type



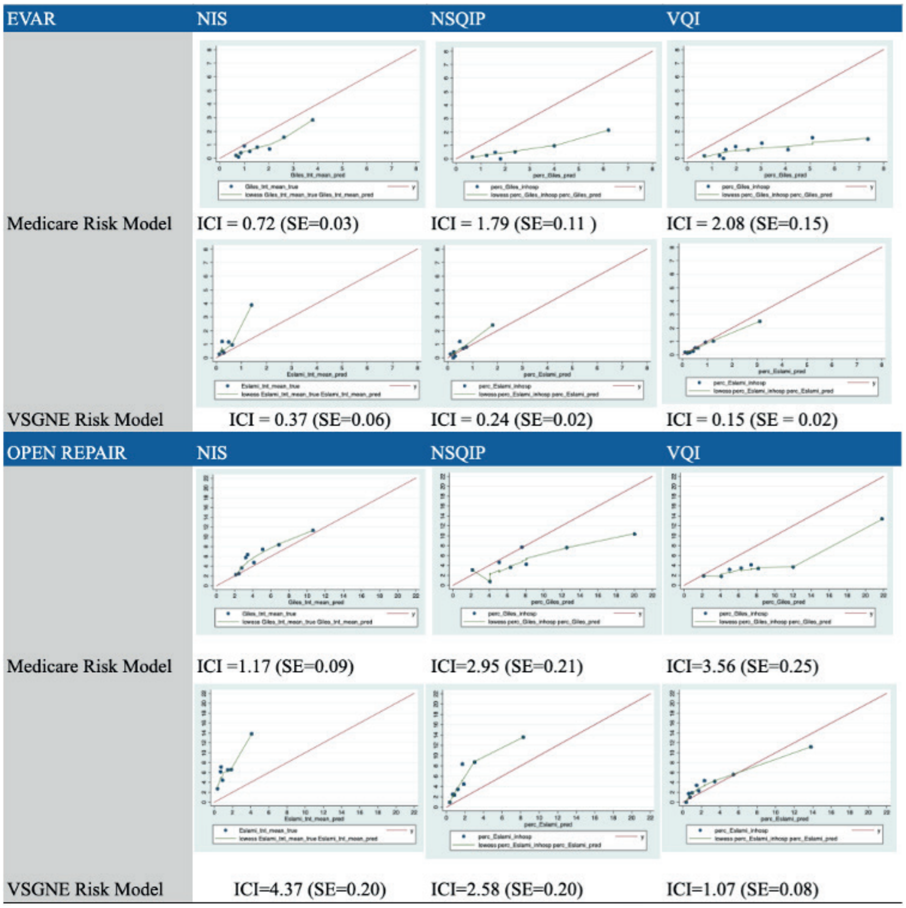
NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score

Table 3. Integrated Calibration Index of each Risk Score per dataset.

_	NIS	VQI	NSQIP
Medicare	**EVAR**: ICI: 0.72 (SE=0.03) **Open**: ICI: 1.17 (SE=0.09)	**EVAR**: ICI: 2.08 (SE=0.15) **Open**: ICI: 3.56 (SE=0.25)	**EVAR**: ICI: 1.79 (SE=0.11) **Open**: ICI: 2.95 (SE=0.21)
VSGNE	**EVAR**: ICI: 0.37 (SE=0.06) **Open**: ICI: 4.37 (SE=0.20)	**EVAR**: ICI: 0.15 (SE=0.02) **Open**: ICI: 1.07 (SE=0.08)	**EVAR**: ICI: 0.24 (SE=0.02) **Open**: ICI: 2.58 (SE=0.20)
GAS	-	-	-

NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score

Figure 3: Calibration curves plotting the predicted mortality against the actual mortality, stratified by risk score and database.



EVAR: endovascular aneurysm repair; NIS: National Inpatient Sample; NSQIP: National Surgical Quality Improvement Program; VQI: Vascular Quality Initiative; VSGNE Vascular Study Group of New England; GAS: Glasgow Aneurysm Score; ICI: Integrated Calibration Index; SE: Standard error

Discrimination - open repair

In the NIS, the Medicare, VSGNE, and GAS risk scores had similar ROC AUC of 0.64, 0.61, and 0.63, respectively (Medicare vs. GAS: P=.29; VSGNE vs. GAS: P=.37; Medicare vs. VSGNE: P=.08)(Table 2, Figure 1).

In the VQI registry, the Medicare risk score had a ROC AUC of 0.66, the VSGNE risk score AUC was 0.73 and the GAS AUC was 0.69(Table 2, Figure 1). These differences were associated with significantly improved discrimination for the VSGNE risk score compared to the Medicare risk score (Medicare vs. GAS: P=.22; VSGNE vs. GAS: P=.06; Medicare vs. VSGNE: P=.008).

In the NSQIP registry, the respective ROC AUCs for the Medicare, VSGNE, and GAS risk scores were 0.67, 0.74, 0.73(Table 2, Figure 2). No significant differences in the discrimination between risk scores was evident (Medicare vs. GAS: P=.13; VSGNE vs. GAS: P=.0.84; Medicare vs. VSGNE: P=.16).

The Medicare risk score was not associated with better discrimination in any database compared to any other risk score. However, the VSGNE risk score was associated with a significantly higher AUC in VQI compared to NIS(P<0.001) and in NSQIP compared to the NIS risk score(P=0.001). Additionally, the GAS risk score was associated with a higher AUC in the VQI compared to the NIS database(P=0.02).

Calibration - open repair

After open repair, observed in-hospital mortality in the NIS was 5.4% and expected mortality was 3.2% using the Medicare risk score and 0.75% using the VSGNE risk score. In the VQI, the observed mortality was 3.5% and the expected mortality was 5.0% using the Medicare risk score and 1.6% using the VSGNE risk score. Finally, in the NSQIP registry, observed in-hospital mortality was 4.0% and expected mortality was 5.1% using the Medicare risk score and 0.85% using the VSGNE risk score (Figure 2). In the NIS, the Medicare risk score showed improved calibration compared with the VSGNE risk score(P<.001) and NSQIP scores(P<.001) while in VQI registry, the VSGNE risk score showed improved calibration compared with the Medicare risk score. The Medicare risk score had improved calibration in the NIScompared to both VQI (P<0.01) and NSQIP (P<.001). The VSGNE risk score showed improved calibration in VQI compared to both NIS and NSQIP, and in NSQIP compared to NIS (Table 3, Figure 3). Finally, for all databases and risk scores, calibration was improved after EVAR compared to open repair.

Discussion

The aim of the current analysis was examine how different risk scores perform in two QI registries and one administrative database. Overall, the Medicare risk score had a propensity to overestimate mortality in the QI registries while the VSGNE risk score underestimated mortality in all databases. In contrast, the VSGNE risk score showed the best overall discrimination and calibration in the QI registries while the Medicare risk score demonstrated better calibration in the administrative NIS dataset after open repair.

The improved ability to discriminate between higher and lower risk patients by the VSGNE risk score in the VQI registry and the Medicare risk score in the NIS could be explained by multiple factors. First, there are differences in the variable definitions and availability between the databases which were used to create the risk models and the datasets to which we subsequently applied each risk score. For example, the VSGNE is a regional registry of the VQI database, so the definitions used in the original derivation of the VSGNE risk score exactly match the VQI database definitions. This observation is relevant since the NSQIP registry has some variable definition discrepancies compared to the VQI while the NIS lacks some clinical variables such as preoperative AAA diameter and cross clamp location that are used in the VSGNE risk score. Analogous to these differences, the Elixhauser index was used to identify risk factors for the original generation of the Medicare risk score so improved performance in a claims database like the NIS is more likely given variable similarities.[8] Moreover, the Medicare risk score used the Elixhauser definition for Chronic Renal Insufficiency which included stages I to IV. This broad definition of renal disease applied to a majority of the patients in the QI registries.[7] Since increased perioperative mortality risk is predicted based upon increasing renal disease severity, applying the Medicare definition in QI registries likely decreases its discrimination and calibration abilities.

Secondly, the different patient populations represented within the datasets have different distributions of risk factors. For example, centers who participate in a QI registry are more likely to be higher volume referral centers while nationwide administrative databases are likely to have more heterogenous AAA populations.[7] Therefore, risk scores that are developed using registry data could be less applicable in an administrative database and vice versa.

When evaluating calibration (the ability to accurately predict the risk level), the VSGNE risk score performed better in all databases when predicting EVAR in-hospital mortality risk whereas the Medicare risk score overestimated the risk in all three databases. After open repair, the VSGNE risk model performed better in the VQI database compared to the Medicare risk score; however, they both underestimated the mortality risk in all three databases. Notably, the Medicare risk score performed better compared to the VSGNE in the NIS database. Similar to EVAR, the Medicare risk score overestimated mortality after elective open AAA repair in the two QI registries.

The overestimation of EVAR mortality risk could be influenced by the increased use and improvement of EVAR outcomes over time.[10,11] The VSGNE risk score was created using more contemporaneous data (2003–2013) when EVAR use was more established compared to the Medicare risk score which was developed using data from repairs performed between 2001 and 2004. This observation would emphasize the ephemeral nature of risk scores and the importance of updating and developing scores over time so that they more closely align with changes in practice pattern. Also, another reason for the mortality risk overestimation by the Medicare risk score and underestimation by the VSGNE risk score, is the inherent differences between patient populations captured by administrative databases and QI registries.

As hospitals elect to participate in QI registries, the centers represented in VQI and NSQIP are frequently larger centers and care networks, focused on QI and therefore often achieve improved outcomes compared to administrative nationwide databases.[7] Furthermore, the centers that are participating in QI registries may have more standardized post-operative pathways to recognize a patient who is at risk for failure to rescue.[12] This difference in patient population and processes of care could contribute to this discrepancy in calibration outcomes and highlight the importance of updating risk scores to reflect contemporary mortality outcomes. If the intended use of a risk score is to inform clinical decision making by adequately predicting mortality risk for a patient, the result should be as specific as possible to the hospital and repair type.

Our findings have several important implications for perioperative decision-aid risk prediction model development. Derivation of a perfect model is practically impossible, and it is important to control model complexity. Also, transparency in terms of variable definitions, methods and results is essential. In this study, we were not able to analyze the calibration of the GAS as they did not provide the intercept of the risk score model. Also, for the VSGNE and Medicare risk score, the manuscripts describing the risk score do not define the individual variables that are used in the model. An important limitation of risk scores in the rapidly evolving field of AAA surgery is that older scores might not be applicable to newer data as techniques and outcomes evolve over time.

Elective EVAR in-hospital mortality rates are $<1\%$ across a variety of databases, so the question arises if perioperative mortality outcome is still the best marker of quality? The more rare the outcome becomes, the harder it is for models to reliably predict the event. Accordingly, it is our recommendation that a shift from focusing on in-hospital mortality to long-term survival, reintervention, cost and late rupture should occur and would likely be more appropriate surrogates to define quality of EVAR delivery nationally. Updating risk scores using contemporary data while incorporating other relevant outcomes is therefore essential. Despite the limitations of risk scores, they remain an important clinical decision-making tool in the discussion of AAA repair in the era of value-based healthcare and increasing patient autonomy.

The usefulness of prediction scores depends on the intended application. The use of the VSGNE risk score is recommended by the SVS and our analysis shows good discrimination and calibration in the QI registries. The clinical variables in in the VSGNE risk score are also available in the preoperative setting, so the VSGNE score is well suited to facilitate point of care decision-making. However, the VSGNE risk incorporates anatomic and operative variables and is therefore limited in its application within administrative datasets so the Medicare score seems to remain most appropriate to use in this data source. In contrast, retrospective application of the VSGNE score for inter-hospital comparisons using claims data would be less likely to produce accurate risk adjusted comparisons.

The results of the current manuscript need to be interpreted within the context of its limitations. We evaluated the predictive ability of the Medicare, VSGNE, and GAS risk scores in three different databases so our results reflect the performance in these databases while accepting the inherent limitations of each database. Broader generalizability of our findings and recommendations towards the universal applicability in clinical and research settings is therefore not straightforward. However, we believe that examination of the three most commonly used risk scores among three well known data sources that inform the field represents an important contribution. We were also restricted by the availability of the variable definitions and risk score descriptions presented in the index publications that reported the risk scores. When we applied the VSGNE risk score to the NIS, the risk score potentially underestimated the mortality by assuming patients all had an infrarenal clamp. The VSGNE risk score would likely perform better if we were able to determine which patients underwent repair with suprarenal clamping. Also, since the GAS does not provide the intercept of the risk model, we could not perform a calibration validation for this risk score. This underscores the importance of the peer review and editorial process to demand that all the relevant information be made available when introducing a risk score into publication.

Conclusion

Overall, the VSGNE risk score, while underestimating mortality, performed better in QI registry data; however, the Medicare risk score performed better in an administrative dataset, particularly in patients undergoing open repair. This is likely a reflection of the different patient populations that are used to build the risk scores compared to the patient populations that are used when the risk score is applied. An updated algorithm based on current VQI data may be less prone to underestimate mortality. Also, administrative data has less granular variable definitions and does not provide anatomical and clinical variables needed for the VSGNE risk score, negatively impacting its predictive ability. Therefore, the Medicare score continues to deliver the most value for claims-based analysis but an iteratively updated model accounting for procedure and patient level risk factors is needed to align with the changing landscape of AAA care provision. These important differences in different risk scores can inform clinicians, patients and researchers when attempting to make clinical decisions and define quality to improve AAA care delivery nationally.

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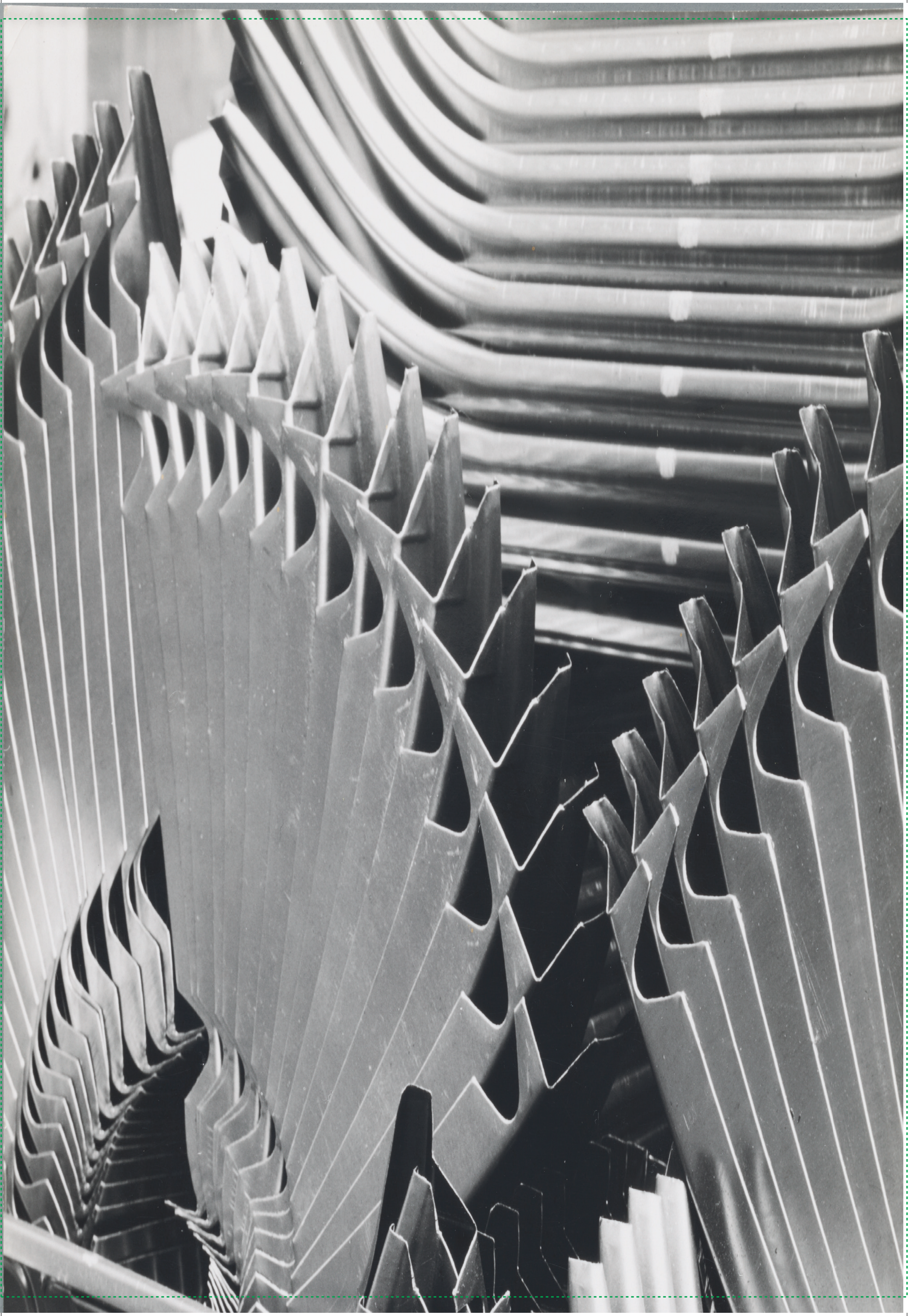

PART II

Management of AAA repair in specific subpopulations

Chapter 5

Sex differences in perioperative outcomes after complex abdominal aneurysms repair

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Abstract

Objective: Female sex is associated with worse outcomes following infrarenal abdominal aortic aneurysm (AAA) repair. However, the impact of female sex on complex AAA repair is poorly characterized. Therefore, we compared outcomes between female and male patients following open and endovascular treatment of complex AAA.

Methods: We identified all patients who underwent complex aneurysm repair between 2011 and 2017 in the American College of Surgeons National Surgical Quality Improvement Program Targeted Vascular Module. Complex repairs were defined as those for juxtarenal, pararenal or suprarenal aneurysms. We compared rates of perioperative adverse events between females and males, stratified by open and endovascular repair (EVAR). We calculated propensity scores and used inverse probability weighted logistic regression to identify independent associations between female sex and our outcomes.

Results: We identified 2,270 complex aneurysm repairs, of which 1,260 were EVARs (21.4%% female) and 1,010 were open repairs (30.7% female). Following EVAR, female patients had higher rates of perioperative mortality (6.3% vs 2.4%; P=.001) and major complications (15.9% vs. 7.6%, P<.001) compared to males. In contrast, following open repair, perioperative mortality was not significantly different (7.4% vs. 5.6%, P=.3) and the rate of major complications was similar (29.4% vs. 27.4%, P=.53) between females and males. Furthermore, even though perioperative mortality was significantly lower after EVAR compared to open repair for male patients (2.4% vs. 5.6%, P=.001), this difference was not significant for women (6.3% vs. 7.4%, P=.60). On multivariable analysis, female sex remained independently associated with higher perioperative mortality (OR, 2.5; 95% CI, 1.3-4.9; P=.007) and major complications (OR, 2.0; 95% CI, 1.3-3.2; P=.002) in patients treated with EVAR, but showed no significant association with mortality (OR, 0.9; 95% CI, 0.5-1.6; P=.69) or major complications (OR, 1.1; 95% CI, 0.8-1.5; P=.74) after open repair. However, the association of female sex with higher perioperative mortality in patients undergoing complex EVAR was attenuated when diameter was replaced with Aortic Size Index in the multivariable analysis (OR, 1.9; 95% CI, .9-3.9; P= .091).

Conclusion: Female sex is associated with higher perioperative mortality and more major complications than male patients following complex EVAR, but not following complex open repair. Continuous efforts are warranted to improve the sex discrepancies in patients undergoing endovascular repair of complex AAA.

Introduction

Abdominal aortic aneurysms (AAAs) are 4-6 times more common in men than in women.[1] However, female sex is associated with a higher rupture risk and worse perioperative outcomes after infrarenal AAA repair.[2,3] Although the etiology of these differences is not fully understood, the influence of sex hormones, more complex anatomy, more graft related complications, and a higher incidence of undiagnosed cardiovascular disease, have all been suggested as potential causes.[4,5]

Abdominal aneurysms involving the renal and visceral segment of the aorta, also known as complex AAAs, present additional technical challenges to both open and endovascular aortic repair (EVAR). The introduction of new endovascular repair strategies such as fenestrated and branched endografts, or chimney and snorkel techniques, have made endovascular repair of these complex aneurysms possible with good results.[6–11] However, the previously reported promising outcomes for complex EVAR may not be applicable to the female population as females are typically underrepresented in these studies and are less likely to meet the necessary endograft anatomic criteria than male patients.[6–12]

As compared to infrarenal aneurysms, the impact of female sex on aneurysms involving the renal and visceral segment of the aorta is poorly characterized and studies have shown contradicting results.[13,14] Therefore, we evaluated the association of female sex and perioperative outcomes after endovascular and open complex AAA repair in a nationwide registry. We hypothesize that female sex will impact complex AAA outcomes even more than in infrarenal repair due to the more challenging procedures with stiffer devices in female patients with smaller vessels and more complex anatomy.

Methods

Data Source

We performed a retrospective cohort study including patients from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) targeted vascular module. The NSQIP targeted vascular module is a multi-institutional collaboration with prospectively collected clinical data of patients undergoing vascular interventions. The data are collected by trained and certified surgical clinical reviewers and include demographics, comorbid conditions, intraoperative variables and 30-day mortality and complications. Moreover, the NSQIP database has previously been validated and the data are routinely audited for accuracy and reliability.[15,16] Further information is available at www.facs.org/quality-programs/acs-nsqip. The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the requirement for patient consent owing to the retrospective and deidentified nature of the NSQIP database.

Patient Cohort

We included patients undergoing endovascular or open repair of complex AAAs between 2011 and 2017 within the vascular targeted NSQIP database. We defined complex aneurysms as those with a proximal extent listed as juxtarenal, pararenal or suprarenal according to the predefined variable in the dataset. In addition, we considered open procedures coded as repair of a AAA involving visceral vessels (CPT 35091) and EVAR using the Cook Zenith Fenestrated Endovascular Graft (Cook Medical, Bloomington, IN) as complex repairs. We excluded patients undergoing open repair with an infrarenal proximal clamp position. We additionally excluded patients undergoing emergency repair (n=407), patients with prior AAA repair with unsatisfactory result (n=127), ruptured AAAs (n=54), and thoracoabdominal aneurysms (n=38).

Definitions and variables

The NSQIP registry codes age as a continuous variable. However, in order to maintain deidentification, all patients above the age of 89 are recorded as 90 years old. We calculated the estimated glomerular filtration rate (eGFR) in accordance with the Chronic Kidney Disease Epidemiology Collaboration equation using a single preoperative creatinine value.[17] We defined renal function categories as an eGFR value above 60 mL/min/1.73m^2, an eGFR between 30 and 60 mL/min/1.73m^2, and an eGFR below 30 mL/min/1.73m^2 or preoperative dialysis requirement. We calculated body mass index (BMI) and body surface area (BSA) according to the standard weight (kg)/height^2 (m) formula and Du Bois and Du Bois weight$^{0.425}$ (kg) x height$^{0.725}$ (cm) x 0.007184 formula respectively.[18] We classified BMI categories as underweight (BMI<18.5), normal (BMI 18.5 - 25), overweight (BMI 25-30) obese

(BMI 30-40) and, morbidly obese (BMI>40). Aortic size index (ASI) was defined as aneurysm diameter/BSA.[19,20]

Our primary outcome was perioperative mortality and our secondary outcomes included any complication, major complications and its distinctive constituents which all occurred within 30 days after the index procedure. We defined major complications as the presence of one of the following: intraoperative or postoperative cardiac complications comprising cardiac arrest or myocardial infarction; major pulmonary complications including prolonged ventilator requirement (>48h); unplanned reintubation or intraoperative or postoperative pulmonary embolism; renal complications comprising acute renal failure requiring dialysis; progressive renal insufficiency, which is defined by NSQIP as a creatinine concentration increase >2 mg/dL from preoperative value; intraoperative or postoperative stroke; ischemic colitis; lower extremity ischemia requiring intervention; postoperative aneurysm rupture; any unplanned reoperation; or postoperative sepsis. Patients with preoperative dialysis requirement were excluded from analyses of postoperative renal complications.

Statistical Analysis

We univariately compared male and female patients baseline and operative characteristics, perioperative mortality, and postoperative complications, stratified by open and endovascular repair. We presented categorical variables as counts and percentages and continuous variables as median (interquartile range). We compared patient and operative characteristics between female and male patients using the χ^2 or Fischer exact test for categorical variables where appropriate, and the Wilcoxon rank-sum for continuous variables.

We investigated the independent associations between female sex and our outcomes, stratified by EVAR and open repair. We also examined independent associations between endovascular and open repair with the outcomes, for female and male patients separately. We calculated propensity scores using logistic regression models and used these propensity scores to create inverse probability weights. We opted for propensity scores instead of multivariable regression as the relatively low event rates of our primary outcome precluded us from robust multivariable adjustment. This allowed us to adjust for all a priori selected covariates without the risk of overfitting our model. Our primary model was adjusted for demographics, comorbid conditions and aneurysm diameter; However, in a secondary model, BMI and diameter were replaced with ASI. The model included age, race (white, black, other or unknown), BMI category, smoking status, insulin dependent diabetes mellitus (IDDM), hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), renal function, steroid use for a chronic condition, weight loss (>10% in the 6 months prior to surgery), bleeding disorders, systemic inflammatory response syndrome (SIRS) within 48 hours prior to surgery, symptomatic aneurysm, and diameter. By not adjusting for variables reflecting the anatomical complexity, we allowed the inherent anatomical differences between female and males to persist. All variables had less than 5% missing data except race for which we used an indicator variable. We tested the propensity scores for adequacy of overlap by plotting the distribution of propensity scores between the study groups. To adjust for extreme weights, we truncated weights below the 5^{th} and above the 95^{th} percentile. After weighting, all the standardized differences showed minimal imbalance (£10%). Statistical significance was assumed at a P-value below .05. We performed additional sensitivity analyses using a subgroup of the study cohort excluding patients with symptomatic aneurysms. Statistical analyses were performed using Stata 15 software (StataCorp LP, College Station, Texas).

Results

Patient Characteristics

We identified 2,270 complex aneurysm repairs, of which 1,010 were EVARs and 1,260 open repairs. Complex EVAR was performed in 270 females (21.4%) complex open repair was performed in 310 females (30.7%). Female patients were older (median age 75, [IQR: 69-80] vs. 73 [67-79], P=.002), were less commonly overweight (60.5% vs. 70.6%, P<.001), were more often current smokers (46.9% vs. 37.0%, P<.001), less commonly had normal renal function (55.6% vs. 65.7%, P<.001), and were more often symptomatic (12.8% vs. 7.6%, P<.001). (Table 1).

Table 1. Baseline characteristics

	Complex Repair (n=2,270)		
	Female (n=580)	**Male (n=1,690)**	**P-value**
Age	75 (69, 80)	73 (67, 79)	**0.002**
Race			0.11
White	479 (82.6%)	1373 (81.2%)	
Black	29 (5.0%)	62 (3.7%)	
Other	4 (0.7%)	29 (1.7%)	
Unknown	68 (11.7%)	226 (13.4%)	
BMI categories			**<0.001**
Normal (BMI 18.5-25)	193 (33.7%)	459 (27.5%)	
Underweight (BMI <18.5)	33 (5.8%)	31 (1.9%)	
Overweight (BMI 25-30)	199 (34.7%)	690 (41.3%)	
Obese (BMI 30-40)	125 (21.8%)	452 (27.1%)	
Morbidly obese (BMI >40)	23 (4.0%)	37 (2.2%)	
Smoker	272 (46.9%)	625 (37.0%)	**<0.001**
IDDM	14 (2.4%)	43 (2.5%)	0.86
Hypertension	465 (80.2%)	1387 (82.1%)	0.31
CHF	10 (1.7%)	39 (2.3%)	0.40
COPD	129 (22.2%)	333 (19.7%)	0.19
Renal Function			**<0.001**
eGFR >60	315 (55.6%)	1076 (65.7%)	
eGFR 30-60	218 (38.4%)	485 (29.6%)	
eGFR <30 or on dialysis	34 (6.0%)	77 (4.7%)	
Steroid Use	29 (5.0%)	59 (3.5%)	0.10
Weight loss	10 (1.7%)	15 (0.9%)	0.096
Bleeding disorders	66 (11.4%)	188 (11.1%)	0.87
SIRS symptoms	11 (1.9%)	22 (1.3%)	0.30
Symptomatic	74 (12.8%)	128 (7.6%)	**<0.001**

EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; Age (years); BMI: Body Mass Index (kg/m2); IDDM: Insulin Dependent Diabetes Mellitus; CHF: chronic hearth failure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; SIRS: systemic inflammatory response syndrome.
Values are median (inter quartile range) or total events (percentages)
Values of polytomous variables may not sum to 100% due to rounding
Boldface P values represent significance (P<.05).

Operative characteristics

Female patients who underwent EVAR had a longer operative time, though this difference did not reach statistical significance (152 [110-252] vs. 146 [103-234], P=.055). AAA diameter in females was not significantly different compared to men (5.5 [5.1-6] vs. 5.6 [5.1-6.2], P=.087), however female patients had a higher ASI (3.3 [2.8-3.8] vs. 2.8 [2.5-3.2], P<.001). Use of percutaneous access (32.6% vs. 35.3%, P=.4), iliac conduit (8.1% vs. 7.2%, P=.6) and brachial arterial access (5.2% vs. 4.7%, P=.8) was similar between female and male patients. Also, female patients less often underwent complex EVAR with a Cook Zenith Fenestrated (ZFEN) device than male patients (17.9% vs. 25.7%, P=.008).

Female patients who underwent open repair had a shorter operative time (235 [176-299] vs. 242 [191-314], P=.049). Females in the open cohort had a smaller AAA diameter compared to male patients (5.7 [5.2-6.4] vs. 6 [5.5-6.8], P<.001), however, they had a higher ASI (3.4 [3-3.9] vs. 3 [2.7-3.5], P<.001). Also, female patients underwent repair with a retroperitoneal approach more often than men, but this was not statistically significant (47.2% vs. 40.6%, P=.052) (Table 2).

Table 2. Operative characteristics

	Complex EVAR (n=1,260)			Complex Open AAA repair (n=1,010)		
	Female (n=270)	**Male (n=990)**	**P-value**	**Female (n=310)**	**Male (n=700)**	**P-value**
Diameter	5.5 (5.1, 6)	5.6 (5.1, 6.2)	0.087	5.7 (5.2, 6.4)	6 (5.5, 6.75)	**<0.001**
Aortic Size Index	3.3 (2.8, 3.8)	2.8 (2.5, 3.2)	**<0.001**	3.4 (3, 3.9)	3 (2.7, 3.5)	**<0.001**
Distal Aneurysm Extent			0.17			0.13
Aortic	82 (35.8%)	245 (29.0%)		170 (63.7%)	343 (55.1%)	
Common iliac	86 (37.6%)	348 (41.2%)		88 (33.0%)	248 (39.9%)	
External iliac	24 (10.5%)	81 (9.6%)		5 (1.9%)	15 (2.4%)	
Internal iliac	37 (16.2%)	171 (20.2%)		4 (1.5%)	16 (2.6%)	
Operative time	152 (110, 252)	146 (103, 234)	0.055	235 (176, 299)	242 (191, 314)	**0.049**
Percutaneous Access	88 (32.6%)	348 (35.3%)	0.41	-	-	-
Hypogastric Embolization	18 (6.7%)	70 (7.1%)	0.82	-	-	-
Iliac Conduit	22 (8.1%)	71 (7.2%)	0.59	-	-	-
Iliac Branched Device	46 (17.0%)	184 (18.6%)	0.56	-	-	-
Brachial Arterial Access	14 (5.2%)	47 (4.7%)	0.77	-	-	-
Retroperitoneal Approach	-	-	-	145 (47.2%)	280 (40.6%)	0.052

EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; Diameter (cm).Values are median (inter quartile range) or total events (percentages). Values of polytomous variables may not sum to 100% due to rounding. Boldface P values represent significance (P<.05).

