Aortic Biomechanics and Surgical Outcomes

Multidisciplinary Perspectives

Tim J. Mandigers

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Multidisciplinary Perspectives

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Multidisciplinary Perspectives

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Voor Mama, Oma en Oma

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Part I

Introduction

1

Introduction, objectives, and thesis outline

INTRODUCTION

For readers familiar with key aortic terminology and concepts involving anatomy, function, biomechanics, disease, and surgical management, please proceed to thesis objectives and outline on page 20.

Anatomy of the aorta

The aorta is the largest artery of the human body. It originates from the left ventricle of the heart, rises upward, forward and to the right, then arches over the heart in a left-posterior manner, and descends through the left hemithorax and abdomen to the iliac bifurcation.[1] Along its course, multiple arterial branches originate from the aorta, and it consists of a thoracic and abdominal section – separated by the diaphragm – which can be divided in different segments (i.e., thoracic aorta: attachment zones 0 – 5, abdominal aorta: zones 6 – 9) (**Figure 1**).[2] The thoracic aorta consists of the aortic root, ascending aorta, aortic arch, and descending aorta, whereas the abdominal aorta consists of a visceral, renal, and infrarenal segment up to the iliac bifurcation (**Figure 1**).[3,4]

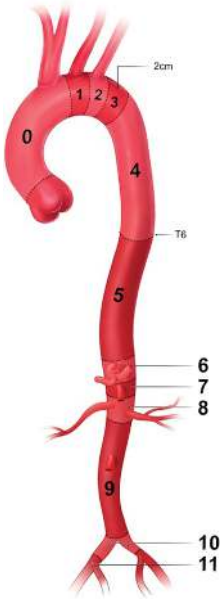

Figure 1. The thoraco-abdominal aorta divided according to the thoracic endovascular aortic repair (TEVAR) attachment zones with origination of major side-branches. Zone 0: Ascending aorta and proximal aortic arch up to the distal border of the brachiocephalic trunk (BCT); Zone 1: Aortic arch with origin of the left common carotid artery (LCCA); Zone 2: Distal aortic arch with origin of the left subclavian artery (LSA); Zone 3: The first 2 cm of descending aorta starting from the distal border of the LSA; Zone 4: ≥2 centimeter from the distal border of the LSA to the mid-descending aorta (T6 level); Zone 5: The distal half of the descending thoracic aorta up to the proximal border of the celiac trunk; Zone 6: Celiac origin to the proximal border of the superior mesenteric artery (SMA); Zone 8: Including at least one of the renal arteries; Zone 9: Infrarenal; Zone 10: Common iliac artery; Zone 11: External iliac artery (From Czerny *et al.*[2] (2019); with permission from Elsevier and Copyright Clearance Center to reuse in thesis/dissertation).

The aortic wall and its microstructure

From inside to outside, the aortic wall consists of three layers: intima, media, and adventitia. While the histological, microstructural components of the thin intima

(e.g., endothelial cells) and adventitia (e.g., vasa vasorum, nerves) are important for maintaining vascular function, the medial wall components are crucial in defining the biomechanical properties of the aorta.[5] Besides smooth muscle cells, the medial wall layer consists of elastic lamellae containing elastin and collagen proteins. Together with connective fibers, elastin and collagen impart the unique combination of elasticity and strength.[3–7]

In the medial wall layer of healthy thoracic aorta, the proportions of elastin and collagen are relatively equal.[7] Despite this, the biomechanical properties of different segments seem to differ, as well as their extensibility and distensibility.[8,9] Shifting towards the abdominal aorta, the proportion of collagen gradually increases while elastin gradually decreases, to about double the proportion of collagen with respect to elastin in the abdominal aorta (**Figure 2**).[7]

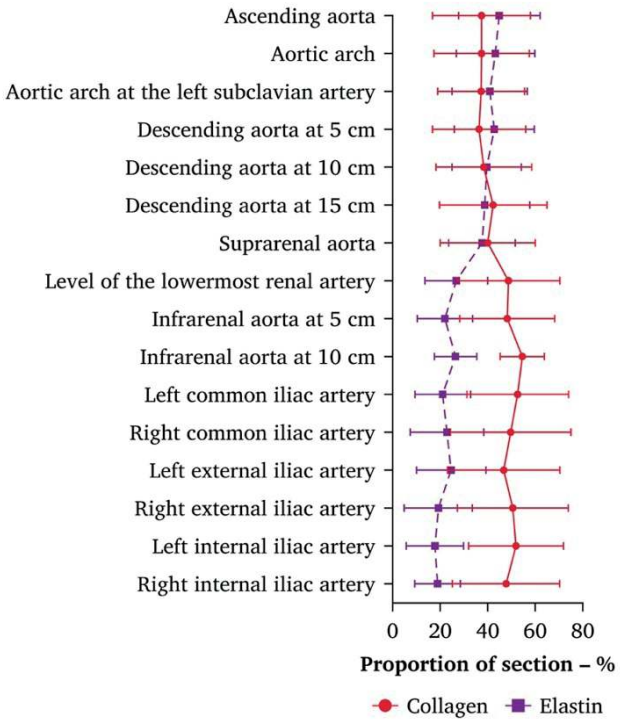

Figure 2. Structural analysis showing proportions of elastin and collagen at different sections of the thoracoabdominal aorta. A decline in the proportion of elastin is noted in the lower renal segment, infrarenal segment and iliac arteries compared with thoracic aortic segments and the suprarenal aorta (From Liyanage *et al.*[7] (2022); with permission from Elsevier and Copyright Clearance Center to reuse in thesis/dissertation).

Physiological functions of the aorta

The healthy aorta is in continuous, harmonious movement, synchronized to the systolic and diastolic phases of the cardiac cycle and serves as the main arterial conduit transporting oxygenated blood with nutrients to the rest of the organs. This is a dynamic process. During systole, the aorta distends and partially absorbs the stroke volume and pulsatile energy exerted by the heart. During diastole, the aorta recoils and propagates the oxygenated blood forward to peripheral arterial beds, as a secondary pump.[4] This Windkessel function helps providing continuous, steady state peripheral arterial flow, maintains diastolic blood pressure, and is of utmost importance for coronary perfusion.[4,5]

In addition, baroreceptors in the adventitial wall layer play a central role in the rhythmic coordination between the aorta and the heart, by maintaining systemic vascular resistance and heart rate. If blood pressures drop, this results in an increased systemic vascular resistance, heart rate, and vice versa.[5,10]

Blood flow, aortic stiffness, and cardiovascular health

The rhythmic coordination of the heart and aorta thus creates a wave of blood flow over the arterial wall, propagating down the aorta from proximal to distal aortic segments at a given speed, and into originating branches. This forward wave gets reflected at numerous sites of impedance mismatch throughout the entire arterial circulatory bed, such as branching arteries, changes in wall diameter, or at changes in the microstructural properties of the arterial wall. These reflections merge into a net backward wave, which returns at the aorta during diastole in young, healthy, and compliant aortas.[11]

If the arterial wall gets stiffer and less elastic, distensible, or compliant, this equilibrium changes. Reasons are aging, various pathologic states like atherosclerosis, or other changes to the biomechanical properties of the arterial wall like intraluminal stent-graft deployment.[11,12] By a loss in cushioning function, the speed of pulse wave travel increases, and backward wave reflections may arrive in mid-to-late systole, thereby enhancing systolic blood pressure (i.e., systolic hypertension[13]), and reducing diastolic blood pressure. Moreover, an adverse cardiac afterload pattern occurs, diastolic coronary perfusion reduces, whereas target organs operating at low microvascular resistance and high arterial flow (e.g., kidneys, brain, placenta) absorb more pulsatile energy, in terms of blood pressure (barotrauma) and blood flow (higher shear forces with higher velocity) (**Figure 3**).

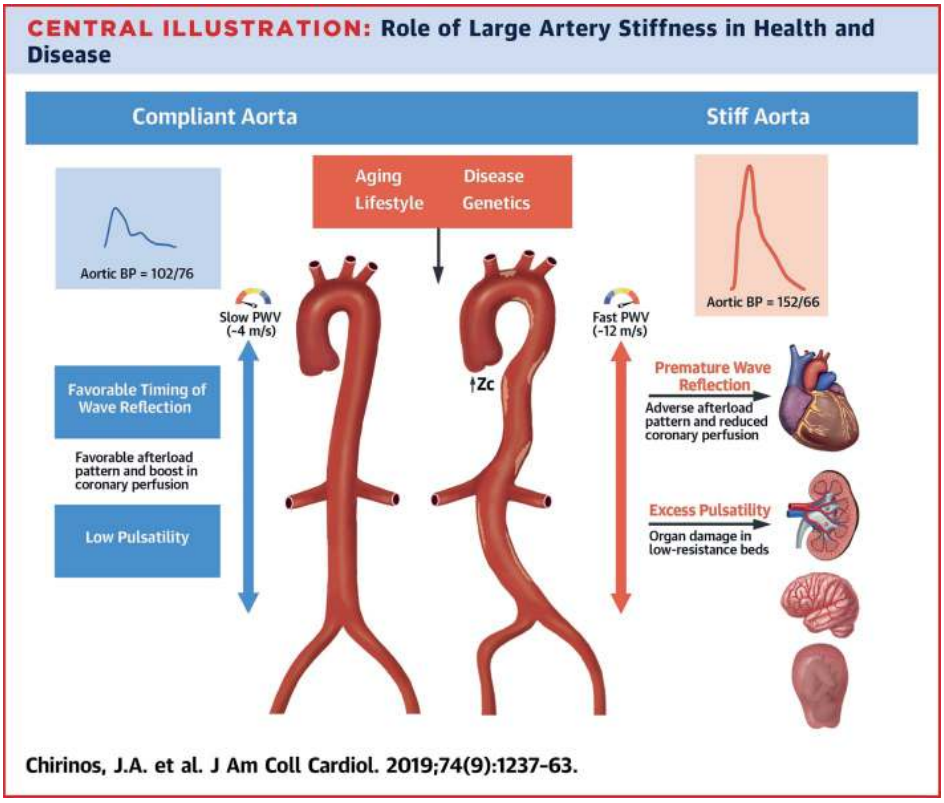

Figure 3. Illustration of healthy blood flow dynamics and the consequences of aortic stiffening (From Chirinos *et al.*[11] (2019); with permission from Elsevier and Copyright Clearance Center to reuse in thesis/dissertation).

Since the aorta is the largest and most distensible artery, it is the primary target to measure clinically relevant arterial stiffness, as mostly performed by non-invasive *in vivo* measurement of carotid-femoral aortic pulse wave velocity (PWV).[11,12] Aortic stiffness, or thus higher or faster aortic PWV, independently predicts the risk of adverse cardiovascular events and plays an important role in determining a patient's cardiovascular health.[11,12,14]

Aortic diseases

Besides aortic stiffening, there is a myriad of aortic diseases occurring at all segments, but with a different incidence, depending on lifestyle factors, familial history, and genetic history.[3,4] The most common aortic disease besides atherosclerosis is an aneurysm, generally defined as a dilatation of 1.5 times the normal diameter and occurring in multiple shapes (e.g., fusiform, saccular).[3,4] Other aortic diseases include acute aortic syndromes

(AAS), in which there is a defect in any of the aortic wall layers. The most common AAS is aortic dissection, where an intimal entry tear allows blood to flow within the medial wall layer, creating a true and false lumen for blood flow. Other AAS include intramural hematoma, where there is no identifiable intimal tear but blood within the media, and penetrating atherosclerotic ulceration, where an ulceration of an atherosclerotic plaque causes a focal disruption of the intima and blood penetration into the media. The aorta may also get damaged by traumatic events, both penetrating and blunt.[3,4,15] Other pathologies of the aorta may be related to or include inflammation, infection, atherosclerotic disease, aortic coarctation, and congenital abnormalities.[3,4]

Aortic surgery

In general, aortic surgery is performed to prevent against aortic rupture, or treat rupture or other life-threatening complications such as end-organ malperfusion.[4] Nowadays, the aortic surgical armamentarium consists of open, endovascular, and hybrid repair techniques. Open surgery consists of replacing a segment of aortic disease by surgical interposition grafting, after opening the respective cavity of the body and approaching the aorta (**Figure 4**). In contrast, endovascular repair consists of the deployment of a stent-graft in the aortic lumen and is considered minimally invasive with lower morbidity and mortality rates (**Figure 4**); however, choice of specific treatment modality also depends on other factors including patients' demographics, comorbidities, clinical presentation, aortic anatomy, surgeon and hospital experience and case-volume, and/or access to endovascular devices.[3,16]

In the thoracic aorta, while thoracic endovascular aortic repair (TEVAR) is increasingly applied to treat the proximal aorta, open surgery remains the first choice for treating zones 0 – 1 (**Figure 1**).[3] Open surgery is also recommended for patients with disease in zone 1 – 2 with a low or intermediate surgical risk, while endovascular repair should be considered for the treatment of zones 1 – 2 in the presence of suitable anatomy as well.[2,3] Endovascular repair is the first choice for aortic disease in zones 3 – 5, while open surgery is complementary in the descending aorta, and remains important as primary treatment option in case of connective tissue disease, unsuitable anatomy, small access vessel diameter, in young patients with a life expectancy exceeding 10 years, or in case of endovascular failure.[2,3,15,18,19] Moreover, similar as for disease involving zones 0 – 2, surgical treatment of zones 6 – 8 necessitates management of vital aortic side-branches (**Figure 1**). On the other hand, surgical treatment of zones 3 – 5 and 9 does not include major side-branch management and is also based on operative risk and aortic anatomy, among the aforementioned factors.[3,16] In any case, surgical options should complement each other, and depend on an informed shared decision-making process between the patient and operating team.