Outcomes

When comparing the outcomes of females and males among the patients treated with EVAR, perioperative mortality was higher in female patients (6.3% vs 2.4%; P=.001). Also, the rates of any complication (19% vs 9.7%; P<.001) and major complications (15.9% vs. 7.6%, P<.001) were higher in female patients. Significantly different rates of individual major complications were major respiratory complications (4.8% vs 1.8%, P=.012), renal complications (4.4% vs 1.4%, P=.006), ischemic colitis (2.2% vs 0.5%, P=.016), aneurysm rupture (1.1% vs 0.1%, P=.033), and return to the operating room (7.8% vs 3.7%, P=.008). The most common reasons for reoperations were lower extremity revascularization (15.5%), bleeding (12.1%), ischemic colitis (10.3%), and aneurysm related (5.2%). No significant differences were found between female and male patients for these reoperation subcategories.

Table 3. Perioperative outcomes

	Complex EVAR (n=1,260)			Complex Open AAA repair (n=1,010)		
	Female (n=270)	Male (n=990)	P-value	Female (n=310)	Male (n=700)	P-value
Perioperative Mortality	17 (6.3%)	24 (2.4%)	**0.001**	23 (7.4%)	39 (5.6%)	0.26
Any Complication	51 (19.0%)	96 (9.7%)	**<0.001**	110 (35.5%)	223 (31.9%)	0.26
Major Complication	43 (15.9%)	75 (7.6%)	**<0.001**	91 (29.4%)	192 (27.4%)	0.53
Cardiac complication	8 (3.0%)	17 (1.7%)	0.22	18 (5.8%)	52 (7.4%)	0.42
Major Respiratory Complication	13 (4.8%)	18 (1.8%)	**0.012**	48 (15.5%)	92 (13.1%)	0.32
Renal complication	12 (4.4%)	14 (1.4%)	**0.006**	25 (8.1%)	58 (8.3%)	1.00
Stroke	4 (1.5%)	7 (0.7%)	0.26	0 (0.0%)	4 (0.6%)	0.32
Ischemic Colitis	6 (2.2%)	5 (0.5%)	**0.016**	17 (5.5%)	31 (4.4%)	0.52
Lower Extremity Ischemia	7 (2.6%)	15 (1.5%)	0.29	8 (2.6%)	19 (2.7%)	1.00
Aneurysm Rupture	3 (1.1%)	1 (0.1%)	**0.033**	1 (0.3%)	1 (0.1%)	0.52
Reoperation	21 (7.8%)	37 (3.7%)	**0.008**	41 (13.2%)	93 (13.3%)	1.00
Sepsis	0 (0.0%)	4 (0.4%)	0.58	8 (2.6%)	11 (1.6%)	0.32

EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; Major complications (cardiac complications, major pulmonary complications, renal complications, stroke, ischemic colitis, lower extremity ischemia requiring intervention, postoperative aneurysm rupture, an unplanned reoperation, or postoperative sepsis). Values are total events (percentages). Boldface P values represent significance (P<.05).

Among patients treated with open repair, perioperative mortality was 7.4% in female patients and 5.6% in males (P=.30), and there was no significant difference in any complications (35.5% vs. 31.9%, P=.26) and major complications (29.4% vs. 27.4%, P=.53) rates (Table 3).

When comparing the perioperative events between EVAR and open repair, for female and male patients separately, perioperative mortality for male patients was significantly lower after EVAR compared to open repair (2.4% vs. 5.6%, P=.001), while this difference was not seen for female patients (6.3% vs. 7.4%, P=.60).

Multivariable analysis

After adjustment with inverse-probability weighted logistic regression, in patients undergoing EVAR, female sex was significantly associated with higher perioperative mortality (OR, 2.5; 95% CI, 1.3-4.9; P=.007), any complication (OR, 2.1; 95% CI, 1.4-3.2; P<.001), major complication (OR, 2.0; 95% CI, 1.3-3.1; P=.002), reoperation (OR, 1.9; 95% CI, 1.0-3.6; P=.047), major respiratory complication (OR, 2.6; 95% CI, 1.2-5.6; P=.017), renal complication (OR, 3.1; 95% CI, 1.4-7.2; P=.007) and ischemic colitis (OR, 4.1; 95% CI, 1.2-14.1; P=.025) (Table 4). However, when we replaced BMI and diameter with ASI in the propensity score, the association between female sex and perioperative mortality rate attenuated and was no longer statistically significant (OR, 1.9; 95% CI, .9-3.9; P= .091). Adjusted analysis for open repair showed no significant associations of female sex with perioperative mortality (OR, 0.9; 95% CI, 0.5-1.6; P=.69), any complications (OR, 1.2; 95% CI, 0.9-1.7; P=.22) or major complications (OR, 1.1; 95% CI, 0.8-1.5; P=.74) (Table 4). Replacing diameter with ASI in the model showed similar results.

Sensitivity analyses excluding symptomatic patients showed similar associations with perioperative mortality and major complications in the open and EVAR cohort. When comparing the outcomes between EVAR and open repair in male patients, after adjustment for demographics, comorbid conditions and diameter, the patients undergoing EVAR experienced lower rate of perioperative mortality compared to open repair (OR, 0.4; 95% CI, 0.2-0.7; P=.003). However, this difference was not observed in the female subgroup (OR, 0.8; 95% CI, 0.4-1.7; P=.61). Lower major complication rates were associated with EVAR in both male patients and female patients.

Table 4. Odds Ratios (95% Confidence Intervals) for female patients undergoing open AAA repair or EVAR and perioperative outcomes

	Complex EVAR (n=1,260)			Complex Open (n=1,010)		
	OR	**P-value**	**95% CI**	**OR**	**P-value**	**95% CI**
Mortality, perioperative	2.5	**0.007**	1.3 - 4.9	0.9	0.69	.5 - 1.6
Any complication	2.1	**<0.001**	1.4 - 3.2	1.2	0.22	.9 - 1.7
Major Complication	2.0	**0.002**	1.3 - 3.1	1.1	0.74	.8 - 1.5
Reoperation	1.9	**0.047**	1.0 - 3.6	0.9	0.49	.6 - 1.3
Cardiac complication	1.1	0.8	.4 - 2.9	0.7	0.19	.4 - 1.2
Major Respiratory Complication	2.6	**0.017**	1.2 - 5.6	1.1	0.60	.7 - 1.7
Renal complication	3.1	**0.007**	1.4 - 7.2	1.0	0.88	.6 - 1.8
Stroke*	1.8	0.356	.5 - 6.5	-	-	-
Ischemic Colitis	4.1	**0.025**	1.2 - 14.1	1.0	0.98	.5 - 1.9
Lower Extremity Ischemia	2.5	0.074	.9 - 6.8	0.7	0.48	.3 - 1.8
Aneurysm Rupture	8.0	0.074	.8 - 78.6	1.8	0.68	.1 - 28.9
Sepsis*	-	-	-	1.3	0.58	.5 - 3.8

EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; OR: Odds Ratio; CI: Confidence Interval; Major complications (cardiac complications, major pulmonary complications, renal complications, stroke, ischemic colitis, lower extremity ischemia requiring intervention, postoperative aneurysm rupture, an unplanned reoperation, or postoperative sepsis). The model is adjusted for age (years), race (white (ref), black, other, unknown), body mass index category (BMI<18.5, BMI 18.5-25(ref), BMI 25-30, BMI 30-40, BMI>40 kg/m2), current smoking status, insulin dependent diabetes mellitus, hypertension requiring medication, congestive heart failure, chronic obstructive pulmonary disease, renal function (eGFR>60(ref), eGFR30-60, eGFR<30 or preoperative dialysis), steroid use for a chronic condition, weight loss (> 10% in the 6 Months Prior to Surgery), bleeding disorders, systemic inflammatory response syndrome within 48 Hours Prior to Surgery, symptomatic aneurysm and diameter. Boldface P values represent significance (P<.05).
** Results not shown given the lack of any septic events among female patients undergoing EVAR and any stroke among female patients undergoing open repair.*

Discussion

In this study, we demonstrated that females experienced higher rates of complications and mortality following complex EVAR when compared to males. However, when substituting ASI for diameter in the model, no significant association was found with perioperative mortality. Following open repair, the rate of perioperative mortality and major complications were similar between female and male patients. Furthermore, the benefit in terms of perioperative mortality of EVAR over open repair in male patients was not seen in female patients.

Our findings in female patients undergoing complex EVAR are consistent with the demographics and results found in studies focusing on the influence of sex on infrarenal aneurysm repair. In a previous study using the NSQIP database, we showed that female sex was associated with a higher mortality and major complication rates in patients undergoing infrarenal EVAR.[2] Our findings in female patients undergoing EVAR for complex aneurysms are further supported by the study of Rieß et al., who studied sex disparities following fenestrated and branched EVAR using health insurance claims in Germany.[13] However, compared to our results, they reported a higher 30-day mortality rate of 12.3% in female patients and 5.4% in male patients (compared to the 6.3% in females and 2.4% in males we found).[13] This difference is likely explained by their inclusion of thoracic and thoraco-abdominal AAA and patients with dissection. In contrast to this previous study, Timaran et al. did not find a significant difference in major adverse events between female and male patients after FEVAR apart from more severe renal function impairment (defined as a 30% or greater increase of serum creatinine from baseline).[14] However, this single center study was limited by a small sample size, with only 16 female patients included in the analysis, and therefore may have lacked power to detect a difference in major adverse events.

Despite the older age and more prevalent comorbid conditions in our female population, adjustment for these factors did not alter our conclusion. However, replacing aortic diameter with ASI in the multivariate model attenuated our results, supporting the idea that the use of ASI is a more accurate measurement than diameter alone to determine optimal threshold for repair in female patients. We have previously shown that, unlike in men where aortic diameter is the most predictive determinant, ASI is more predictive of rupture in female patients.[20] Prior data have shown that patients with a larger aneurysm diameter have worse outcomes and it has previously been shown with NSQIP data that obesity was not associated with worse perioperative mortality after EVAR.[21,22] Therefore we believe that the attenuation of the mortality difference when we account for ASI rather than diameter reflect that a specific aneurysm diameter represents a proportionately greater aortic dilatation in female patients compared to male patients.[19] Therefore, female patients would have a more progressed aortic aneurysm at a similar diameter. We therefore suggest that ASI should be taken into account when identifying a treatment plan for female patients with complex AAAs.

The benefits of infrarenal EVAR over open repair are predicated in several randomized controlled trials and large retrospective studies showing lower mortality and complications after EVAR.[23–25] For treatment of complex AAA repair it was found that EVAR was associated with a lower incidence of 30-day mortality and adverse outcomes than open repair.[26] However, our study found that females did not experience the benefit in perioperative mortality following complex EVAR that the male cohort experienced. A factor which has been hypothesized to contribute to this disparity in outcomes is that female patients have smaller access vessels possibly making an endovascular intervention more challenging.[27] The available data in our study do not clearly support this as the use of an iliac conduit and use of percutaneous access was similar in female and male patients. However, the trend towards longer operative times in female patients undergoing EVAR but shorter operative times in female patients undergoing open repair could indicate a more complex endovascular procedure, a factor which may contribute to the differences in outcomes between these two procedures in female patients. Also, we found that women less often underwent complex EVAR with a ZFEN device than men (17.9% vs. 25.7%) which could be an indication that women are less likely to meet ZFEN instructions-for-use criteria due to their smaller access vessels and higher angulations. As ZFEN devices have been shown to have low perioperative mortality this could contribute to the sex disparities we found.[11] This shows the importance of focusing on sex disparities when developing endovascular procedures and highlights an important target for improvement of the accessibility and quality of endovascular repair.

This study should be interpreted in the context of its design. The NSQIP only collects data of patients undergoing AAA repair, precluding us from commenting on patients with complex AAAs who did not undergo surgery and the influence of surgical choice. Given the lack of technical data in the NSIQP database, we were unable to account for the exact technical approaches. Therefore, the effect of the specific complex repair technique could not be evaluated. Also, the NSQIP does not include anatomical data other than maximum diameter, specifically aortic neck length, angulation, and access vessel diameter, and therefore, we could not show the anatomical differences between female and male patients. Finally, follow-up data after 30 days are not recorded in NSQIP. Future studies assessing the association of female sex with long-term outcomes in complex repair are warranted, and future research initiatives should aim at determining causation of these sex differences and implementing sex-specific treatment strategies.

Conclusion

Female sex is independently associated with higher perioperative mortality and complications after complex endovascular repair, even after adjustment for demographics, comorbid conditions, and aneurysm diameter, and this association is not seen following complex open repair. The use of ASI in determining the optimal threshold for complex AAA repair and more sex-specific research may help reduce these sex discrepancies.

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Chapter 6

Sex Specific Thresholds for Repair Should be Utilized in Patients Undergoing Aortic Aneurysm Repair

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Abstract

Objective: Female patients are more likely to undergo repair of intact and ruptured abdominal aortic aneurysm (AAA) at smaller aortic diameter compared with male patients. By adjusting for inherent anatomic differences between sexes, aortic size index (ASI) and aortic height index (AHI) may provide an alternative method for guiding treatment. We therefore identified thresholds for repair in female and male patients using aortic diameter, ASI, and AHI.

Methods: We identified all patients who underwent AAA repair between 2003-2019 in the Vascular Quality Initiative database. The Dubois and Dubois formula was used to calculate body surface area (BSA), aortic diameter was divided by BSA to calculate ASI. Aortic diameter was divided by height to calculate AHI. Cumulative distribution curves were used to plot the proportion of patients who underwent repair of ruptured aneurysm according to aortic diameter, ASI, and AHI. Multivariable logistic regression modeling was used to identify the association of female sex with perioperative mortality and any major postoperative complication.

Results: We identified 55,647 patients, of whom 12,664 were female (20%). For both intact and rupture repair, female patients were older, less likely to undergo EVAR, and more likely to have comorbid conditions. Female patients underwent repair at smaller median aortic diameter compared with male patients for intact (5.4 vs 5.5cm, $P<.001$) and rupture repair (6.7 vs 7.7cm, $P<.001$). However, ASI was higher in female patients for both intact (3.1 vs 2.7cm/m^2, $P<.001$) and rupture repair (3.8 vs 3.7cm/m^2, $P<.001$). Whereas AHI was higher in female patients for intact repair (3.3 vs 3.1cm/m, $P<.001$) but lower for rupture repair (4.1 vs 4.3cm/m, $P<.001$). When analyzing the cumulative distribution of rupture repair in male patients, 12% of rupture repairs were performed at a diameter below 5.5cm. To achieve the same proportion of rupture repair in female patients, the repair diameter was only 4.9cm. However, when ASI and AHI were used, female and male patients both reached 12% of rupture repair at an ASI of 2.7cm/m^2 and an AHI of 3.0cm/m.

Conclusion: Our study provides data to strongly support the sex-specific 5.0cm aortic diameter threshold suggested for repair in female patients by the Society for Vascular Surgery. The high percentage of patients undergoing rupture repair below 5.5cm in male patients and 5.0cm in female patients highlights the need to better identify patients at risk of rupture at smaller aortic diameters.

Introduction

Abdominal aortic aneurysm (AAA) diameter of 5.5cm or greater had previously been used as a threshold for repair in both male and female patients. This was based on four randomized controlled trials in which female patients comprised only 3.7%-17.1% of the entire study cohort.[1–4] The United Kingdom Small Aneurysm Trial, which had the largest proportion of female patients (17.1%) demonstrated female patients were more likely to present with ruptured AAA at a smaller aortic diameter compared with male patients.[1] Contemporary studies have also found that female patients have smaller aortic diameter at the time of repair for both intact and ruptured AAA compared with males.[5–8] Therefore, the Society for Vascular Surgery (SVS) suggests young healthy female patients, with an aortic diameter of 5.0cm-5.4cm may benefit from early repair[9] and the European Society for Vascular Surgery (ESVS) suggests repair should be considered in female patients with an aortic diameter of 5.0cm.[10]

This difference in aneurysm diameter by sex at the time of repair may be due to baseline differences in aortic anatomy. Female patients have aortic diameter measurements approximately 2-6mm smaller than male patients along the entire length of the aorta.[11–13] Aortic size index (ASI), which indexes the aortic diameter to body surface area, and aortic height index (AHI), which indexes aortic diameter to height, can account for differences in body size and provides information on relative as opposed to absolute aortic aneurysm dilation.[14–16] However, the ideal threshold for AAA repair using ASI and AHI is unclear. Additionally, the SVS and ESVS sex-specific aortic diameter thresholds for repair are suggestions and not recommendations. Both societies cite a lack of strong quality of evidence as a reason for the weaker recommendation (Table 1). Therefore, the purpose of this analysis was to determine sex-specific thresholds for AAA repair using aortic diameter, ASI, and AHI.

Table 1. Level of recommendation and supporting quality of evidence cited by the SVS and ESVS for sex-specific aortic diameter thresholds for repair

	SVS	ESVS
Level of Recommendation	2 (Weak) Benefits closely balanced with harms and burdens	IIB Usefulness/efficacy is less well established by evidence/opinion
Quality of evidence	B (Moderate) Evidence from RCTs with important limitations or unusually strong evidence from unbiased observational studies. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	C Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Methods

Data Source

We performed a retrospective cohort study including patients from the SVS Vascular Quality Initiative (VQI). The VQI is a prospectively collected quality improvement registry. With over 550 participating centers, VQI captures over 350 pre-defined variables including patient characteristics, procedural and anatomical characteristics, as well as in-hospital outcomes and long-term mortality data. More information can be found at www.vqi.org. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards for observational studies.[17] The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the need for patient consent due to the retrospective and de-identified nature of the study.

Patient Cohort

We identified all patients undergoing open and endovascular repair of intact and ruptured AAA's between January 2003 and December 2019 (n=64,603). To avoid multiple evaluations of the same patients, we excluded secondary repair procedures when patients had multiple entries in the database (n=314). When evaluating patients who underwent intact repair, we aimed to include only those who had an elective repair indicated by AAA diameter threshold. Therefore, we excluded intact repairs that were performed on the weekend and were therefore most likely not truly elective (n=253). Additionally, patients with an isolated iliac aneurysm (n=730) or those undergoing repair within 24 hours of onset of pain and/or tenderness (n=5,836) were also excluded, as we did not want the repair to be driven by iliac aneurysm disease or symptomatic status. Finally, we excluded patients with essential missing data (missing sex n=6; admission status n=218; diameter n=1,028; or height/weight n=571).

Definitions and Variables

ASI was defined as aneurysm diameter divided by body surface area (cm/m^2); body surface area was calculated using the Dubois and Dubois formula (0.20247 x [height (m)$^{0.725}$ x weight (kg)$^{0.425}$]). AHI was defined as aneurysm diameter divided by height (cm/m). Ruptured presentation was defined by CT angiography or operative evidence of rupture. Aortic diameter measurements immediately preceding rupture were not available, therefore aortic diameter in patients with ruptured aneurysm may not reflect the true measurement right before rupture. Body mass index (BMI) was calculating using the standard weight/height^2(kg/m^2) formula. We classified patients with a BMI$<$18.5 as underweight an $\geq$30kg/m^2 as obese. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[8] We defined chronic kidney disease (CKD) as an eGFR$<$30mL/min/1.73m^2 or currently on dialysis. Major complication was defined as the presence of one of the following: reoperation, postoperative congestive heart failure (CHF), stroke, myocardial infarction, reintubation, dialysis requirement, surgically treated intestinal ischemia, surgical site infection or lower extremity ischemia/emboli.

Statistical Analysis

We stratified our analysis by urgency of AAA repair (intact or rupture). Within each group, we used univariate analysis to compare demographics, coexisting conditions, anatomical and procedural characteristics between female and male patients. Categorical variables were presented as counts and percentages and compared using χ^2 test. Continuous variables were presented as median and interquartile ranges and compared using the Wilcoxon rank-sum test. We then constructed box plots of the repair diameter, ASI, and AHI for male and female patients. The box spans the interquartile range with the median value

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represented by the horizontal line within the box. Cumulative distribution curves were used to plot the proportion of male and female patients who underwent repair of ruptured aneurysm according to aortic diameter, ASI, and AHI. We used multivariable logistic regression modeling to assess the independent association between female sex and perioperative mortality as well as any major post-operative complication. We adjusted the models for covariates selected a priori including age, race, current smoker, insulin dependent diabetes mellitus, hypertension, CHF, chronic obstructive pulmonary disease (COPD), CKD, prior AAA repair, coronary artery disease, familial history of AAA, preoperative medication use (aspirin, statin, and betablocker), AAA diameter, and type of repair (open or endovascular). Subsequently, we replaced AAA diameter with ASI and AHI. We assessed for interactions between female sex and the remaining covariates. We did not include BMI in the multivariable model as the formula to calculate ASI includes height and weight and the formula to calculate AHI contains height. We did not include BMI in the model using aortic diameter as we wanted all three models to contain the same covariates.All varia bles had <5% missing. All analyses were performed using Stata 15.1(StataCorp, College station, Texas, USA).

Results

Aneurysm presentation

We identified 55,647 patients of whom 51,136 underwent elective repair and 4,511 underwent rupture repair. Female patients represented a larger proportion of rupture repair compared with elective repair (22% vs 20%; P=.002), however, the absolute difference was small. Female patients underwent intact repair at a slightly smaller median aortic diameter compared with male patients (5.4 vs. 5.5cm; P<.001) but larger ASI (3.1 vs. 2.7cm/m^2; P<.001) and AHI (3.3 vs 3.1 cm/m; P<.001) (Figure 1). Female patients also underwent rupture repair at a smaller aortic diameter (6.7 vs. 7.7cm; P<.001) and AHI (4.1 vs 4.3cm/m; P<.001), but larger ASI (3.8 vs 3.7cm/m^2; P=.03) compared with male patients (Figure 1). For both intact and rupture repair, female patients were older, less likely to undergo EVAR, and more likely to be Black. Female patients were also more likely to have hypertension, COPD, or CKD but were less likely to be on preoperative ASA/aspirin or statin therapy (Table 2).

Figure 1. Vertical box plots showing the median and interquartile ranges of (A) aortic diameter, (B) ASI, and (C) AHI in male and female patients undergoing intact and rupture repair.

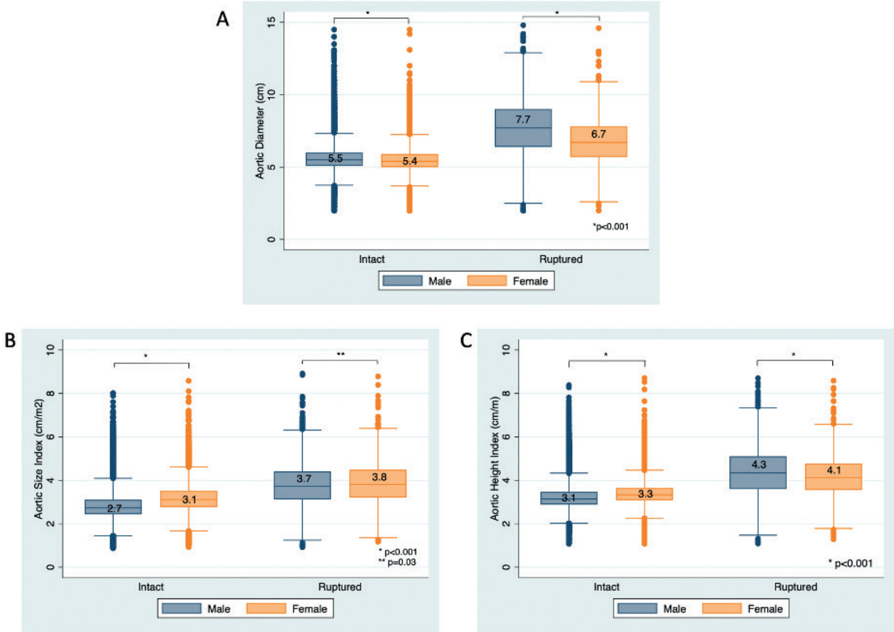


Table 2. Baseline Characteristics for female and male patients undergoing AAA repair stratified by (A) intact and (B) rupture repair

A. Intact Repair	Female (N=10,118)		Male (N=41,018)		P-value
Diameter, median (IQR)	5.4	(5.0, 5.9)	5.5	(5.1, 6.0)	<0.001
BSA, median (IQR)	1.7	(1.6, 1.9)	2.0	(1.9, 2.2)	<0.001
ASI, median (IQR)	3.1	(2.8, 3.5)	2.7	(2.4, 3.1)	<0.001
AHI, median (IQR)	3.3	(3.1, 3.6)	3.1	(2,9, 3.5)	<0.001
EVAR	7,893	(78%)	34,643	(85%)	<0.001
Age, median (IQR)	75	(69, 80)	73	(67, 79)	<0.001
Race/Ethnicity					<0.001
Non-Hispanic white	8768	(89%)	36588	(92%)	
Black or African American	710	(7.2%)	1570	(3.9%)	
Hispanic	249	(2.5%)	1094	(2.7%)	
Asian	101	(1.0%)	535	(1.3%)	
Other	44	(0.5%)	151	(0.4%)	
Underweight	539	(5.3%)	728	(1.8%)	<0.001
Obese	2957	(29%)	12922	(32%)	<0.001
Current smoker	3665	(36%)	13008	(32%)	<0.001
Hypertension	8605	(85%)	34170	(83%)	<0.001
Insulin Dependent Diabetes	322	(3.2%)	1474	(3.6%)	0.045

A. Intact Repair	Female (N=10,118)		Male (N=41,018)		P-value
Coronary Artery Disease	3176	(31%)	18204	(44%)	<0.001
CHF					<0.001
None	9070	(90%)	36196	(88%)	
Asymptomatic/Mild	914	(9.0%)	4141	(10%)	
Moderate/Severe	130	(1.3%)	660	(1.6%)	
COPD	4203	(42%)	12920	(32%)	<0.001
CKD	609	(6.1%)	1462	(3.6%)	<0.001
Prior Aortic Aneurysm Repair	322	(3.2%)	1428	(3.5%)	0.14
Family History of AAA	1048	(10%)	3575	(8.8%)	<0.001
Preop. ASA/Aspirin use	6284	(62%)	27526	(67%)	<0.001
Preop. Beta-Blocker use	5626	(56%)	23178	(57%)	0.10
Preop. Statin use	6847	(68%)	29704	(72%)	<0.001

BSA: Body Surface Area; ASI: Aortic Size Index; AHI: Aortic Height Index; EVAR: Endovascular Aneurysm Repair; Underweight: body mass index below 18.5; Obese: body mass index of 30 or above; CHF: Congestive Heart Failure; COPD: chronic obstructive pulmonary disease; CKD: Chronic Kidney Disease; AAA: abdominal aortic aneurysm
Categorical variables are presented as counts and percentages and continuous variables as median and interquartile ranges.

B. Rupture Repair	Female (N=978)		Male (N=3,533)		P-value
Diameter, median (IQR)	6.7	(5.7, 7.8)	7.7	(6.4, 9.0)	<0.001
BSA, median (IQR)	1.7	(1.6, 1.9)	2.0	(1.9, 2.2)	<0.001
ASI, median (IQR)	3.8	(3.2, 4.5)	3.7	(3.1, 4.4)	0.030
AHI, median (IQR)	4.1	(3.6, 4.8)	4.3	(3.6, 5.1)	<0.001
EVAR	562	(58%)	2097	(60%)	0.29
Age, median (IQR)	76	(70, 83)	72	(65, 78)	<0.001
Race/Ethnicity					0.001
Non-Hispanic white	834	(88%)	3075	(90%)	
Black or African American	80	(8.5%)	184	(5.4%)	
Hispanic	23	(2.4%)	97	(2.8%)	
Asian	6	(0.6%)	55	(1.6%)	
Other	3	(0.3%)	7	(0.2%)	
Underweight	73	(7.5%)	102	(2.9%)	<0.001
Obese	320	(33%)	1187	(34%)	0.61
Current smoker	409	(42%)	1619	(46%)	0.019
Hypertension	784	(80%)	2730	(78%)	0.068
Insulin Dependent Diabetes	35	(3.6%)	117	(3.3%)	0.69
Coronary Artery Disease	236	(24%)	1132	(32%)	<0.001
CHF					0.18
Asymptomatic/Mild	91	(9.4%)	314	(9.0%)	
Moderate/Severe	26	(2.7%)	62	(1.8%)	
COPD	361	(37%)	999	(29%)	<0.001
CKD	171	(18%)	418	(12%)	<0.001
Prior Aortic Aneurysm Repair	47	(4.8%)	232	(6.6%)	0.041
Family History of AAA	58	(6.1%)	200	(5.8%)	0.78

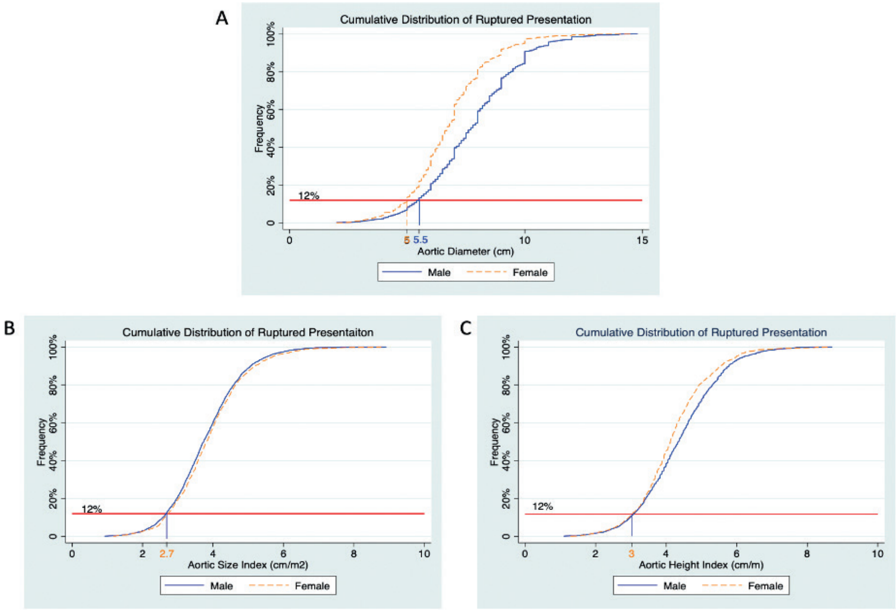
B. Rupture Repair	Female (N=978)		Male (N=3,533)		P-value
Preop. ASA/Aspirin use	356	(37%)	1412	(41%)	0.054
Preop. Beta-Blocker use	388	(40%)	1345	(39%)	0.31
Preop. Statin use	406	(42%)	1518	(44%)	0.46

BSA: Body Surface Area; ASI: Aortic Size Index; AHI: Aortic Height Index; EVAR: Endovascular Aneurysm Repair; Underweight: body mass index below 18.5; Obese: body mass index of 30 or above; CHF: Congestive Heart Failure; COPD: chronic obstructive pulmonary disease; CKD: Chronic Kidney Disease.
Categorical variables are presented as counts and percentages and continuous variables as median and interquartile ranges.

Rupture repair below threshold

When cumulative distribution of rupture repair was plotted against aortic diameter, 12% of all rupture repairs in male patients were performed at an aortic diameter below 5.5cm (Figure 2). The same 12% frequency of rupture repair in female patients occurred at an aortic diameter threshold of 4.9cm. However, 12% of the rupture repairs occurred at similar thresholds for female and male patients when using ASI (2.7 vs. 2.7cm/m^2) and AHI (3.0 vs 3.0cm/m).

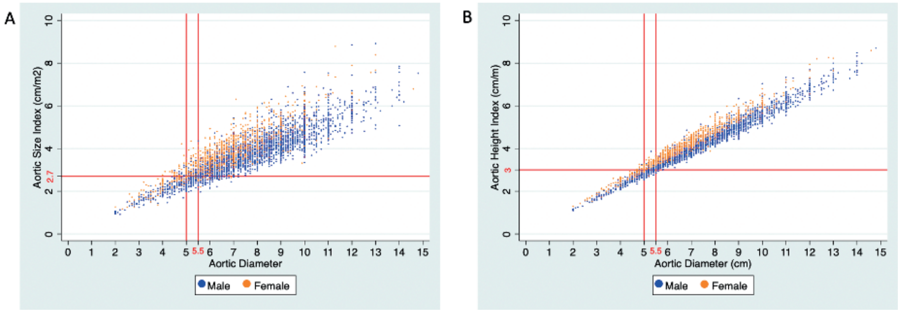
Figure 2. Plot of the cumulative distribution function for male and female patients undergoing ruptured AAA repair by (A) aortic diameter, (B) ASI, and (C) AHI



Of female patients undergoing rupture repair (n=978), 20% had an aneurysm diameter below 5.5cm,14% had an aneurysm diameter at or below 5cm, and 12% had an aneurysm diameter at or below 4.9cm. Additionally, 12% of female patients undergoing rupture repair had an ASI below 2.7cm/m^2 and an AHI below 3.0cm/m. Of the female patients undergoing rupture repair below 5.0cm (n=134), 31% had an ASI above the 2.7cm/m^2 threshold, 22% had an AHI above the 3.0cm/m threshold, and 20% had an aortic diameter above the 4.9cm threshold (Figure 3).

Of male patients undergoing rupture repair (n=3533), 12% had an aneurysm diameter below 5.5cm and 8.4% had an aneurysm diameter at or below 5cm. Additionally, 12% of male patients undergoing rupture repair had an ASI below 2.7cm/m^2 or an AHI below 3.0 cm/m. Of the male patients undergoing rupture repair below 5.5cm (n=415), 16% had an ASI above the 2.7cm/m^2 threshold and 14% had an AHI above the 3.0cm/m threshold (Figure 3).

Figure 3. Distribution of male and female patients undergoing ruptured AAA repair stratified by (A) aortic diameter and ASI or (B) aortic diameter and AHI at the time of repair



Perioperative outcomes

Female patients had higher perioperative mortality after intact EVAR (1.4% vs. 0.7%; P<.001), intact open repair (5.1% vs. 3.2%; P<.001), ruptured EVAR (26% vs. 20%; P<.001), and ruptured open repair (42% vs. 31%; P<.001). Female patients also had higher major complication rates after intact EVAR (6.3% vs. 3.2%; P<.001) and intact open repair (24% vs. 20%; P<.001). However, the major complication rates were similar after ruptured EVAR (34% vs. 35%; P=.79) and lower in female patients following ruptured open repair (54% vs. 60%; P=.03). Female patients were more likely to be discharged to a skilled nursing facility after intact EVAR (7.7% vs.

3.6%, P<.001), intact open repair (26% vs. 15%, P<.001), or rupture EVAR (35% vs. 21%, P<.001). However, the discharge disposition was similar between female and male patients after ruptured open repair (32% vs. 29%, P=.22). (Table 3)

Table 3. Perioperative outcomes for female and male patients undergoing AAA repair stratified by (A) intact and (B) rupture repair

A. Intact Repair	**EVAR**			**Open repair**		
	Female N=7,893	Male N=34,643	p-value	Female N=2,225	Male N=6,375	p-value
Perioperative Mortality	1.4%	0.7%	<.001	5.1%	3.2%	<.001
LOS (median)	2 (1, 3)	1 (1, 2)	<.001	7 (6, 9)	7 (5, 9	<.001
Any Major Complication	6.3%	3.2%	<.001	24%	20%	<.001
Cardiac complications	3.9%	2.6%	<.001	17%	17%	0.93
Renal complications	4.4%	2.7%	<.001	16%	17%	0.1
Respiratory complication	1.9%	1.1%	<.001	12%	9.6%	<.001
Access related complication	2.9%	1.8%	<.001	-	-	-
Postoperative Stroke	0.2%	0.2%	0.27	1.0%	0.8%	0.33
Intestinal Ischemia	0.7%	0.3%	<.001	4.3%	3.3%	0.044
Discharged to SNF	7.8%	3.6%	<.001	26%	15%	<.001
B. Rupture repair	**EVAR**			**Open repair**		
	Female N=562	Male N=2,097	p-value	Female N=416	Male N=1,436	p-value
Perioperative Mortality	26%	20%	<.001	42%	31%	<.001
LOS (median)	5 (3, 10)	5 (3, 10)	0.73	8.5 (2, 17)	10 (5, 19)	0.002
Any Major Complication	34%	35%	0.80	54%	60%	0.03
Cardiac complications	20%	21%	0.47	34%	37%	0.19
Renal complications	25%	26%	0.81	41%	41%	0.84
Respiratory complication	20%	20%	0.86	33%	39%	0.036
Access related complication	4.9%	4.0%	0.36	-	-	-
Postoperative Stroke	2.8%	2.2%	0.45	3.3%	3.6%	0.76
Intestinal Ischemia	6.4%	6.2%	0.91	18%	18%	0.96
Discharged to SNF	35%	21%	<.001	32%	29%	.22

LOS, length of stay; SNF, skilled nursing facility Categorical variables are presented as counts and percentages and continuous variables as median and interquartile ranges.

Adjusted outcomes

After adjustment for demographics, coexisting conditions, type of repair, and aortic diameter, female sex remained associated with higher perioperative mortality after intact repair (OR 1.5; 95%CI[1.3-1.8]; P<.001) and rupture repair (OR 1.3; 95%CI[1.1-1.6]; P=.003). (Table 4) When aortic diameter was replaced with ASI in the model, the association between female sex and perioperative mortality remained significant for both intact repair (OR 1.3; 95%CI[1.1-1.6]; P=.003) and rupture repair (OR 1.3; 95%CI[1.1-1.5]; P=.01). When aortic diameter was replaced with AHI in the model, the association between female sex and perioperative mortality again remained significant for both intact repair (OR 1.4; 95%CI[1.2-1.7]; P<.001) and rupture repair (OR 1.3; 95%CI[1.1 – 1.5]; P=.006). There was no interaction between female sex and the remaining covariates within the models.

Table 4. Multivariable adjusted analysis of the effect of female sex on perioperative mortality following (A) intact repair and (B) ruptured repair adjusted for aortic diameter, ASI, or AHI.

A. Intact Repair			
Model Adjusted For	Odds Ratio	95% CI	p-value
Aortic diameter	1.5	1.3, 1.8	<0.001
ASI	1.3	1.1, 1.6	0.003
AHI	1.4	1.2, 1.7	<0.001

B. Rupture Repair			
Model Adjusted For	Odds Ratio	95% CI	p-value
Aortic diameter	1.3	1.1, 1.6	0.003
ASI	1.3	1.1, 1.5	0.010
AHI	1.3	1.1, 1.5	0.006

ASI: Aortic Size Index; AHI: Aortic Height Index; CI: Confidence Interval
Models also adjusted for age, race, current smoking status, insulin dependent diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, prior abdominal aortic aneurysm repair, coronary artery disease, family history of abdominal aortic aneurysm, preoperative aspirin use, preoperative statin use, preoperative betablocker use, and type of repair (endovascular vs open).

When adjusted for demographics, coexisting conditions, type of repair, and aortic diameter, female sex was significantly associated with any major complication after intact repair (OR 1.5; 95%CI[1.4-1.7]; P<.001) but not after rupture repair (OR 0.9; 95%CI[0.7-1.0]; P=.06) (Table 5). When aortic diameter was replaced with ASI in the model, female sex was associated with higher risk of any major complication after intact repair (OR 1.4; 95%CI[1.3-1.5]; P<.001) however, female sex was associated with a lower risk of any major complication after rupture repair (OR 0.8; 95%CI[0.7-0.9]; P=.016. Similarly, when aortic diameter was replaced with AHI, female sex was associated with higher risk of any major complication after intact repair (OR 1.4; 95%CI[1.3-1.6]; P<.001) and lower risk of any major complication after rupture repair (OR 0.8; 95%CI[0.7-0.9]; P=.027). Again, there was no interaction between female sex and the remaining covariates within the models.

Table 5. Multivariable adjusted analysis of the effect of female sex on any major complication following (A) intact repair and (B) ruptured repair adjusted for aortic diameter, ASI, or AHI.

A. Intact Repair			
Model Adjusted For	Odds Ratio	95% CI	p-value
Aortic diameter	1.5	1.4, 1.7	<0.001
ASI	1.4	1.3, 1.5	<0.001
AHI	1.4	1.3, 1.6	<0.001

B. Rupture Repair			
Model Adjusted For	Odds Ratio	95% CI	p-value
Aortic diameter	0.9	0.7, 1.0	0.06
ASI	0.8	0.7, 0.9	0.016
AHI	0.8	0.7, 0.9	0.027

ASI: Aortic Size Index; AHI: Aortic Height Index; CI: Confidence Interval
Models also adjusted for age, race, current smoking status, insulin dependent diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, prior abdominal aortic aneurysm repair, coronary artery disease, family history of abdominal aortic aneurysm, preoperative aspirin use, preoperative statin use, preoperative betablocker use, and type of repair (endovascular vs open).

Discussion

When compared with male patients, female patients had smaller aortic diameter but larger ASI at the time of intact and rupture AAA repair. Female patients had larger AHI at the time of intact AAA repair, but smaller AHI at the time of rupture repair. When comparing the cumulative distribution of rupture repair in male and female patients, the currently recommended threshold for repair in males of 5.5cm represented an ASI of 2.7cm/m^2, an AHI of 3.0cm/m, or an aortic diameter of 4.9cm in female patients. When adjusting for demographics, coexisting conditions, and aortic diameter, female patients had higher odds of perioperative mortality and any major complication for both intact and rupture repair. When aortic diameter was replaced with ASI and AHI, the association of female sex with perioperative mortality following both intact and rupture repair, and the association with any major complications after intact repair remained significant.

The ASI threshold of 2.7cm/m^2 and the AHI threshold of 3.0cm/m were chosen as these measurements represent the point where 12% of male patients and 12% of female patients with ruptured aneurysms were treated. The 12% frequency was chosen to correspond to the proportion of male patients who underwent repair of ruptured aneurysm below the current 5.5cm aortic diameter threshold for repair. However, as a society, we must determine if it is acceptable to have a threshold of repair, whether it be aortic diameter, ASI, or AHI, below which 12% of the population is at risk for presenting with ruptured aneurysm. Further studies are warranted to identify patients with smaller aneurysms who are at risk for rupture.

Within our study population, we found that of the proportion of female patients who presented below an aortic diameter of 5.0cm, 31% had an ASI above the 2.7cm/m^2 threshold and 22% had an AHI above the 3.0cm/m threshold. While these data suggest ASI would more accurately identify female patients at risk of rupture, our study does not capture the true population of female patients with small aneurysms, and therefore this cannot be determined from our study. Our study population only includes those patients who underwent vascular intervention. In order to determine the true validity of ASI or AHI we would need prospective data that identifies all female patients with small aneurysms who are at risk of rupture, not just those with small aneurysms who undergo repair. Until such data are available, we cannot propose the superiority of ASI or AHI over aortic diameter. Therefore, our study primarily supports aortic diameter thresholds of 5.0cm in female patients and 5.5cm in male patients.

The most recent SVS practice guidelines for AAA management suggest repair in female patients with an AAA between 5.0cm and 5.4cm, however the guidelines note only young, healthy females would derive benefit from repair at this smaller aortic diameter.[9] Likewise, the European Society for Vascular Surgery (ESVS) practice guidelines state aneurysm repair should be considered in female patients with an aortic diameter of 5.0cm.[10] Our study found that 20% of female patients undergoing repair for ruptured aneurysm had an aortic diameter less than 5.5cm compared with only 12% of males. Furthermore, 14% of female patients underwent rupture repair at an aortic diameter less than 5.0cm. It should be noted that earlier repair in female patients is not a “recommendation” in either practice guideline, rather these are suggestions and considerations to be made by the individual surgeon based on patient presentation and health status. While the guidelines suggest repair in young, healthy female patients, there may be older patients with comorbid conditions who would also benefit from repair. Therefore, operative risk should be calculated for each patient[18] and considered together with their estimated life-expectancy when considering eligibility for operative repair.[19,20] Our findings suggest a change in practice guidelines to provide a stronger recommendation for sex-specific elective AAA repair threshold for all female patients with an aortic diameter ≥5.0cm.

Studies across multiple databases including the VQI, NSQIP, and National Inpatient Sample (NIS) have found that female patients derive less benefit from repair of aortic aneurysms. When compared with males, female patients had increased 30-day mortality,[6,21–26] post-operative complications,[6–8,22,24,26] type IA endoleak,[26,27] and were more likely to be discharged to skilled nursing facilities.[7,22,23,28] The worse outcomes observed in female patients in our study and in previously published works cannot be refuted. However, by comparing demographics, patient anatomy, and current practice guidelines, we can begin to understand the causes of these disparate outcomes and identify targeted strategies for improvement. As shown in our study and several others, female patients present with smaller aortic diameter at the time of both intact and rupture repair.[6–8,22,26] Furthermore, female patients are more likely to undergo repair for ruptured aneurysm compared with their male counterparts.

These findings suggest that we may be under-diagnosing aortic aneurysms in female patients and failing to intervene in a timely manner. The effectiveness of screening guidelines are dependent on the prevalence of disease, cost and accuracy of testing, and the expected reduction in morbidity and mortality following intervention. Currently, the United States Preventive Services Task Force and Canadian Task Force on Preventative Care both recommend against AAA screening in females.[29,30] The low prevalence of AAA in females and adverse outcomes following repair have been the mainstay for recommending against screening. However, due to increased prevalence of AAA in several high-risk groups, the SVS recommends screening women aged 65 years or older who have a history of smoking or a family history of AAA.[9] The ESVS also recommends screening women with a family history of AAA and those with a true peripheral arterial aneurysm.[10] The current sex-neutral definition for diagnosis of AAA may also contribute to the low prevalence in female patients. Several population-based studies have shown the aortic diameter in female patients is 2-6mm smaller than males.[11–13] When aortic aneurysm diagnosis was defined as the median aortic diameter plus two standard deviations, Wanhainen et al. found infrarenal AAA diagnosis should be defined as an aortic diameter greater than 3.0cm in male patients and 2.7cm in female patients.[11] If sex-specific thresholds for diagnosis were implemented to reflect baseline anatomic differences, the prevalence of AAA in female patients would increase, positively influencing the value of expanding screening guidelines.

Furthermore, female patients are more likely to present with challenging anatomy including shorter neck length, more angulated neck, and smaller iliac artery diameter.[6–8,22,26,27,31] These anatomic differences may further contribute to fewer female patients being offered EVAR and the worse outcomes observed in female patients following endovascular repair. When contemporary low-profile stent graft use was analyzed using the ENGAGE registry, female patients were found to have more challenging anatomy at the time of repair and were more likely to be treated outside the manufacturer's instructions for use (IFU). Despite these anatomic differences, female patients experienced similar perioperative outcomes, long-term survival, freedom-from aneurysm related reinterventions, late rupture, and open conversion compared to male patients.[27,31] Device development dedicated to stent grafts with lower profile, widely applicable IFU, and conformability better suited for complex anatomy may further help reduce the disparity in outcomes between male and female patients undergoing EVAR.

The vast majority of practice patterns for both open and endovascular aortic aneurysm repair are based on randomized controlled trials in which female patients were only modestly represented.[1–4] Female patients have also been underrepresented in pivotal trials for current FDA-approved infrarenal devices.[32–36] As female patients are less likely to undergo endovascular repair, expanding device development to account for sex-specific anatomy may enhance the range of endovascular repair options. Increasing female representation and treating males and females as two separate entities in future studies may further improve our understanding of the varied outcomes seen in these two groups.

This study should be interpreted within the context of its retrospective design. As the VQI is a voluntary quality initiative registry, the participating centers are likely to have a dedicated focus on quality improvement and are more likely to be high volume centers. Therefore, these outcomes might not be generalizable to the wider population.[37] However, as of 2015, AAA repairs in VQI accounted for 24% of all US AAA repairs, and the proportion is increasing over time.[37] Device specific information was blinded for the investigators, therefore potential device related confounding could not be accounted for. Furthermore, only patients who have undergone vascular interventions are included in the VQI, introducing a selection bias. We do not have data on patients with small aortic aneurysms who did not undergo repair, therefore patients with small intact AAAs are not included in our analysis. Patients with ruptured aneurysms that either did not reach the hospital to receive medical care, those who turned down an operation, or those who were deemed to be too high risk for operative repair are not accounted for in our analysis. As a result, our findings are likely to underrepresent the true mortality rate associated with rupture presentation. Furthermore, without data on this sub-population we are unable to analyze the effect of aortic diameter, ASI, and AHI for patients that do not undergo repair. ASI should also be used cautiously in obese patients as the Dubois and Dubois formula has been found to underestimate the true BSA in this population.[38]

Conclusion

Our study provides data to strongly encourage the 5.0cm aortic diameter threshold suggested for repair in female patients by the SVS and ESVS. However, sex-specific repair thresholds alone are not likely to overcome the current sex discrepancies observed in AAA repair. Treating males and females as two separate entities in future research studies, as well as device development research, may expand our understanding of disease pathology and ultimately lead to improved practice patterns in female patients. This study does not include data on patients who were deemed inoperable or those who were unable to seek timely medical attention. Therefore, our study likely underestimates the true severity of ruptured aneurysm. Lastly, the high percentage of male and female patients undergoing repair of ruptured AAA below the current elective repair threshold highlights the need to better identify patients at risk of rupture at smaller aortic diameters. While the ASI shows promise, prospective data are needed.

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Chapter 7

Racial differences in isolated aortic, concomitant aortoiliac and isolated iliac aneurysms

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Abstract

Objective: Our aim was to describe the racial and ethnic differences in presentation, baseline and operative characteristics, and outcomes after aortoiliac aneurysm repair. Previous studies have demonstrated racial and ethnic differences in prevalence of abdominal aortic aneurysms and showed more complex iliac anatomy in Asian patients.

Methods: We identified all White, Black, Asian, and Hispanic patients undergoing aortoiliac aneurysm repair in the VQI from 2003 to 2019. We compared baseline comorbidities, operative characteristics, and perioperative outcomes by race and ethnicity.

Results: In our 60,435 patient cohort, Black patients, followed by Asian patients, were most likely to undergo repair for aortoiliac (W:23%, B:38%, A:31%, H:22%, P<.001) and isolated iliac aneurysms (W:1.0%, B:3.1%, A:1.5%, H:1.6%, P<.001), and White and Hispanic patients were most likely to undergo isolated aortic aneurysm repair (W:76%, B:59%, A:68%, H:76%, P<.001). Black patients were more likely to undergo symptomatic repair and underwent rupture repair at a smaller aortic diameter. The iliac aneurysm diameter was largest in Black and Asian patients. Asian patients were most likely to have aortic neck angulation above 60°, graft oversizing above 20%, and completion endoleaks. Also, Asian patients were more likely to have a hypogastric artery aneurysm and to undergo hypogastric coiling.

Conclusion: Asian and Black patients were more likely to undergo repair for aortoiliac and isolated iliac aneurysms compared to White and Hispanic patients who were more likely to undergo repair for isolated aortic aneurysms. Moreover, there were significant racial differences in the demographics and anatomic characteristics that could be used to inform operative approach and device development.

Introduction

Racial and ethnic differences with regards to demographics, urgency, and repair strategy exist at the time of presentation for abdominal aortic aneurysm (AAA) repair.[1–5] Despite varying severity in preoperative comorbidities and presentation, contradicting conclusions have been made about the impact of race/ethnicity on postoperative outcomes.[1–5] Additionally, compared with White patients, Black and Asian patients more often present with concurrent iliac artery aneurysms at the time of abdominal aortic repair, with the mean diameter of the iliac aneurysm greatest in Asian patients.[3] This could potentially make operative planning more complex. Also, the presence of concurrent iliac artery aneurysms with abdominal aortic aneurysm repair has been associated with worse outcomes.[6]

Documentation of racial and ethnic differences is an important step in advancing health equity. However, it is essential to be cautious when associating racial or ethnic categories with causation and outcomes in healthcare. Racial and ethnic categories are sociocultural constructs based on physical attributes such as skin color for race and shared cultural characteristics such as language for ethnicity. Historically, racial and ethnic categories have been used in biomedical research as a proxy for genetic biology. However, with recent evolutions in the ability to sequence the whole human genome, it has been shown that all humans regardless of race/ethnicity are more than 99% the same at the DNA sequence level, and the majority of variations (87%-91%) are within racial groups rather than between racial groups.[7,8]

However, despite the limited biological significance of race and ethnicity, the understanding of racial and ethnic differences is essential to identify potential areas for quality improvement. Therefore, we performed an observational descriptive study assessing racial and ethnic differences among patients with isolated aortic, aortoiliac and isolated iliac aneurysms. We describe the prevalence of comorbidities, aneurysm anatomical characteristics, operative characteristics, and outcomes after repair, stratified by race and ethnicity, in a national prospective registry.

Methods

Data Source & Patient cohort

We identified all White, Black, Asian, and Hispanic patients who underwent open or endovascular isolated aortic, concomitant aortoiliac, and isolated iliac aneurysm repair in the Society of Vascular Surgery Vascular Quality Initiative (VQI) between 2003 and 2019. The registry does not include patients who had an aneurysm but did not undergo repair. We excluded patients with missing race (N=2,307) or race categories other than White, Black, or Asian as the small sample size of these groups (<0.5%) prohibits robust analyses (American Indian or Alaskan Native, N=150; Native Hawaiian or other Pacific Islander, N=74; More than 1 race, N=65). As Black and Asian Hispanic patients represented less than 0.01% of the cohort we only categorized White patients with Hispanic ethnicity as Hispanic. We also excluded patients with missing data on iliac aneurysm presence (N=1,572). The VQI is a quality improvement initiative incorporating data from over 500 centers. It contains demographic, procedural and outcome data. More information about the VQI can be found at www.vqi.org. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards for observational studies.[9] The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the need for patient consent due to the study design and minimal risk to human subjects.

Definitions and variables

We defined isolated aortic aneurysms as those with an abdominal aneurysm without aneurysm extent in the iliac artery; aortoiliac aneurysms as those with an abdominal aneurysm and an iliac aneurysm; and isolated iliac aneurysms as patients with an iliac aneurysm but no aortic aneurysm. The VQI classifies race the same as the United States census bureau methodology with White race as a person having origins in Europe, the Middle East, or North Africa; Black race as a person having origins in Africa; and Asian race as a person having origins in the Far East, Southeast Asia, or the Indian subcontinent. Hispanic ethnicity is defined as a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin. To calculate body mass index (BMI), we used the standard weight (kg)/height^2 (m^2) formula, and the estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[10] We defined chronic kidney disease (CKD) as an eGFR<30mL/min/1.73m^2 or currently on dialysis. We classified patients with a BMI<18.5 as underweight and ≥30 as obese. We calculated body surface area (BSA) according to the Du Bois and Du Bois weight$^{0.425}$ (kg) x height$^{0.725}$ (cm) x 0.007184 formula. Aortic size index (ASI) was defined as aneurysm diameter/BSA. Symptomatic aneurysms were defined as those undergoing surgery within 24 hours of pain and/or tenderness without rupture. We defined major complications as the presence of one of the following: postoperative myocardial infarction, congestive heart failure (CHF), reintubation, dialysis requirement not present prior to admission, stroke, surgically treated intestinal ischemia, surgically treated leg ischemia/embolism, surgically treated surgical site infection, or reoperation. Iliac diameter, concomitant procedures, and unplanned graft extension (extension location is not specified) were only available for patients undergoing EVAR prior to 2014 (17,143 (28%)); percutaneous access, neck-AAA angulation, aortic neck diameter, aortic neck length, and, hypogastric aneurysm were only available for patients undergoing EVAR after 2014 (31,222 patients (52%)); and insurance status was only available after 2012 (50,086 patients (83%)).

Statistical analysis

Normally distributed continuous variables were presented as mean and standard deviation and non-normally distributed continuous variables as median and interquartile range (IQR). We presented categorical variables as counts and percentages. We compared baseline, operative characteristics, and outcomes amongst White, Black, Asian, and Hispanic patients. In addition, the comparisons between races were also performed stratified by anatomical group (isolated aortic vs. aortoiliac vs. isolated iliac aneurysms). In this study, our aim was to perform an observational descriptive study assessing racial/ethnic differences and associations with outcomes even if these can't be interpreted causally. We decided to describe the racial differences in outcomes without adjustment for potential confounders as our aim was to emphasize the actual racial differences. Racial differences are confounded and mediated by many factors including socioeconomic factors, background and cultural context. We are limited by the available data and our understanding of these complex relations and therefore we could not demonstrate and interpret the cause of racial disparities correctly with our data. Creating a multivariable model which tries to account for these factors can result in misinterpretation of the "effect" of race on outcomes.[11] Therefore, we allowed for the confounding factors to persist in our results. Statistical analyses were performed using Stata 15 (StataCorp LP, College Station, Tex).

Results

Patient Cohort

We identified 60,435 patients, of whom 55,200 (91%) were White, 3,208 (5.3%) were Black, 803 (1.3%) were Asian, and 1,224 (2%) were Hispanic. A total of 42,128 (70%) patients underwent isolated aortic repair, 14,603 (24%) aortoiliac repair and 704 (1.2%) isolated iliac repair. Black patients were the most likely to undergo aortoiliac (W:23%, B:38%, A:31%, H:22%, P<.001) and isolated iliac aneurysm repair (W:1.0%, B:3.1%, A:1.5%, H:1.6%, P<.001) rather than isolated aortic repair (W:76%, B:59%, A:68%, H:76%, P<.001). Also, Black and Hispanic patients most often underwent endovascular repair (W:80%, B:83%, A:79%, H:83%, P=.001) and were most likely to undergo repair for a symptomatic aneurysm (W:9.3%, B:18%, A:11%, H:13%, P<.001). All groups had similar rates of rupture repair (W:7.9%, B:9.1%, A:8.1%, H:8.0%, P=.15). Patients with isolated iliac aneurysms were more likely to present with a ruptured aneurysm (isolated aortic: 8.3%, aortoiliac: 7%, isolated iliac:11%, P<.001). The prevalence of race categories varied between the VQI regions with White race varying between 79% and 97%, Black race between 0.7% and 12%, Asian race between 0.2% and 13%, and Hispanic between 0.3% and 9.3%. Also, Asian, Black, and Hispanic patients were more likely to be on Medicaid or Self-pay (Table 1). When stratifying between regions with more and less than 90% white patients, the trends in aortoiliac repair, EVAR and urgency rates remained similar.

Baseline characteristics

Among all aneurysm cohorts, Black patients were more likely to be younger, female, underweight, current smokers, have a history of prior AAA repair, and have IDDM, hypertension, CHF, and CKD. White patients were more likely to have a history of coronary artery disease, COPD, and a family history of AAA. White patients more likely to undergo repair in high-volume centers by high-volume surgeons than in medium and low-volume centers and by medium and low-volume surgeons. Asian patients were least likely to be obese and to have ever smoked. Black patients were less likely to be taking statins preoperatively and on discharge, while Hispanic and Asian patients were least likely to take preoperative and discharge Beta-blocker medication and White patients were most likely to be taking antiplatelet medication preoperatively and on discharge (Table 1).

Table 1. Baseline characteristics

	All patients (n=60,435)				
	White (n=55,200)	**Black (n=3,208)**	**Asian (n=803)**	**Hispanic (n=1,224)**	**P-value**
Age	73 (67, 79)	71 (64, 78)	75 (68,81)	73 (67,80)	<.001
Female sex	11017 (20%)	1011 (32%)	126 (16%)	229 (19%)	<.001
Underweight (BMI <18.5)	1457 (2.7%)	159 (5.0%)	37 (4.6%)	32 (2.6%)	<.001
Obese (BMI >30)	17012 (31%)	929 (29%)	70 (8.8%)	347 (29%)	<.001
IDDM	1834 (3.3%)	193 (6.0%)	22 (2.7%)	64 (5.2%)	<.001
Ever smoker	48194 (88%)	2683 (84%)	519 (65%)	974 (80%)	<.001
Current smoker	19037 (35%)	1300 (41%)	157 (20%)	381 (31%)	<.001
Hypertension	45591 (83%)	2932 (92%)	679 (85%)	1019 (83%)	<.001
Coronary Artery Disease	22775 (41%)	1081 (34%)	277 (35%)	452 (37%)	<.001
CHF					
Asymptomatic/Mild	5413 (9.8%)	417 (13%)	51 (6.4%)	112 (9.2%)	<.001
Moderate/Severe	897 (1.6%)	90 (2.8%)	9 (1.1%)	21 (1.7%)	
COPD	18909 (34%)	858 (27%)	155 (19%)	271 (22%)	<.001
CKD	2557 (4.7%)	328 (10%)	60 (7.5%)	63 (5.2%)	<.001
Prior AAA Repair	2259 (4.1%)	203 (6.3%)	40 (5.0%)	48 (3.9%)	<.001
Family History of AAA	5027 (9.2%)	129 (4.1%)	35 (4.4%)	58 (4.8%)	<.001
Center Volume	57 (35,83)	49 (30,73)	41 (26,65)	56 (32,98)	<.001
Surgeon Volume	13 (8,20)	11 (6,18)	11 (6,18)	11 (6,20)	<.001
Preoperative Statin Use	37570 (68%)	2064 (64%)	565 (70%)	802 (66%)	<.001
Preoperative Antiplatelet Use	36657 (67%)	1958 (61%)	475 (59%)	711 (58%)	<.001
Preoperative Beta-blocker Use	30246 (55%)	1783 (56%)	403 (50%)	620 (51%)	.001
Discharge Statin Use	39718 (75%)	2278 (73%)	596 (76%)	878 (74%)	.06
Discharge Antiplatelet Use	43755 (82%)	2501 (80%)	621 (79%)	926 (78%)	<.001
Discharge Beta-blocker Use	31542 (59%)	1961 (63%)	403 (50%)	675 (57%)	<.001
Insurance status[a]					<.001
Insured	46235 (97%)	2679 (91%)	685 (92%)	1037 (91%)	
Medicaid	452 (1.0%)	68 (2.3%)	15 (2.0%)	42 (3.7%)	
Self-pay	936 (2.0%)	212 (7.2%)	46 (6.2%)	64 (5.6%)	

Age (years); BMI: Body Mass Index (kg/m2); IDDM: Insulin Dependent Diabetes Mellitus; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease eGFR: estimated glomerular filtration rate; Values are median (inter quartile range) or total events (percentages)

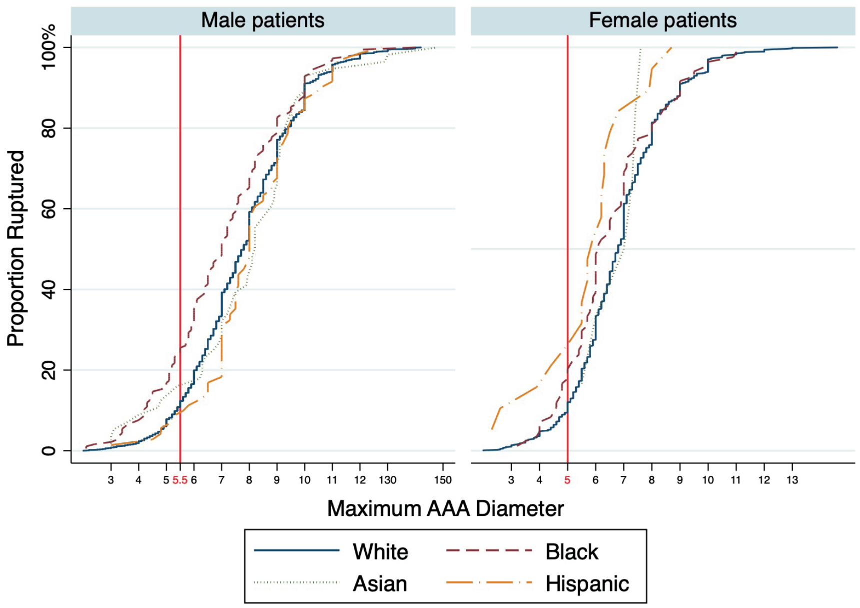
[a] This variable was only available after 2012 and therefore this analysis was done in the subgroup with the available data

7

Operative characteristics

Black patients were more likely to undergo urgent repair among all three aneurysm groups. No racial difference was found in AAA diameter among patients presenting with a symptomatic AAA. However, among patients who presented with a ruptured AAA, Black patients presented with the smallest AAA diameter when undergoing repair (EVAR: W:74, B:69, A:76, H:71mm, P=.002; Open: W:78, B:70, A:83, H:83mm, P <.001). Black patients were more likely to undergo rupture repair at a diameter below the 55mm threshold for male patients and below the 50mm threshold for female patients (W:12%, B:24%, A:15%, H:13%, P<.001) (Figure 1). This difference was not attenuated by using ASI. Among patients presenting for elective endovascular repair, although Black patients had a smaller aortic diameter, the absolute difference was very low (EVAR: W:56, B:55. A:56mm, H:56 P<.001). However, when accounting for body size, Asian patients had a substantially higher ASI compared with White and Black patients (W:28, B:28, A:32, H:30 P<.001).). Also, when undergoing elective open repair, there were no racial differences in AAA diameter, while Asian patients had a larger ASI at repair (W:31, B:31, A:34, H:31, P<.001).