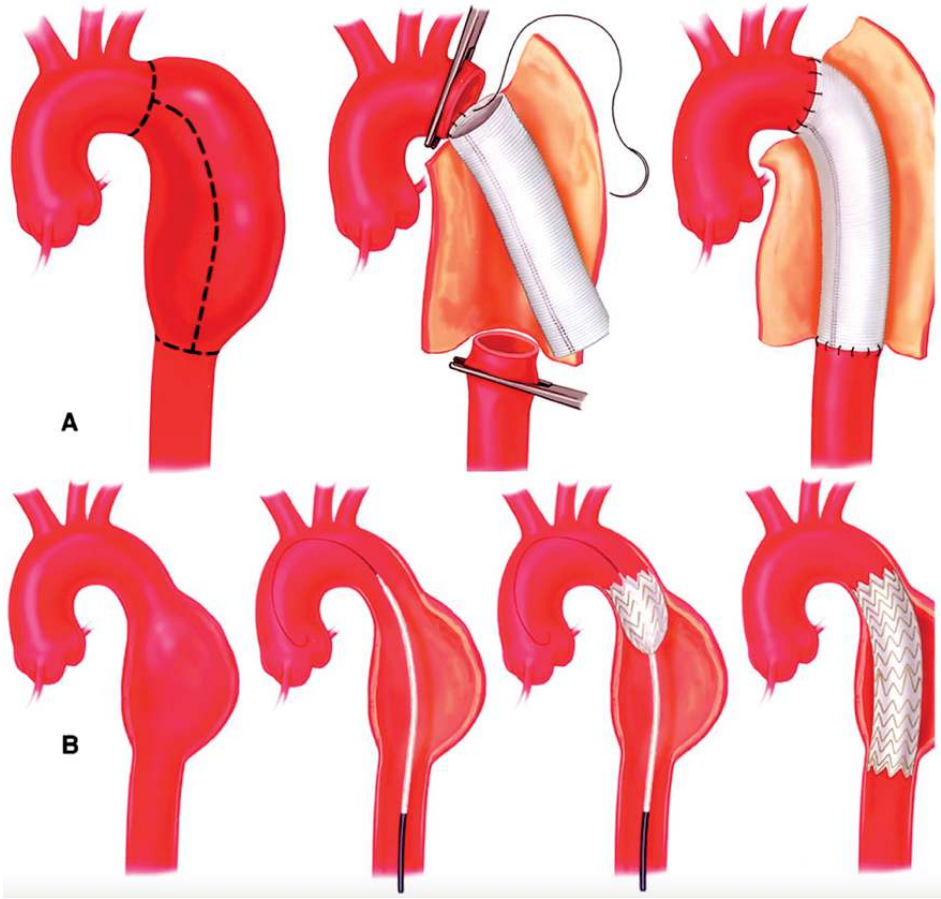

Figure 4. (A) Open surgical interposition grafting of a descending thoracic aortic aneurysm; (B**)** Intraluminal stent-graft deployment of a descending thoracic aortic aneurysm (i.e., thoracic endovascular aortic repair [TEVAR]) (From Isselbacher *et al.*[17] (2005); with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center to reuse in thesis/dissertation).

OBJECTIVES AND THESIS OUTLINE

The above-described key aortic terminology and concepts including anatomy, function, biomechanics, disease, and surgical management are the fundament on which this thesis is built.

The aim of this thesis is to provide multidisciplinary perspectives on aortic biomechanics, anatomy, and open surgical or endovascular treatment of the aorta and its side branches. In light of contemporary advancements in terms of available technologies, medical devices, and expanding indications for surgery (more frequent use of endovas-

cular repair), these aspects and their interaction deserved further exploration. Thereby, this thesis ultimately aims to contribute to the improvement of clinical outcomes of patients with aortic disease.

Part I continues introducing this thesis with **Chapter 2**, a systematic review that assessed the available literature on changes in cardiovascular haemodynamics after endovascular repair of blunt thoracic aortic injury (BTAI).

In **part II**, this thesis presents three experimental studies that utilize a mock cardiovascular circulatory flow loop to perform porcine *ex vivo* analyses on aortic biomechanics including blood flow dynamics, more specifically, on changes in aortic stiffness with different arch geometries and after aortic surgery, as quantified by aortic pulse wave velocity (PWV). **Chapter 3** investigates the role of arch geometry (i.e., angulation) in defining aortic PWV and blood pressures. **Chapter 4** investigates aortic PWV and blood pressures before and after open surgical descending aortic interposition grafting and compares this with TEVAR-induced aortic stiffening. **Chapter 5** investigates potential intergenerational differences in TEVAR-induced aortic stiffening.

Part III of this thesis starts with two studies on *in silico* computational (numerical) tools to virtually simulate endovascular repair of the thoracic aorta, potentially useful for predicting technical and clinical TEVAR outcomes. **Chapter 6** is a scoping review that explores the currently available TEVAR procedure and stent-graft modelling options. **Chapter 7** presents the application of a novel high-fidelity numerical TEVAR simulation methodology to a clinical case. Then, **Part III** continues with two imaging-based studies (i.e., computed tomography and ultrasound) of the proximal thoracic and abdominal aorta. **Chapter 8** is a morphometric analysis of the ascending aorta and aortic arch based on electrocardiogram-gated computed tomography angiography scans. **Chapter 9** is a meta-analysis assessing the most reproducible method of ultrasound caliper placement to measure abdominal aortic diameters.

Part IV of this thesis consists of five clinical studies based on the data from international collaborative registries (i.e., Global Registry for Endovascular Aortic Treatment, Vascular Quality Initiative, International Registry of Acute Aortic Dissection) and single-center experiences. **Chapter 10** presents the long-term (i.e., 5-year) sex-related outcomes of thoracic endovascular aortic repair for any disease, and then performed stratified subgroup analyses for each aortic disease. **Chapter 11** investigates the impact of annual surgeon TEVAR volume on the outcomes of TEVAR for blunt thoracic aortic injury. **Chapter 12** reports long-term (i.e., 10-year) patency rates of surgical left subclavian artery revascularization in the setting of TEVAR with zone 2 proximal seal. **Chapter 13** is a

comparative analysis of in-hospital complications and mortality in patients undergoing zone 2 TEVAR with left subclavian artery revascularization, stratified by revascularization type (i.e., open *vs.* any endovascular). Finally, **Chapter 14** evaluates the role of the International Registry of Acute Aortic Dissection (IRAD) in promoting the understanding and management of acute aortic dissection over its first 25 years of existence.

In **Part V**, we discuss the findings of the different chapters of this thesis in **Chapter 15** and conclude with a summary and discussion in Dutch in **Chapter 16**.

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2

Cardiac and Aortic Modifications after Endovascular Repair for Blunt Thoracic Aortic Injury: A Systematic Review☆

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WHAT THIS PAPER ADDS

This systematic review describes aortic stiffness, blood pressure, cardiac mass, and aortic size increases after follow up of thoracic endovascular aortic repair for blunt thoracic aortic injury. These modifications could have potential adverse effects on both the cardiovascular system and target organs (e.g., kidneys and brain), which emphasise the need for continuous surveillance and patient specific, tailored medicine, particularly in young patients with a long life expectancy.

ABSTRACT

Objective: Blunt thoracic aortic injury (BTAI) is a devastating condition that commonly occurs in healthy and young patients. Endovascular treatment is the first choice; however, it has also been demonstrated to alter cardiovascular haemodynamics. The aim of this systematic review was to describe the cardiovascular modifications after thoracic endovascular aortic repair (TEVAR) for BTAI.

Data Sources: PubMed (MEDLINE), Scopus, and Web of Science were systematically searched for eligible studies reporting on modifications in aortic stiffness, blood pressure, cardiac mass, and aortic size.

Review Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed. The Newcastle-Ottawa Scale was used to assess the methodological quality of included studies.

Results: A total of 12 studies reporting on 265 patients were included. Severe heterogeneity existed among the included studies with regard to demographics, BTAI grade, endograft specifications, reported outcomes, and the method of evaluation. Regarding aortic stiffness, two studies found a significant increase in pulse wave velocity (PWV) in patients after TEVAR compared with a control group, while one did not find a significant increase in PWV and augmentation index after > 3 years of follow up. Five studies reported an increase in the incidence of post-TEVAR hypertension up to 55% (range 34.8% e 55.0%) vs. baseline. One study found a statistically significant increase in left ventricular mass and left ventricular mass index during follow up. Nine studies report data regarding aortic dilatation or remodelling after TEVAR. One found a 2.4 fold faster growth rate in ascending aortic diameter vs. controls, while other studies described significant changes in aortic size at different locations along the aorta and endograft after TEVAR.

Conclusion: This systematic review highlights adverse cardiac and aortic modifications after TEVAR for BTAI. The results stress the need for lifelong surveillance in these patients and the necessity of developing a more compliant endograft to prevent cardiovascular complications in the long term.

INTRODUCTION

Blunt thoracic aortic injury (BTAI) remains a life threatening condition usually occurring at relatively fixed sections of the thoracic aorta such as the aortic isthmus following acute decelerative traumatic events.[1,2] Thoracic endovascular aortic repair (TEVAR) is considered the treatment of choice for grade II, III, and IV lesions[3] according to the clinical practice guidelines of the European and American societies for vascular surgery and cardiology.[2,4,5] TEVAR is associated with a lower morbidity and mortality rate than open surgical aortic repair in the presence of suitable anatomical characteristics.[2,4,5]

However, there is a paucity of available data on the long term adverse effects of aortic endograft implantation on the cardiovascular system and target organs for both abdominal and thoracic aortic diseases.[6] The implantation of an aortic endograft, "a rigid tube" not conforming to the intrinsic elastic mechanical properties of the aortic wall, immediately alters cardiac and aortic haemodynamics by reducing the important cushioning function of the native aorta, thereby inducing segmental vascular or aortic stiffness that plays a central role in the development of cardiovascular disease.[7-10] Increased aortic stiffness, as quantified by pulse wave velocity (PWV, m/s), causes systolic hypertension, puts target organs operating at low local microvascular resistance at risk of pulsatile damage, reduces coronary perfusion pressure, increases cardiac afterload, and promotes left ventricular remodelling.[11-14] Ex vivo porcine experiments have also shown an increase in PWV after the implantation of an aortic endograft.[15,16]

The adverse effects of TEVAR on the cardiovascular system and target organs can be detrimental in the long term, particularly in young patients with a long life expectancy, making BTAI an appropriate disease entity in which to investigate these side effects and discover possible preventive mechanisms.[17]

The aim of this systematic review was to evaluate the available literature and to highlight cardiovascular modifications after TEVAR for BTAI; to describe and analyse baseline patient characteristics, aortic lesion locations, BTAI grades, endograft specifications, cardiovascular modifications, and method of evaluation; and to better understand and improve the associated morbidity and mortality of TEVAR in the long term.

METHODS

Review design

The protocol and methodology of this systematic review was registered with the International prospective register of systematic reviews (PROSPERO) prior to starting the systematic search (ID: 246485). The most recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the recommendations by Koelemay and Vermeulen were followed.[18,19]

PICO framework and objective

Before developing the search strategy, the Patient, Intervention, Comparison, Outcome (PICO) framework[20] was determined to specify the clinical question and objective of this study:

- Patient ("thoracic aortic injury", "aortic trauma");
- Intervention ("endovascular repair", "endovascular treatment","TEVAR");
- Comparison (not applicable for this research question due to the objective stated below);
- Outcome ("vascular stiffness", "pulse wave velocity", "cardiovascular remodelling", "cardiac remodelling", "aortic remodelling").

The main objective of this systematic review was to describe and analyse cardiac related (e.g., cardiac mass and cardiac function) and aorta related modifications (e.g., aortic stiffness, aortic length and diameter, and aortic tortuosity) after TEVAR for BTAI. Related modifications in blood pressure and markers of target organ damage (e.g., renal function) were also addressed.

Literature sources and search strategy

Two authors (T.J.M. and D.B.) independently performed the research process, including the systematic search, study selection with application of inclusion and exclusion criteria, data acquisition and management, data analysis, and quality assessment. In the event of disagreement, a third author (M.D.) was consulted to make the final judgement and provide consensus. The systematic search was performed on 27 August 2021. The study selection process was performed from 28 August to 2 September 2021.

The search was conducted on PubMed (MEDLINE), Scopus, and Web of Science. A study range filter from 1 January 2000 to 31 December 2021 and an English language filter were applied. No registers were queried. The PICO framework was applied to develop and facilitate the search strategy. For every PICO category, relevant keywords, Medical Subject Headings (MeSH) and related free words were applied to the PubMed search to

gather all relevant articles related to this topic. When possible, MeSH terms were used to capture most relevant keywords and to avoid irrelevant and redundant results. Per category, the MeSH terms and free words were combined with "OR". Subsequently, the Patient, Intervention and Outcome categories were combined with "AND". The search strategy used for PubMed was consecutively translated to comparable systematic searches for Scopus and Web of Science. The full search strategy for the three databases, including search terms and applied filters, can be found in Supplementary Table S1.

Study selection

The full search strategy was applied to the three databases to search the available literature systematically. After the removal of duplicates, articles were screened for eligibility starting with title and abstract followed by the retrieval of full text articles and screening on full text eligibility. Consecutively, full text and reference lists of included articles were assessed for other relevant articles possibly eligible for inclusion. EndNote version 20 (Clarivate Analytics, London, UK) was used for reference management and to accelerate the process of duplicate removal. No automation tools were used to perform title, abstract, or full text screening.

Inclusion and exclusion criteria

Every English language original clinical article reporting cardiac and/or aortic modifications after TEVAR treatment for BTAI was included. The exclusion criteria included reviews (both systematic and non-systematic); case report and case series; no separate report of outcomes for BTAI; and no relevant cardiovascular outcomes reported.

Data acquisition

Data were extracted and summarised on a data extraction form using a previously established Excel spreadsheet (Microsoft, Redmond, WA, USA). When possible, groups were created to pool data. Data were extracted regarding study characteristics (e.g., first author, year of publication, study location and design, and study period), baseline patient and control characteristics (e.g., sex, age, weight, height, body mass index [BMI], and duration of follow up), aortic lesion location, blunt thoracic aortic injury grades, endograft specifications (e.g., type, number, length, diameter, percentage oversizing, left subclavian artery coverage, and eventual revascularisation), relevant reported outcomes (e.g., regarding aortic stiffness, blood pressure, cardiac mass and function, and aortic size), and the methods of evaluation and follow up (e.g., computed tomography angiography [CTA] and echocardiography).

Statistical analysis and data description

Data were reported in textual form, as number (frequency), as mean ± standard deviation (SD) or median (range or interquartile range [IQR]). Missing data were reported as (-). To create homogeneity among data in tables, if deemed necessary, mean ± SD from median, range or IQR and sample size were estimated using the formulas provided by Luo et al. and Wan et al.[21,22]

Quality assessment

Possible risk of bias was assessed using the Newcastlee Ottawa scale (NOS) for each included study; this scoring system ranges from 0 to 9.[23] A score of 8-9 was categorized as a low risk of bias and high quality study; 6-7 represented a moderate risk of bias; and a score < 6 was categorised as a study at high risk of bias and of low quality.

Definitions

The location of the aortic lesion was grouped according to its occurrence in specific Criado-Ishimaru aortic zones (zone 1, 2, 3, or 4), and present disease severity was assessed following Azizzadeh et al. and Society of Vascular Surgery defined BTAI grades I, II, III, or IV.[3,4,24,25] Grade I is defined as an intimal tear, grade II as an intramural haematoma, grade III as a pseudoaneurysm, and grade IV as an aortic rupture. The more recent Harborview Grade, classifying different lesions as minimal (grade I and II), moderate (grade III), or severe (grade IV) was obtained if reported.[26] Depending on the study, blood pressure values are reported as the presence or absence of arterial hypertension (defined as a peak systolic blood pressure [SBP] > 140 mmHg, a SBP ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, undefined), or as absolute SBP and pulse pressure (PP) values (Table 4).

RESULTS

Study selection

A total of 846 articles were identified after primary database searching (Fig. 1). After duplicate removal, 525 articles were screened. Altogether, 508 studies were not eligible based on title and abstract screening and availability. Seventeen full text articles were retrieved and assessed. The most important reasons for exclusion were the lack of a separate investigation for BTAI patients specifically, or the lack of relevant cardiovascular outcomes. Finally, 12 articles were included in the qualitative analysis.[27,38] Supplementary Tables S2 and S3 provide a detailed overview of study characteristics and NOS scores.

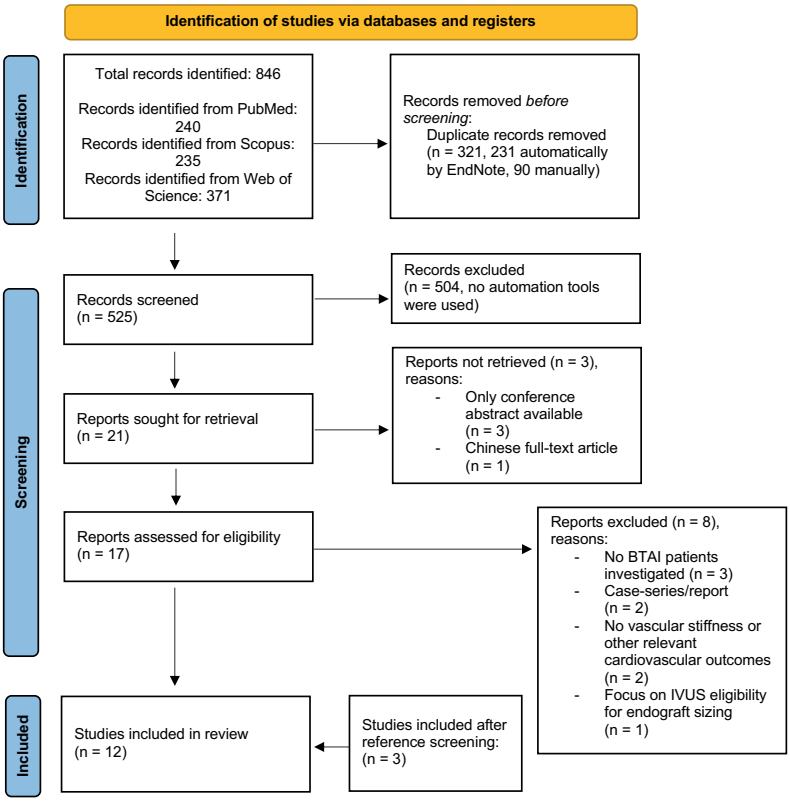

Figure 1. Study selection flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 for new systematic reviews to identify studies reporting cardiac and aortic modifications after endovascular repair of blunt thoracic aortic injury. BTAI = blunt thoracic aortic injury; IVUS = intravascular ultrasound.

Patient and control characteristics

In total, the included studies reported on 265 patients with BTAI and 67 control subjects (Supplementary Table S4). The combined mean age of the entire patient cohort was 45.0 ± 5.7 years, with a median percentage of male patients of 88% (range 68.8% e 100%). The 67 controls were matched for age,[27,28,30] duration of follow up,[27] sex,[28,30] height and BMI,[30] and had a combined mean age of 32.9 ± 5.8 years with a median percentage of male patients of 90% (range 50% e 100%).[27,28,30] The follow up period among studies ranged from a minimum of 0.1 years to a maximum of 14.3 years. Overall, few comorbidities were present, and a detailed specification of the baseline patient and control characteristics is available in Supplementary Tables S4 - S6.

Aortic lesion location and grades

Seven studies[27,28,30-32,34,38] reported the location of the aortic lesion for 134 subjects in total which was located mostly in zone 3 (n = 74, 55.2%), or zone 2 (n = 39, 29.1%) (Table 1). Nine studies[28,30-35,37,38] reported BTAI grades for a total of 204 patients treated by TEVAR. Of these, five were treated for grade I lesions (2.5%), 30 were grade II lesions (14.7%), most were grade III lesions (n = 114, 55.9%), and more than a quarter were grade IV lesions (n = 55, 27.0%; Table 1).

Endograft specifications

Table 2 provides an overview of the endograft specifications. Different types of endografts were used, predominantly TAG (n . 34; 17% [W.L. Gore, Flagstaff, AZ, USA]), CTAG (n = 33; 16% [W.L. Gore]), Relay (n = 33; 16% [Bolton Medical, Sunrise, FL, USA]), and Valiant (n = 31; 15% [Medtronic, Santa Rosa, CA, USA]). The median endograft length and diameter were 100 mm (range 80 - 162 mm) and 26 mm (range 21 - 40 mm), with severe heterogeneity in the amount of oversizing (range 10% - 43%) and aortic coverage (maximum 250 mm or 53.1%), when reported. Because more than one endograft was used in 17 patients, the aortic coverage could exceed the maximum endograft length. Four studies[28-30,33] investigated, but did not find, a correlation between endograft features (e.g., diameter and length) and PWV[28-30] or aortic diameter/axis remodelling.[33]

Main outcomes

Table 3 provides an overview of the reported outcomes per study and the method applied for outcome evaluation. All studies except for one used contrast enhanced CTA as the primary evaluation method to measure predefined outcomes.[27,28,30-36,38] Transoesophageal[28,30] and/or transthoracic[29,30] echocardiography were also adopted.

Table 1. Aortic lesion locations and blunt thoracic aortic injury grades of 265 patients with blunt thoracic aortic injury among the 12 studies included in this systematic review

Author, year	Reported disease	Aortic lesion location	Grade I	Grade II	Grade III	Grade IV	Harborview grade
Kamenskiy, 2020 [27]	Blunt thoracic aortic trauma	Zone 4: 1 (5), Zone 3: 14 (70), Zone 2: 3 (15), Zone 1: 2 (10)	-	-	-	-	-
Tzilalis, 2012 [28]	Thoracic aortic transection (TAT)	Zone 3: 11 (100)	3 (27)	2 (18)	3 (27)	3 (27)	-
Vallerio, 2019 [29]	Thoracic aortic injury (TAI)	-	-	-	-	-	-
Youssef, 2020 [30]	Blunt thoracic aortic injury (TBAI)	Zone 2: 14 (100)	0 (0)	0 (0)	0 (0)	14 (100)	-
Bero, 2020 [31]	Blunt thoracic aortic injury (BTAI)	Zone 4: 4 (12.5), Zone 3: 10 (31.2), Zone 2: 18 (56.2)	0 (0)	8 (25.0)	13 (40.6)	11 (34.4)	-
Fontana, 2018 [32]	Blunt traumatic thoracic aortic injuries (BTTAIs)	Zone 4: 1 (4.3), Zone 3-4: 10 (43,5%), Zone 3: 9 (39.1), Zone 2-3: 3 (13.1)	0 (0)	4 (17)	10 (43)	9 (39)	-
Gennai, 2020 [33]	Blunt thoracic aortic injuries (BTAI)	-	1 (2.1)	7 (14.9)	39 (83)	0 (0)	-
Kim, 2017 [34]	Acute traumatic transection of the thoracic aorta (TTA)	Mean transection to LSA distance: 14 ± 9 (0–31) mm	0 (0)	0 (0)	15 (88)	2 (12)	-
Tran, 2020 [35]	Traumatic blunt thoracic aortic injuries (BTAI)	-	1 (5)	1 (5)	18 (90)	0 (0)	Moderate: 14 (70), Severe: 6 (30)
Forbes, 2010 [36]	Blunt traumatic thoracic aortic injuries (BTAI)	-	-	-	-	-	-
Tigkiropoulis, 2018 [37]	Blunt thoracic aortic injury (BTAI)	-	0 (0)	0 (0)	9 (39.1)	14 (60.9)	-
Canaud, 2015 [38]	Acute traumatic transection of the thoracic aorta	Zone 3: 13 (76), Zone 2: 4 (24)	0 (0)	8 (47%)	7 (41)	2 (12)	-

Data are presented as *n* (%). BTAI = blunt thoracic aortic injury; TAT = thoracic aortic transection; TAI = thoracic aortic injury; BTTAI = blunt traumatic thoracic aortic injury; TTA = acute traumatic transection of thoracic aorta; LSA = left subclavian artery.