Figure 1: Cumulative distribution of ruptured repair as a function of preoperative aortic diameter (in mm), stratified by race and ethnicity.



Among patients with an aortoiliac or isolated iliac aneurysm undergoing elective repair, White patients had the smallest iliac diameters (EVAR: W:30, B:36, A:37, H:33mm, P< .001; Open: W:32, B:37, A:38, H:39mm, P<.001), Black patients were more likely to have bilateral iliac aneurysms (EVAR: W:46%, B:58%, A:44%, H:47%, P<.001; Open: W:55%, B:74%, A:46%, H:57%, P<.001), and Asian patients were most likely to have a concomitant hypogastric aneurysm (W:12%, B:12%, A:24%, H:7.9, P<.001). Asian patients had the smallest aortic neck diameter (W:24, B:23, A:21, H:23mm, P<.001), the largest percentage of aortic aneurysm neck angle above 60 degrees (W:6.5%, B:7.6%, A:15%, H:5.9%, P<.001), while Hispanic patients had the shortest neck (W:24, B:25, A:25, H:22mm, P<.001). Asian and Black patients most often had concomitant procedures done (W:32%, B:41%, A:41%, H:35%, P<.001) with higher hypogastric coiling rates (W13%, B:27%, A:30%, H:18%, P<.001). Among patients undergoing isolated aortic repair, hypogastric coiling rates were still highest in Asian patients (W:2.5%, B:5.6%, A:14%, H:3.0%, P<.001). Asian patients had the highest rates of unplanned graft extension (W:9.7%, B:9.4%, A:15%, H:10%, P=.04) and percutaneous access (W:72%, B:74%, A:83%, iH:69%, P<.001). For both EVAR and open repair, the procedure time was longest in Black patients (EVAR: W:115, B:123, A:121, H:106, P<.001; Open: W:224, B:270, A:232, H:210 minutes, P<.001). Conversion rates were low and similar between races after EVAR (Table 2).

Table 2. Operative characteristics

	EVAR					Open repair				
	White (n=44,064)	**Black (n=2,652)**	**Asian (n=637)**	**Hispanic (n=1,012)**	**p-value**	**White (n=11,136)**	**Black (n=556)**	**Asian (n=166)**	**Hispanic (n=212)**	**p-value**
General Anesthesia	91%	93%	86%	94%	<.001	100%	100%	100%	100%	-
Total procedure time	115 (86,159)	123 (90,179)	121 (90,177)	106 (80,147)	<.001	224 (172,295)	270 (207,350)	232 (180,291)	210 (160,281)	<.001
Concomitant procedure[a]	32%	41%	41%	35%	<.001	-	-	-	-	-
Hypogastric coil[b]	13%	27%	30%	18%	<.001	-	-	-	-	-
Unplanned Graft Extension[a]	9.7%	9.4%	15%	10%	.04	-	-	-	-	-
Conversion to Open Repair	0.3%	0.3%	0.3%	0.4%	1	-	-	-	-	-
Percuntaneous acces[b]	72%	74%	83%	69%	<.001	-	-	-	-	-
Elective AAA Diameter	56 (10)	55 (12)	56 (11)	56 (11)	.002	60 (13)	60 (15)	60 (15)	58 (13)	.28
Elective AAA ASI	28 (6.1)	28 (7.2)	32 (7.1)	30 (6.5)	<.001	31 (7.4)	31 (8.4)	34 (8.7)	31 (7.3)	<.001
Rupture AAA Diameter	74 (19)	69 (21)	76 (22)	71 (20)	.002	78 (19)	70 (20)	83 (24)	83 (18)	<.001
Symptomatic AAA Diameter	62(17)	62 (16)	59 (17)	60 (15)	.43	69 (19)	67 (19)	67 (17)	63 (19)	0.33
Elective Iliac Diameter*[a]	30 (14)	36 (14)	37 (17)	33 (14)	<.001	32 (14)	37 (17)	38 (15)	39 (23)	<.001
Rupture Iliac Diameter*[a]	39 (21)	51 (26)	40 (26)		.16	40 (22)	54 (27)	45 (26)	49 (26)	.01
Symptomatic Iliac Diameter*[a]	34 (18)	35 (17)	40 (22)	54 (22)	.04	39 (20)	40 (16)	39 (15)	48 (35)	0.75
Neck-AAA angle above 60[b]	6.5%	7.6%	15%	5.9%	<.001	-	-	-	-	-
Aortic Neck diameter[b]	24 (21,26)	23 (20,26)	21 (20, 24)	23 (20,25)	<.001	-	-	-	-	-
Aortic Neck length[b]	24 (17,31)	25 (16,33)	25 (20, 35)	22 (17,30)	<.001	-	-	-	-	-

	EVAR					Open repair				
	White (n=44,064)	**Black (n=2,652)**	**Asian (n=637)**	**Hispanic (n=1,012)**	**p-value**	**White (n=11,136)**	**Black (n=556)**	**Asian (n=166)**	**Hispanic (n=212)**	**p-value**
Oversizing >20%[b]	85%	89%	90%	83%	<.001	-	-	-	-	-
Iliac Aneurysm	24%	41%	31%	23%	<.001	25%	47%	40%	26%	<.001
Hypogastric artery aneurysm*[b]	12%	12%	24%	7.9%	.014					
Unilateral Iliac Aneurysm*	54%	42%	56%	53%	<.001	45%	26%	54%	43%	<.001
Bilateral Iliac Aneurysm*	46%	58%	44%	47%	<.001	55%	74%	46%	57%	<.001
Symptomatic AAA	7.9%	16%	10%	11%	<.001	11%	20%	11%	17%	<.001
Ruptured AAA	5.4%	7.9%	6.6%	5.3%	<.001	18%	15%	14%	21%	.1

** Rates within the patients undergoing concomitant aortoiliac or isolated iliac repair*
EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; Time between symptoms and repair (hours); Total procedure time (minutes); Diameter (mm); Aortic Neck Length (mm).
Values are median (inter quartile range) or total events (percentages).
[a] These variables were only available for patients undergoing EVAR prior to 2014 and therefore this analysis was done in the subgroup with the available data
[b] These variables were only available for patients undergoing EVAR after 2014 and therefore this analysis was done in the subgroup with the available data

Outcomes for Intact aneurysm repair

After intact EVAR, there was no significant difference in perioperative mortality among the three racial groups (W:1.1%, B:1.2%, A:0.5%, H:0.8%, P=.41). However, Black patients were found to have the highest rates of major complications (W:4.3%, B:5.4%, A:3.4%, H:3.7%, P=.039). After intact open repair, perioperative mortality (W:4.1%, B:5.1%, A:4.2%, H:2.4, P=.50) and major complication rates (W:22%, B:23%, A:30%, H:17%, P=.06) were similar between the three racial groups. After EVAR, Black patients were most likely to have intestinal ischemia (W:0.4%, B:0.8%, A:0.3, H:0.1%, P=.006) and had the highest rates of reoperation during the index hospitalization (W:2.0%, B:2.8%, A:0.5%, H:1.8%, P<.001). Also, Black patients were most likely to have a longer length of stay (W:1, B:2, A:1, H:1 day, P<.001) and to be discharged to a rehab unit or nursing home (W:5.0%, B:8.3%, A:3.9%, H:5.2%, P<.001). Asian patients were most likely to have any endoleak at the completion of the index procedure (W:23%, B:20%, A:27%, H:22%, P<.001); specifically, Asian patients had higher type I endoleaks (W:3.3%, B:3.0%, A:5.4%, H:3.3%, P=.028) and Black patients had lower type II endoleak rates (W:17%, B:13%, A:17%, H:16%, P<.001). Type III and type IV endoleaks were relatively uncommon for all races and were not different between races. After open repair, Asian patients had the highest rates of myocardial infarction (W:5.1%, B:3.6%, A:15%, H:3.0%, P<.001). Black patients had lower rates of CHF (W:4%, B:1.7%, A:3.5%, H:2.4%, P=.054) and higher rates of new dialysis (W:1.1%, B:2.7%, A:0.7%, H:0.7%, P=.010), reoperation (W:8%, B:11%, A:9.8%, H:5.4%, P=.042), and longest length of stay (W:7, B:8, A:7, H:7, P<.001) (Table 3a).

Outcomes for Ruptured aneurysm repair

After ruptured EVAR, there were no significant differences among the three racial groups in perioperative mortality (W:23%, B:18%, A:24%, H:22% P=.44) or major complications (W:35%, B:37%, A:38%, H:32%, P=.81). After ruptured open repair, there were no significant racial differences in perioperative mortality (W:37%, B:26%, A:22%, H:43%, P=.062) and major complication rates (W:60%, B:56%, A:62%, H:73%, P=.38). After EVAR, Asian patients had the highest rates of myocardial infarctions (W:9.6%, B:3.4%, A:12%, H:5.6%, P=.018), intestinal ischemia (W:5.6%, A:6.8%, A:17%, H:5.6%, P=.020) and surgically treated intestinal ischemia (W:3.2%, B:1.9%, A:12%, H:1.9%, P=.007). Black patients had the longest median length of stay after open rupture repair (W:9, B:12, A:10, H:10 days, P=.024) (Table 3b).

Table 3a. Outcomes Intact repair

	EVAR (n=45,636)					Open repair (n=9,948)				
	White (n=41,644)	**Black (n=2,440)**	**Asian (n=594)**	**Hispanic (n=958)**	**p-value**	**White (n=9,163)**	**Black (n=474)**	**Asian (n=143)**	**Hispanic (n=168)**	**p-value**
Perioperative Mortality	1.1%	1.2%	0.5%	0.8%	.41	4.1%	5.1%	4.2%	2.4%	.50
Any Major Complication	4.3%	5.4%	3.4%	3.7%	.039	22%	23%	30%	17%	.06
Postoperative Stroke	0.2%	0.1%	0.3%	0.0%	.32	0.8%	1.1%	1.4%	0.6%	.80
Myocardial Infarction	0.9%	1.0%	1.5%	0.5%	.20	5.1%	3.6%	15%	3.0%	<.001
New Dysrhythmia	2.1%	2.3%	2.5%	1.5%	.37	13%	9.7%	15%	8.3%	.059
CHF	0.8%	0.6%	1.0%	0.7%	.77	4.0%	1.7%	3.5%	2.4%	.054
Pneumonia	0.5%	0.6%	0.7%	0.3%	.62	3.2%	3.8%	4.9%	4.2%	.55
Reintubation	1.0%	1.4%	0.7%	0.7%	.22	8.2%	9.5%	6.3%	6.0%	.41
Intestinal Ischemia	0.4%	0.8%	0.3%	0.1%	.006	4.1%	3.8%	4.2%	3.6%	.98
Surgically Treated Intestinal Ischemia	0.2%	0.3%	0.0%	0.1%	.47	1.9%	2.1%	1.4%	0.6%	.59
New Dialysis	0.2%	0.3%	0.2%	0.1%	.68	1.1%	2.7%	0.7%	0.6%	.010
Endoleak (any)	23%	20%	27%	22%	<.001	-	-	-		-
Endoleak (type I)	3.3%	3.0%	5.4%	3.3%	.028	-	-	-		-
Endoleak (type II)	17%	13%	17%	16%	<.001	-	-	-		-
Endoleak (type III)	0.3%	0.4%	0.0%	0.2%	.45	-	-	-		-
Endoleak (type IV)	0.4%	0.5%	0.3%	0.3%	.86	-	-	-		-
Reoperation	2.0%	2.8%	0.5%	1.8%	.001	8.0%	11%	9.8%	5.4%	.042
Popstop LOS	1 (1, 2)	2 (1, 3)	1 (1, 2)	1 (1, 2)	<.001	7 (5, 9)	8 (6, 11)	7(6, 12)	7 (5, 9)	<.001
Discharge to rehab or SNF	5.0%	8.3%	3.9%	5.2%	<.001	20%	23%	17%	21.1%	.28

EVAR: endovascular aneurysm repair; Major complications (postoperative myocardial infarction; congestive heart failure; reintubation; new onset dialysis requirement not present prior to admission; stroke; surgically treated ischemic colitis; surgically treated leg ischemia/embolism; surgically treated surgical site infection or; reoperation); CHF: Congestive Heart Failure; LOS: length of stay; SNF: skilled nursing facility.
Values are total events (percentages).

Table 3b. Outcomes ruptured repair

	EVAR (n=2,701)					Open repair (n=2,120)				
	White (n=2,397)	**Black (n=208)**	**Asian (n=42)**	**Hispanic (n=54)**	**p-value**	**White (n=1,971)**	**Black (n=82)**	**Asian (n=23)**	**Hispanic (n=44)**	**p-value**
Perioperative Mortality	23%	18%	24%	22%	.44	37%	26%	22%	43%	.062
Any Major Complication	35%	37%	38%	32%	.81	60%	56%	62%	73%	.38
Postoperative Stroke	2.1%	2.9%	2.4%	3.7%	.73	3.2%	3.7%	9.5%	5.4%	.38
Myocardial Infarction	9.6%	3.4%	12%	5.6%	.018	16%	12%	29%	11%	.26
New Dysrhythmia	14%	10%	17%	7.4%	.25	24%	24%	19%	41%	.13
CHF	4.7%	2.9%	7.3%	5.6%	.53	8.5%	6.2%	9.5%	8.3%	.90
Pneumonia	4.9%	4.4%	12%	1.9%	.12	8.8%	8.6%	19%	2.6%	.21
Reintubation	14%	18%	2.4%	13%	.073	30%	28%	19%	42%	.27
Intestinal Ischemia	5.6%	6.8%	17%	5.6%	.020	17%	22%	4.8%	8.1%	.12
Surgically Treated Intestinal Ischemia	3.2%	1.9%	12%	1.9%	.007	9.8%	16%	0.0%	5.4%	.087
New Dialysis	2.7%	3.9%	0.0%	0.0%	.29	5.2%	8.9%	9.5%	5.3%	.45
Endoleak (any)	17%	17%	17%	20%	.93	-	-	-		-
Endoleak (type I)	4.0%	3.9%	9.5%	7.4%	.20	-	-	-		-
Endoleak (type II)	9.1%	9.3%	2.4%	11%	.46	-	-	-		-
Endoleak (type III)	0.8%	0.0%	2.4%	0.0%	.32	-	-	-		-
Endoleak (type IV)	0.1%	0.0%	0.0%	0.0%	.94	-	-	-		-
Reoperation	16%	21%	12%	19%	.16	31%	38%	38%	37%	.44
Popstop LOS	5 (2, 10)	5 (3, 13)	5 (3, 9)	5 (2, 9)	.051	9 (3, 17)	12 (7, 21)	10 (7, 24)	10 (4, 18)	.024
Discharge to rehab or SNF	24%	25%	24%	23%	.99	29%	34%	35%	14%	.098

EVAR: endovascular aneurysm repair; Major complications (postoperative myocardial infarction; congestive heart failure; reintubation; new onset dialysis requirement not present prior to admission; stroke; surgically treated ischemic colitis; surgically treated leg ischemia/embolism; surgically treated surgical site infection or; reoperation); CHF: Congestive Heart Failure; LOS: length of stay; SNF: skilled nursing facility.
Values are total events (percentages).

Discussion

Black patients, followed by Asian patients, were most likely to undergo repair for aortoiliac or isolated iliac aneurysm and less likely to undergo isolated aortic repair compared with White and Hispanic patients. Black patients were more likely to undergo urgent repair, presented with a smaller aortic diameter when undergoing rupture repair, and were more likely to have a rupture at diameters below typical repair thresholds. Among aortoiliac and isolated iliac aneurysms, iliac diameter was largest in Black and Asian patients. Also, Asian patients were most likely to have a hypogastric artery aneurysm and to undergo hypogastric coiling, even in the absence of iliac aneurysms. These anatomic differences likely reflect unclear biological mechanisms and risk factors that need further exploration. Also, differences in patient demographics, comorbid conditions and operative characteristics were found that may be a reflection of differences in access and quality of care.

Several racial differences in presentation and anatomy were described in this study. We found that Black and Asian patients were more likely to undergo repair for aortoiliac and isolated iliac aneurysm while White and Hispanic patients were more likely to undergo repair for isolated aortic aneurysms. In a study assessing racial differences in outcomes after intact AAA repair a higher rate of concomitant iliac artery aneurysm repairs in Black followed by Asian patients compared with White patients was previously described. However, the cause of these discrepancies in aortoiliac and isolated iliac aneurysm presentation are unclear. This could reflect a more “advanced” disease given the higher burden of comorbidities in Black patients and the larger iliac diameter and ASI in Asian patients. In a study evaluating possible mechanisms for site specificity of aneurysms, factors increasing the bifurcation angles between the aorta and the common iliac artery that lead to disturbed blood flow through this area and increased susceptibility to aneurysm formation have been cited as a possible explanation.[12] These factors included the loss of elastic tissue tone with increasing age and smoking. In our study, Asian patients were the oldest and Black patients were most likely to be current smokers; therefore, the mechanism previously described could contribute to the observed higher iliac aneurysm rate in the Black and Asian populations. Also, our results indicate that Black patients rupture at a smaller diameter, with 24% of Black patients undergoing ruptured repair being below the recommended thresholds for elective repair. While one might wonder if the threshold for AAA repair should be decreased in the Black population, the higher postoperative complication rate following AAA repair in the Black population would mandate a thorough assessment of the risk/benefit profile as part of a robust discussion before any such dialog can be fully contemplated. Overall, the biological mechanisms behind racial differences in the formation of aneurysms are unclear, and more studies examining the potential risk factors for iliac aneurysm formation are needed.

Among patients undergoing aortoiliac and isolated iliac aneurysm repair, Black and Asian patients were found to have the largest iliac diameter. Previous research showed that Chinese patients had larger aortic aneurysm diameters, larger common iliac artery diameters, and shorter common iliac artery lengths compared with American and European patients.[13] Also, coverage of the hypogastric artery was necessary in more than half of the Asian patients undergoing EVAR due to short or aneurysmal common iliac arteries.[13] Unfortunately, the VQI does not report common iliac artery lengths. However, we found that Asian patients most often underwent hypogastric coiling in both isolated aortic and aortoiliac aneurysm repairs, and as a common indication for hypogastric coiling is graft extension beyond the hypogastric artery, this suggests that there was inadequate common iliac artery length in Asian patients more so than others. Also, hypogastric artery embolization or coverage has been associated with increased morbidity among patients, including buttock claudication, erectile dysfunction and in rare cases intestinal or spinal ischemia.[10] Except intestinal ischemia, which was more likely in Asian or Black patients after EVAR, these post-operative symptoms were not collected in the VQI. Complex aortoiliac anatomy has been documented among Asian patients which may pose additional challenges for endovascular repair. We found that Asian patients had higher rates of any endoleak at completion, specifically in Type I and Type II endoleaks. The higher rate of type I endoleak may be related to the higher rates of severe neck angulation found in Asian patients.[14] The high rates of type II endoleaks in Asian patients could be associated with hypogastric artery coil embolization and distal graft extension in Asian patients.[15] This suggests the need for new devices designed for use in patients with complex iliac anatomy such as short common iliac length in particular for those who do not have dilated common iliac arteries.

Racial differences in medical care are complex and multifactorial and, increasing evidence-based research will be needed to further understand these disparities[16]

However, in our cohort, we highlight several differences which could reflect inequality in access and quality of care. First, Black, Asian, and Hispanic patients were less likely to have their aneurysm repair in high-volume centers by high-volume surgeons compared with White patients, and previous research shows this is associated with worse outcomes.[17] Second, our study found that Black, Asian, and Hispanic patients were most likely to have Medicaid or self-pay. Studies have demonstrated that physicians may alter clinical management based on a patient's insurance status, resulting in changes in preventive services, diagnostic evaluations and therapeutic treatments.[18] Third, Black, Asian, and Hispanic patients were less likely to receive appropriate medical management, both preoperatively and on discharge. Preventive strategies for chronic disease, such as optimal medical management with statins and aspirin, are pivotal in the prevention and progression of vascular pathologies.[19] As Black patients are younger with higher rates of comorbidities and are more likely to be current smokers, this suggests potential inequity in access to or efficacy of current preventive strategies. Also, racism is deeply ingrained in the structures of our society resulting in differences in the distribution of opportunities and exposure to risks based on one's racial identity that impacts an individual's health.[20] Physicians and researchers should understand the effects of access to quality education, affordable housing, food security, gainful employment, social support, and a clean environment which can be important factors affecting one's health.[21,22,23] The majority of clinical registries do not capture these social determinants of health, leading to gaps in our understanding of major drivers of these differences and potential solutions for quality improvement.[24] Lastly, provider level factors such as implicit or unconscious bias in the delivery of care might influence outcomes or clinical decisions.[16] Therefore, at a physician level, awareness of biases that may lead to variation of care and increased training is essential. Also, developing a healthcare workforce that is reflective of the racial diversity of the population that it serves can improve health care delivery.[25]

These results must be interpreted within the context of the study design. First, the VQI only captures patients who undergo repair and therefore limits our interpretation of ruptured AAA prevalence when repair is not offered. Second, the VQI lacks specific information on iliac diameter in open repair and EVAR after 2014. Third, our database lacks data including complications related specifically to iliac interventions such as buttock claudication or erectile dysfunction. Fourth, the VQI includes data from centers focused on quality improvement and therefore might not be generalizable to the overall population.[26] Finally, we were not able to analyze the extent of the influence of socioeconomic status on these racial differences as the VQI lacks variables that reflect the socioeconomic status such as income or zip code.

Conclusion:

Black and Asian patients were most likely to undergo repair for aortoiliac and isolated iliac aneurysms compared with White patients, while White and Hispanic patients were most likely to undergo isolated aortic aneurysm repair. Also, Black patients were more likely to undergo urgent repair and presented with a ruptured aneurysm at a smaller diameter compared with White, Asian, and Hispanic patients. Asian patients have been documented to have more complex iliac anatomy and this may be contributing to higher rates of concomitant procedures such as hypogastric coiling and higher rates of operative complications such as completion endoleaks. The observations in this study provide a framework for race-specific quality improvement with improved patient selection for repair, preventive measures such as smoking cessation and optimization of medications, and device development for complex iliac anatomy. However, more research needs to be conducted to understand the risk factors contributing to the formation of iliac aneurysms, the likelihood of rupture at small diameters, the socioeconomic factors that lead to racial disparities.

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PART III

Practice patterns and appropriate application of EVAR

Chapter 8

Long-term Implications of Elective EVAR That is Non-compliant with Clinical Practice Guideline Diameter Thresholds

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Abstract

Objective: Compliance with SVS AAA clinical practice guideline (CPG) diameter thresholds is variable for EVAR. In order to evaluate the implications and appropriateness of repairs that are non-compliant with current guidelines, we investigated the long-term outcomes, adherence to imaging follow-up, and associated healthcare costs in patients undergoing EVAR for AAA who do or do not meet recommended diameter thresholds.

Methods: All patients receiving elective EVAR from 2003-2016 in the SVS-VQI with linked Medicare claims were reviewed. Weekend procedures, isolated iliac aneurysm, as well as symptomatic and ruptured presentations were excluded. Diameter thresholds for non-compliant repairs were defined as: men <55mm; women<50mm who did not have an iliac diameter ≥30mm. We evaluated adherence to postoperative imaging surveillance, reimbursement amounts, reintervention, rupture, and all-cause mortality. We defined an EVAR quality metric as performance of the index procedure with freedom from conversion to open repair, five-year rupture-free survival, and adherence to minimum imaging surveillance (at least one CT scan documented between 6-24 months postoperatively).

Results: Among 19,018 elective EVARs, 35% did not meet CPG diameter thresholds (26% within 5mm of threshold). The rate of non-compliant repairs increased over time (24%-2003 vs. 36%-2016; P<.001). Patients undergoing non-compliant repairs were younger, less likely to have multiple comorbidities, and more likely to receive EVAR with adherence to instructions for use criteria (89% vs. 79%; P<.001). Patients undergoing non-compliant repairs had greater five-year freedom from reintervention (86% vs. 81%; P<.001), rupture-free survival (94% vs. 92%; P=.01), and overall survival rates (71% vs. 61%;P<.001) compared with repairs that complied with CPG diameter thresholds.

Although non-compliant repairs had higher rates of one-year imaging surveillance, overall differences were modest (68% vs. 65%; P=.003). Importantly, for the entire cohort, follow-up imaging surveillance decreased over time (93%-2003 vs. 63%-2014; P<.001). Notably, although non-compliant repairs had higher rates of achieving the composite quality metric compared with compliant repairs (43% vs. 38%; P<.001), failure occurred with a significant majority of all repairs.

Conclusion: Compliance with SVS endorsed CPG diameter thresholds for elective EVAR is poor, and rates of non-compliance are increasing. Non-compliant repairs appear to be offered more commonly to patients with fewer comorbidities and favorable anatomy, and these repairs are associated with improved rates of reintervention, rupture and survival compared to procedures meeting CPG diameter thresholds. Importantly, non-compliant repairs fail to meet minimum quality standards in a majority of cases, which underscores the need for further policies to improve the overall quality and appropriateness of AAA care delivery nationally.

Introduction

The Society for Vascular Surgery clinical practice guidelines (CPGs) currently recommend offering elective abdominal aortic aneurysm (AAA) repair in men with an AAA diameter that is ≥ 5.5cm and in women with a diameter ≥5.0cm.[1] These threshold recommendations are based on large randomized controlled trials that have demonstrated no advantage of small aneurysm repair compared with surveillance.[2] While medical and technological advancements have lowered the perioperative risk of EVAR, these improvements still have not led to a clear benefit of EVAR over surveillance for small AAA.[3,4] However, previous research has identified that 41% of patients underwent elective repair below the recommended CPG diameter thresholds.[5]

In combination with the high costs and limited long-term durability of EVAR, high rates of small AAA repair may indicate overtreatment and inappropriate application of this technology.[6,7] However, there is significant international variation in the rate of small intact AAA repair, with the US among the countries with the highest rates.[8,6] Also, within the US, there is regional and center variation in repair diameters.[9] In order to justify repair outside the current CPGs, EVAR for small intact AAA should result in excellent survival, as well as low reintervention and complication rates.

Due to the lack of evidence supporting small AAA repair and the fact that the US is an outlier in performing small AAA repair, it is questionable whether this practice is appropriate in the era of value-based care and cost containment. Understanding the clinical decision-making surrounding repairs below the recommended diameter thresholds and the long-term outcomes after these procedures is essential to evaluate the appropriateness of offering elective EVAR that is non-compliant with CPGs. Therefore, our objective was to investigate the long-term outcomes, adherence to imaging follow-up, and associated healthcare costs in patients undergoing EVAR for AAA that does or does not comply with recommended diameter treatment thresholds.

Methods

Data Source

We retrospectively identified patients who underwent elective EVAR between 2003 and 2016 in the Vascular Quality Initiative (VQI) registry linked to their respective Medicare claims file. Linkage was performed by a previously described methodology.[10,11] The VQI prospectively collects granular clinical, technical, and in-hospital outcome data. More information can be found at www.vqi.org. The Medicare data contains reimbursed inpatient claims for Medicare Beneficiaries and linkage with this longitudinal data allow long-term follow-up with analyses of late outcomes. The linkage methodology has been previously described.[10] The study was performed in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.[12]

The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the need for further patient consent due to the nature of the design and minimal risk to human subjects.

Patient Cohort

We identified all patients who underwent elective EVAR between 2003 and 2016 in the VQI with linked Medicare claims to determine long-term outcomes (n=23,253). We excluded patients undergoing rupture (n= 1,173) and symptomatic repairs (n=1,819) as well as those with missing urgency status (n=90). Also, when patients had two entries in the database (n=16), the second procedure was excluded to avoid the biasing effect of non-independence of observations in our analyses. To ensure elective AAA repair was being analyzed and decrease likelihood that repair was driven by an indication other than aneurysm diameter, we excluded weekend procedures (n=98), patients with isolated iliac aneurysms (n=246) or subjects with a prior AAA repair history (n=528). Finally, we excluded patients with missing AAA diameter (n=265).

Definitions and Variables

Non-compliant repairs were defined as AAA procedures performed for an aortic diameter less than 55mm in men and less than 50mm in women who also did not have an iliac diameter above 30mm. We subcategorized non-compliant repair patients as those undergoing repairs at diameters less than 5mm, between 5 and 10mm, and more than 10mm below CPG thresholds. Age above 90 is coded as 90 years old in the VQI. Race/Ethnicity was stratified into non-Hispanic White, Hispanic, Black, Asian, and Other and was included in the analyses despite its limited biological significance, as we believe describing the racial differences is essential to identify potential areas for quality improvement. We used the standard weight (kg) / height^2 (m^2) formula for body mass index (BMI) and defined underweight as a BMI below 18.5 and obese as a BMI of 30 or above. We calculated estimated glomerular filtration (eGFR) rate with the Chronic Kidney Disease Epidemiology Collaboration equation formula using the most recent preoperative creatinine value. Chronic kidney disease (CKD) was defined as preoperative eGFR <30 or dialysis. Congestive heart failure (CHF) was classified into asymptomatic/mild and moderate/severe presentations. COPD was categorized as no COPD, untreated COPD and treated COPD (with medication or oxygen). Neck angulation, length, and diameter were introduced into the EVAR VQI registry in December 2014 and therefore neck characteristics and IFU adherence were only included after that date. IFU adherence was based on common device IFU cutoffs: β-neck angulation <60°, α-neck angulation <45°, neck length ≥10mm, neck diameter ≤32mm, and iliac diameter ≥7mm.

We defined an EVAR quality metric based on the composite outcomes of freedom from open conversion after the index procedure, 5-year rupture-free survival, and adequate one-year follow-up imaging. Adequate one-year follow-up imaging compliance was defined as at least one CT scan documented between 6-24 months postoperatively. The index procedure reimbursement amount was a summation of Medicare facility payment (Part A), pass-through amount, and professional services payment (Part B). The reintervention Medicare payment amount combined the MedPar payment, MedPAR pass through, and part B claim payment.

Statistical Analysis

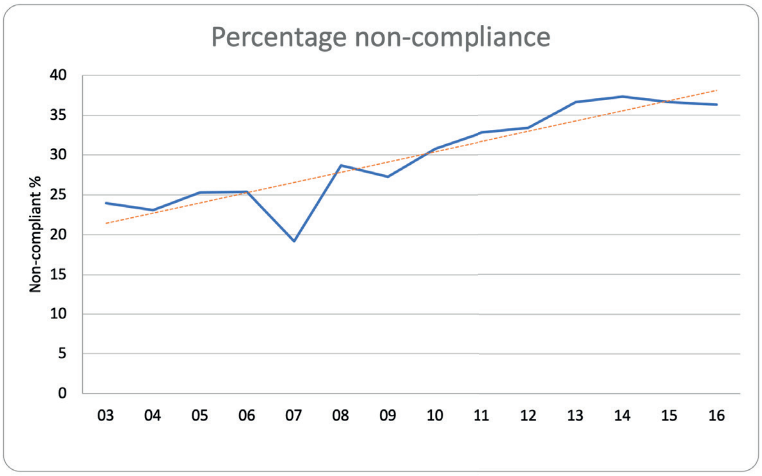
We reported counts and percentages of categorical variables and median and interquartile range or mean and standard deviation for continuous variables, where appropriate. We performed descriptive analyses of the demographics, comorbidities, reimbursement amounts, one-year imaging rates, and re-admissions. We assessed CPG diameter threshold and follow-up imaging compliance rates over time using logistic regression. Five-year reintervention, rupture, and mortality rates were calculated using Kaplan-Meier survival analyses with hazard function estimation. Patients were censored at their date of death. Also, as longitudinal data were not available for patients who left Medicare fee-for-service and entered into a non-fee-for-service program such as Medicare Advantage, we censored these patients at the time of their switch. Comparison of long-term outcomes was performed using the log-rank test. As we wanted to allow the patient selection criteria to persist, we compared our outcomes univariately without performing a multivariable analysis. To assess the cumulative cost of reinterventions after EVAR, we performed a subgroup analysis in a cohort for which follow-up was available through 5 years or until death. Finally, we performed a sensitivity analysis comparing the outcomes between patients that underwent repair above the recommended thresholds and those that were less than 5mm below the threshold. All statistical analyses were performed using Stata 15 software (StataCorp LLC, College Station, Texas).