Table 2. Specifications of the endografts used to treat 265 patients with blunt thoracic aortic injury among the 12 studies included in this systematic review

Author, year	Type (patients)	Endografts per patient (patients)	Length - mm	Diameter - mm	Oversizing - %	DTA-aortic coverage - % or mm	LSA coverage	Secondary LSA revascularization	Time from trauma to TEVAR - d
Kamenskiy, 2020 [27]	Excluder (10), CTAG (6), TAG (3), Talent (1)	Excluder: 1 stent (3), 2 stents (4), 3 stents (3), Talent: 2 stents (1)	-	-	-	32.2 ± 11.3 (13.0–53.1)	-	-	-
Tzilalis, 2012 [28]	Talent (7), TAG (3), Relay (1)	-	114 (100-150)	34 (30-38)	-	-	-	-	-
Vallerio, 2019 [29]	CTAG (11), Valiant (9)	Not specified: 2 stents (1)	100 (100-150)	-	17.2 ± 6.7 (CTAG), 17.9 ± 2.3 (Valiant)	-	7 (35)	-	-
Youssef, 2020 [30]	TAG (11), Valiant (3), Endurant II (1)	TAG: 2 stents (2), TAG+Valiant: 1 stent each (1)	100 (82-150)	Proximal: 26 (21-31), distal 26 (21-31)	10-20	- (100-250)	14 (100)	-	-
Bero, 2020 [31]	-	-	-	-	19 (11-43)	101.7 ± -	18 (56.2)	5 (15.6)	3 ± - (0-42)
Fontana, 2018 [32]	Excluder (3), Talent (1), Zenith TX2 (1), TAG (10), Valiant (8)	Single stent (23)	100 (100-150)	28 (21-36)	10.5 (6.5-20)	110.65 ± - (100-150)	3 (13)	0 (0)	-
Gennai, 2020 [33]	Relay (32), Zenith Alpha (6), Talent (2), TAG (7)	-	100 (80-162)	26.9 ± 3.5 (21-34)	18.1 ± 9.6 (Relay), 22.5 ± 13.1 (Valiant), 19.4 ± 9.3 (TAG), 22.2 ± 3.1 (Talent)	112.81 ± 3.54 (80-155)	16 (34)	4 (9)	-
Kim, 2017 [34]	S&G Biotech, Seongnam, Korea (17)	-	110 ± 19	30 ± 3	15-20	-	Full: 4 (24), Partial: 8 (47)	0 (0)	0.83 ± 1.13 (max 10 days)
Tran, 2020 [35]	CTAG (16), Zenith Alpha (4)	Single stent (20)	100 [100-102.5 IQR]	26 [21-28 IQR]	30.3 [16-32.5 IQR]	-	0 (0)	0 (0)	0.90 [0.08-3 IQR]
Forbes, 2010 [36]	Talent-Valiant (11), Zenith TX2 (10)	-	-	- (22-34)	Maximum 10%	-	12 (57)	1 (4.8)	-
Tigkiropoulis, 2018 [37]	TAG (2), Relay (2), Ankura (3), Endofit (15), Valiant (1)	TAG: 2 stents (1), Endofit: 2 stents (1)	-	-	-	-	6 (26)	1 (4.3)	-
Canaud, 2015 [38]	Excluder (7), Talent (9), Zenith distal extension cuff (1)	-	104 ± 27 (100-150)	28.4 ± 3 (22-40)	25 ± 9	-	4 (24)	2 (12)	5.2 ± 7.8

Data reported as *n* (%), median (range) or mean ± standard deviation (range). DTA = descending thoracic aorta; LSA = left subclavian artery; TEVAR = thoracic endovascular aortic repair; IQR = interquartile range.

Table 3. Reported outcomes, evaluation method, and duration of follow up among the 12 studies included in the systematic review evaluating cardiac and aortic changes after endovascular repair for blunt thoracic aortic injury

Author, year	Reported outcomes per study	Evaluation method	Follow-up, mean ± SD (range), years	Follow-up, median (range), years
Kamenskiy, 2020 [27]	LV mass, LVMi, hypertension, ATA diameter, ATA length	Contrast-enhanced CTA	5.1 ± 3.1 (1.1-12.3)	-
Tzilalis, 2012 [28]	PWV, SBP, PP	CTA, TEE, Micro Medical Pulse Trace, Sphygmomanometry in the brachial artery	(1.08-5.5)	(1.08-5.5)
Vallerio, 2019 [29]	PWV, AIx, SBP, aortic root-ascendens-arch at LCCA origin diameter, LV mass index-deceleration time-ascendens index diameter	CTA, Mobil-O-Graph ABPM device, echocardiography	-	5.0 ± 3.5†
Youssef, 2020 [30]	PWV, hypertension, heart failure: NT-proBNP levels and echocardiography	CTA, TEE, MRA, AngE Pro8 software, echocardiography	5.3 ± 1.8	-
Bero, 2020 [31]	Ascending aorta-midaortic arch-PLZ-DLZ diameter, ascending aorta-aortic arch length	High-resolution CTA	1.7 ± - (0.06-8)	-
Fontana, 2018 [32]	Aortic diameters at 4 locations*	CTA	5.45 ± - (1-14.25)	-
Gennai, 2020 [33]	Aortic remodeling: diameter variation >2mm, angle modification between distal endograft and aortic axis	CTA	-	5.62 ± 4.68 (1.67-12.75)†
Kim, 2017 [34]	Aortic diameter: mean, at LSA level	CT	3.75 ± 2.67 (0.5-8.5)	-
Tran, 2020 [35]	Aortic dilatation at 6 locations*	CTA	-	3.9 (1-6.67)
Forbes, 2010 [36]	Aortic dilatation at 4 locations*	CT	2.6 ± - (1-5.5)	-
Tigkiropoulis, 2018 [37]	Post-implant hypertension	Sphygmomanometry in the brachial artery	-	8.33 (1.5-10)
Canaud, 2015 [38]	Proximal and distal aortic neck dilatation	Contrast-enhanced CT	-	11.7 (10-13.2)

Data are presented as mean ± standard deviation (SD) (range) or as median (range). LV = left ventricular; LVMi = LV mass index; ATA = ascending thoracic aorta; CTA = computed tomography angiography; PWV = pulse wave velocity; SBP = systolic blood pressure; PP = pulse pressure; TOE = transoesophageal echocardiography; AIx = augmentation index; LCCA = left common carotid artery; ABPM = ambulatory blood pressure monitoring; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; MRA = magnetic resonance angiography; PLZ = proximal landing zone; DLZ = distal landing zone; LSA = left subclavian artery; CT = computed tomography.

* Reported in the respective study as median ± SD.

† See Table 6.

Aortic stiffness and blood pressure modifications. Table 4 provides an overview of the aortic stiffness and blood pressure outcomes. Two studies[28,30] reported an increase in PWV in patients after TEVAR vs. a control group (10.41 ± 0.85 m/s vs. 7.45 ± 0.66 m/s [p =. .006] and 10.34 ± 2.07 m/s vs. 7.42 ± 1.22 m/s [p < .001]). Five studies[27-30,37] reported an increase in the incidence of arterial hypertension, ranging from 34.8% to 55% post-operatively.

Cardiac findings. Table 5 provides an overview of the cardiac outcomes. Three studies[27,29,30] evaluated cardiac modifications after TEVAR for BTAI. Kamenskiy et al.[27] reported an increase in left ventricular (LV)mass and LV mass index (LVMi) at a mean follow up of 5.1 3.1 years, evaluated with three dimensional CTA. LV mass and LVMi showed significant growth rates in the patient group, while LV mass and LVMi remained stable over time. Two studies[29,30] evaluated cardiac modifications using echocardiography: Vallerio et al.[29] reported an increase in LVMi after division for time after treatment (> 3 years), while Youssef et al.[30] did not find significant changes in LV mass, systolic wall function, or elevated N-terminal pro-brain natriuretic peptide levels. However,Youssef et al.[30] reported diastolic dysfunction grade I in 60% of post-operatively hypertensive patients (36%).

Aortic dilatation. Table 6 provides an overview of the aortic dilatation outcomes. In total, nine studies[27,29,31-36,38] reported aortic modifications after TEVAR for BTAI, three[27,29,31] evaluated changes in the ascending aorta (AA), and eight[27,29,31,33-36,38] in the aortic arch. Kamenskiy et al.[27] found a 2.4 fold faster AA diameter growth rate in the patient group. Moreover, Vallerio et al.[29] found a greater AA diameter and diameter at the left common carotid artery runoff after division for time after treatment (> 3 years). Bero et al.[31] found changes in AA and aortic arch diameter and length over time, while the diameters of the proximal landing zone (PLZ), distal landing zone (DLZ), and distal seal zone also changed. Canaud et al.[38] reported a net increase in PLZ and DLZ diameter and found a greater net PLZ increase in younger patients after division for age (< 30 years), while Gennai et al.[33] found that the aortic axis between the distal part of the endograft and the curvature of the thoracic descending aorta distal to the endograft decreased over time.

Table 4. Aortic stiffness and blood pressure outcomes for the five studies included in the systematic review that evaluated this after endovascular repair for blunt thoracic aortic injury

Author, year	Group	HT, baseline - %	HT, FU - %	SBP, FU - mmHg	PP, FU - mmHg	Anti-hypertensive drug treatment at FU (*n*)	Risk factors for post-implant HT	PWV, location	PWV, FU - m/sec	AIx - %
Kamenskiy, 2020 [27]	Patient	5	50	-	-	-	-	-	-	-
	Control	24	29	-	-	-	-	-	-	-
	Males / females	19 / 24	19 / 38							
Tzilalis, 2012 [28]	Patient	-	-	134.1 ± 13.75, p = .016	60.45 ± 19.42, p = .020	Irbesartan-Metoprolol (1), Irbesartan (1), Captopril-Metoprolol (1)	-	RCCA to RFA	10.41 ± 0.85, p = .006	-
	Control	-	-	121.36 ± 7.1	44.1 ± 4.37	-	-	RCCA to RFA	7.45 ± 0.66	-
Vallerio, 2019 [29]	Patient	0	55	<3 years: 120.1 ± 6.6, >3 years: 128.3 ± 14.3, p <.01	-	(12; 55%) treated	-	-	<3 years: 6.3 ± 1.1, >3 years: 7.5 ± 1.9, NS	<3 years: 16.2 ± 7.4, >3 years: 19.1 ± 7.6, NS
Youssef, 2020 [30]	Patient	0	36	-	-	(5; 36%) treated, 3-5 diastolic dysfunction grade I without AoI	-	Right upper limb to both thighs	10.34 ± 2.07, p <0.01	-
	Control	-	-	-	-	-	-	Right upper limb to both thighs	7.42 ± 1.22	-
Tigkiropoulis, 2018 [37]	Patient	-	34.8 (previously non-HT)	-	-	B-blockers (8), Ca-channel-blocker (4), ACE-I (2), Clonidine (1)	Younger age, p = .027; LSA coverage, p = .01	-	-	-

Data are presented as *n* (%), median (range) or mean ± standard deviation (range). HT = hypertension; FU = follow up; SBP = systolic blood pressure; PP = pulse pressure; PWV = pulse wave velocity; AIx = augmentation index; RCCA = right common carotid artery; RFA = right femoral artery; NS = not significant; AR = aortic regurgitation; ACEi = angiotensin converting enzyme inhibitor.

Table 5. Cardiac outcomes for the three studies included in the systematic review that evaluated this after endovascular repair for blunt thoracic aortic injury

Author, year	Group	LV mass, baseline at 3D CTA - g	LV mass, FU at 3D CTA - g	LV mass index, baseline, at 3D CTA - g/m^2	LV mass index, FU, at 3D CTA - g/m^2	LV mass growth at 3D CTA - g/year	LV mass index growth at 3D CTA - g/m^2/year
Kamenskiy, 2020 [27]	Patient	138.5 ± 39.6, p=.33	173.5 ± 50.1, p<0.01	72.35 ± 15.17, p=.06	85.48 ± 18.34, p<0.01	10.03 ± 12.79, p<0.01	6.25 ± 10.28, p<0.01
	Control	113.8 ± 27.6	116.3 ± 30.3	58.29 ± 11.64	58.44 ± 11.74	−0.01 ± 3.75, p=0.98	−0.25 ± 1.90, p=0.40
	Male / Female	128.3 ± 24.5 / 99.4 ± 22.9	133.4 ± 28.7, p=0.24 / 99.3 ± 21.2, p=0.95	64.04 ± 11.65 / 52.53 ± 8.52	64.09 ± 10.83, p=0.98 / 52.79 ± 9.89, p=0.85	0.84 ± 4.27, p=0.38 / −0.87 ± 3.02, p=0.20	−0.15 ± 1.66, p=0.68
		LVMi, FU in echo - g/m^2	**E wave deceleration time, FU in echo**	**Diastolic dysfunction in echo**	**LV mass in echo**	**Systolic wall function in echo**	**Elevated NT-proBNP, FU**
Vallerio, 2019 [29]	Patient	<3 y: 70.2 ± 9.4, >3 y: 91.2 ± 34.7, p<0.05	<3 y: 205.6 ± 22.9, >3 y: 164.4 ± 22.9, p<0.01	-	-	-	-
Youssef, 2020 [30]	Patient	-	-	3 out of 5 hypertensive TEVAR patients, grade I	NS change in patients vs. controls	NS change in patients vs. controls	2-14 patients, NS
	Control	-	-	3 out of 5 hypertensive TEVAR patients, grade I	NS change in patients vs. controls	NS change in patients vs. controls	2-14 patients, NS

Data are presented as *n* (%), median (range) or mean ± SD (range). 3D = three dimensional; CTA = computed tomography angiography; LV = left ventricle; FU = follow up; LVMi = LV mass index; ECHO = echocardiography; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; TEVAR = thoracic endovascular aortic repair; NS = not significant.

Table 6. Aortic dilatation outcomes for the nine studies included in the systematic review that evaluated this after endovascular repair for blunt thoracic aortic injury

Author, year	Group	ATA diameter, baseline - mm	ATA diameter, FU - mm	ATA length, baseline - mm	ATA length, FU - mm	ATA diameter growth - mm/year	ATA length growth - mm/year
Kamenskiy, 2020 [27]	Patient	27.6 ± 3.4, p=.29	30.3 ± 3.8, p<0.01	75.5 ± 13.7, p=.65	79.6 ± 10.5, p<0.01	0.60 ± 0.80, *p* <0.01, 2.4-fold faster compared to control cohort, p=.04)	0.58 ± 1.43, p=.04
	Control	28.9 ± 4.7	30.1 ± 5.0, p<0.01	73.9 ± 11.6	76.2 ± 12.5, p=0.02	0.25 ± 0.44, p<0.01	0.58 ± 1.96, p=0.03
	Male / Female	29.7 ± 4.7 / 28.0 ± 4.6	30.9 ± 4.8, p=0.25 / 29.3 ± 5.1, p=0.30	76.3 ± 11.9 / 71.5 ± 11.1	79.3 ± 14.1, p=0.02 / 73.1 ± 10.1, p=0.28	0.27 ± 0.5 / 0.22 ± 0.37	0.78 ± 1.78, p=0.03 / 0.38 ± 2.16, p=0.22
		Aortic root diameter in CTA, FU - mm	**AA diameter in CTA, FU - mm**		**Aortic diameter at LCCA runoff in CTA, FU - mm**		**Ascendens indexed diameter, FU - cm/m²**
Vallerio, 2019 [29]	Patient	<3 y: 31.4 ± 5.1, >3 y: 31.9 ± 5.2, p<0.05	<3 y: 29.9 ± 6.9, >3 y: 32.0 ± 5.1, p<0.01		<3 y: 27.3 ± 3.6, >3 y: 28.3 ± 3.6, p<0.01		<3 y: 1.6 ± 0.2, >3 y: 1.9 ± 0.5, p<0.01
		Δ Aorta ascendens diameter - mm	**Δ Midaortic arch diameter - mm**	**Δ PLZ diameter - mm**	**Δ DLZ diameter - mm**	**Δ DSZ diameter - mm**	**Δ Ascendens length - mm**	**Δ Aortic arch length - mm**
Bero, 2020 [31]	Patient	Pre-post TEVAR: 1.5 ± 1.5, p<0.001, Post-TEVAR-each interval: 0.3 ± 2.6, p=0.594	Pre-post TEVAR: 1.3 ± 1.7, p<0.001, Post-TEVAR-each interval: 0.6 ± 1.4, p<0.001	Pre-post TEVAR: 1.9 ± 2.1, p<0.001	Pre-post TEVAR: 2.2 ± 1.6, p<0.001	Post-TEVAR-each interval: 0.9 ± 0.8, p<0.001	Pre-post TEVAR: 5.7 ± 4.6, p<0.001, Post-TEVAR-each interval: 3.0 ± 4.4, p<0.05	Pre-post TEVAR: 0 ± 3.2, p=0.962, Post-TEVAR-each interval: -0.5 ± 2.5, p=0.334
		Growth diameter A* - mm	**Growth diameter D* - mm**	**Growth diameter B* - mm**		**Growth diameter C* - mm**	**Division for age ≤30 years / >30 years, median increment - mm**	**Division for FU duration >60months / ≤60months, median increment - mm**
Fontana, 2018 [32]	Patient	0.7 ± 0.4379 (median 0.7, range 0.0-1.9)	0.5 ± 0.3976 (median 0.4, range 0.0-2.2)	0.5 ± 0.4446 (median 0.4, range 0.0-1.7)		0.5 ± 0.5304 (median 0.5, range 0.0-1.7)	A: 0.8 / 0.65, D: 0.5 / 0.25, B: 0.4 / 0.4, C: 0.4 / 0.5 (all NS)	A: 0.9 / 0.4, D: 0.55 / 0.1, B: 0.6 / 0.3, C: 0.5 / 0.2 (A: p=0.0046, B: p=0.013, rest NS)
		Kaplan-Meier freedom from remodeling at 1, 3, 6, 10 years	**Mean increment D1/2† at 1, 6, 10 years - mm**	**Mean increment D3† at 1, 6, 10 years - mm**	**Mean increment D4† in last available FU CT - mm**	**Increase in D1/D2† and D3† influenced by:**	**Distal aortic axis angulation**	**Relation oversizing / proximal diameter remodeling**
Gennai, 2020 [33]	Patient	85.1%, 61.9%, 30.9%, 24.7%	2.1, 3.0, 4.3	0.4, 2.0, 3.4	0.1	Time from intervention, age, LSA coverage	Decreased over time	10% increase in oversizing associated with 3.4% D1/D2 increase

Table 6. Aortic dilatation outcomes for the nine studies included in the systematic review that evaluated this after endovascular repair for blunt thoracic aortic injury (*continued*)

Author, year	Group	ATA diameter, baseline - mm	ATA diameter, FU - mm		ATA length, baseline - mm		ATA length, FU - mm	ATA diameter growth - mm/year		ATA length growth - mm/year
		Increase in aortic diameter at LSA level - mm	Significant aortic remodeling‡ - *n* (%)	Δ diameter landmark A‡ - mm	Δ diameter landmark B‡ - mm	Δ diameter landmark C‡ - mm	Δ diameter landmark D‡ - mm	Δ diameter landmark E‡ - mm	Δ diameter landmark F‡ - mm	Landmark D‡, growth rate
Kim, 2017 [34]	Patient	2 ± 1 (0-5)	-	-	-	-	-	-	-	-
Tran, 2020 [35]	Patient	-	14 (70)	0.7 ± 1.2, p=0.89	0.9 ± 0.7, p=0.009	1.2 ± 1.2, p=0.0007	1.8 ± 1.6, p=0.0006	1.7 ± 1.3, p=0.003	0.2 ± 0.4, p=0.287	0,67mm/y, p=0.006 (nearly linear)
		D1§, growth rate - mm/y	D2§, growth rate - mm/y	D3§, growth rate - mm/y	D4§, growth rate - mm/y			Net increase proximal neck diameter - mm		Net increase distal neck diameter - mm
Forbes, 2010 [36]	Patient	0.71, (95% CI 0.42-1.06), p=0.07	0.83 (95% CI 0.55-1.11), p=0.025	0.63 (95% CI 0.37-0.89), p=0.06	0.47 (95% CI 0.27-0.67), no p-value			-		-
Canaud, 2015 [38]	Patient	-	-	-	-			3.3 ± 1.5 at 10 y FU: significantly greater in <30 y group vs. >30 y group: 4 ± 1.2 mm vs. 1.5 ± 1.7 mm, p=0.0037		2.7 ± 1

Data are presented as *n* (%), median (range), or mean ± standard deviation (range). ATA = ascending thoracic aorta; FU = follow up; CTA = computed tomography angiography; AA = ascending aorta; LCCA = left common carotid artery; PLZ = proximal landing zone; DLZ = distal landing zone; DSZ = distal seal zone; TEVAR = thoracic endovascular aortic repair; NS = not significant; LSA = left subclavian artery; CI = confidence interval.

Landmarks: A = proximal take off of LSA; B = proximal edge endograft; C = 2 cm distal to proximal endograft edge; D = 2 cm proximal to distal endograft edge; E = distal endograft edge; F = 2 cm distal to distal endograft edge.

* A: 1 cm proximal to endograft edge; B: 2 cm distal to proximal endograft edge; C: 2 cm proximal to distal endograft edge; D: 1 cm distal to endograft edge.

† D1: landing zone 2 diameter, 2 mm proximal to top of endograft; D2: landing zone 3 diameter, 2 mm proximal to top of endograft; D3: distal neck diameter distal end of endograft; D4: diameter 15 mm distal to endograft.

‡ Aortic dilatation was considered significant as average diameter growth >5%.[35]

§ D1: proximal to LSA origin; D2: distal to LSA origin; D3: distal end endograft; D4: 15 mm distal to distal end endograft.

DISCUSSION

This systematic review highlights important increases in aortic stiffness, blood pressure, cardiac mass, and aortic size after endovascular aortic repair in young patients suffering BTAI. Young patients generally have less aortic stiffness,[9] fewer comorbidities, and fewer cardiovascular risk factors, and are thus healthier when an endograft is deployed into their elastic, native aorta than elderly patients with aortic disease. Therefore, the use of TEVAR in younger patients requires specific attention, and possible adverse effects on the cardiovascular system and target organs need to be prevented in both the immediate post-operative phase and in the long term wherever possible, without questioning the application of TEVAR for aortic emergencies such as BTAI.

The main findings and the paucity of available data (265 patients with BTAI in total) confirm that BTAI is a rare disease entity and that patients are generally young (combined mean age 45.0 ± 5.7 years), and male (median 88%). Moreover, the main findings confirm that BTAI mostly occurs in the region of the aortic isthmus with more than 80% occurrence in zone 3 and 2 and that 80% of TEVAR was performed for grade III or IV lesions, which is in line with most recent treatment guidelines.[2,4,5] However, 35 patients (17.2%) were treated for grade I and grade II lesions. This contrasts with the current treatment guidelines,[2,4,5] where TEVAR is not recommended for grade I aortic lesions, but rather active blood pressure control with close follow up imaging. There is also increasing evidence supporting the safety of non-operative management for grade II aortic lesions.[17,39]

The main findings regarding the cardiovascular changes after TEVAR for BTAI confirm the expected increase in aortic stiffness, as quantified by PWV. As a surrogate for aortic stiffness, an increase in the PWV represents an increase in aortic stiffness, which is an established risk factor for the development of cardiovascular and target organs damage via the aforementioned mechanisms.[9] A recent systematic review and meta-analysis investigated the impact of abdominal endovascular aortic repair (EVAR) and TEVAR vs. open surgical aortic repair on aortic stiffness.[40] This systematic review demonstrated a significant increase in aortic stiffness after both EVAR and TEVAR, but not after open surgical aortic repair, and highlights the possible deleterious impact of endograft deployment on the cardiovascular system.[40]

An ex vivo experiment has also shown that the degree of PWV increase is dependent on the length of aortic coverage,[15] providing a possible option to develop shorter endografts to treat BTAI and minimise subsequent increases in PWV, or to use the shortest available endograft when possible. However, in contrast to these findings, clinical investigations by Yamashita et al. and Moulakakis et al. did not find a relationship between the length

of aortic coverage and subsequent increase in PWV.[41,42] Therefore, this aspect might merit further investigation.

As BTAI occurs after an acute traumatic event, this explains why baseline PWV measurements are not available in these patients and why two studies accounted for this complexity by comparing the PWV values of patients at follow up with matched controls. If pre-operative PWV values are obtained in the future, then these values can be compared with values at follow up, which could aid in the understanding of PWV increases following TEVAR for specific aortic disease entities and give insight into possible preventive strategies.

Pre-operative blood pressure values are usually known, and five studies[27-30,37] reported significant increases in the incidence of arterial hypertension or absolute SBP and PP values post-TEVAR, underlining the need for active blood pressure control in the immediate post-operative phase and at regular long term follow up visits. When interpreting the post-operative incidences of arterial hypertension, potential confounders must be emphasised (e.g., pre-operative blood pressure, time of measurement, definition of arterial hypertension, and comparison against controls).

Depending on the type of measurement, cardiac data deriving from post-operative CTA can be compared with baseline pre-operative values, as reported by Kamenskiy et al.,[27] who found significant increases in LV mass, LVMi, and associated growth rates per year of follow up. Interestingly, the predominantly male (85%) patient group was compared with a male subgroup of controls in this study, taking a lower LV mass for females into account. These findings correspond to computational findings of increased LV stroke work and mass due to the stiffness mismatch between the endograft and the aorta in descending thoracic aortic pathology.[43] If cardiac data is assessed by transoesophageal or transthoracic echocardiography, comparison with pre-operative values might not be possible owing to the lack of an available pre-operative echocardiogram. Again, if these data are available, a better comparison and understanding of cardiac changes after endovascular aortic repair could be obtained.

The main findings regarding aortic size are mostly assessed by CTA, which allows for a comparison between post-operative and pre-operative aortic data. However, Tran et al.[35] compared the last available follow up CTA with the first post-operative CTA, within one month post-operatively. It is important to note the associated difficulties in choosing the appropriate amount of oversizing when treating BTAI, because aortic diameters at different locations are significantly reduced in the pre-operative hypovolaemic shock

state, as shown in a case report and porcine model.[44,45] This might also influence the pre-operative and post-operative comparison of aortic diameters in patients with BTAI.

In summary, nine studies[27,29,31-36,38] confirm significant aortic dilatation in different aortic segments after TEVAR with increases in AA diameter and AA growth rate, among other findings. Interestingly, Canaud et al.[38] found a greater net PLZ increase in younger patients after division for age, which might suggest that young patients have more elastic mechanical wall properties compared with older patients, which corresponds to the concept that aortic stiffness develops over time.[9,10] Moreover, it can be hypothesised, according to the Windkessel effect,[46] that the reduced storage of blood volume during systole in stented aortic segments might be (partially) compensated for by more proximal and distal unstented aortic segments, thus influencing aortic growth in these segments, potentially causing device related complications (e.g., endoleaks and endograft migration) in the long term. This stresses the need for lifelong surveillance.