Results

Patient cohort

We identified 19,018 patients who underwent elective EVAR, of which 35% (n=6,730) did not meet the CPG diameter thresholds for AAA repair. Specifically, 4,902 (26%) underwent repair less than 5mm below the thresholds, 1,126 (5.9%) received repair between 5 and 10mm below the thresholds, and 702 (3.7%) underwent repair more than 10mm below the thresholds. The rate of non-compliant repairs increased over time with non-compliant repairs being performed at a rate of 24% in 2003 and 36% in 2016 (OR per year: 1.05, P<.001, 95%CI: 1.04-1.06; Figure 1).

Figure 1. Percentage of non-compliance with clinical practice guideline diameter thresholds over time



Non-compliant repair rate
X-axis represent the calendar year

Baseline and anatomic characteristics

Compared with patients undergoing guideline-compliant repairs, patients undergoing non-compliant repairs were less often female (10.2% vs. 25.3%, P<.001), younger (Median 74 [IQR: 69; 79] vs. 76 [70; 82]; P<.001), more likely White (95.2% vs. 94.2%), less likely Black (3.5% vs. 4.5%, P=005), and less likely underweight (1.8% vs. 2.6%; P<.001). These patients were also less likely to have CKD (2.3% vs. 4.1%, P<.001), Asymptomatic/Mild CHF (9.5% vs. 11.3%; P<.001) Moderate/Severe CHF (1.1% vs. 1.8%; P<.001), COPD (31% vs. 35%; P<.001), and COPD on home oxygen (3.3% vs. 6.0%). Also, patients undergoing non-compliant repairs were more likely to have prior coronary artery disease (45.7% vs. 42.7%, <.001), and use preoperative Statin, Aspirin, and P2Y12 inhibitors (Table 1).

Table 1: Baseline characteristics, stratified by compliance with clinical practice guideline diameter thresholds

	Non-compliant N=6,730		Compliant N=12,288		P-value
Female	686	10.2%	3,108	25.3%	<.001
Age	74	69, 79	76	70, 82	<.001
Race					.005
White	6,298	95.2%	11,328	94.2%	
Black	232	3.5%	539	4.5%	
Other	85	1.3%	160	1.3%	
Underweight	122	1.8%	317	2.6%	<.001
Obese	2033	30.3%	3,621	29.6%	.31
Current Smoker	1,864	27.7%	3,385	27.6%	.82
Ever Smoked	5,808	86.4%	10,515	85.7%	.16
CKD	152	2.3%	497	4.1%	<.001
CHF					<.001
No	6,010	89.4%	10,667	86.9%	
Asymptomatic/Mild	642	9.5%	1,389	11.3%	
Moderate/Severe	73	1.1%	221	1.8%	
Family History of AAA	623	9.3%	1,033	8.5%	.053
Hypertension	5,616	83.5%	10,306	83.9%	.45
IDDM	262	3.9%	436	4.6%	.22
COPD					<.001
No	4,616	68.6%	8,007	65.2%	
Untreated	640	9.5%	1,219	9.9%	
On Medication	1243	18.5%	2,319	18.9%	
On home O2	225	3.3%	738	6.0%	
CAD	3,074	45.7%	5,243	42.7%	<.001
Preoperative Statin use	4,907	72.9%	8,561	69.7%	<.001
Preoperative Aspirin use	4,561	67.8%	8,077	65.8%	.005
Preoperative P2Y12 inhibitor use	873	13.0%	1,416	11.5%	.003
Large Neck diameter*	150	8.8%	316	10.1%	.14
Short neck length*	319	18.4%	721	22.6%	<.001
Beta angulation > 60°*	43	2.7%	266	8.9%	<.001
Adherence to IFU*	1,734	89.2%	2,783	78.5%	<.001

Age (years); Other race: Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific Islander or more than 1 race; Underweight: body mass index below 18.5; Obese: body mass index of 30 or above; CKD: Chronic Kidney Disease; CHF: Congestive Heart Failure; AAA: abdominal aortic aneurysm; IDDM: Insulin Dependent Diabetes Mellitus; COPD: chronic obstructive pulmonary disease; CAD: Coronary Artery Disease; IFU: Instructions for Use.
Categorical variables are presented as counts and percentages and continuous variables as median and interquartile ranges.
** Neck anatomy variables were introduced in 2014, these rates are therefore from a subset of patients undergoing repair after 2014 (n=5490, 29%)*

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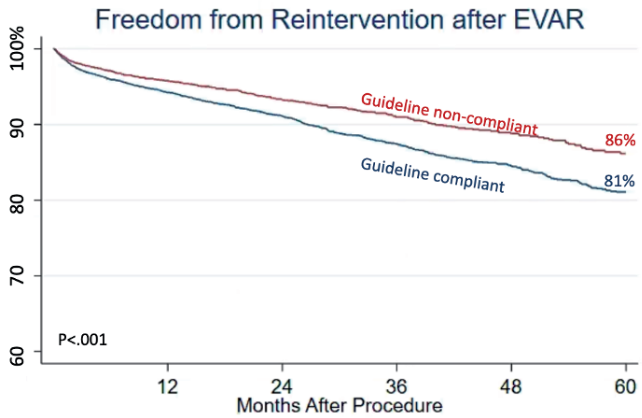
Outcomes and follow-up adherence

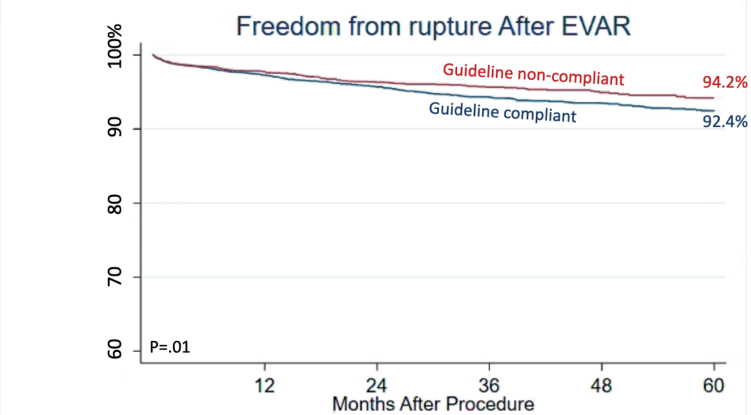
Compared with patients undergoing guideline-compliant repairs, patients undergoing non-compliant repairs had lower perioperative mortality (0.7% vs. 1.6%, P<.001), postoperative CHF (0.5% vs. 1.0%, P<.001), postoperative intestinal ischemia (0.3% vs. 0.6%, P=.014), and postoperative new dialysis (0.6% vs. 1.0%, P=.013). Also, the were less likely to be readmitted within 30-days (7.7% vs. 9.9%, P<.001) and within 90-days (14% vs. 18%, P<.001). Those undergoing non-compliant repairs also had greater five-year freedom from reintervention (86% vs. 81%, HR: 1.4, P<.001, 95%CI: 1.2-1.5; Figure 2), rupture (94.2% vs. 92.4%, HR: 1.3, P=.016, 95%CI: 1.0-1.5; Figure 3), and higher five-year survival rates (71% vs. 61%, HR: 1.6, P<.001, 95%CI: 1.4-1.7; Figure 4). In addition, patients undergoing non-compliant repairs had higher rates of adherence to one-year CT-scan follow-up (68% vs. 65%, P=.003); however, rates of one-year follow-up imaging decreased significantly over time (93%-2003 vs. 63%-2014; P<.001). A minority of all patients achieved the quality metric, but the rate was higher in those undergoing non-compliant repairs compared with guideline-compliant repairs (43% vs. 38%; HR:1.3, P<.001; 95%CI: 1.1-1.3; Figure 5).

Figure 2. Five-year freedom from reintervention, stratified by compliance with clinical practice guideline diameter thresholds



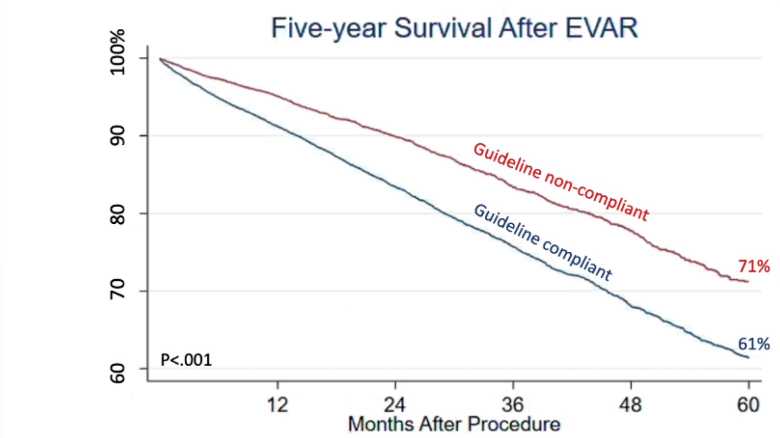
Months after repair	12	24	36	48	60
Off-guideline repairs					
Number at risk	N=3366	N=2255	N=1370	N=766	N=391
Survivor % (Standard error)	**95.8%** (0.003)	**93.3%** (0.004)	**91.0%** (0.005)	**89%** (0.007)	**86%** (0.009)
Guideline compliant repair					
Number at risk	N=5937	N=3997	N=2520	N=1509	N=780
Survivor % (Standard error)	**94.2%** (0.003)	**91.1%** (0.004)	**87%** (0.005)	**85%** (0.006)	**81%** (0.007)

Figure 3 : Five-year freedom from rupture, stratified by compliance with clinical practice guideline diameter thresholds



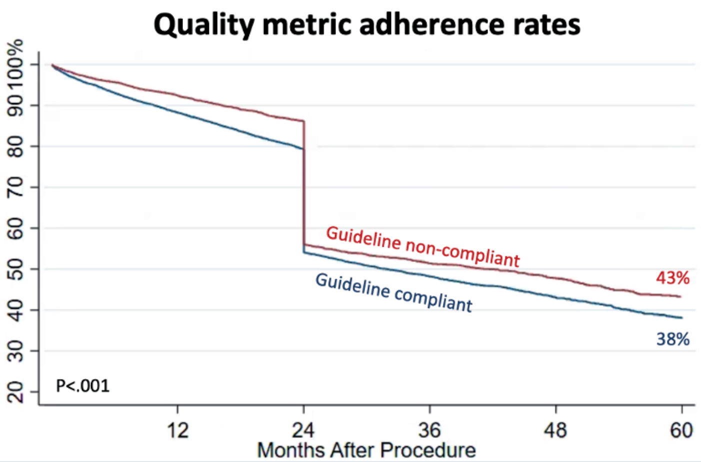
Months after repair	12	24	36	48	60
Off-guideline repairs					
Number at risk	N=3430	N=2342	N=1443	N=832	N=434
Survivor % (Standard error)	**97.7%** (0.002)	**96.3%** (0.003)	**95.7%** (0.004)	**94.9%** (0.004)	**94.2%** (0.006)
Guideline compliant repair					
Number at risk	N=6122	N=4242	N=2750	N=1679	N=895
Survivor % (Standard error)	**97.3%** (0.002)	**95.7%** (0.003)	**94.3%** (0.003)	**93.5%** (0.004)	**92.4%** (0.005)

Figure 4. Five-year survival, stratified by compliance with clinical practice guideline diameter thresholds



Months after repair	12	24	36	48	60
Off-guideline repairs					
Number at risk	N=5008	N=3416	N=2041	N=1111	N=554
Survivor % (Standard error)	95% (0.003)	90% (0.004)	83% (0.006)	78% (0.008)	71% (0.01)
Guideline compliant repair					
Number at risk	N=8877	N=6006	N=3755	N=2189	N=1135
Survivor % (Standard error)	91% (0.003)	83% (0.004)	76% (0.005)	68% (0.006)	61% (0.007)

Figure 5. Five-year adherence to the quality metric, stratified by compliance with clinical practice guideline diameter thresholds



Months after repair	12	24	36	48	60
off-guideline repairs	N=3414 **92%** (0.4%)	N=2321 **86%** (0.6%)	N=947 **51%** (1.0%)	N=557 **48%** (1.0%)	N=298 **43%** (1.1%)
Guideline compliant repair	N=6083 **88%** (0.4%)	N=4191 **79%** (0.5%)	N=1872 **48%** (0.7%)	N=1162 **43%** (0.7%)	N=647 **38%** (0.8%)

The quality metric is a composite outcome of freedom from open conversion after the index procedure, 5-year rupture-free survival, and adequate one-year follow-up imaging (defined as at least one CT scan documented between 6-24 months postoperatively)

Reimbursement amounts

The median Medicare reimbursement amount for non-compliant index EVAR procedures was $22,314 (IQR $5,306-27,488) and $23,520 (IQR $5,233-29,649) for guideline compliant repairs. When only including patients with 5-year follow-up (n=3,872), 28% underwent repair below the threshold (21% <5mm, 4.6% 5-10mm, 2.4% >10mm). The median Medicare payment for the index procedure was lower in the patients undergoing non-compliant repair ($24,418 vs. $26,713, P<.001). However, the total reimbursement amount for all reinterventions among patients who had at least one reintervention was similar ($23,662 vs. $24,092, P=.95). Also, the total payments during the study period for all patients undergoing non-compliant repairs represented 26% of the total payment for all repairs ($29,179,856 vs. $83,430,936 ($112,610,792)). Similarly, for reintervention costs, non-compliant repairs represented 27% of the reintervention costs ($6,555,525 vs.

$17,811,076 ($24,366,601)). Also, the number of reinterventions was similar (13% vs. 12% undergoing 1 reintervention, 1.7% vs. 2.3% undergoing 2 reinterventions, and 1.3% vs. 1.1% undergoing 3 or more reinterventions; P=.41).

Sensitivity analysis

Compared with patients undergoing guideline-compliant repairs, patients receiving non-compliant EVAR but within 5mm of CPG thresholds had lower five-year mortality (29% vs. 39%, P<.001), reintervention (15% vs. 19%, P<.001), and rupture rates (5.5% vs. 7.7%, P=.07), similar to our primary analysis.

Subgroup analysis in patients with available neck anatomy data

When assessing IFU compliance in the subgroup with available neck characteristics (variables introduced in 2014, n=5490, 29%), 2,783 (51%) were both above the CPG repair threshold and compliant with IFU, 763 (14%) were above the threshold but non-compliant with IFU, 1,734 (32%) were below the thresholds and compliant with IFU, and 210 (3.8%) were below CPG thresholds and non-compliant with IFU. Compared with patients undergoing guideline-compliant repairs, patients undergoing non-compliant repairs were more likely to adhere to IFU criteria (89% vs. 79%, P<.001). The total index procedure costs were higher for patients non-compliant with IFU both among patients above the repair threshold (109,375$ vs. 99,582$) and below the threshold (99,023$ vs. 97,924$, P<.001). Also, the percentage of patients that reached the quality metric after 2 years was similarly low across all four comparison groups (39% vs. 39% vs. 38% vs. 41%; P=.39).

Discussion

While CPGs recommend AAA repair for diameters ≥ 5.5cm in men and ≥5.0cm in women, 35% of elective EVARs in the VQI are performed in patients who have not reached these thresholds, and this rate is increasing. In our study population, patients who were selected for non-compliant repair had fewer comorbidities, more favorable anatomy, and improved rates of reintervention, rupture, and survival when compared with patients undergoing repairs compliant with current CPG diameter thresholds. However, longer term reintervention and mortality rates remain high and follow-up rates low. Therefore, elective EVARs that are non-compliant with CPG diameter thresholds fail to meet minimum quality standards in a majority of cases.

The goal of elective AAA repair is to prevent rupture and its associated significant morbidity and mortality. Contemporary rupture risk for patients with a small AAA is low and therefore the procedure-related risk has to be even less to warrant early repair.[2] Moreover, surveillance studies have demonstrated that many small AAAs do not grow and/or patients die of other causes before reaching the appropriate diameter threshold. In fact, only 27.2% of monitored small AAAs (defined as an aneurysm with a diameter between 3 and 5.5cm) end up undergoing repair.[13] It is therefore essential that patients are made aware of the risks associated with the operation, as well as those associated with the natural history of AAA disease.

In patients undergoing AAA repair, EVAR has become the dominant treatment modality. Despite the short-term advantages of EVAR, the long-term outcomes after EVAR remain a concern.[14] Clinical decision-making needs to take into account the high costs, life-long surveillance requirements, and substantial reintervention risk after EVAR. Given these challenges, appropriate application of this technology is essential. Patients undergoing repair before reaching the CPG diameter thresholds in our study had worse outcomes compared with patients undergoing EVAR for small AAA (4.1 to 5.4 cm) in the CAESAR trial, with higher long-term mortality (17% vs. 14.5%), reintervention rates (9% vs. 5.7%), and rupture rates (4.4% vs. 0%) after three years of follow up.[3] These differences are potentially partially explained by the strict patient and anatomical selection in the CAESAR trial and study setting with specific surgeons and centers performing operations. In the UK small aneurysm trial, 12-year mortality was 63.9% in the early surgery group. While patients in the UK small aneurysm trial underwent open repair between 1991 and 1995, the approximately 27% 5-year mortality rate in the UK small aneurysm trial was similar to the 29% mortality rate at 5-years in our study. Finally, EVAR remains associated with significant procedure-associated costs and previous studies showed a negative procedure-associated margin for EVAR, which is primarily driven by the high device costs.[6] However, of the total elective EVAR reimbursement, 26% was for repair that were below the recommended threshold for repair. The financial impact of these procedures is therefore significant and needs to be considered when selecting patients for repair.

Patients repaired below diameter thresholds have fewer comorbidities, which may make their outcomes look better relative to those who were treated at appropriate diameter thresholds. Also, the higher rates of prior vascular diseases and preoperative medication use in the non-compliant group could suggest that the patients were under the care of a vascular specialist. Several factors, such as fewer comorbidities or favorable anatomy, might influence repair before reaching the diameter threshold as the perioperative risk may be lower than the risk of the aneurysm rupture in these low-risk patients. Also, available skill and technology, patient preferences, and surgeon behavior can influence the decision for AAA repair. Finally, indications for repair such as saccular-shaped aneurysm or rapid growth might drive repair below the recommended diameter thresholds. However, a previous study comparing national quality registries from 11 countries across 3 continents, including the VQI, showed a large impact of healthcare systems and reimbursement on indication for surgery and suggested an association between small intact AAA repair rates and positive financial incentives.[8]

Even if there is a reasonable rationale for offering repair below CPG thresholds in some patients, appropriate high-quality care is essential. This includes adherence to recommended imaging follow-up for ongoing AAA surveillance after EVAR, in an effort to reduce risk of late rupture and allow for timely reinterventions when indicated. However, our results show that 32% of patients do not receive a one-year CT-scan, and this rate is increasing over time. When offering elective repair below the recommended diameter thresholds, early mortality, late rupture, conversion, and lack of sufficient imaging follow-up should be considered a treatment failure of EVAR. Importantly, in a majority of non-compliant repairs, these metrics were not met. Therefore, the willingness and ability of patients to adhere to strict surveillance programs needs to be taken into account prior to offering repair, and patients with risk factors affecting survival with no other indications for repair should not undergo repair below the diameter thresholds.

This study has several limitations. The VQI database does not include indication for repair, therefore we could not verify that diameter alone was the only indication for repair or if other high-risk variables drove the decision to offer repair. Although we excluded patients with urgent/symptomatic repair, as well as iliac aneurysm repair, weekend repairs, and patients with prior AAA repair, we could not assess patient anxiety, growth rate, embolization, or aneurysm morphology. Also, while the VQI includes tenderness in the definition of symptomatic patients, this might not be clear when inputting data. Therefore, not all of the repairs evaluated in this study should be considered as inappropriate and this highlights the importance of documenting the indication for surgery in registries. Secondly, the VQI only captures patients undergoing repair and therefore a control group showing natural history of AAA under imaging surveillance was not available. Also, generalizability of our results to national practice patterns might be limited as participation in the VQI is voluntary and therefore represents hospitals that have elected to participate in quality improvement. Finally, as our analyses were performed using data with Medicare linkage, only enrolled Medicare beneficiaries age ≥ 65 years old were included.

Conclusion

Compliance with SVS-endorsed AAA CPG diameter thresholds for elective EVAR is poor, and rates of non-compliance are increasing. Non-compliant repairs appear to be offered more commonly to patients with fewer comorbidities and favorable anatomy, and these repairs are associated with improved rates of reintervention, rupture, and survival when compared with procedures following the recommended thresholds. Importantly, non-compliant repairs fail to meet minimum quality standards in a majority of cases and therefore the appropriateness of many of these repairs below the diameter threshold needs to be questioned. Judicious use of EVAR and adequate follow-up when performing non-compliant repairs is imperative. These results underscore the need for further policy development to improve the overall quality and appropriateness of AAA care delivery nationally.

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Chapter 9

Late Outcomes after Endovascular and Open Repair of Large Abdominal Aortic Aneurysms

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Abstract

Objective: The risk of AAA rupture increases with increasing aneurysm diameter. However, the impact of AAA diameter on late outcomes after aneurysm repair is unclear. Therefore, we assessed the association of large AAA diameter with late outcomes in patients undergoing open and endovascular AAA repair.

Methods: We identified all patients who underwent elective open or endovascular infrarenal aneurysm repair between 2003 and 2016 in the Vascular Quality Initiative linked to Medicare claims for long-term outcomes. A large AAA diameter was defined as above 65 mm. We assessed five-year reintervention, rupture, mortality and follow-up rates. We constructed propensity scores and used inverse probability weighted Kaplan-Meier estimations and Cox proportional hazard models to identify independent associations between large AAA repair and our outcomes.

Results: Of the 21,119 aneurysm repairs identified, 15.2% were for large AAAs. There were 19,017 endovascular and 2,102 open repairs. The large AAA cohort was less likely to undergo EVAR (84.9% vs. 91%, $P<.001$), older (median age 76 vs. 75 years, $P<.001$), and less likely female (16.2% vs. 21.7%, $P<.001$). After EVAR, patients with large AAAs had lower adjusted five-year freedom from reintervention (73.9% vs. 84.6%, $P<.001$), freedom from rupture rates (88.5% vs. 93.6%, $P<.001$), survival (58.0% vs. 66.4%; $P<.001$) and freedom from loss to follow-up (77.7% vs. 83.3%; $P<.001$) compared with patients with smaller AAAs. However, after open repair, the adjusted five-year freedom from reintervention (95.8% vs. 93.3%, $P=.11$), freedom from rupture rates (97.4% vs. 97.8%, $P=.32$), survival (70.4% vs. 74.0%, $P=.13$), and loss to follow-up (60.5% vs. 62.8%, $P=.86$) were similar compared with patients with smaller AAAs. For patients with large AAA, adjusted five-year survival was lower after EVAR compared with open repair (55.3% vs. 63.7%) but not after smaller AAA repair (67.3% vs. 70.6%).

Conclusion: Five-year adjusted reintervention, ruptures, mortality, and loss to follow-up rates in patients undergoing large AAA EVAR were higher compared with smaller AAA EVAR and large AAA open repair. Therefore, in patients with large AAAs who are medically fit, open repair should be strongly considered. Furthermore, these findings highlight the necessity for rigorous long-term follow-up after EVAR.

Introduction

The Society for Vascular Surgery, in their guidelines, currently recommends elective aortic abdominal aneurysm (AAA) repair at a maximum AAA diameter of 5.5 cm in men and 5 cm in women.[1] In addition, previous studies show an increasing rupture risk and intact repair mortality risk in patients with larger aortic diameter.[2,3] However, large variations exist in repair diameter and a large proportion of patients undergo surgery above the threshold of 5 and 5.5cm.[4,5]

The perioperative benefit and improvement over time of endovascular aneurysm repair (EVAR) has led to an increasing majority of AAA repair being performed endovascularly.[6,7] However, long-term survival data showed that the perioperative benefit after EVAR persisted only up to 3 years following the index procedure, after which time survival was similar in the open and endovascular repair cohorts.[8] Also, endovascular repair has been associated with higher rupture and reintervention rates, and procedural costs.[8] Therefore, the true benefit and appropriate selection of patients for EVAR must be carefully considered, especially in specific higher risk cohorts such as patients with large aneurysm diameters.

Therefore, our aim was to investigate the association of large AAA diameter with late outcomes and compare EVAR and open repair in patients with large AAAs.

Methods

Data Source

We performed a retrospective cohort study using Vascular Quality Initiative (VQI) registry data linked with Medicare claims. Patients identified in the VQI were linked to the Medicare claims files using a previously described methodology.[9,10] This method combines the advantages of a prospectively collected vascular quality improvement registry and administrative data. The VQI has granular clinical, technical and in-hospital outcome data available which were specifically designed per procedure and by vascular surgeons. More information can be found at www.vqi.org. However, long-term data are limited. The Medicare linkage provides long-term follow-up data enabling us to study late reinterventions, ruptures, follow-up imaging, and mortality. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards for observational studies.[11] The Beth Israel Deaconess Medical Center Institutional

Review Board approved this study and waived the need for patient consent due to the retrospective and de-identified nature of the study.

Patient Cohort

We identified all patients undergoing endovascular or open repair of an infrarenal AAA between 2003 and 2016 with linked records (89% matched). We excluded patients if they presented with a symptomatic AAA (n=2,423), ruptured AAA (n=2,163) or unknown urgency status (n=102). Also, to improve comparability with the infrarenal EVARs we excluded patients undergoing open repair with a clamp location above the infrarenal level (n=1,877). To ensure that we only captured true elective repairs we further only included the first entry of a patient with multiple entries (n=30). Also we excluded a repair performed on the weekend (n=106), patients with small AAA (<50 mm) for whom the indication for repair was an iliac aneurysm (n=274) and those with a prior AAA repair noted at the time of their first VQI entry (n=649). Finally, we excluded patients with missing aortic diameter data (n=283).

Definitions and Variables

We defined large AAA as an aneurysm with a maximum AAA diameter above 65 mm as previous research showed that this was a clinically relevant threshold.[3,12] Medium AAA was defined as a diameter above the SVS recommended thresholds of 55 mm for men and 50 mm for women and below 65 mm.[1] We defined small AAAs as patients undergoing repair at a diameter below the SVS recommended thresholds. Aortic Size Index was defined as the aneurysm diameter divided by body surface area; body surface area was calculated according to the Dubois and Dubois formula (0.20247 x [height (m)$^{0.725}$ x weight (kg)$^{0.425}$]).[13–15] Age above 90 is coded as 90 years old in the VQI. Race was stratified into White, Black and Other (including Asian, American Indian or Alaskan native, Native Hawaiian, other Pacific Islander or more than 1 race). We included race in our analyses despite its limited biological significance, as we believe describing the racial differences is essential to identify potential areas for quality improvement. We used the standard weight (kg) / height^2 (m^2) formula for body mass index (BMI) and considered a BMI below 18.5 underweight and a BMI of 30 or above obese. The most recent preoperative creatinine value was used to estimate the glomerular filtration rate (eGFR) for each patient using the Chronic Kidney Disease Epidemiology Collaboration equation.[16] Chronic kidney disease (CKD) was defined as a preoperative eGFR<30 or currently being on dialysis. Congestive heart failure (CHF) includes asymptomatic and mild, moderate, and severe CHF presentations. Insulin dependent diabetes, any preoperative history of hypertension, and any severity of chronic obstructive pulmonary disease (COPD) were included. Current smoker was defined as any patient smoking in the month prior to surgery and family history was defined as a first-degree relative with an AAA diagnosis. Preoperative medication use was included if the medication was used within 36 hours of procedure. Neck characteristics were only available for patients undergoing EVAR after 2014 and a hostile neck was defined as the presence of at least one of the following and based on common device IFU cutoffs: neck angulation >60°, neck length <15 mm, or neck diameter >30 mm. Our prespecified primary outcomes were five-year mortality, reinterventions, loss to imaging follow-up, and ruptures.

Statistical Analysis

We univariately compared baseline and operative characteristics between patients with larger and smaller AAA diameter. Categorical variables were presented as counts and percentages and continuous variables as median and interquartile ranges. We calculated propensity scores using separate logistic regression models for the smaller vs. large AAA diameter comparison, stratified by EVAR and open repair. And similarly, for the EVAR vs. open repair comparison, stratified by small and large AAA diameter. Our logistic model constrained the following a priori selected covariates: age, sex, race (white, black, other), underweight, obese, smoking status, renal disease, insulin-dependent diabetes mellitus, hypertension, CHF, COPD, family history, coronary artery disease, statin use, aspirin use, and p2Y12 use. The propensity scores were tested for adequacy of overlap by plotting the distribution of propensity scores between the study groups. After weighting, there was minimal imbalance with all standardized differences ≤10%. We used these propensity scores to create inverse probability weights and reweighted the data to ensure that the distribution of confounders is the same between our comparison groups. By using this method, rather than propensity matching, we could adjust for all relevant confounders and retain the entire sample size, which makes the study more generalizable. We used inverse probability weighted

Kaplan-Meier estimations and Cox proportional hazard models to compare five-year reinterventions, ruptures, follow-up and survival. Standard errors were below 0.1 at five-years for all outcomes. For five-year reintervention, rupture and follow-up assessment, patients who died were censored at the date of death and patients who left Medicare fee-for-service for an alternative program were censored on the date of the switch. As neck anatomy data were only introduced in 2014 in the EVAR database, we performed a post-hoc sub-analysis in patients with available neck anatomy data comparing large AAA EVAR in the cohort without hostile neck characteristics with smaller AAA EVAR without hostile neck characteristics and with large AAA open repair. We also compared patients undergoing large AAA EVAR with and without hostile neck characteristics. Previous studies showed that female patients generally have a smaller body habitus and therefore a specific aneurysm diameter might represent a greater relative increase in aortic diameter in female patients compared with males.[14,15] Therefore we analyzed the mean ASI of male patients at a diameter of 65mm and used this threshold to define large AAA in female patients. A post-hoc subgroup analysis comparing large and smaller AAA repair using this ASI threshold was performed in female patients. Also, we performed a post-hoc sensitivity analysis in patients undergoing repair after 2010 and comparing patients with a large AAA to patients with a diameter which was below 65 mm but above the SVS guideline threshold of 55 mm for male and 50 mm for female patients.[1]

In order to evaluate the predicted open perioperative mortality we used the VQI risk score to evaluate patients with large aneurysms undergoing EVAR.[17] This risk score includes open aortic surgery, age above 75 years, female sex, history of myocardial disease, history of cerebrovascular disease, history of COPD, creatinine, and AAA diameter in its model. With this analysis we aim to risk stratify these patients to evaluate if the larger AAA diameter pushes the risk score to exceed the accepted open repair perioperative mortality of 5%.[1]

All variables had <2% missing data. All statistical analyses were performed using Stata 16 software (StataCorp LLC, College Station, Tex).

Results

Patient cohort

Of the 21,119 patients identified,19,017 underwent EVAR (2,729 (14.4%) large AAAs) and 2,102 underwent open repair (484 (23%) large AAAs). Overall, 15.2% underwent repair for a large AAA. The proportion of repairs for large AAAs compared with smaller AAAs decreased over time with 22.5% large AAA repairs in 2003 and 13.5% large AAA repairs in 2016. Also, EVAR usage for large AAA repairs increased over time, with 34.9% endovascular repairs in 2003 and 90.6% endovascular repairs in 2016.

Baseline and anatomic characteristics

The large AAA cohort compared with patients with smaller aneurysms was older (median age 76 vs. 75 years, P<.001), less likely to be female (16.2% vs. 21.7%, P<.001), to have a family history (8.2% vs. 9.4%, P=.030), to have hypertension (82.6% vs. 84.1%; P=.037) or to have a history of CAD (41.4% vs. 43.8%; P=.011). Also, patients undergoing large AAA repair were more likely to be underweight (3% vs. 2.4%, P=.027), have renal disease (4.6% vs. 3.4%, P<.001) and have CHF (13.7% vs. 11.4%, P<.001). Finally, patients undergoing large AAA repair were less likely to use preoperative statin (65.3% vs. 71.7%, P<.001), aspirin (63.0% vs. 67.5%, P<.001), and P2Y12 (9.3% vs. 12.1%, P<.001) (Table 1).