Future perspectives

A wider array of pre-operative assessments may possibly help in discovering more preventive strategies to improve outcomes in young patients receiving TEVAR. To increase the comparability of future studies, authors could aim to assess cardiac and aortic modifications in a standardized manner by obtaining both pre- and post operative values at certain intervals, using the same imaging techniques (e.g., morphological and functional cardiac evaluation using echocardiography, and PWV using the carotid-femoral method). Future studies might also focus on the short, mid, and long term outcomes of the non-operative management for grade III aortic lesions with close monitoring and compare this with endovascular treatment options. In this way, treatment modalities in terms of associated morbidity and mortality for specific BTAI grades could be improved. Device manufacturers can focus on developing more compliant endografts to improve the stiffness mismatch between the endograft and the aorta. Finally, obtaining long term follow up data after TEVAR in young patients remains an important issue to improve current and future endovascular treatment modalities.

Limitations

The strength of the results is limited by the number of available studies; the rarity of BTAI, which is associated with a high mortality before reaching hospital (80% - 90%[2]); poor long term follow up after BTAI treatment;[47] and thus a small number of cases to investigate. The included studies showed great heterogeneity in addressing different outcomes of TEVAR for BTAI, while applying different methods of outcome evaluation. Moreover, a meta-analysis was not performed as the added value was expected to be low owing to the small number of studies reporting the same outcome. Thus, the pool-

ing of data would have been inappropriate, and a robust comparison could not be made. Furthermore, for nine studies (75%), the risk of bias was estimated to be moderate. Nevertheless, this is the first systematic review to address this specific topic and highlights important cardiovascular modifications after TEVAR in young patients.

Conclusion

Expanding indications for endovascular aortic repair in a younger patient group raises several concerns regarding the possible adverse effects on the cardiovascular system and target organs. The main findings illustrate several significant modifications at the cardiac and aortic level but with great clinical heterogeneity. These might have detrimental effects in the long term, and lifelong surveillance with patient specific tailored medicine to prevent complications are warranted, focusing not only on technical results, but also on adverse cardiovascular changes. Endograft manufacturers should focus on the development of more compliant and possibly shorter endografts for the treatment of BTAI.

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Part II

Experimental Perspectives

3

Type III aortic arch angulation increases aortic stiffness: Analysis from an ex vivo porcine model☆

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CENTRAL MESSAGE

Increased aortic arch angulation – as observed in a type III arch – is associated with higher aortic PWV and blood pressures in this porcine *ex vivo* study.

PERSPECTIVE

Previous literature has highlighted increases in systolic pulse wave reflections, central aortic stiffness, and hypertension in patients with postoperative geometrical configurations with an increased aortic arch angulation. The close relationship among these aspects remains to be further clarified and was studied by this experimental study utilizing a mock cardiovascular circulatory loop.

ABSTRACT

Objective: The relationship among increased aortic arch angulation, aortic flow dynamics, and vessel wall stiffness remains unclear. This experimental ex vivo study investigated how increased aortic arch angulation affects aortic stiffness and stent-graft induced aortic stiffening, assessed by pulse wave velocity (PWV).

Methods: Porcine thoracic aortas were connected to a circulatory mock loop in a Type I and Type III aortic arch configuration. Baseline characteristics and blood pressures were measured. Proximal and distal flow curves were acquired to calculate PWV in both arch configurations. After that, a thoracic stent-graft (VAMF2626C100TU) was deployed in aortas with adequate proximal landing zone diameters to reach 10% t0 20% oversizing. Acquisitions were repeated for both arch configurations after stent-graft deployment.

Results: Twenty-four aortas were harvested, surgically prepared, and mounted. Cardiac output was kept constant for both arch configurations (Type I: 4.74 ± 0.40 and Type III: 4.72 ± 0.38 L/minute; $P = .703$). Compared with a Type I arch, aortic PWV increased significantly in the Type III arch (3.53 ± 0.40 vs 3.83 ± 0.40 m/second; $P < .001$), as well as blood pressures. A stent-graft was deployed in 15 aortas. After deployment, Type I arch PWV increased (3.55 ± 0.39 vs 3.81 ± 0.44 m/second; $P < .001$) and Type III arch PWV increased although not significantly (3.86 ± 0.42 vs 4.03 ± 0.46 m/second; $P = .094$). Type III arch PWV resulted the highest and significantly higher compared with the Type I arch after stent-graft deployment (3.81 ± 0.44 vs 4.03 ± 0.46 m/second; $P = .023$).

Conclusion: Increased aortic arch angulation—as in a Type III arch—is associated with higher aortic PWV and blood pressures and this may negatively influence cardiovascular health.

INTRODUCTION

Successful thoracic endovascular aortic repair (TEVAR) of the aortic arch and proximal descending thoracic aorta is largely dependent on the anatomical characteristics of the landing zone of interest.[1,2] The Modified Arch Landing Areas Nomenclature has characterized several geometric parameters associated with different aortic arch types in zones 0 through 3, and found increased angulation in the distal parts of the Type III arch.[3] Such increased angulation has been associated with stent-graft malapposition, bird beak occurrence, and hostile hemodynamic displacement forces at the proximal landing zone (PLZ).[4-6]

In other postoperative geometrical configurations with an increased aortic arch angulation, like in patients who underwent successful open surgical repair of aortic coarctation or transposition of the great arteries, hypertension, increased systolic pulse wave reflections, and central aortic stiffness were also observed.[7–10] Aortic pulse wave velocity (PWV), widely adopted to quantify aortic stiffness, reflects the speed of pulse wave propagation along the aortic wall following left ventricular ejection, and independently predicts adverse cardiovascular events.[11–13] Changes in aortic PWV have been investigated by numerous clinical and experimental studies after TEVAR, which showed that TEVAR increases aortic PWV.[11,14-17] Although the direct effect of TEVAR on aortic stiffening is known, the role of aortic arch angulation in this setting is less clear.

Therefore, this study aims to investigate the effect of an increased aortic arch angulation—as present in a Type III arch—on aortic PWV, using an ex vivo porcine model. The hypothesis was tested whether or not an angulated Type III arch, compared with a less angulated Type I arch, increases aortic PWV. Additionally, the study investigated if a Type III arch configuration influences TEVAR-induced aortic stiffening.

MATERIALS AND METHODS

Although the experimental setup of this study has been utilized to perform previous ex vivo analyses,[15–19] several components (eg, ventricular compliance and transit-time derivation from flow curves) and protocol steps (eg, experiments within 12 hours of aortic sample procurement) have been updated, as described in detail below. The experimental protocol has not been previously published.

Aortic Samples

Thoracic aortas of young healthy pigs (commercial hybrid, aged 10-12 months, weighing 160-180 kg) were procured at a local slaughterhouse from the ascending aorta to the level of the renal arteries. The pigs were evaluated by a veterinary physician, were solely raised for commercial purposes, and not killed for this study. Therefore, ethical approval by the local animal ethics committee was waived. The aortas were sealed and transported to the experimental β-lab of the University of Pavia. The experiments were performed on the same day, within 12 hours of procurement. The aortas were surgically prepared (T.J.M.) from the aortic root to the level of the celiac trunk by removing excess connective tissue and cardiac tissue. This allowed ligation of the 2 supra-aortic trunks, spinal arteries, and attachment of a proximal connector to the aortic root and a distal connector to the descending aorta.

Experimental Setup and Components

Figure 1 provides a schematic overview of the experimental setup and its components. The aortas were connected to a circulatory mock loop using silicone tubes and positioned in an open plastic box. The circulatory mock loop allowed for intraluminal pressurization under continuous steady state or pulsatile flow in a controlled manner. A centrifugal pump (Biomedicus 550; Medtronic) provided the continuous pressurization and a custom-made pulsatile pump resembling the left ventricle and containing both biomorphic inlet and outlet valves, provided pulsatile flow.[20] A ventricular compliance has been added to this pulsatile pump to obtain stable pressure curves and to mitigate the high-frequency pressure variation due to the closure of the mechanical valves of the system. Water was utilized as circulatory fluid and kept at body temperature with a liquid heater (542 Heizer Titan [100 Watt]; Schego) in the water reservoir. Intraluminal pressures were recorded using a pressure sensor (40pc015g series; Honeywell) positioned in zone 3. Aortic flow was measured using a flow meter (Em·tec part of PSG, a Dover Company).

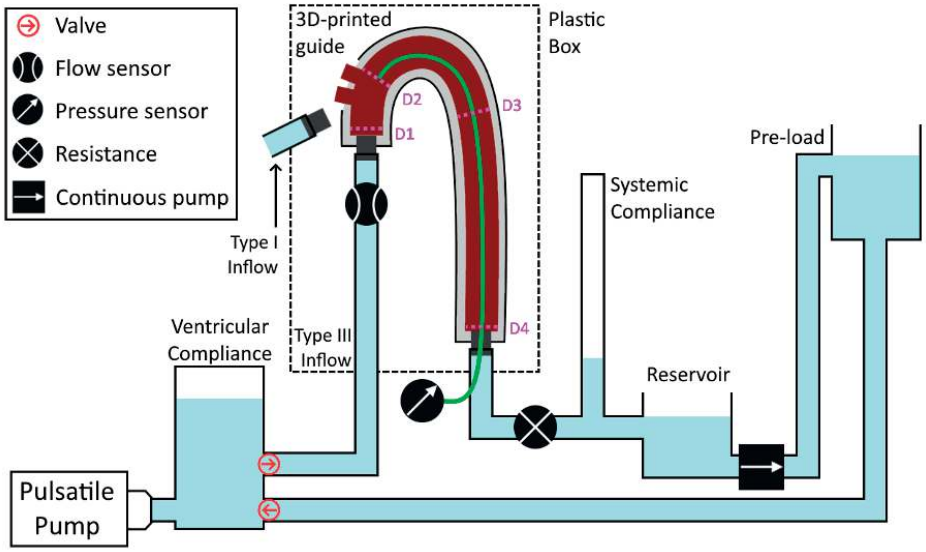

Figure 1. Schematic representation of the experimental set-up and its components. *3D*, Three dimensional.

Aortic Arch Guides

The aortas were guided into the desired aortic arch configuration utilizing 2 aortic guides with the geometrical characteristics of a Type I or a Type III aortic arch, as specified below. First, the aortic guides were virtually developed using computer-aided design. A basic virtual aortic model was created of which the geometry could be adjusted. According to baseline calibers of previously characterized thoracic porcine aortas (n = 20),[17] mean aortic length, diameters at different points, and 2 supra-aortic trunks were inserted, so that the basic model virtually resembled a porcine thoracic aorta from the ascending aorta to the level of the celiac trunk.

Next, following the aortic arch classification, the basic virtual model was adjusted to create a Type I and Type III aortic arch model based on the vertical distance between the onset of the brachiocephalic trunk and the top of the aortic arch.[21] Moreover, the geometric characteristics associated with a Type I or Type III aortic arch as defined by a previous study, were applied to both virtual models using similar methodology.[3] These consisted of radius of curvature, aortic arch centerline length, tortuosity index, and ß-angle.

Both the Type I and III aortic arch guides were virtually designed around the Type I and Type III aortic models and a hatch was included for both supra-aortic trunks. The 2 vir-

tual guides were consequently 3–dimensional-printed and utilized in the experimental setup (Figure 2).

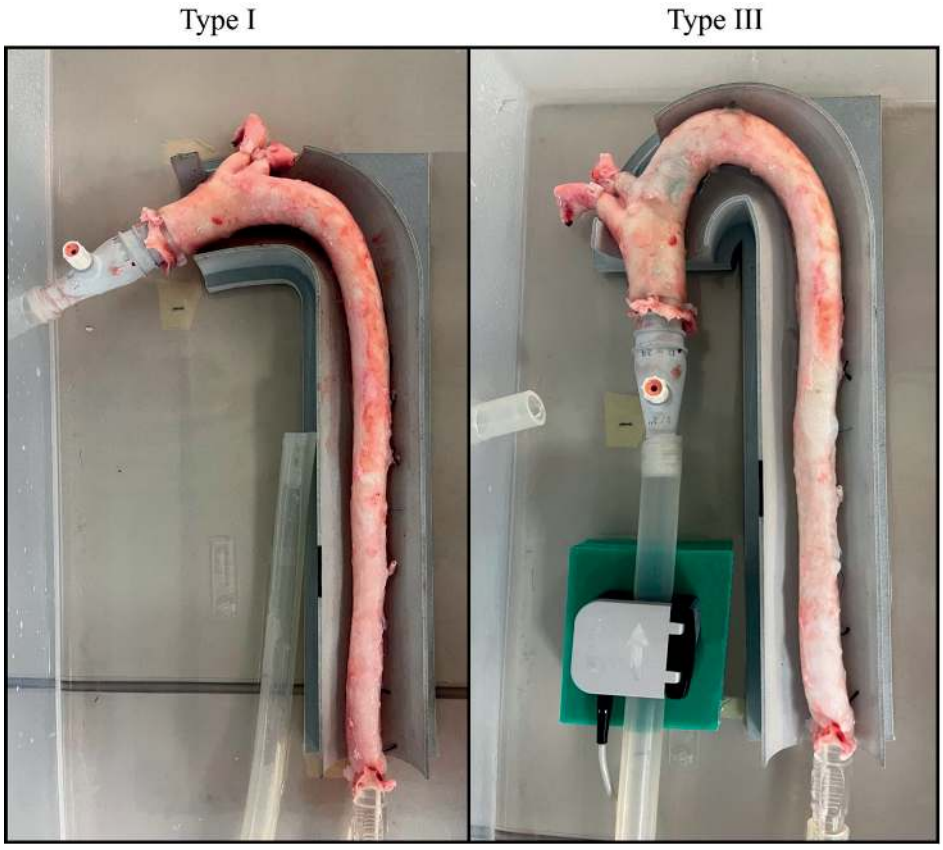

Figure 2. Thoracic porcine aortas with a Type I and Type III aortic arch configuration, connected to the experimental setup.

Experimental Workflow

The aorta was connected to the loop in the type I arch configuration and pressurized by continuous steady state flow. A planar image of the aorta was taken with a digital camera parallel to the aortic plane at arterial pressure levels of 80, 100, and 120 mm Hg to measure centerline length. At 100 mm Hg, baseline anteroposterior aortic diameters were measured using ultrasound (Accuvix XQ; Medison) by 2 operators (T.J.M. and A.F.P.) using an inner-to-inner calliper placement. Diameters were measured at 4 predefined locations: ascending aorta just distal to the proximal connector, just distal to the second

supra-aortic trunk (ie, the PLZ), 112 mm distal to point 2 (ie, the distal landing zone), and descending aorta just before the distal connector (see dashed lines in Figure 1).

After baseline caliber measurements, pulsatile flow was installed and peripheral resistance, ventricular compliance, heart rate (75 beats per minute), and cardiac output (4.5-5.5 L/minute) were set to obtain physiologic baseline diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure (PP), and mean arterial pressure (MAP) values of 75 to 85, 115 to 125, 40 to 50, and 90 to 100 mm Hg, respectively. PP was defined as the difference between SBP and DBP.[22] MAP was defined as DBP plus one-third of PP.[22]

Consequently, pressure values and aortic flow curves at the proximal and distal end of the aorta were acquired for at least 25 consecutive cardiac cycles. Next, the aorta was disconnected and guided into a Type III arch configuration utilizing the Type III arch guide. Planar images at the 3 MAP levels were retaken under continuous pressurization as in the Type I arch configuration. Then, the flow regime was changed to pulsatile and cardiac output (quantified as flow) was adjusted to achieve an equal cardiac output as in the Type I arch configuration if a flow reduction was noted. Here, the aim was to mimic physiologic compensation mechanisms of the heart with increases or decreases in pre- and/or afterload.[23] Consequently, pressure values and proximal and distal aortic flow curves were acquired in the Type III arch configuration.

Stent-Grafts and Implantation

A Valiant thoracic aortic stent-graft with the Captivia delivery system (Medtronic Inc) with a proximal and distal diameter of 26 mm and 112 mm covered length (Code: VAM-F2626C100TU) was deployed in cases where an oversizing of 10% to 20% at the PLZ (just distal to the second supra-aortic trunk) could be achieved (following our stent-graft diameter, upper and lower cutoff aortic diameters to reach 10%-20% oversizing were 21.7-23.6 mm). A custom-made delivery system was utilized.[17] Consequently, the stented aorta was reconnected to the circulatory loop, planar images, pressure values, and proximal and distal flow curves were acquired in both arch configurations, following the steps described above.

Aortic PWV

Aortic PWV was calculated by dividing the centerline length of the aortic sample by the transit time over this distance. Transit time was obtained mechanically by applying the cross-correlation method[24] between the proximal and distal flow curves, synchronized with the heart rate. Centerline length measurements were obtained by importing the planar images at different pressure values to Matlab (Mathworks), and manually placing a minimum of 15 points between the proximal and distal connector (A.F.P. and

S.J.) (Figure E1). Pixels were scaled to centimeters using a reference line of 2.5 cm on the aortic guide. The change in length for different pressure levels and different arch configurations was accounted for: the length value used to compute aortic PWV was obtained by fitting a linear regression line between the pressure values at continuous flow and different length values. Consequently, length at the MAP levels during pulsatile flow was used to compute aortic PWV.

Primary and Secondary Analyses

The primary analysis assessed changes in aortic PWV with increased aortic arch angulation (Type I vs Type III arch), without deployment of the stent-graft. The secondary analysis was the assessment of changes in aortic PWV for both arch configurations after stent-graft deployment and assessed whether an increased arch angulation affects TEVAR induced aortic stiffening.

Sample Size Calculation

A power analysis was conducted based on a previous study that found a significant increase in aortic PWV in patients with an increased angulation of the aortic arch.[9] With a 2-sided paired samples *t* test significance level of 5% ($\alpha = .050$) and a power of 95%, the resulting required sample size was 10. To account for a potential margin of error, the number of experiments was set at a minimum of 15.

Data analysis

Data were analyzed using Microsoft Excel (Microsoft), Matlab version R2020b, and IBM SPSS Statistics version 28 (IBM-SPSS Inc). Data were reported as number and percentage, mean ± SD or median (interquartile range) where appropriate. Boxplots were created to graphically summarize results. Shapiro-Wilk test was performed to test for normality on all studied variables. Paired samples *t* test was performed to compare the means of 2 groups of normally distributed measurements and Wilcoxon signed rank test in case of nonnormally distributed data. A variability analysis was performed for the operator-dependent centerline length measurements, included in the calculation of aortic PWV. Intra- and interobserver reliability (ie, the extent to which the measurements can be replicated) was assessed for both arch configurations by calculating the intraclass correlation coefficient (ICC) (model: 2-way mixed, single rater/measurement, type: absolute agreement).[25]

RESULTS

Baseline Aortic Sample Characteristics

A total of 24 aortas were harvested (November 2022-February 2023) and connected in both arch configurations for the primary analysis. In a subgroup of 15 aortas with an adequate diameter at point 2 (ranging from 21.7 to 23.6 mm) the stent-graft was deployed, and the aortas were connected in both arch configurations again for the secondary analysis. Table 1 reports baseline diameters and centerline length for the aortic samples. In the subgroup of 15 out of 24 (62.5%) aortas, PLZ oversizing at point 2 was controlled and was 14% ± 2%, which gradually increased toward the distal landing zone inherent to the tapering of the thoracic porcine aortas from proximal to distal aortic zones (Table 1).

Table 1. Baseline diameters and length of the thoracic aortic samples utilized for the primary and secondary analyses

	Aortas for primary analysis, n = 24	Subgroup of aortas for secondary analysis with stent-graft, n = 15/24
Diameter point 1*, mm	25.4 ± 1.8	25.3 ± 1.6
Diameter point 2*, mm	22.8 ± 1.6	22.8 ± 0.5
Diameter point 3*, mm	16.3 ± 1.0	16.2 ± 1.0
Diameter point 4*, mm	14.6 ± 1.3	14.5 ± 1.3
Centreline length, type I arch, cm	36.2 ± 2.6	35.9 ± 3.1
Centreline length, type III arch, cm	36.9 ± 2.7	36.7 ± 3.0

Values are presented as mean ± SD. *See the Materials and Methods section for a specification of the 4 diameter measurement locations.

Primary Analysis

Table 2 reports the cardiac output, DBP, SBP, PP, MAP, and aortic PWV for both the Type I and Type III arch configuration. Cardiac output (flow), being a controlled parameter, was stable in both arch configurations (Type I: 4.74 ± 0.40 L/minute, Type III: 4.72 ± 0.38 L/minute; $P = .703$). With a change from Type I to Type III arch configuration, DBP, SBP, PP, and MAP significantly increased (Table 2). Figure 3 shows the changes in DBP, SBP, and MAP with respect to a change in arch configuration. Aortic PWV was significantly higher in the more angulated Type III arch with respect to the Type I configuration (Type I: 3.53 ± 0.40 m/second, Type III: 3.83 ± 0.40 m/second; $P < .001$), corresponding to a 9.0% ± 10% increase. Figure 4 shows the increase in aortic PWV with respect to a change in arch configuration for the 24 harvested aortas.

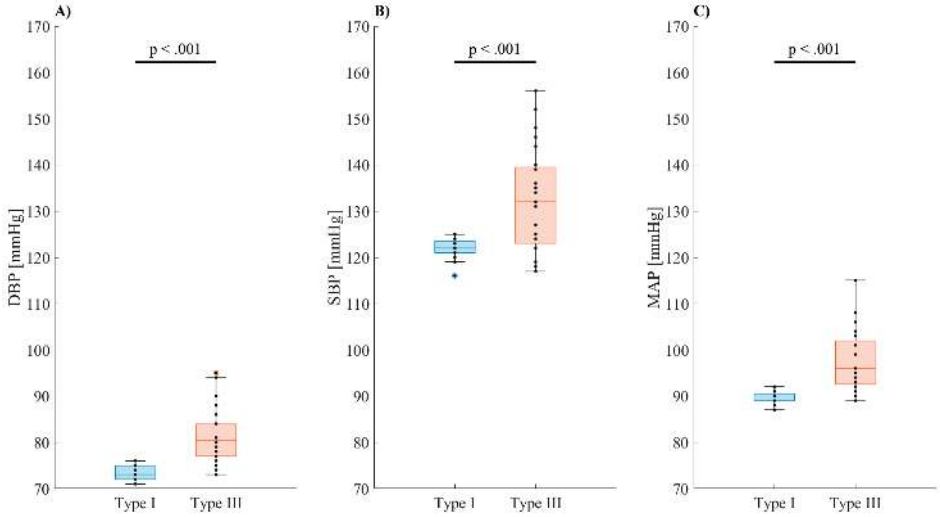

Figure 3. Boxplots of the diastolic (A), systolic (B), and mean arterial blood pressures (C) in both arch configurations for the 24 thoracic aortic samples. *Middle lines of the boxplots* represent median values. *Lower and upper border of the box* represent the 25th and 75th percentile (interquartile range), respectively. Lower and upper whiskers represent the minimum and maximum values of nonoutliers, respectively. Points represent individual data points and positive or negative outliers. *DBP*, Diastolic blood pressure; *SBP*, systolic blood pressure; *MAP*, mean arterial pressure.

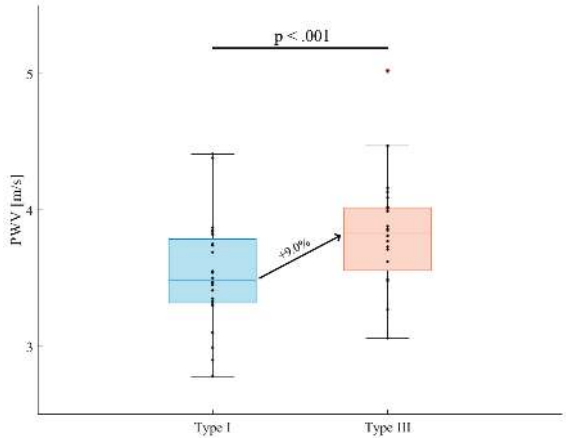

Figure 4. Boxplots of the aortic pulse wave velocity in both arch configurations for the 24 thoracic aortic samples. *Middle lines of the boxplots* represent median values. *Lower and upper border of the box* represent the 25th and 75th percentile (interquartile range), respectively. *Lower and upper whiskers* represent the minimum and maximum values of nonoutliers, respectively. *Points* represent individual data points and positive or negative outliers. *PWV*, Pulse wave velocity.

Table 2. Aortic flow, blood pressure, and pulse wave velocity values in both arch configurations for the primary and secondary analyses

Variable	Primary analysis (N = 24)			Subgroup of aortas for secondary analysis with stent-graft (n = 15)		
	Type I	Type III	*P* value	Type I	Type III	*P* value
Flow (L/min)	4.74 ± .40	4.72 ± .38	.703	4.70 ± .37	4.68 ± .33	.410
Diastolic blood pressure (mm Hg)	73 ± 2	81 ± 6	<.001	74 ± 3	77 ± 6	.030
Systolic blood pressure (mm Hg)	122 ± 2	133 ± 11	<.001	125 ± 6	133 ± 11	.002
Pulse pressure (mm Hg)	49 ± 2	51 ± 7	.024	51 ± 6	56 ± 8	<.001
Mean arterial pressure (mm Hg)	90 ± 1	98 ± 7	<.001	91 ± 3	96 ± 7	.008
Pulse wave velocity (m/sec)	3.53 ± .40	3.83 ± .40	<.001	3.81 ± .44	4.03 ± .46	.023

Values are presented as mean ± SD.

Secondary Analysis

In the subgroup of 15 aortas, there was an increase in aortic PWV after stent-graft deployment in the Type I arch (baseline PWV: 3.55 ± 0.39 m/second, PWV after TEVAR: 3.81 ± 0.44 m/second; $P < .001$). In the Type III arch, there was an increase in aortic PWV after stent-graft deployment; however, not statistically significant (baseline PWV: 3.86 ± 0.42 m/second, PWV after TEVAR: 4.03 ± 0.46 m/second; $P = .094$). As demonstrated in the primary analysis, the baseline aortic PWV before stent-graft deployment was higher in the Type III arch configuration compared with the Type I arch configuration. The mean percent TEVAR-induced increase in aortic PWV for the Type I arch configuration was 7.3% ± 5.3% and 4.7% ± 9.1% in the Type III arch configuration. Figure 5 shows the changes in aortic PWV for the subgroup of 15 aortic samples in which the stent-graft was deployed.