Table 1: Baseline Characteristics

	AAA <65mm N=17,906		AAA≥65mm N=3,213		P-value
EVAR	16,289	91%	2729	84.9%	<.001
Female	3,889	21.7%	522	16.2%	<.001
Age	75	70, 80	76	70, 82	<.001
Race					.16
White	16,645	94.7%	2,965	94.6%	
Black	714	4.1%	118	3.8%	
Other	218	1.2%	51	1.6%	
Underweight	419	2.4%	96	3.0%	.027
Obese	5,261	29.5%	902	28.3%	.15
Current Smoker	5,119	28.6%	931	29%	.63
Ever Smoked	15,456	86.4%	2,766	86.2%	.82
EGFR ≤ 30	599	3.4%	146	4.6%	<.001
CHF	2,040	11.4%	441	13.7%	<.001

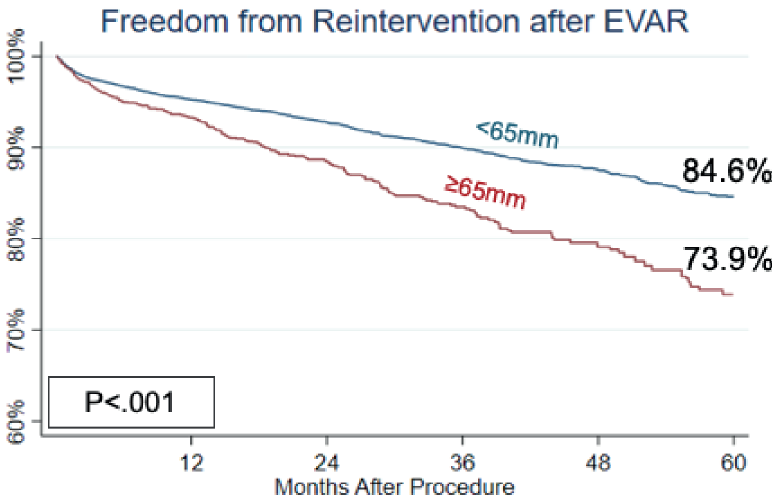
	AAA <65mm N=17,906		AAA≥65mm N=3,213		P-value
Family History of AAA	1,659	9.4%	258	8.2%	.030
Hypertension	15,046	84.1%	2,651	82.6%	.037
IDDM	631	3.5%	117	3.6%	.74
COPD	6,017	33.6%	1,111	34.6%	.29
CAD	7,839	43.8	1,328	41.4%	.011
Preoperative Statin use	12,838	71.7%	2,097	65.3%	<.001
Preoperative Aspirin use	12,075	67.5%	2,020	63%	<.001
Preoperative P2Y12 inhibitor use	2,156	12.1%	300	9.3%	<.001

AAA: Abdominal Aortic Aneurysm; EVAR: Endovascular Aneurysm Repair; Other race: Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific Islander or more than 1 race; Underweight: body mass index below 18.5; Obese: body mass index of 30 or above; EGFR: Estimated Glomerular Filtration Rate; CHF: Congestive Heart Failure; IDDM: Insulin Dependent Diabetes Mellitus; COPD: chronic obstructive pulmonary disease; CAD: Coronary Artery Disease. Categorical variables are presented as counts and percentages and continuous variables as median and interquartile ranges.

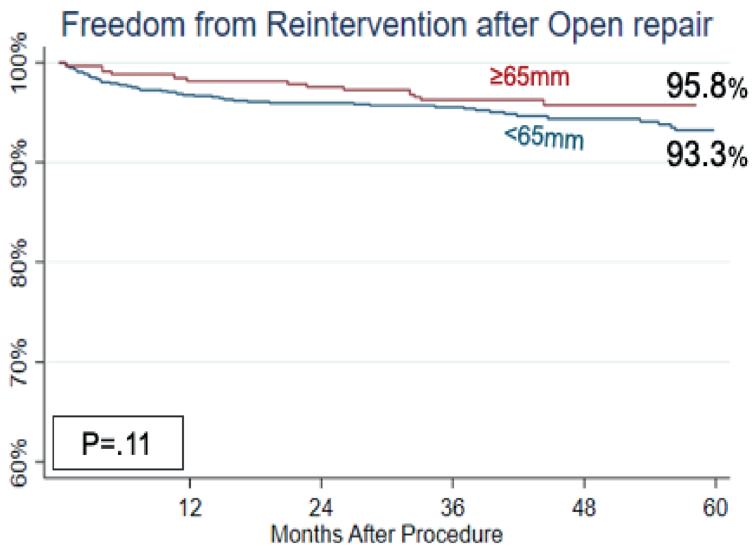
Large vs. Small EVAR and open repair

Adjusted five-year freedom from reintervention after EVAR was lower after large AAA EVAR with 73.9% compared with 84.6% in smaller AAA EVAR (HR: 1.70, 95%CI: 1.46-1.98, P<.001; Figure 1A). However, after open repair reintervention rates were similar between larger and smaller aneurysms (95.8% vs. 93.3%, HR: 0.63, 95%CI: 0.32-1.21, P=0.17; Figure 1B). Adjusted freedom from late rupture after EVAR was lower after large AAA EVAR with 88.5% vs. 93.6% after smaller AAA EVAR (HR: 1.53, 95%CI: 1.22-1.93, P<.001; Figure 2A). However, after open repair, freedom from late rupture was similar between aneurysm sizes (97.5% vs. 97.8%, HR:1.52, 95%CI: 0.63-3.64, P=.35; Figure 2B). Also, adjusted five-year survival after EVAR was lower after large AAA repair compared with smaller AAA EVAR with 58.0% vs. 66.4% (HR: 1.52, 95%CI: 1.40-1.67, P<.001; Figure 3A) while after open repair, there was no significant difference in five-year survival between large and smaller AAA repair (70.4% vs. 74.1%, HR: 1.22, 95%CI: 0.95-1.56, P=.12, Figure 3B). After EVAR, patients with a large AAA repair had lower adjusted freedom from loss to imaging follow-up (77.7% vs. 83.3%; P<.001) and after open repair there was no significant difference in loss to imaging follow-up (60.5% vs. 62.8%, P=.86).

Figure 1. Adjusted Freedom from Reintervention after EVAR (A) and after open repair (B)



Inverse Probability Weighted number at risk					
<65mm	N=8905	N=6015	N=3766	N=2194	N=1122
≥65mm	N=7891	N=5104	N=2954	N=1681	N=794



Inverse Probability Weighted number at risk					
<65mm	N=1180	N=936	N=721	N=548	N=422
≥65mm	N=1141	N=907	N=709	N=528	N=423

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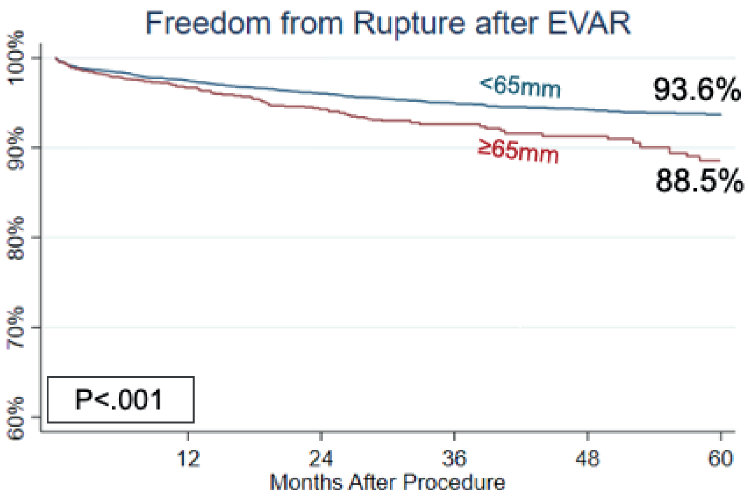
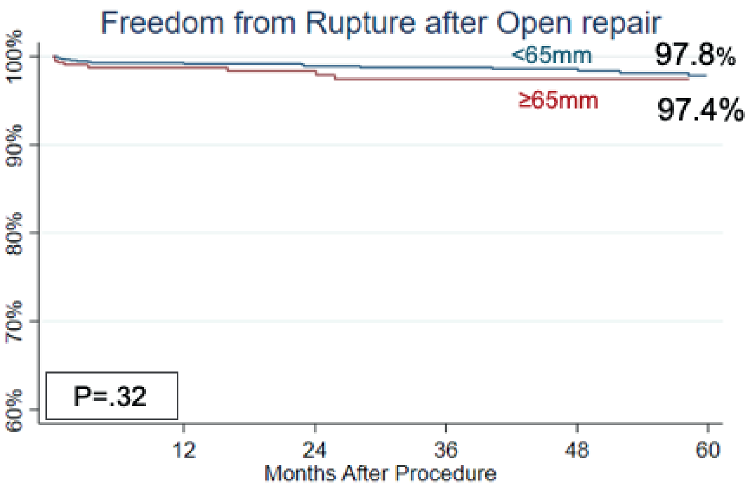
Figure 2. Adjusted Freedom from Rupture after EVAR(A) and open repair (B)

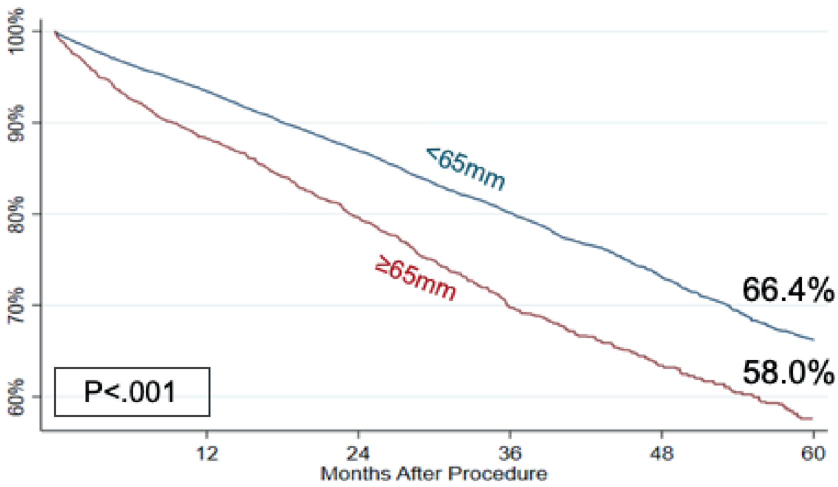


Inverse Probability Weighted number at risk					
<65mm	N=9056	N=6213	N=3945	N=2338	N=1208
≥65mm	N=8152	N=5485	N=3337	N=1979	N=945

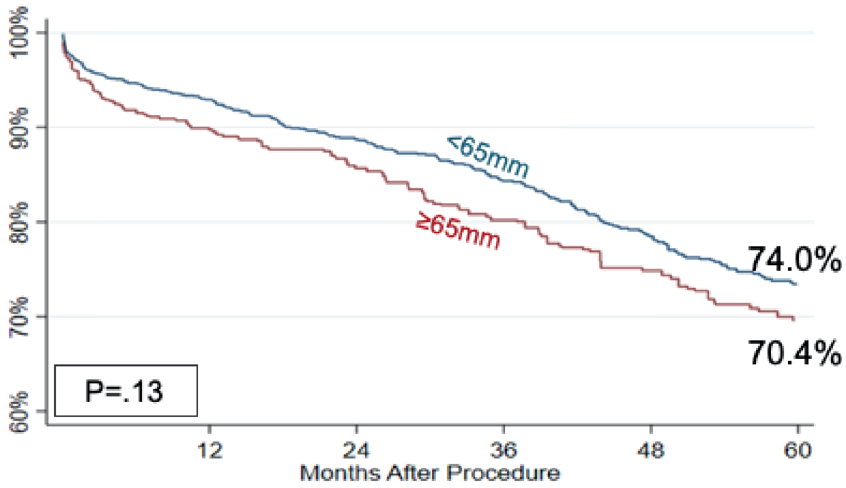


Inverse Probability Weighted number at risk					
<65mm	N=1202	N=955	N=741	N=571	N=438
≥65mm	N=1149	N=914	N=715	N=541	N=429

Figure 3. Adjusted Survival after EVAR (A) and open repair (B)



Inverse Probability Weighted number at risk					
<65mm	N=13246	N=9014	N=5553	N=3135	N=1575
≥65mm	N=12501	N=8246	N=4851	N=2752	N=1368



Inverse Probability Weighted number at risk					
<65mm	N=1584	N=1235	N=924	N=682	N=518
≥65mm	N=1517	N=1159	N=867	N=643	N=496

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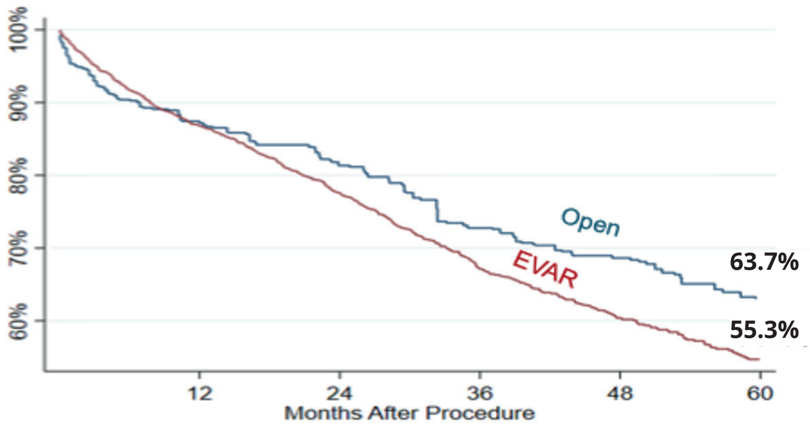
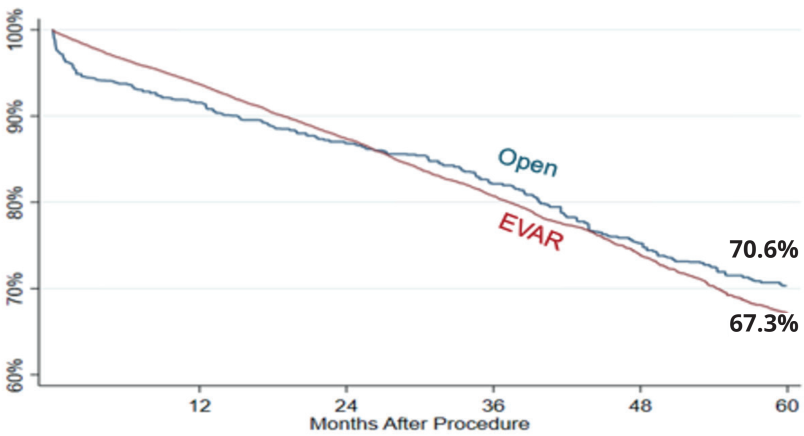
EVAR vs. Open Large and smaller repair

Patients undergoing large AAA repair had a perioperative adjusted survival benefit after EVAR that lasts less than a year and after five years adjusted survival is lower after EVAR with 55.3% compared with 63.7% after open repair (Figure 4A). Also, freedom from reintervention was lower after EVAR compared with open repair (74.0% vs. 93.6%, HR: 4.54, 95%CI: 2.20-9.37, $P<.001$) and freedom from rupture was similar (89.2% vs. 96.5%, HR: 2.04, 95%CI: 0.79-5.26, $P=.14$). Patients undergoing smaller aneurysm repair with EVAR had a longer survival benefit compared with open repair and adjusted five-year survival was similar (67.3% vs. 70.6%; Figure 4B). Freedom from reintervention was lower after EVAR compared with open repair (84.6% vs. 93.7%, HR: 2.30, 95%CI: 1.72-3.09, $P<.001$) and freedom from rupture (93.7% vs. 98.2%, HR: 3.95, 95%CI: 2.32-6.73, $P<.001$).

Figure 4. Adjusted Survival after large AAA repair (A) and after small/medium AAA repair (B)



Inverse Probability Weighted number at risk					
Open repair	N=2112	N=1506	N=958	N=629	N=362
EVAR	N=2134	N=1464	N=920	N=566	N=337

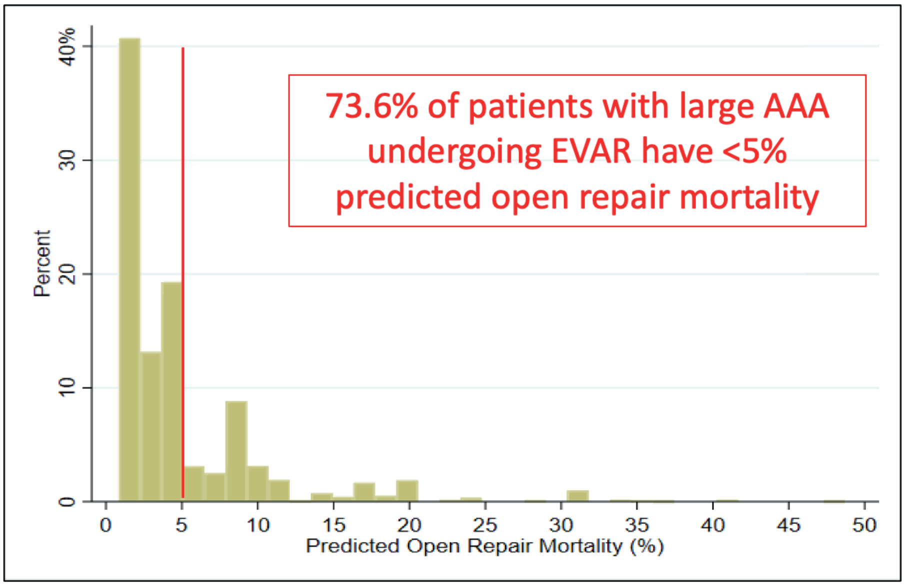


Inverse Probability Weighted number at risk					
Open repair	N=11817	N=8153	N=5162	N=3024	N=1673
EVAR	N=12593	N=8641	N=5416	N=3159	N=1693

Predicted mortality risk

When applying the VSGNE risk score to calculate the predicted open mortality for large AAA patients that are undergoing EVAR, 73.6% had a predicted open repair mortality below 5% (median 3.2%, IQR 1.8 - 6.3%) (Figure 5).

Figure 5. Predicted open mortality for patients undergoing large AAA EVAR using the VSGNE risk score



Hostile neck anatomy

A sub-analysis in patients with available neck anatomy variables (EVAR patients from December 2014 onward; N=4,544) showed that patients with large AAAs undergoing EVAR were more likely to have hostile neck characteristics (47.4% vs. 35.0%; P=.007). Also, in the subgroup of patients with no hostile neck characteristics undergoing EVAR, large AAA diameter was associated with lower two-year adjusted survival rates (84.6% vs. 88.9%, P=.007) compared with patients with smaller AAAs. In this same subgroup, although two-year freedom from reintervention and rupture was lower in those with a large AAA diameter compared with patients with smaller AAAs, this was not significant (90.3% vs. 94.6%, P=.17; 94.0% vs. 96.7%, P=.20). Also, patients with a large AAA and without hostile neck anatomy undergoing EVAR compared with patients undergoing large AAA open repair had lower two-year freedom from reinterventions (89.9% vs. 97.4%, HR: 3.80, 95%CI: 1.01-14.3, P=.049) and similar freedom from rupture rate (93.1% vs. 96.6%, HR: 1.38, 95%CI: .29-6.63, P=.68). The survival benefit of EVAR lasted less than a year and at two-years, survival was similar (83.7% vs 85.9%, HR: 1.04, 95%CI: .51– 2.14, P=.91). After smaller AAA repair, patients without hostile neck characteristics undergoing EVAR and patients undergoing open repair has similar freedom from two-year reinterventions (94.5% vs. 96.2%, HR: 1.53, 95%CI: .80-2.93, P=.20), and two-year rupture (96.8% vs. 97.5%, HR: 2.32, 95%CI: .99-5.40, P=.052). In patients undergoing smaller AAA repair, patients without hostile neck undergoing EVAR had higher two-year survival rates compared with patients undergoing open repair (89.6% vs. 87.8%, HR:.65, 95%CI: .45-.94, P=.021).

Finally, no significant difference was found when comparing patients with a large AAA with and without hostile neck characteristics (n=567) for two-year freedom from reinterventions (92.8% vs. 90.7%, HR: .76, 95%CI: .28-2.06, P=.59), freedom from rupture (94.0% vs. 92.9%, HR:1.20, 95%CI: .41-3.50, P=.74) and survival (84.3% vs. 83.2%, HR:1.13, 95%CI: .67-1.90, P=.64).

Female sex

In male patients, the mean ASI of patients with a AAA diameter of 65mm was 3.25cm/m^2. When using 3.25cm/m2 as a threshold for large AAA in female patients, female patients undergoing EVAR (n=7,188) for large AAAs compared with smaller AAAs were less likely to have adjusted five-year freedom from reintervention (75.5% vs. 86.3%, HR:1.66, 95%CI:1.23-2.23, P<.001), while in the subgroup of female patients undergoing open repair (n=617), patients undergoing large AAA repair had similar adjusted five-year freedom from reintervention (95.6% vs. 93.6%, HR: .58, 95%CI: .20 – 1.74, P=.33) compared with patients undergoing smaller AAA repair. Also, female patients undergoing large AAA EVAR were less likely to have adjusted five-year freedom from rupture (87.4% vs. 94.4%, HR:1.78; 95%CI: 1.20-2.66; P=.005) compared with smaller AAA EVAR, while after open repair adjusted five-year freedom from rupture (97.0% vs. 95.0%, HR:.67, 95%CI: .19-2.36, P=.53) was similar in female patients undergoing large AAA open repair compared with smaller AAA open repair. Finally, after EVAR, female patients undergoing large AAA repair were less likely to have adjusted five-year survival (53.1% vs. 64.3%, HR: 1.49, 95%CI

1.26-1.77, P<.001) compared with patients undergoing smaller AAA repair. Also, after open repair, adjusted five-year survival was lower patients undergoing large AAA compared with smaller AAA repair (63.7% vs. 73.2%, HR:1.55, 95%CI:1.02-2.35, P=.040).

Sensitivity analysis

A sensitivity analysis comparing patients with a large AAA to patients with a diameter which was below 65 mm but above the SVS guideline threshold gave the same results as our primary analysis. Large AAA repair compared with medium AAA repair showed significantly lower freedom from reintervention (73.6% vs. 83.3%, P<.001), rupture (88.1% vs. 93.2%, P=.002), survival (54.9% vs. 62.5%, P<.001) and lower adherence to imaging follow-up (77.5% vs. 83.1%, P<.001) in EVAR patients but not in patients undergoing open repair. (Reintervention: 95.9% vs. 94.2%, P=42; Rupture: 97.4% vs. 97.6%, P=.59; Survival: 68.4% vs. 71.5%, P=.34; Imaging follow-up: 58.2% vs. 62.9%, P=.93).

Also, in a subgroup of patients undergoing repair after 2010, patients with large AAAs had a perioperative adjusted survival benefit after EVAR compared with open repair that lasts less than a year and after five years adjusted survival was lower after EVAR with 55.2% compared with 61.0% after open repair. Patients undergoing smaller aneurysm repair with EVAR had a longer survival benefit compared with open repair and adjusted five-year survival was similar (66.8% vs. 71.3%).

Discussion

Patients with large AAA diameter (≥65 mm) compared with smaller AAA (<65 mm) undergoing EVAR had higher mortality, reintervention, rupture and loss to imaging follow-up rates while after open repair, these outcomes were similar. Also, EVAR in large AAA repair is associated with higher adjusted five-year mortality in patients compared with open repair which is not observed in patients with smaller aneurysms.

Previous research shows that above 55 mm the untreated aneurysm related rupture risk outweighs the operative risk in the majority of patients.[1] However, in our study, 15.2% of elective repairs were performed in patients with a AAA which is over 65 mm. While it is possible that patients with identified AAA have surgery deferred until they reach larger diameters because of high comorbidity rates, we believe this is unlikely in practice. Our analysis showing low predicted open operative mortality in patients undergoing large AAA repair supports this assumption. It is more likely that patients remain undiagnosed until initial presentation with an incidental large AAA.

It is also possible that delays in care delivery result in repair at a larger diameter, emphasizing the need for screening and early vascular referral. The United States implemented a Medicare screening program in 2007 for male patients between 65 and 75 years old with a smoking history or patients with a family history of AAA.[18] The decrease over time in large AAA repair could reflect the effect of screening and improved access to healthcare. Although, patients with large AAA repair were less likely to have a family history of AAA, smoking rates were similar, and patients were more likely male. Therefore, expansion of screening guidelines or separate strategies to improve access to vascular care are warranted. Also, indicators for optimal medical management with statin, and aspirin or P2Y12 inhibitors in patients undergoing large AAA repair were lower and could therefore suggest that this group had less exposure to guideline-based medical care before detection or were recently diagnosed. This potential diminished access to preoperative care vascular care in patients with large AAAs could also influence the adherence to follow-up as we found lower imaging follow-up rates in patients with large AAAs undergoing EVAR. The high reintervention rates and rupture rates combined with lower imaging follow-up rates and potential diminished access to vascular care in patients with large AAAs highlight the need for improved follow-up especially in this high-risk patient group.

The worse adjusted outcomes in patients undergoing large AAA EVAR compared with smaller AAA EVAR and large AAA open repair raise serious concerns regarding the durability of endovascular repair in large AAAs. Large diameter was found to be associated with more complex anatomy which would likely predispose to a less advantageous seal, limiting the suitability of EVAR. As neck characteristic variables were only introduced after 2014, our sub-analyses regarding hostile neck characteristics had limited follow-up and a smaller study population. However, in the subgroup analyses, patients with no hostile neck characteristics undergoing EVAR for a large AAA compared with both smaller AAA EVAR and large AAA open repair showed similar effect sizes and directions compared with the primary analysis. Therefore, we expect that our conclusions will remain applicable in patients without hostile neck characteristics. The mechanisms causing worse outcomes in patients with a large AAA remain unclear and warrant further exploration but are likely to include factors not associated with neck anatomy. Furthermore, when considering the value of EVAR, the higher procedural costs and lifelong surveillance requirement need to be taken into account.[19,20]

Especially in patients with an acceptable operative risk and suboptimal access to vascular care. The SVS suggests that elective open repair for AAA be performed at centers with a documented perioperative mortality of 5% or less.[1] Our application of a validated predictive model shows that a majority of all patients currently undergoing large AAA EVAR have an acceptable open repair operative risk. This would indicate that patients who undergo EVAR because they are unfit for open surgery are likely a minority of the patients with a large AAA and shows the room for quality improvement in optimal treatment selection in this cohort.

When interpreting the results of this study, the potential selection bias of the VQI and Medicare data has to be considered. Hospitals elect to participate in the VQI and therefore are likely to have a dedicated QI focus.[21] Furthermore, Medicare only includes individuals who are ≥65 years of age and select individuals aged <65 years. Also, we excluded patients undergoing symptomatic or rupture repair. Therefore, generalizability to younger patient populations or patients undergoing non-elective repair might not be warranted. Finally, aneurysm neck characteristics were not available in the open repair database and were only available after 2014 in the EVAR database. Therefore, when longer follow-up will be available, further study of the long-term impact of hostile neck characteristics is warranted.

Conclusion

In conclusion, large AAA repair is associated with higher adjusted five-year mortality reintervention and rupture rates after EVAR, but not after open repair. Despite the higher adjusted five-year mortality in patients with large AAAs undergoing EVAR compared with open repair, an increasing majority of patients with large AAAs are undergoing EVAR. Therefore, in patients with large AAAs who are medically fit, open repair should be strongly considered even in patients with anatomy suitable for EVAR. Furthermore, the high reintervention rates and late ruptures highlight the necessity for rigorous long-term follow-up after EVAR.

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Chapter 10

The Association between Device Instructions for Use Adherence and Outcomes after Elective Endovascular Aortic Abdominal Aneurysm Repair

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Abstract

Objective: Aortic neck anatomy has a significant impact on the complexity of endovascular aortic aneurysm repair (EVAR), with concern that neck characteristics outside of instructions for use (IFU) may result in worse outcomes. Therefore, this study determined the impact of neck characteristics outside of IFU on perioperative and one-year outcomes and mid-term survival after EVAR.

Methods: We identified all patients undergoing elective infrarenal EVAR from December 2014 to May 2020 in the Vascular Quality Initiative database. Neck characteristics outside of IFU were determined based the specific device IFU neck characteristics (Neck diameter, length, and angulation). Patients without one-year follow-up were excluded for the 1-year outcomes analyses (n=6,138 (40%)). We used multivariable adjusted logistic regression and Cox proportional hazard models to identify the independent associations between neck characteristics outside of IFU and our outcomes.

Results: Of the 15,448 patients identified, 22.1% had neck characteristics outside of IFU, including 6.6% with a infrarenal angle, 6.8% with a neck length, 10.4% with a neck diameter, and 1.1% with a suprarenal angulation outside of IFU. Of these, 2.4% had more than one neck characteristic outside of IFU. Patients with neck characteristics outside of IFU were more often female (27.9% vs. 15.0%, $P<.001$) and were older (median age 75 vs. 73, $P<.001$). EVAR patients with neck characteristics outside of IFU had higher rates of type Ia endoleaks at completion (4.8% vs. 2.5%, $P<.001$), perioperative mortality (1.2% vs. 0.6%, $P<.001$), one-year sac expansion (7.1% vs. 5.3%, P=.017), and one-year reinterventions (4.4% vs. 3.2%, P=.03). In multivariable adjusted analyses, neck characteristics outside of IFU were independently associated with type Ia completion endoleaks (OR 1.6, [1.3–2.0], $P<.001$), perioperative mortality (OR 1.8; [1.2–2.7]; P=.005), one-year sac expansion (OR 1.4; [1.0–1.8]; P=.025) and one-year reinterventions (OR 1.4; [1.0–1.9]; P=.039). Unadjusted mid-term survival was lower for patients with neck characteristics outside of IFU than for patients without (5-year survival 84.0% vs. 86.7%, log-rank<.001). However, after adjustment, survival was similar for patients with neck characteristics outside of IFU to those within (HR: 1.1; [1.0-1.3]; P=.22).

Conclusion: Neck characteristics outside of IFU are independently associated with completion type Ia endoleaks, perioperative mortality, one-year sac expansion and

one-year reinterventions among patients undergoing elective EVAR. These results indicate that continued effort is needed to improve the proximal seal in patients with neck characteristics outside of IFU undergoing EVAR. Also, in patients with severe hostile neck characteristics, alternative approaches such as open repair, use of a fenestrated or branched device, or endoanchors should be considered.

Introduction

Since its first description in 1991,[1] endovascular aortic aneurysm repair (EVAR) has become the dominant repair technique for abdominal aortic aneurysms (AAAs). Subsequently, perioperative mortality and complication rates have greatly decreased.[2,3] Attaining adequate proximal seal is essential for the technical success of EVAR. However, EVAR is frequently performed in patients who do not meet the device-specific instructions for use (IFU), commonly due to excessive neck angulation, short length, or large diameter.[4–6] Also, contradicting results have been reported as to the impact of these anatomic criteria on outcomes.[6–9]

Neck anatomy outside of IFU, characterized mainly by shorter, more angulated necks with larger diameters, increases the complexity of EVAR and presents challenges to achieving proximal seal. Type Ia endoleaks at the completion of the index procedures occur when the seal at the proximal attachment site is incomplete and is considered a technical failure according the Society for Vascular Surgery reporting standards.[10–12] Consequently, patients with neck characteristics outside of IFU potentially have an increased risk of type Ia endoleaks which could lead to reinterventions, device migration, and aneurysm rupture.[4] Also, sac expansion, regardless of the presence or absence of endoleak is associated with late rupture and mortality.[13,14]

Therefore, the aim of this study was to examine the impact of proximal neck characteristics outside of IFU on outcomes after EVAR in terms of type Ia endoleaks at completion, reinterventions, sac behavior, and survival.

Methods

Patient Cohort

We identified all patients undergoing elective EVAR for infrarenal AAA from December 2014 to May 2020 in the Vascular Quality Initiative (VQI) registry. The VQI registry is a quality improvement initiative that prospectively collects clinical data from, at the time of this study, 290 centers in 19 regions. The over 350 collected variables include patient demographics, comorbid conditions, anatomical and operative characteristics, perioperative complications, follow-up data and long-term. More information about the VQI can be found at https://www.vqi.org/. The VQI registry includes data since 2003, however, as neck anatomy variables were introduced in December 2014 we used this date as the start date of our study. We excluded non-elective procedures (n=5,078) and patients without neck characteristic IFU data (n=857). As a sensitivity analysis, we used multiple imputation for missing neck characteristic IFU variables and analyzed the associations with our primary outcome. Long-term mortality is captured in the VQI through linkage with the Social Security Death Index and follow-up data including the 1-year outcomes described in this manuscript are captured in the VQI long-term follow-up module. As this long-term module only captures data on a subset of the patients, patients without one-year follow-up were excluded for the 1-year outcomes analyses (n=6,138 (40%)). This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards for observational studies.[15] The Columbia University Institutional Review Board approved this study and waived the need for patient consent because of the retrospective nature and minimal risk to the participants.

Definitions and study end points

Neck characteristics outside of IFU were defined using the device specific IFU criteria. In a fashion blinded to the investigators, the VQI provided a variable indicating whether each neck characteristic was inside or outside the IFU, without revealing the device. In the VQI, aortic neck length was measured from lowest renal artery to where aortic neck diameter had expanded by 10% and ranged from 1mm to 60mm. Aortic neck diameter was determined as the outer aortic wall diameter at the largest portion of the seal zone planned for implantation and ranged from 10mm to 40mm. Neck angulation is defined by VQI as angulation <45°, 45-60°, 61-75°, 76-90°, and >90°. This is reported for both the suprarenal angle which was defined as the maximum angle between the axis of the suprarenal aorta and the aneurysm neck; and the infrarenal angle which was defined as the maximum angle between the axis of the aneurysm neck and the proximal portion of the aneurysm sac. Only 20% of endografts have an IFU requirement for suprarenal angulation but 75% have a requirement for infrarenal angulation. We used the standard weight (kg) / height^2 (m^2) formula for body mass index (BMI) and considered a BMI below 18.5 underweight and a BMI of 30 or above obese. A single preoperative creatinine value was used to estimate the glomerular filtration rate (eGFR) for each patients using the Chronic Kidney Disease Epidemiology Collaboration equation.[16]

An eGFR < 60 mL/min/1.73 m^2 or current dialysis were considered as decreased renal function.

Our outcomes included the presence of type Ia endoleaks at completion of the index procedure, perioperative mortality (within 30 days or within the index hospitalization), in-hospital and one-year reinterventions, one-year presence of type Ia endoleak and sac expansion, and four-year survival. Specific in-hospital reinterventions included reintervention for any endoleak, for type Ia endoleak, for graft migration, and for rupture. One-year sac expansion was defined as an increase of more than 5mm between preoperative aortic diameter and aortic diameter measured at a scan between 6 and 18 months postoperatively, as not all patients received follow-up at exactly one-year. One-year endoleak and reintervention rates were included if they occurred within 18 months postoperatively to allow a grace period for the 1-year follow-up appointment. We included any one-year reintervention, reintervention for any endoleak, graft migration, sac growth and late rupture.

Statistical Analysis

We present categorical variables as counts and percentages, normally distributes continuous variables as mean and standard deviation and non-normally distributed continuous variables as median and interquartile range (IQR). We compared patient characteristics and outcomes between patients with and without any neck characteristics outside of IFU using Fisher exact and Pearson's χ^2 tests for categorical variables and the Wilcoxon rank sum test for continuous variables, where appropriate. Kaplan-Meier survival estimates were stratified by IFU status and compared using log-rank tests. We used multivariable adjusted logistic and cox proportional hazard regression modeling to assess the independent association between neck characteristics outside of IFU and the outcomes. We controlled the models for covariates selected a priori including age, sex, race, underweight, obesity, current smoking status, insulin dependent diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, decreased renal function, prior AAA repair, coronary artery disease, cerebrovascular disease, familial history of AAA, aspirin use, statin use, betablocker use, and AAA diameter. All covariates had less than 1% missing data, except the race variable (3.7%). As missing race data was equally distributed between patients with and without neck characteristics outside of IFU and to maintain maximal statistical power, we created a dummy variable to account for the missing race data in our models. As secondary analyses, we investigated the association of the individual characteristics with the outcomes compared to patients with no neck characteristics outside of IFU. Statistical analyses were performed using Stata 15 software (StataCorp LLC, College Station, Tex).

Results

Patient Characteristics

We identified 15,448 patients who underwent elective infrarenal EVAR, of which 3,420 had neck characteristics outside of IFU (22.1%). Median neck length was 24mm (IQR: 18-31) and 6.8% of the patients had a neck length outside of IFU. Median neck diameter was 23.5mm (IQR: 21-26) and 10.4% had a neck diameter outside of IFU (3.4% were larger than the IFU and 7% were lower than the IFU). For neck angulation, 6.6% of the patients had a infrarenal angle outside of IFU and 1.1% had a suprarenal angle outside of IFU. Patients with neck characteristics outside of IFU were older (median age 75 [IQR: 69-81] vs. 73 [68-79], P<.001), were more likely female (27.9% vs. 15.0%, P<.001), non-White (8.3% vs. 5.5%, P<.001) and underweight (3.1% vs. 2.1%, P<.001) and less likely to be obese (27.9% vs. 34.4%, P<.001). They were also more likely to have chronic obstructive pulmonary disease (COPD) (35.5% vs. 33.1%, P=.009) and prior AAA repair (3.0% vs. 1.8%, P<.001). Finally, patients with neck characteristics outside of IFU had larger maximum aneurysm diameter. However, the absolute difference was small. (56.7 mm [SD 11.4] vs. 55.7 mm [SD 9.7], P<.001) (Table 1).

Table 1. Baseline Characteristics, stratified by the presence of neck characteristics outside of

	Outside IFU N=3,420		Within IFU N= 12,028		P-value
Age	75	69, 81	73	68, 79	<0.001
Female Gender	955	27.9%	1806	15.0%	<0.001
Race					<0.001
White	3023	91.7%	10925	94.5%	
Black or African American	190	5.8%	461	4.0%	
Other Race	84	2.5%	171	1.5%	
Unknown Race	123	3.6%	471	3.9%	
Underweight	107	3.1%	255	2.1%	<0.001
Obese	951	27.9%	4118	34.4%	<0.001
Current smoker	1074	31.4%	3616	30.1%	0.13
CHF	134	3.9%	456	3.8%	0.73
IDDM	439	12.8%	1489	12.4%	0.48
COPD	1213	35.5%	3979	33.1%	0.009
Hypertension	2827	82.9%	9897	82.3%	0.47
eGFR<30 / On Dialysis	138	4.0%	433	3.6%	0.24
Prior Aortic Aneurysm Repair	103	3.0%	217	1.8%	<0.001
Prior CAD	1360	39.8%	4989	41.5%	0.071
Prior CVD	370	10.8%	1207	10.0%	0.18
Family History of AAA	277	8.1%	1085	9.0%	0.092
Preoperative ASA/Aspirin use	2236	65.4%	8013	66.6%	0.17
Preoperative Statin use	2465	72.1%	8737	72.7%	0.50
Preoperative Beta Blocker use	1791	52.4%	6267	52.1%	0.79
Percutaneous access	2546	74.6%	8901	74.1%	0.62
Concomitant Iliac Aneurysm	897	26.4%	3075	25.6%	0.35
Maximum AAA Diameter	55	51,60.2	55	51, 59	<0.001

IFU: Instructions for use; Age (years); IDDM: Insulin dependent diabetes mellitus; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; CAD: Coronary artery disease; CVD: Cerebrovascular disease; AAA: abdominal aortic aneurysm; ASA: Acetylsalicylic Acid; Maximum AAA Diameter (in millimeter)
Values are median (inter quartile range) or total events (percentages)

Outcomes

The rate of type Ia endoleak at completion was higher in patients with neck characteristics outside of IFU (4.8% vs. 2.5%, P<.001). Also, patients with neck characteristics outside of IFU had higher perioperative mortality (1.2% vs. 0.6%, P<.001) compared with patients with no neck characteristic outside of IFU while rates of postoperative stroke (0.2% vs. 0.1%, P=.10), myocardial infarction (0.6% vs. 0.6%, P=.81), and chronic heart failure (0.6% vs. 0.4%, P=.23) were similar. Overall reintervention rates during the index hospitalization were similar between patients with and without neck characteristics outside of IFU (0.4% vs. 0.2%, P=.057). However, neck characteristics outside of IFU were associated with reinterventions for an endoleak (0.15% vs. <0.1%, P=.016), and reinterventions for a type Ia endoleak (0.12% vs. 0%, P<.001) (Table 2a). Stratified by anatomic characteristics, type Ia endoleak at completion was associated with infrarenal angulation outside of IFU (7.2% vs. 2.7%, P<.001), neck length outside of IFU (5.6% vs. 2.8%, P<.001), and suprarenal neck angulation outside of IFU (6.8% vs. 2.9%, P=.004)) compared to patients with no neck characteristic outside of IFU, but not neck diameter larger than the IFU (4.7% vs. 2.8%, P=.012) after Bonferroni correction for multiple testing and not neck diameter smaller than the IFU (2.3% vs. 3.0%, P=.15). Perioperative mortality was higher in patients with infrarenal angulation outside of IFU (1.5% vs. 0.6%, P=.001) and neck diameter larger than the IFU (1.9% vs. 0.6%, P<.001) but similar in patients with only neck diameter smaller than the IFU (0.8% vs. 0.7%, P=.53), neck length outside of IFU (1.0% vs. 0.7%, P=.32), and suprarenal neck angulation outside of IFU (0.6% vs. 0.7%, P=92). Also, infrarenal angulation outside of IFU was associated with reinterventions for any endoleak (0.3% vs. <0.1%, P<.001) and reinterventions for type Ia endoleak (0.2% vs. <0.1%, P<.001) compared to patients with no infrarenal angulation outside of IFU. (Table 3a)

At one year, no difference was seen in the rates of type Ia endoleaks between patients with and without neck characteristics outside of IFU (0.9% vs. 0.8%, P=.75). However, patients with neck characteristics outside of IFU more often experienced one-year sac expansion (7.1% vs. 5.3%, P=.017). Also, reintervention rates were higher (4.4% vs. 3.2%, P=.032) and reinterventions for migration were more often performed in patients with neck characteristics outside of IFU (0.3% vs. <0.1%, P=.002). One-year reinterventions for endoleak, rupture, and sac expansion were very low and not significantly different between patients with and without neck characteristics outside of IFU (Table 3b). When looking at individual neck characteristics compared to patients with no neck characteristics outside of IFU, patients with infrarenal angulation outside of IFU more often experienced sac expansion (9.5% vs. 5.4%, P=.002), underwent any reintervention (6.4% vs. 3.3%, P<.001) and reinterventions for endoleaks (3.8% vs. 1.5%, P<.001). Patients with a neck diameter larger than the IFU were associated with one-year sac expansion (9.3% vs. 5.5%, P=.042) but this association lost significance after Bonferroni correction. Patients with neck diameter smaller than the IFU were not associated with one-year endoleak, sac expansion or reintervention. Patients with neck length outside of IFU were associated with reinterventions for migration (0.6% vs. <0.1%, P<.001). (Table 3b).

Table 2. Perioperative and in-hospital outcomes (A) and one-year outcomes (B) comparing patients with and without neck characteristics outside of IFU

A. In-hospital complications	**Outside IFU (n=3,420)**		**Within IFU (n=12,028)**		**P - value**
Endoleak (type Ia)	162	(4.8%)	300	(2.5%)	<0.001
Perioperative Mortality	40	(1.2%)	67	(0.6%)	<0.001
Reintervention	13	(0.4%)	24	(0.2%)	0.057
Reintervention - Endoleak	5	(0.15%)	4	(<0.1%)	0.016
Reintervention - Migration	0	(0.0%)	1	(<0.1%)	0.59
Reintervention - Rupture	3	(<0.1%)	6	(<0.1%)	0.42
Reintervention - Endoleak Ia	4	(0.12%)	0	(0%)	<0.001

B. One-year complications	**Outside IFU (n=2,123)**		**Within IFU (n=7,187)**		**P - value**
Endoleak (type Ia)	11	(0.9%)	35	(0.8%)	0.75
Sac expansion	83	(7.1%)	222	(5.3%)	0.017
Reintervention	65	(4.4%)	160	(3.2%)	0.032
Reintervention - Endoleak	29	(1.9%)	76	(1.5%)	0.33
Reintervention - Migration	4	(0.3%)	1	(0<.1%)	0.002
Reintervention - Rupture	1	(0.1%)	4	(0.1%)	0.87
Reintervention - Sac expansion	7	(0.5%)	21	(0.4%)	0.80

IFU: Instructions for use

Table 3. Perioperative and in-hospital outcomes (A) and one-year outcomes (B) comparing patients with and without neck characteristics outside of IFU, stratified by neck characteristic

A. In-hospital outcomes

	Beta Angle outside IFU			**Neck Diameter larger than the IFU**			**Neck Length outside IFU**			**Alpha Angle outside IFU**		
	No 14,068	Yes 1,001	P value	No 16,428	Yes 516	P value	No 14,279	Yes 1,033	P value	No 15,230	Yes 162	P value
Endoleak (type Ia)	2.7%	7.2%	<.001	2.8%	4.7%	.012	2.8%	5.6%	<.001	2.9%	6.8%	.004
In-hospital mortality	0.6%	1.5%	.001	0.6%	1.9%	<.001	0.7%	1.0%	.32	0.7%	0.6%	.92
Reintervention	0.2%	0.4%	.26	0.2%	0.0%	.26	0.2%	0.4%	.70	0.2%	0.0%	.54
Reintervention - Endoleak	0.0%	0.3%	<.001	0.0%	0.0%	.62	0.0%	0.2%	.57	0.1%	0.0%	.77
Reintervention - Migration	0.0%	0.0%	.79	0.0%	0.0%	.86	0.0%	0.0%	.62	0.0%	0.0%	.92
Reintervention - Rupture	0.0%	0.1%	.59	0.0%	0.0%	.59	0.0%	0.1%	.71	0.1%	0.0%	.76
Reintervention - Endoleak Ia	0.0%	0.2%	<.001	0.0%	0.0%	.76	0.0%	0.0%	.62	0.0%	0.0%	.86

B. One-year outcomes comparing patients with and without neck characteristics outside of IFU

	Beta Angle outside IFU			Neck Diameter outside IFU			Neck Length outside IFU			Alpha Angle outside IFU		
	No 8,479	Yes 597	P value	No 14,783	Yes 516	P value	No 8,557	Yes 1,674	P value	No 9,163	Yes 111	P value
Endoleak (type Ia)	0.8%	1.1%	.48	0.8%	1.2%	.56	0.8%	1.0%	.69	0.8%	3.2%	.037
Sac expansion	5.4%	9.5%	.002	5.5%	9.3%	.042	5.6%	6.7%	.35	5.6%	5.1%	.85
Reintervention	3.3%	6.4%	<.001	3.4%	4.8%	.30	3.5%	4.1%	.49	3.5%	5.6%	.34
Reintervention - Endoleak	1.5%	3.8%	<.001	1.6%	2.4%	.35	1.6%	1.5%	.83	1.6%	2.8%	.42
Reintervention - Migration	0.1%	0.2%	.24	0.1%	0.5%	.036	<0.1%	0.6%	<.001	0.1%	0%	.81
Reintervention - Rupture	0.1%	0.2%	.24	0.1%	0.5%	.036	0.1%	0%	.53	0.1%	0%	.81
Reintervention -Sac expansion	0.4%	1%	.11	0.4%	1.0%	.23	0.5%	0%	.14	0.4%	1.4%	.21

FU: Instructions for use

Multivariable adjusted analyses

After adjustment, neck characteristics outside of IFU were associated with type Ia endoleak on completion angiogram (OR 1.6, 95% confidence interval (CI) [1.3-2.0], P<.001), and perioperative mortality (OR 1.8 [1.2-2.7], P=.005) but no significant association with in-hospital reinterventions (OR 1.9 [0.9-3.8], P=.077) (Table 4). Type Ia completion endoleaks were associated with infrarenal angulation (OR 2.0 [1.5-2.7], P<.001) and neck length outside of IFU (OR 2.0 [1.5-2.8], P<.001), while smaller neck diameter was protective (OR .5 [.3-.8], P=.009); and trended towards association with large neck diameter (OR 1.5 [1.0-2.5], P=.075), and suprarenal angulation outside of IFU (OR 1.7 [.9-3.3], P=.097). Also, perioperative mortality was associated with large neck diameter outside of IFU (OR 2.8 [1.3-6.0], P=.007) and infrarenal angulation outside of IFU (OR 1.8 [1.0-3.3], P=.044) (Table 5).

When evaluating one-year outcomes, neck characteristics outside of IFU were associated with one-year sac expansion (OR 1.4; [1.0-1.8]; P=.025) and one-year reintervention (OR 1.4; [1.0-1.9]; P=.039) but not one-year type Ia endoleak rates (Table 4). When stratifying per specific characteristics, infrarenal neck angulation was independently associated with one-year sac expansion (OR 2.1; [1.4-3.2]; P=<.001) and reinterventions (OR 2.1; [1.3-3.2]; P=.001). Also, large neck diameter outside of IFU was associated with one-year sac expansion (OR 2.1; [1.1-3.7]; P=.017) (Table 5).

On secondary analysis, the rate of type Ia endoleaks at completion varied directly with the number of neck characteristics outside of IFU, compared to patients with no neck characteristics outside of IFU; patients with one neck characteristic outside of IFU (OR 1.6; [1.2-1.9]; P<.001), and two characteristics outside of IFU (OR 2.5, [1.6-3.9]; P<.001).

Table 4. Adjusted odds Ratios (95% Confidence Intervals) for patients with neck characteristics outside IFU

	OR	P-value	95% CI
Endoleak (type Ia)	1.6	<.001	1.3 - 2.0
Perioperative mortality	1.8	.005	1.2 – 2.7
Reintervention during index hospitalization	1.9	.077	.9 – 3.8
1-year endoleak (type Ia)	1.0	.926	.5 – 1.9
1-year sac expansion	1.4	.025	1.0 – 1.8
1-year reintervention	1.4	.039	1.0 – 1.9

IFU: Instructions for use; OR: Odds Ratio; CI: Confidence Interval
The model is adjusted for age (years), sex, race (white (ref), black, other, missing), underweight, obesity, current smoking status, insulin dependent diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, decreased renal function, prior AAA repair, coronary artery disease, cerebrovascular disease, familial history of AAA, aspirin use, statin use, betablocker use, and AAA diameter

Survival analyses

Overall survival was lower for patients with neck characteristics outside of IFU at 5 years (84.0% vs. 86.7%, log-rank<.001; Figure 1). However, after adjustment, there was no association between neck characteristics outside of IFU and 5-year mortality (HR: 1.1; [1.0-1.3]; P=.22).

Figure 1. Mid-term survival for patients with and without neck characteristics outside of IFU

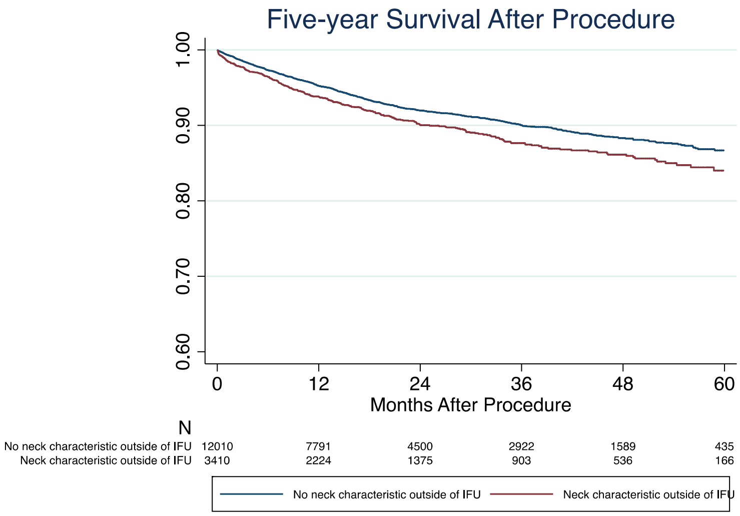

Table 5. Adjusted odds Ratios (95% Confidence Intervals) for patients with neck characteristics outside of IFU, stratified per characteristic

	Beta angulation outside IFU			Neck diameter larger than IFU			Neck length outside IFU			Alpha angulation outside IFU		
	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI
Endoleak (type Ia)	2.0	<.001	1.5–2.7	1.5	.075	1.0–2.5	2.0	<.001	1.5–2.8	1.7	.097	.9–3.3
Perioperative mortality	1.8	.044	1.0–3.3	2.8	.007	1.3–6.0	1.2	.65	.5–2.6	.6	.65	.1–4.7
1-year sac expansion	2.1	<.001	1.4–3.2	2.1	.017	1.1–3.7	1.2	.46	.7–2.0	.8	.69	.2–2.6
1-year reintervention	2.1	.001	1.3–3.2	1.6	.19	.8–3.2	1.3	.35	.8–2.2	1.6	.37	.6–4.6

IFU: Instructions for use; OR: Odds Ratio; CI: Confidence Interval
The model is adjusted for age (years), sex, race (white (ref), black, other, missing), underweight, obesity, current smoking status, insulin dependent diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, decreased renal function, prior AAA repair, coronary artery disease, cerebrovascular disease, familial history of AAA, aspirin use, statin use, betablocker use, and AAA diameter

Sensitivity analysis

After using multiple imputation for missing neck characteristics data, similar adjusted associations were found of neck characteristics outside of IFU with our primary outcomes, type Ia completion endoleaks (OR 1.3, [1.1-1.7], P<.001), perioperative mortality (OR 1.4 [1.0-2.1], P=.064) or long-term mortality (HR: 1.1; [.9-1.2]; P=.360).

Discussion:

This study evaluated the impact of neck characteristics outside of IFU on outcomes after EVAR using a large vascular registry of prospectively collected multicenter data. We found that 22.1% of our study population had at least one neck characteristic outside of IFU and this was independently associated with completion type Ia endoleak, perioperative mortality, one-year sac expansion, and one-year reinterventions.

Despite anatomically restrictive device IFU's, a large proportion of patients treated with EVAR have neck characteristics outside of IFU. This anatomic complexity was more common in females, older patients, and those with greater comorbid burdens, which could explain the unadjusted association with lower survival which was attenuated after adjustment. However, even though there was no independent association of neck characteristics outside of IFU with five-year survival, the increased rates of type Ia endoleaks, endoleak related perioperative reinterventions, and one-year sac expansion likely reflects a worse proximal endograft seal in these patients and could have important implications in long-term outcomes after EVAR. Although neck characteristics outside of IFU were associated with type Ia endoleaks at completion and type Ia endoleak related perioperative reinterventions, the rates of perioperative reinterventions were low. This is likely a consequence of the increasing evidence showing spontaneous resolution of selected type Ia endoleaks at completion in carefully selected patients.[17–19]

Previous studies have examined device IFU criteria compliance. The study by Walker et al. found non-adherence to neck angulation criteria of 4.3% compared with 6.6% infrarenal angulation outside of IFU in our study; 26.2% of the patients had a shorter neck length than recommended in the IFU compared to 6.8% neck length outside of IFU in our study; and 3.1% did not meet neck diameter criteria compared to 3.4% large neck diameter and 7% small neck diameter outside of IFU in our study population.[7] The study showed that IFU adherence, mainly determined by proximal neck characteristics, was not associated with worse survival, similar to our study. The study by Walker et al. examined adherence to IFU between 2000 and 2010 while our study analyzed repairs between 2014 and 2020. Therefore, the larger discrepancy in neck length outside of IFU could reflect the increased availability over time of new devices allowing treatment of shorter necks within IFU. However previous studies show contradicting results concerning the association of adherence to device IFU and postoperative complications and reinterventions and long-term results of off-label EVAR are scarcely published.[6,20,21]

In our study, infrarenal angulation outside of IFU was independently associated with higher rates of type Ia endoleaks at completion, perioperative mortality, one-year sac expansion, and one-year reinterventions compared to patients with no neck characteristics outside of IFU, while larger neck diameter outside of IFU only showed an association with perioperative mortality and one-year sac expansion, and neck length with type Ia endoleaks at completion. Small neck diameter, and suprarenal angulation outside of IFU did not show these associations. A similar association between severe infrarenal neck angulation and proximal type I endoleak was shown in the EUROSTAR registry; however it is not clear if these endoleaks warranted a reintervention.[22] Associations with neck angulation that could contribute to these outcomes and have been show in previous studies are incomplete graft expansion or device kinking at the angled segments of the aorta, or altered blood flow patterns due to angulation.[23–25] Also, potential causes for the stronger association of patients with angulated neck with worse outcomes compared to the other neck characteristics outside of IFU could be a lack of devices that expand IFU for angulated neck compared to short neck length. However, the long-term durability of these strategies in hostile necks remains to be seen.

The inferior outcomes after EVAR in patients with neck characteristics outside of IFU shown in this study warrant the consideration of alternative approaches in these patients. In patients with severe or additive hostile neck characteristics in which an adequate proximal seal is not likely to be achieved, open repair should be considered in patients of appropriate operative risk.[26] However, with technological advancement, the endovascular repair strategies for patients with hostile neck characteristics are continuously expanding. Contemporary devices have been designed to allow patients with more complex neck anatomy to be treated with EVAR with good results. The Aorfix endovascular endograft (Lombard Medical, Oxfordshire, United Kingdom) was designed for patients with highly angulated necks,[27] and the Endurant stent graft (Medtronic Vascular, Santa Rosa, CA), the Ovation stent graft (Trivascular Inc, Santa Rosa, CA), and the TREO stent graft (Terumo Aortic Limited, Sunrise, FL) enable repair for patients with short necks although the long-term results in this subgroup of patients with hostile necks remains to be seen.[28–30] Also, adjunctive use of endoanchors or complex endovascular repair techniques with fenestrated or branched endografts have shown promising results and might provide an important treatment alternative in patients with severe hostile neck characteristics but again; long-term data are lacking.[31–34]

There are several limitations which should be considered when interpreting the results of this study. Information concerning the specific device and endoanchor use was blinded for the investigators, therefore we could not account for potential device related confounding. Also, we could not distinguish between those with and without a suprarenal stent. However, for cases where endoanchors were used, the IFU was changed for the Endurant device. Also, we could not evaluate the performance within the IFU of individual grafts specifically designed for patients with short or angulated neck characteristics for that cohort of patients. Secondly, the VQI database only includes patients who underwent EVAR at a hospital that voluntarily participates in a quality improvement registry, and therefore, these results might not be representative for all hospitals.[35] Thirdly, as follow-up data concerning sac expansion, reinterventions and endoleak occurrence are only available in approximately 60% of the patients included in the VQI we could only assess one-year outcomes in a subset of our cohort. Therefore, the outcomes could underestimate or overestimate the true occurrence. Finally, although the anatomical variables in the VQI are collected with input from the surgical team, inter-rater and intra-rater variability is likely. However, since clinical trials require strict adherence to the IFU and are typically performed in high-volume centers by high-volume surgeons, evaluating the clinical practice in a real-world setting is essential and these results give important insights into the impact of neck anatomy and the appropriate role of EVAR in patients with neck characteristics outside of IFU.

Conclusion:

In conclusion, neck characteristics outside of IFU are independently associated with type Ia endoleaks, perioperative mortality, one-year sac expansion, and one-year reinterventions among patients undergoing elective EVAR. Continuous efforts are warranted to improve the proximal seal in patients with neck characteristics outside of IFU. Also, alternative approaches to standard EVAR should be considered in patients with severe or additive hostile neck characteristics including use of adjuvants to EVAR such as open repair, use of a fenestrated or branched device, or endoanchors.

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PART IV

SUMMARY AND DISCUSSION

Chapter 11

Summary, general discussion and future perspectives

While abdominal aortic aneurysms (AAA) have a decreasing prevalence, the burden on health care remains important.[1] The goal of elective AAA repair is to prevent aneurysm rupture which is associated with a high morbidity and mortality risk. Therefore, the decision to treat an AAA must balance the risk of aneurysm rupture and risk of aneurysm repair, within the context of the patient's overall life expectancy and patient preference. Aneurysm diameter is the most commonly used predictor of rupture of AAA and is therefore often used for patient selection. However, a single diameter-based threshold is not applicable for all and higher rupture rates are seen in female patient. Therefore, the recommended threshold for elective repair is an aortic diameter of 5.5cm in male patients and 5cm in female patients.[2] To improve accurate operative risk prediction, several risk scores have been created and are recommended in the guidelines.[3–5] However, optimal patient selection and risk prediction remains a challenge. The management of AAA is a rapidly evolving field with a decreasing prevalence of AAA, increasing use of endovascular repair and decreasing operative mortality over time.[6–8] Outcome research with contemporary real-life data is therefore essential to observe shifts in the paradigm and identify areas for improvement.

Endovascular devices and technique are constantly evolving and have pushed the frontier for the treatment of AAA. However, the long-term durability and the limits of appropriate application remain unclear. While endovascular repair shows an initial survival advantage compared with open repair, long-term outcomes indicated similar mortality to open repair.[9] Also, the increased potential of late rupture following endovascular repair necessitates commitment to long-term imaging surveillance and timely reinterventions for complications, when indicated.[10,11] Therefore, appropriate application of this technology to achieve high value-based care and rapid assessment over time through database studies are essential.

Traditional randomized controlled trials are a gold standard in clinical research and they have helped transform the management of AAA. Observational database studies however can overcome several of the limitations of clinical trials and address important research questions. The generalizability of randomized controlled trials is limited by strict inclusion and exclusion criteria and by the time results are published they may no longer reflect contemporary practice in the context of rapid technological advances. In contrast, database studies complement clinical trials and offer large-scale contemporary assessments in a broad patient population at a relatively low cost. Administrative databases such as the National (Nationwide) Inpatient Sample (NIS) and the Medicare Database use codes which are used for insurance reimbursement purposes. In contrast, quality improvement registries use pre-determined metrics to analyze the quality of patient care received at each participating center. Granular, procedure-specific data is entered by trained clinical staff with the intent to improve patient care. Well-known surgical quality improvement registries in the United States are the National Surgical Quality Improvement Program (NSQIP) and the Vascular Quality Initiative (VQI).

In this thesis we used registry and administrative data to describe contemporary practice patterns in abdominal aortic aneurysm management and repair strategy appropriateness, three decades after the introduction of EVAR and 15 years after the completion of RCTs.[12–14]

The value of outcomes research

Studies using clinical registries or administrative database from real-world settings create many unique opportunities when adequately used. In **chapter 2** we present the most important paradigm shifts in AAA management based on database studies. Database studies with large patients samples and data collection over time have identified the increasing dominance and the decreasing perioperative adverse outcomes of EVAR over time.[15,16] Also, long-term outcomes in database studies confirmed and complemented results of randomized controlled trials comparing EVAR and open repair. When using high quality databases to answer the right questions database studies have given essential insights into the impact of practice patterns such as centralization of open repair, endoleak management and graft use outside of instructions for use (IFU). Also, they have enabled studies with specific populations which are often underrepresented in clinical trials such as elderly, female patients and patients with rare diseases. Finally, registries combining data from different regions or countries, have provided essential data for identifying best practices or areas for quality improvement.[17–19]

While **chapter 2** identified the promise and opportunities of database research when used adequately, the strengths and limitations of available vascular databases needs to be considered prior to initiating a study.[20] To improve understanding of commonly used databases in AAA research, **chapter 3** gives insight into the differences and best uses of two quality improvement registries and one administrative database. The in-hospital mortality rates gave insight into the inherent differences between the centers captured by administrative databases and quality improvement registries and questions the generalizability of quality improvement registries. Compared to the VQI registry, the administrative NIS database identified a 2% higher in-hospital mortality after open intact AAA repair, 8% higher after rupture EVAR, and 10% higher after open rupture repair. As centers elect to participate in quality improvement registries, these centers are likely larger centers with a dedicated focus on quality improvement. In contrast, administrative databases represent a national experience but lack the granularity for robust adjusted analysis. These differences are important to take into account when interpreting the results of our studies.

This understanding of the differences in patient population, data capturing, and variable definitions between databases is critical when interpreting risk prediction models. In chapter 4 we evaluated how different risk models behave in these databases. Overall, the Medicare risk score had a propensity to overestimate in-hospital mortality in the quality improvement registries. Meanwhile the VSGNE risk score, which was derived from a quality improvement registry, underestimated mortality in all databases. This study emphasized the importance of updating risk scores using contemporary data, and transparency in terms of patient population, variable definitions, and methodology. However, the low contemporary in-hospital mortality rates after elective AAA repair questions if perioperative mortality outcomes are still an appropriate marker of quality.

Outcome measures in registries have historically included perioperative mortality and morbidity. More recently, through linkage with the Social Security Death Index or linkage to Medicare claims, long-term survival, reinterventions and late ruptures have been captured.[21] A shift from focusing on in-hospital mortality to long-term survival, reintervention, late ruptures, and costs would likely be more appropriate measures for quality of EVAR. Also, it is increasingly recognized that traditional outcomes measures of AAA do not fully capture the patient perspective and quality of care. Patient Reported Outcomes measures (PROM) have been underutilized in vascular surgery and should, when possible, be incorporated in outcome studies.[22]

Management of AAA in specific subpopulations

In part II, we addressed sex and racial differences in AAA management and outcomes and discussed strategies for implementing change. While more research is needed to investigate mechanisms that cause disparities upstream of outcomes, our aim was to describe sex and racial disparities and highlight gaps in knowledge that may serve as areas of further investigation.

Previous studies identified that female compared with male patients have a higher rupture risk, smaller aneurysm diameter at rupture, and higher perioperative mortality after aneurysm repair.[23–25] However, uncertainty remains due to the underrepresentation of females in most large studies. **Chapter 5** demonstrated that female patients compared with male patients experienced higher rates of complications and mortality after complex EVAR but not after complex open repair. Also, the perioperative mortality benefit of EVAR over open repair in male patients was not seen in female patients. This study indicated several potential areas for quality improvement such as a focus on sex disparities in developing endovascular procedures and the use of aortic size index (ASI).

As female compared with male patients generally have a smaller body habitus, a specific aneurysm diameter likely represents a relative greater increase in aortic diameter in female compared with male patients. Therefore, aortic diameter might not have the same predictive value of rupture in female patients as in males and ASI, a ratio of diameter and body surface area, might be a more accurate measurement than diameter alone to determine optimal threshold for repair in female patients. In **chapter 6** we found that female patients when compared with male patients underwent intact and rupture repair at smaller median aortic diameter but larger ASI. Also, the cumulative distribution of rupture repair at the currently recommended threshold for repair in males of 5.5cm represented an ASI of 2.7cm/m^2, an AHI of 3.0cm/m, or an aortic diameter of 4.9cm in female patients.

The racial differences found in **chapter 7** give insights into the racial disparities across a patient's healthcare trajectory. Differences in patient demographics, comorbid conditions, and operative characteristics were found that may be a reflection of differences in access and quality of care. Black patients were more likely to undergo urgent repair, and were more likely to undergo rupture repair at aortic diameters below typical repair thresholds. Also, among elective aortoiliac and isolated iliac aneurysms, iliac diameter was largest in Black and Asian patients which could reflect more advanced disease. Asian patients were most likely to have a hypogastric artery aneurysm and to undergo hypogastric coiling, even in the absence of iliac aneurysms, suggesting inadequate common iliac artery length. As we lacked data for robust analysis of the mechanisms behind the racial differences in aortic, aortoiliac, and iliac aneurysms, more studies are needed.

AAA outcomes have improved over time, however significant disparities remain. To address the differences found in chapter 5 and 7, it will be essential to understand the etiology of these disparities, to establish targeted strategies for improvement, and collaborate with all stakeholders. Furthermore, the studies described in this thesis indicate the importance of standardized reporting and subgroup analyses for sex and racial groups. An important area of quality improvement would be to strive towards proportional sex and racial representation in AAA research. Previous RCTs which have greatly influenced the AAA guidelines have often not achieved this and imbalanced enrollment on the basis of sex, or race limits the generalizability. Improved diversity and sub-analyses in research and device development will improve vascular care across populations. Also, broadening variable collection in clinical registries to document social determinants of health will improve our understanding of major drivers of these disparities and give insight into potential solutions for quality improvement.

Practice patterns and appropriate application of EVAR

The introduction of EVAR has improved outcomes for patients with AAA and radically changed the management of AAA. However, continuous assessment of practice patterns and outcomes after the broad introduction of novel technologies is essential. When considering the value of EVAR, the higher procedural costs and the importance of lifelong surveillance need to be taken into account. Therefore, it is essential to select patients who are expected to have a benefit of EVAR compared with open repair or surveillance. In part III, we described the downstream effects of non-adherence to IFU and guideline recommended thresholds for elective EVAR. Also, we compared the use of elective EVAR and open repair for the treatment of large AAAs.

A multinational collaboration of quality improvement registries demonstrated that the United States is among the countries with the highest rates of patients being treated below the recommended diameter threshold and indicated an association of lower repair diameter in fee-for-service countries.[17] As the annual risk of rupture is low for small aneurysms, several large randomized trials identified no benefit of elective repair compared with surveillance for aneurysms that were less than 5.5 cm in diameter.[26] However, **chapter 8** determined that compliance with the guideline recommended AAA diameter threshold for elective EVAR in the United States is poor, and rates of non-compliance were increasing. Non-compliant procedures appear to be offered more commonly to patients with fewer comorbidities and favorable anatomy. While these procedures were associated with improved rates of reintervention, rupture, and survival when compared with procedures following the recommended thresholds, they fail to meet minimum quality standards (defined as 5-year rupture-free survival, and adequate one-year follow-up imaging) in a majority of cases. Therefore, the appropriateness of many of these procedures below the diameter threshold needs to be questioned and adequate follow-up when performing non-compliant procedures is imperative. However, an important limitation is that not all of the procedures evaluated in this study should be considered as inappropriate as the VQI does not capture growth rate, patient preference, embolization, or aneurysm morphology.

While the guidelines recommend that the untreated aneurysm related rupture risk outweighs that operative risk at a diameter above 5.5cm, **chapter 9** shows that 15.2% of elective repair were performed in patients with a AAA diameter above 6.5cm. Patients undergoing EVAR with large aortic aneurysm diameter compared with smaller aneurysms had higher mortality, reintervention, rupture and loss to imaging follow-up rates. These outcomes were similar after open repair for patients with large and smaller aneurysm diameter. Also, in patient with large aneurysms, EVAR was associated with higher adjusted five-year mortality compared with open repair. Therefore, in patients with large aneurysms who are medically fit, open repair should be strongly considered even in patients with anatomy suitable for EVAR. However, while diameter is easily accessible and has been extensively studied, a fixed diameter threshold alone is likely not the most accurate predictor of operative risk as other factors are likely to influence the repair risk. Therefore, we encourage future studies investigating other factors such as aneurysm volume to increase sensitivity when predicting operative risk.

In **chapter 10** we describe that in patients undergoing elective infrarenal EVAR, neck characteristics outside of IFU were present in 22.1% of our study population and were independently associated with type Ia endoleaks at completion of the index procedure, perioperative mortality, one-year sac expansion and one-year reinterventions. While technological advancements are essential to improve the proximal seal in patients with neck characteristics outside of IFU, alternative approaches to standard EVAR should be considered. In patient with severe or additive hostile neck characteristics open repair should be considered in patients of appropriate operative risk. Also, adjunctive use of endoanchors or complex endovascular repair techniques with fenestrated or branched endografts have shown promising results and might provide an important treatment alternative in patients with severe hostile neck characteristics but; long-term data are lacking.[27–30] However, long-term outcomes on the impact of adherence to IFU are needed.

Future perspectives

The balance of rupture risk and repair risk is continuously changing and efforts to reduce both are critical. Selective screening has been introduced to identify patients before the risk of rupture becomes too high. Therefore, many countries recommend screening for AAA in male ever-smokers above 65 years old and in patients with a family history of AAA. However, the screening criteria have been debated and targeted effort for at risk groups will allow earlier detection. Also, potential disadvantages of screening such as higher number of preventive AAA surgeries with associated risks need to be considered. In the US, screening is recommended for high-risk groups and several studies have shown the benefits of this screening program. However, in the Netherlands, a recent evaluation concluded that the added value of a population-based screening program in the Netherlands was limited. Further reduction of rupture risk must be attained through improved prediction of rupture,[31] pharmacologic therapies to influence aneurysm growth rate, and reduction of risk factors such as smoking. Finally, this thesis indicated the limitations of elective EVAR when performing large AAA repairs and repairs who do not comply with IFU or guideline recommended diameter thresholds. While the introduction of new grafts or techniques could potentially allow a larger proportion of patients to undergo endovascular repair, evaluation of long-term outcomes is essential to determine the appropriate patient selection.

While traditional randomized controlled trials are a gold standard in clinical research which have transformed the management of AAA, the value and complementing abilities of database studies are a powerful tool in AAA research. However, database research should be improved by increasing the generalizability of registries by removing barriers for participation such as financial costs and whole country databases such as the Dutch surgical aneurysm audit (DSAA) should be encouraged. Also, broad and accurate capturing of important variables such as socioeconomic status, indications for surgery, aneurysm morphology, device specific information, or quality indicators such as guideline adherence, late outcomes, or patient reported outcomes will increase the potential of registries. Finally, future breakthroughs will be driven from partnerships with different stakeholders through linkage of data or new study designs such as registry based randomized controlled trials with higher enrolment, lower costs, and higher generalizability.[32]

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Chapter 12

Samenvatting en discussie in het Nederlands

Hoewel abdominale aorta aneurysmata (AAA) een afnemende prevalentie hebben, blijft de belasting van de gezondheidszorg belangrijk.[1] Het doel van electieve chirurgische AAA-behandeling is om een aneurysma ruptuur, welke gepaard gaat met een hoog morbiditeits- en mortaliteitsrisico, te voorkomen. Daarom moet bij de beslissing om een AAA te behandelen het risico van aneurysm aruptuur en het risico van de aneurysma behandeling in overweging worden genomen, in de context van de totale levensverwachting en de voorkeur van de patiënt. Aneurysma diameter is de meest gebruikte voorspeller van AAA-ruptuur en wordt daarom vaak gebruikt voor patiënten selectie. Een behandel drempel met één specifieke diameter is echter niet voor iedereen van toepassing. Er worden bijvoorbeeld hogere ruptuur percentages gezien in aneurysmata met een kleinere diameter bij vrouwelijke patiënten. Daarom is de aanbevolen drempel voor electieve chirurgische behandeling een aortadiameter van 5,5 cm bij mannelijke patiënten en 5 cm bij vrouwelijke patiënten.[2] Om een nauwkeurige voorspelling van het operatierisico te verbeteren, bestaan er verschillende risicoscores die worden aanbevolen in de richtlijnen.[3–5] Optimale patiënten selectie en risicovoorspelling blijft echter een uitdaging. De behandeling van AAA is een snel evoluerend gebied met een afnemende AAA-prevalentie, toenemend gebruik van endovasculaire interventies en afnemende perioperatieve mortaliteit in de loop der tijd.[6–8] Database onderzoek met hedendaagse real-life data is daarom essentieel om paradigmaverschuivingen waar te nemen en verbeterpunten te identificeren.

Endovasculaire technologie en interventies zijn voortdurend in ontwikkeling en hebben de grens voor de chirurgische behandeling van AAA verlegd. De bestendigheid op lange termijn en de juiste toepassing blijven echter onduidelijk. Terwijl endovasculaire interventies een vroeg overlevingsvoordeel vertonen in vergelijking met open chirurgische behandeling, laten langetermijnresultaten een vergelijkbare mortaliteit zien.[9] Ook vereist het verhoogde risico op een late ruptuur na endovasculaire interventie een langdurige follow-up met beeldvorming en indien geïndiceerd tijdige reinterventies voor complicaties.[10,11] Om deze vernieuwende technologie adequaat te kunnen toepassen in de praktijk en om dit te evalueren in de loop der tijd zijn databasestudies essentieel.

Traditionele randomized controlled trials (RCT) zijn een gouden standaard in klinisch onderzoek en hebben bijgedragen aan de transformatie van de chirurgische behandeling van AAA. Observationele databasestudies kunnen echter een aantal van de beperkingen van RCT's overwinnen en belangrijke onderzoeksvragen beantwoorden. De generaliseerbaarheid van RCT's wordt beperkt door strikte inclusie- en exclusiecriteria en tegen de tijd dat de resultaten worden gepubliceerd, weerspiegelen ze door de snelle technologische vooruitgang mogelijk niet langer de hedendaagse praktijk. Databasestudies daarentegen vullen klinische studies aan en bieden grootschalige hedendaagse beoordelingen in een brede patiëntenpopulatie tegen relatief lage kosten. Administratieve databases zoals de National Inpatient Sample (NIS) en de Medicare Database gebruiken codes die worden gebruikt voor verzekeringsvergoedingen. Kwaliteitsverbeteringsregisters gebruiken daarentegen vooraf bepaalde variabelen om de kwaliteit van de patiëntenzorg te analyseren in de deelnemende centra. Gedetailleerde, procedure specifieke gegevens worden ingevoerd door getraind klinisch personeel met het doel de patiëntenzorg te verbeteren. Bekende chirurgische kwaliteitsverbeteringsregisters in de Verenigde Staten zijn het National Surgical Quality Improvement Program (NSQIP) en het Vascular Quality Initiative (VQI).

In dit proefschrift gebruikten we register- en administratieve data om hedendaagse praktijkpatronen in AAA-management en behandelstrategieën te beschrijven, drie decennia na de introductie van EVAR en 15 jaar na de voltooiing van RCT's.[12–14]

De waarde van uitkomstenonderzoek

Studies waarbij gebruik wordt gemaakt van klinische registers of administratieve databases creëren veel unieke kansen wanneer ze adequaat worden toegepast. In **hoofdstuk 2** presenteren we de belangrijkste paradigmaverschuivingen in de AAA-behandeling op basis van databasestudies. Databasestudies met grote patiënten aantallen en gegevensverzameling over langere tijd hebben de toenemende dominantie en de afnemende perioperatieve mortaliteit van EVAR in de loop der tijd geïdentificeerd.[15,16] Ook bevestigden en vulden langetermijnresultaten in databasestudies de resultaten aan van RCT's waarin EVAR en open chirurgische behandeling werden vergeleken. Databasestudies hebben essentiële inzichten gegeven in de impact van praktijkpatronen zoals de centralisatie van open chirurgische behandeling, endoleak behandeling en stentgebruik buiten de Instructions For Use (IFU). Ook zijn studies mogelijk gemaakt met specifieke populaties die vaak ondervertegenwoordigd zijn in klinische studies zoals ouderen, vrouwelijke patiënten en patiënten met zeldzame ziekten. Ten slotte hebben registers die gegevens uit verschillende regio's of landen combineren, essentiële gegevens verstrekt voor het identificeren van optimale werkwijzen of gebieden voor kwaliteitsverbetering.[17–19]

Terwijl **hoofdstuk 2** de mogelijkheden van adequaat databaseonderzoek in kaart brengt, moeten de sterke punten en beperkingen van de beschikbare vasculaire databases in overweging worden genomen voordat een onderzoek wordt gestart.[20] Om het begrip van veelgebruikte databases in AAA-onderzoek te verbeteren, geeft **hoofdstuk 3** inzicht in de verschillen en beste toepassingen van twee kwaliteitsverbeteringsregisters en één administratieve database. De perioperatieve sterftecijfers gaven inzicht in de inherente verschillen tussen de centra die zijn vastgelegd in administratieve databases en kwaliteitsverbeteringsregisters en zetten vraagtekens bij de generaliseerbaarheid van kwaliteitsverbeteringsregisters. In vergelijking met het VQI-register identificeerde de administratieve NIS database een 2% hogere perioperatieve sterfte na electieve open AAA behandeling, 8% hoger na EVAR voor geruptureerde AAA en 10% hoger na open chirurgische behandeling voor geruptureerde AAA. Aangezien centra ervoor kiezen om deel te nemen aan kwaliteitsverbeteringsregisters, zijn deze centra waarschijnlijk grotere centra met een specifieke focus op kwaliteitsverbetering. Administratieve databases daarentegen weergeven de nationale ervaring, maar missen de granulariteit voor een robuuste multivariabele analyse. Deze verschillen zijn belangrijk bij het interpreteren van de resultaten van onze studies.

Dit inzicht in de verschillen tussen databases in patiëntenpopulatie, het vastleggen van gegevens en variabele definities is van cruciaal belang bij het interpreteren van risicovoorspellingsmodellen. In **hoofdstuk 4** hebben we geëvalueerd hoe verschillende risicomodellen zich gedragen in de verschillende databases. Over het algemeen had de Medicare risicoscore de neiging om de perioperatieve mortaliteit in de kwaliteitsverbeteringsregisters te overschatten. Daarentegen onderschatte de VSGNE risicoscore, die werd afgeleid van een kwaliteitsverbeteringsregister, de mortaliteit in alle databases. Deze studie benadrukt het belang van het bijwerken van risicoscores met behulp van hedendaagse data en transparantie in de patiëntenpopulatie, variabele definities en methodologie. Echter, de lage hedendaagse perioperatieve sterftecijfers na electieve chirurgische AAA-behandeling roept de vraag op of perioperatieve sterfte nog steeds een geschikte kwaliteitsindicator is.

Uitkomstmaten in registers omvatten van oudsher perioperatieve mortaliteit en morbiditeit. Meer recentelijk, door koppeling van register data met de Social Security Death Index of koppeling aan Medicare claims, zijn overleving op lange termijn, reinterventies en late rupturen vastgelegd.[21] Een verschuiving van de focus op sterfte in het ziekenhuis naar overleving op lange termijn, reinterventies, late rupturen en kosten zouden waarschijnlijk meer geschikte uitkomsten zijn voor de kwaliteit van EVAR. Ook wordt steeds meer erkend dat traditionele uitkomstmaten van AAA het patiënten perspectief en de kwaliteit van zorg niet volledig vastleggen. Patient Reported Outcomes Measures (PROM) zijn onderbenut in vasculaire chirurgie en moeten, indien mogelijk, worden opgenomen in uitkomststudies.[22]

Chirurgische behandeling van AAA in specifieke subpopulaties

In deel II hebben we sekse- en raciale verschillen in AAA-management en resultaten beschreven en verbeter strategieëen voorgesteld. Hoewel er meer onderzoek nodig is om mechanismen te onderzoeken die deze verschillen veroorzaken, was ons doel om sekse- en raciale verschillen te beschrijven en lacunes in kennis te benadrukken die van belang zijn voor verder onderzoek.

Eerdere studies stelden vast dat vrouwelijke patiënten in vergelijking met mannelijke patiënten een hoger ruptuurrisico, een kleinere aneurysmadiameter op het moment van een ruptuur en een hogere perioperatieve mortaliteit na operatieve aneurysma behandeling hebben.[23–25] Onduidelijkheid over sekseverschillen blijft echter bestaan als gevolg van de ondervertegenwoordiging van vrouwen in de meeste grote studies. **Hoofdstuk 5** toont aan dat vrouwelijke patiënten in vergelijking met mannelijke patiënten hogere percentages complicaties en mortaliteit ondervonden na complexe EVAR, maar niet na complexe open chirurgische behandeling. Ook werd het perioperatieve sterftevoordeel van EVAR ten opzichte van open chirurgische behandeling bij mannelijke patiënten niet waargenomen bij vrouwelijke patiënten. Deze studie wees op verschillende mogelijke gebieden voor kwaliteitsverbetering, zoals een focus op sekse verschillen bij het ontwikkelen van endovasculaire procedures en het gebruik van Aortic Size Index (ASI).

Aangezien vrouwelijke patiënten in vergelijking met mannelijke patiënten over het algemeen een kleinere habitus hebben, vertegenwoordigt een specifieke aneurysmadiameter waarschijnlijk een relatief grotere toename van de aortadiameter bij vrouwen in vergelijking met mannelijke patiënten. Daarom kan het zijn dat de aortadiameter bij vrouwelijke patiënten niet dezelfde voorspellende waarde voor een ruptuur heeft als bij mannen en ASI, een verhouding van diameter en lichaamsoppervlak, kan een nauwkeurigere meting zijn dan alleen diameter om een optimale drempel voor electieve behandeling bij vrouwelijke patiënten te bepalen. In **hoofdstuk 6** laten we zien dat vrouwelijke patiënten in vergelijking met mannelijke patiënten electieve en geruptureerde AAA-behandeling ondergingen bij een kleinere mediane aortadiameter maar bij een grotere ASI. Ook vertegenwoordigde de cumulatieve verdeling van geruptureerde AAA-behandeling op de aanbevolen drempel voor electieve behandeling bij mannen van 5,5 cm een ASI van 2,7 cm/ m2, een Aortic Hight Index van 3,0 cm/m, of een aortadiameter van 4,9 cm bij vrouwelijke patiënten.

De raciale verschillen in **hoofdstuk 7** geven inzicht in de raciale verschillen in het zorgtraject van een patiënt. Er werden verschillen gevonden in de demografie van patiënten, comorbide kenmerken en operationele kenmerken die een weerspiegeling kunnen zijn van verschillen in toegang en kwaliteit van zorg. Zwarte patiënten hadden meer kans op een spoedoperatie en hadden meer kans op geruptureerde AAA-behandeling bij aortadiameters onder de aangeraden electieve behandel drempels. Ook, onder patiënten welke electieve aortoiliacale en geïsoleerde iliacale aneurysma behandeling ondergingen, was de iliacale diameter het grootst bij zwarte en Aziatische patiënten wat een meer geavanceerde ziekte zou kunnen weerspiegelen. Aziatische patiënten hadden de meeste kans op een arteria hypogastrica aneurysma en om hypogastrische coiling te ondergaan, zelfs bij afwezigheid van iliacale aneurysmata, wat wijst op onvoldoende arteria iliaca communis lengte. Omdat we geen gegevens hadden voor een robuuste analyse van de mechanismen achter de raciale verschillen in aorta-, aortoiliac- en iliacale aneurysmata, zijn hiervoor meer studies nodig.

AAA-resultaten zijn in de loop van de tijd verbeterd, maar er blijven aanzienlijke sekse en raciale verschillen bestaan. Om de verschillen in **hoofdstuk 5 en 7** aan te pakken, is het van essentieel belang om de etiologie van deze verschillen te begrijpen, gerichte strategieën voor verbetering vast te stellen en samen te werken met alle belanghebbenden. Verder wijzen de studies in dit proefschrift op het belang van gestandaardiseerde rapportage en subgroep analyses voor sekse en raciale groepen. Een belangrijk gebied van kwaliteitsverbetering zou zijn om te streven naar evenredige seksuele en raciale vertegenwoordiging in AAA-onderzoek. Eerdere RCT's die de AAA-richtlijnen sterk hebben beïnvloed, hebben dit vaak niet bereikt en onevenwichtige sekse en raciale verdeling beperkt de generaliseerbaarheid van deze richtlijnen. Verbeterde diversiteit en subanalyses in onderzoek en technologieontwikkeling zullen de vasculaire zorg in verschillende populaties verbeteren. Ook zal het verbreden van variabele verzameling in klinische registers om sociale determinanten van gezondheid te documenteren ons begrip van belangrijke oorzaken van deze verschillen verbeteren en inzicht geven in mogelijke oplossingen voor kwaliteitsverbetering.

Praktijkpatronen en toepassing van EVAR

De introductie van EVAR heeft de resultaten voor patiënten met AAA verbeterd en de behandeling van AAA radicaal veranderd. Een voortdurende beoordeling van praktijkpatronen en -resultaten na de brede invoering van nieuwe technologieën is echter essentieel. Bij de beoordeling van de waarde van EVAR moet rekening worden gehouden met de hogere procedurekosten en het belang van levenslange opvolging. Daarom is het essentieel om patiënten te selecteren waarvan wordt verwacht dat ze een voordeel van EVAR hebben in vergelijking met open chirurgische behandeling of vervolging door middel van beeldvorming. In deel III beschreven we de downstreameffecten van niet-naleving van IFU en de door de richtlijn aanbevolen drempels voor electieve EVAR. Ook vergeleken we het gebruik van electieve EVAR en open chirurgische behandeling voor grote AAA.

Een internationale samenwerking van kwaliteitsverbeteringsregisters toonde aan dat de Verenigde Staten tot de landen behoren met de hoogste percentages patiënten die onder de aanbevolen diameterdrempel worden behandeld en wees op een associatie van een lagere behandel diameter in landen met een fee-for-service systeem.[17] Aangezien het jaarlijkse risico op ruptuur laag is voor kleine aneurysmata, identificeerden verschillende grote RCT's geen voordeel van electieve chirurgische behandeling in vergelijking met vervolging voor aneurysmata met een diameter van minder dan 5,5 cm.[26] Echter, **hoofdstuk 8** stelt vast dat de naleving van de door de richtlijn aanbevolen AAA-diameterdrempel voor electieve EVAR in de Verenigde Staten slecht is en dat de percentages van niet-naleving toenemen. EVAR procedures voor kleine aneurysmata lijken vaker te worden aangeboden aan patiënten met minder comorbiditeiten en gunstige anatomie. Hoewel deze procedures in vergelijking met procedures voor AAA boven de diameter drempel geassocieerd waren met verbeterde percentages van reinterventie, ruptuur en overleving, voldoen ze in de meeste gevallen niet aan de minimale kwaliteitsnormen (gedefinieerd als 5-jarige ruptuur vrije overleving en adequate follow-up beeldvorming binnen één jaar). Daarom moet de geschiktheid van veel van deze procedures voor kleine aneurysmata in twijfel worden getrokken en is een adequate follow-up bij het uitvoeren van deze procedures noodzakelijk. Een belangrijke beperking is echter dat niet alle procedures die in deze studie worden geëvalueerd, als inadequaat moeten worden beschouwd, omdat de VQI geen groeisnelheid, voorkeur van de patiënt, embolisatie of aneurysmamorfologie vastlegt.

Hoewel de richtlijnen aanbevelen dat het onbehandelde aneurysma gerelateerde ruptuur risico opweegt tegen de risico's van een operatie bij een diameter van meer dan 5,5 cm, toont **hoofdstuk 9** aan dat 15,2% van de electieve chirurgische behandeling werd uitgevoerd bij patiënten met een AAA-diameter van meer dan 6,5 cm. Patiënten die EVAR ondergingen met een grote diameter van het aorta-aneurysma in vergelijking met kleinere aneurysmata hadden een hogere mortaliteit, reinterventie, ruptuur en verminderde follow-up percentages. Deze uitkomsten waren vergelijkbaar tussen patiënten met een grotere en kleinere aneurysma diameter na open chirurgische behandeling. Ook bij patiënten met grote aneurysmata werd EVAR geassocieerd met een hogere vijfjaars mortaliteit in vergelijking met open chirurgische behandeling. Daarom moet bij patiënten met grote aneurysmata die medisch fit zijn, open chirurgische behandeling sterk worden overwogen, zelfs bij patiënten met anatomie die geschikt zijn voor EVAR. Hoewel de diameter gemakkelijk toegankelijk is en uitgebreid is bestudeerd, is een drempel met een alleen een vaste diameter waarschijnlijk niet de meest nauwkeurige voorspeller de risico's van een operatie, aangezien andere factoren het behandel risico waarschijnlijk zullen beïnvloeden. Daarom moedigen we toekomstige studies aan om andere factoren zoals aneurysmavolume te onderzoeken om de gevoeligheid te verhogen bij het voorspellen van het operatierisico.

In **hoofdstuk 10** beschrijven we dat bij patiënten die electieve infrarenale EVAR ondergingen, aneurysmanek kenmerken buiten IFU aanwezig waren in 22,1%. De kenmerken waren onafhankelijk geassocieerd met type Ia endoleaks na voltooiing van de indexprocedure, perioperatieve mortaliteit, aneurysma-uitbreiding en reinterventies na een jaar. Hoewel technologische vooruitgang essentieel is om de proximale seal te verbeteren bij patiënten met nekkenmerken buiten IFU, moeten alternatieve benaderingen van standaard EVAR worden overwogen. Bij patiënten met ernstige of additieve beperkende nekkenmerken en een redelijk operatief risico moet open herstel worden overwogen. Ook heeft het aanvullende gebruik van endoanchors of complexe endovasculaire behandeltechnieken met fenestrated of branched endografts veelbelovende resultaten laten zien en kan het een belangrijk behandel alternatief bieden bij patiënten met ernstige beperkende nek kenmerken, maar; lange termijn gegevens ontbreken.[27-30] Ook zijn langetermijnresultaten nodig over de impact van de naleving van IFU.

Toekomstperspectieven

De balans tussen ruptuur risico en behandel risico verandert voortdurend en inspanningen om beide te verminderen zijn van cruciaal belang. Selectieve screening is ingevoerd om patiënten te identificeren voordat het risico op ruptuur te hoog wordt. Daarom raden veel landen screening voor AAA aan bij mannelijke rokers ouder dan 65 jaar en bij patiënten met een familiegeschiedenis van AAA. Over de screeningcriteria wordt echter uitvoerig gediscussieerd en gerichte inspanningen voor hoog risicogroepen zullen eerdere detectie mogelijk maken. Ook moeten mogelijke nadelen van screening, zoals een groter aantal preventieve AAA-operaties met bijbehorende risico's, worden overwogen. In de VS wordt screening aanbevolen voor risicogroepen en verschillende studies hebben de voordelen van dit screeningsprogramma aangetoond. In Nederland concludeerde een recente evaluatie echter dat de toegevoegde waarde van een bevolkingsonderzoek in Nederland beperkt was. Verdere vermindering van het ruptuur risico moet worden bereikt door een betere voorspelling van een ruptuur,[31] farmacologische therapieën om de groeisnelheid van aneurysmata te beïnvloeden en vermindering van risicofactoren zoals roken. Ten slotte gaf dit proefschrift de beperkingen aan van electieve EVAR in de behandeling van grote AAA en van AAA die niet voldoen aan IFU of richtlijn aanbevolen diameterdrempels. Hoewel de introductie van nieuwe grafts of technieken mogelijk een groter deel van de patiënten in staat zou kunnen stellen om endovasculaire behandeling te ondergaan, is evaluatie van langetermijnresultaten essentieel om de juiste patiënten selectie te bepalen.

Hoewel traditionele RCT's een gouden standaard zijn in klinisch onderzoek en deze de behandeling van AAA hebben getransformeerd, zijn databasestudies een krachtig en waardevol hulpmiddel in AAA-onderzoek. Het databaseonderzoek moet echter worden verbeterd door de generaliseerbaarheid van registers te vergroten door belemmeringen voor deelname, zoals financiële kosten, weg te nemen en landelijke databases, zoals de Dutch Surgical Aneurysm Audit (DSAA), aan te moedigen. Ook zal een brede en nauwkeurige registratie van belangrijke variabelen zoals sociaaleconomische status, indicaties voor chirurgie, aneurysmamorfologie, stent specifieke informatie, kwaliteitsindicatoren zoals richtlijn naleving, late resultaten of PROMs het potentieel van registers vergroten. Ten slotte zullen toekomstige doorbraken worden gedreven door partnerschappen met verschillende belanghebbenden door koppeling van gegevens of nieuwe studieontwerpen zoals op register gebaseerde RCT's met grotere aantallen, lagere kosten en hogere generalisatie.[32]

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LIST OF PUBLICATIONS

List of publications

Amelung FJ, de Guerre LEVM, Consten ECJ, Kist JW, Verheijen PM, Broeders I a. MJ, et al. Incidence of and risk factors for stoma-site incisional herniation after reversal. BJS Open. 2018 Jun;2(3):128–34.

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CURRICULUM VITAE

Curriculum Vitae

Livia de Guerre was born on April 28th, 1993 in Amsterdam, the Netherlands. She is the middle child with an older brother and younger sister. When Livia was 9 years old, the family moved to Brussel, Belgium. After graduating high school in 2011 (Insitut Saint André, Brussels), she started Medical School in Utrecht, the Netherlands. During medical school, she spend several months abroad in Hong Kong, Stellenbosch, Moshi, and Paris for internships. She soon developed an interest in surgery and research which eventually evolved into plans for a PhD program under the supervision of Joost van Herwaarden. In April 2018 she obtained her medical degree, whereafter she moved to Boston, USA, to work with Prof. Marc L. Schermerhorn as a research fellow at the Department of Vascular and Endovascular Surgery at Beth Israel Deaconess Medical Center, Harvard Medical School. Her research focussed on aortic aneurysms and the work in this thesis was presented on numerous (inter)national meetings. Currently, Livia works as a surgical resident (not in training) at the Onze Lieve Vrouwe Gasthuis in Amsterdam.