After stent-graft deployment, the increase in aortic PWV associated with a change to the Type III arch was lower compared with the primary analysis without stent-graft (6.4% ± 10% vs 9.0% ± 10%). Nevertheless, aortic PWV in the Type III arch after stent-graft deployment was highest and significantly higher compared with the Type I arch (Type I after TEVAR: 3.81 ± 0.44 m/second, Type III after TEVAR: 4.03 ± 0.46 m/second; $P = .023$) (Figure 5).

Variability Analysis

In the Type I arch configuration, the intra- and interobserver ICCs of the centerline length measurements were 0.990 (95% CI, 0.978-0.996) and 0.990 (95% CI, 0.946-0.997). In the Type III arch configuration, the intra- and interobserver ICCs were 0.994 (95% CI, 0.985-0.997) and 0.978 (95% CI, 0.692-0.994), indicating excellent reliability for both arch configurations (ICC > 0.9).[25]

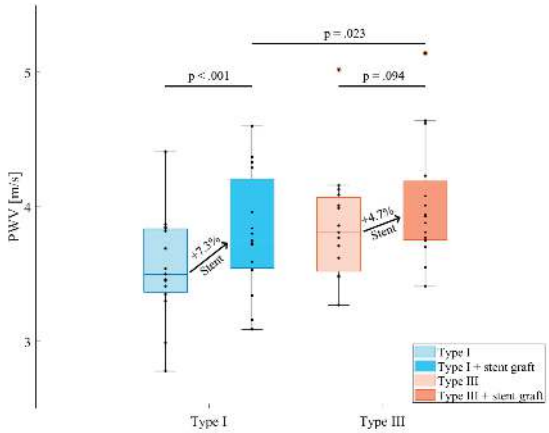

Figure 5. Boxplots of the aortic pulse wave velocity in both arch configurations before and after stent-graft deployment. *Middle lines of the boxplots* represent median values. *Lower and upper border of the box* represent the 25th and 75th percentile (interquartile range), respectively. *Lower and upper whiskers* represent the minimum and maximum values of nonoutliers, respectively. *Points* represent individual data points and positive or negative outliers. *PWV*, Pulse wave velocity.

DISCUSSION

The main findings of this study highlight significant changes in aortic flow dynamics and blood pressure responses following changes in aortic arch geometry (Figure 6). DBP, SBP, PP, and MAP increased with increasing arch angulation as in a Type III arch configuration, compared with a less angulated Type I arch. Moreover, aortic PWV increased in a Type III arch compared with a Type I arch. In addition, the study showed that Type III arch PWV is significantly higher compared with Type I arch PWV after stent-graft deployment. The study also confirms that thoracic stent-graft deployment increases aortic PWV.[11,14-16] TEVAR in zone 3 of a Type I arch increased aortic PWV more than after TEVAR in zone 3 of a Type III arch, probably because aortic PWV was already significantly increased in the Type III arch configuration, as found in this study. These findings further underline that an increased arch angulation as in a Type III arch may be hostile, not only in terms of potential device-related complications, but also in terms of blood pressure responses, cardiac afterload, and aortic stiffness.[4-6] Such changes in aortic flow dynamics could in turn be the cause of TEVAR failure. As an accepted surrogate for aortic stiffness, increases in aortic PWV result in an increased cardiac workload, pulsatile damage to target organs operating at high flow and low vascular resistance (eg, kidneys and brain), and could thereby negatively influence cardiovascular health.[11-14]

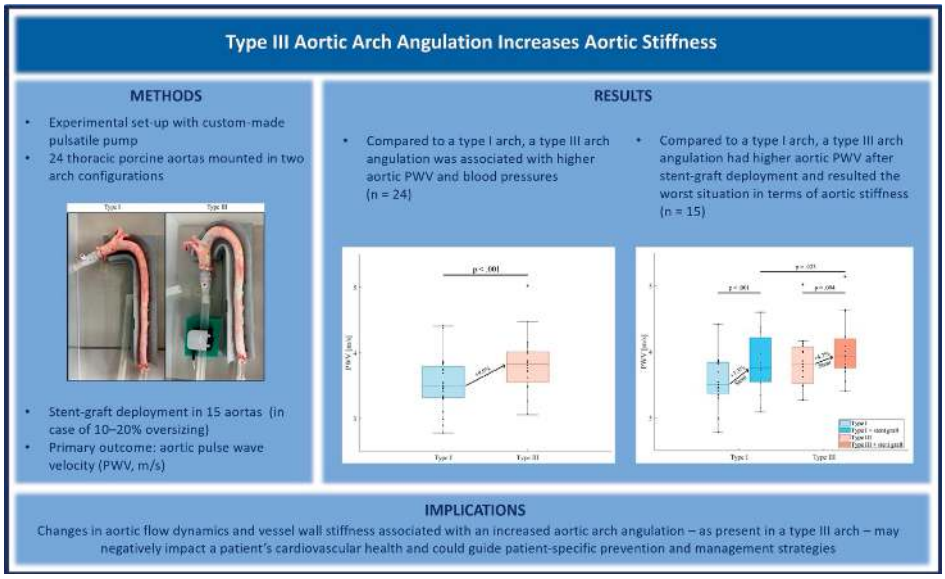

Figure 6. Type III aortic arch angulation increases aortic stiffness. *Middle lines of the boxplots* represent median values. *Lower and upper border of the box* represent the 25th and 75th percentile (interquartile range), respectively. *Lower and upper whiskers* represent the minimum and maximum values of nonoutliers, respectively. *Points* represent individual data points and positive or negative outliers. *PWV*, Pulse wave velocity.

Previous studies have demonstrated that different arch geometries (eg, gothic, crenel, romanesque) exist after successful open surgical repair of aortic coarctation, generally performed in young adults.[7] These studies independently associated the gothic arch geometry with abnormal blood pressure responses, increased central aortic stiffness, and left ventricular mass, and highlighted the potential importance of aortic geometry on aortic flow dynamics.[7-9] Gothic arch was defined as being acutely angulated between the ascending and descending aorta with a shortened or absent inner arch segment. The definitions of such arch geometries were however assessed globally on magnetic resonance imaging, compared with the clear definition of arch types (ie, Type I or Type III) based on multiple geometrical parameters in this study.[3]

A potential reason for the increases in blood pressure and aortic PWV with increases in arch angulation could be an increased systemic vascular resistance and thus cardiac afterload, resulting in compensation mechanisms that may increase mean blood pressure, and consequently aortic PWV. Although there were no structural changes to the aortic wall with changes in aortic arch type in this study, the highly nonlinear mechanical behavior of the aorta and the multiscale organization of lamellae, elastin, and collagen

fiber of the aortic wall might result in a less efficient damping of the pulsatile propulsions during the cardiac cycle as MAPs increase.[26] Moreover, it should be emphasized that this experimental setup utilized thoracic porcine aortas from healthy and young pigs. In patients with thoracic aortic disease, such aspects may even be more or less pronounced. This deserves further exploration to better understand the relationship between geometric arterial changes and blood pressure or aortic PWV responses.

Because a change in aortic geometry does not imply changes to the arterial wall, the validity of utilizing aortic PWV as a surrogate for aortic stiffness in this scenario could be debated. Namely, aortic PWV is dependent on Young's elastic modulus, thickness of the aortic wall, aortic radius, and fluid density following the Moens-Korteweg equation.[27] Aortic PWV should thus not be interpreted as synonym of aortic wall elasticity because there is a complex interplay between Young's elastic modulus and geometric characteristics that play a major role in the estimation of PWV.[27]

Future Perspectives

The results of ex vivo studies on aortic flow dynamics and the mechanical coupling between thoracic aortic stent-grafts and the native aorta could be compared with in-silico or in-vivo analyses to evaluate similarities and differences in findings. The development of a 3-dimensional, printable elastic aortic material strong enough to withstand pulsatile pressurization would allow the development of aortic models with specific geometries (eg, diameter, length, angulation, and tortuosity) with or without disease (eg, aneurysm). The addition of 4–dimensional-flow magnetic resonance imaging may provide additional insights into changes in aortic flow dynamics following changes in arch geometry.[28]

Limitations

This study has limitations that are related to the experimental design and the use of porcine thoracic aortas, inherently limiting the translational value to human beings, and that must be acknowledged.[29] Several aspects have been mentioned by previous studies utilizing this setup such as the use of water as perfusion fluid and the absence of surrounding tissue.[15-19] The setup aims to isolate and analyze a specific parameter (eg, aortic PWV and blood pressure), whereas there is variability in other parameters at the same time (eg, aortic specimen diameters and length and distal oversizing). However, the experimental setup and systematic workflow allows us to control other factors (eg, baseline blood pressures, type of aortic arch, and proximal oversizing) to perform comparative analyses. In the secondary analysis, aortic sample selection bias to reach adequate oversizing might theoretically have influenced our findings. Reusing a single, nontapered, thoracic stent-graft did not result in macroscopic damage of the stent-graft.

CONCLUSIONS

This porcine ex vivo study shows that an increased aortic arch angulation—as present in a Type III aortic arch—increases DBP, SBP, PP, MAP, and aortic PWV. This highlights that changes in arch geometry (eg, increased angulation) can result in altered aortic flow dynamics. Hypertension and aortic PWV, as a surrogate for aortic stiffness, increase a patient's cardiovascular risk. Future studies are needed to better explore the relationship between changes in aortic arch geometry, blood pressure response, and aortic stiffness, which might implicate changes in device materials and designs.

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4

Impact of open surgical descending repair on aortic stiffness and comparison with endovascular repair: Analysis in an ex vivo porcine model☆

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ABSTRACT

Objective: While it is known that stent-graft deployment and acute arch angulation increase aortic stiffness, the impact of surgical interposition grafting remains unclear. We investigated the impact of open surgery on aortic stiffness and compared this with stent-graft induced aortic stiffening, utilising an *ex vivo* model.

Methods: Porcine thoracic aortas were connected to a mock circulatory loop. Baseline characteristics, proximal and distal flow curves (for PWV calculation), and blood pressures were recorded in a type I and III arch configuration. Subsequently, 10cm proximal descending aorta was excised and replaced with Dacron® (IGK0018-40S). After surgery, all measurements were repeated in both arch configurations. Available experimental literature data on stent-graft induced aortic stiffening was used for comparison.

Results: Fifteen aortas were prepared and attached to the circuit. After surgery, with both arch configurations, mean aortic PWV increased (Type I: 3.46 to 3.84m/s (+10.7%),p<.001); Type III: 3.61 to 3.98m/s (+10.4%),p=.001), systolic pressure remained stable, diastolic pressures decreased (Type I: 73 to 65mmHg,p<.001; Type III: 75 to 66mmHg,p<.001), and consequently mean arterial pressure decreased (Type I: 89 to 85mmHg,p=.020; Type III: 92 to 85mmHg,p=.001). Compared with stent-graft induced aortic stiffening and with both arch configurations, baseline aortic PWV was similar, and there was no difference in aortic PWV after open or endovascular repair (Type I open *vs* stent-graft: 3.84 *vs* 3.81m/s,p=.63;Type III open *vs* stent-graft: 3.98 *vs* 4.03m/s,p=.53).

Conclusions: Surgical interposition grafting of the proximal descending aorta increases aortic PWV and decreases diastolic blood pressure. This aortic stiffening is comparable to stent-graft induced stiffening.

INTRODUCTION

In the current endovascular era, open surgical interposition grafting remains the first choice for treating patients with thoracic aortic aneurysms (TAA) and acute aortic syndromes (AAS) involving the aortic root, ascending aorta, and proximal aortic arch (i.e., zones 0 – 1).[1,2] Open surgery is also recommended for patients at low or intermediate surgical risk with arch TAAs (i.e., zones 1 – 2), while thoracic endovascular aortic repair (TEVAR) should be considered in the presence of suitable anatomy.[1–3] For descending aortic pathologies (i.e., zones 3 – 5), open surgery is now complementary to TEVAR, but remains important as primary treatment option in those patients with connective tissue disease, unsuitable anatomy, small access vessel diameters, in young patients with a life expectancy exceeding 10 years, or in case of TEVAR failure.[1–6]

For both open and endovascular thoracic aortic repairs, long-term durability and outcomes remain a concern and point of optimization.[6] One of the factors that might play an important role is aortic stiffness, as it has increasingly been recognized to negatively impact patients' cardiovascular health.[7–9] Aortic stiffness is non-invasively quantified by measuring aortic pulse wave velocity (PWV) which has independently been associated with a higher occurrence of future cardiovascular events, all-cause mortality, and cardiovascular mortality.[7–10]

While prior studies have shown that TEVAR increases aortic stiffness and leads to cardiac and aortic remodelling over time[7,11–15], there is a paucity of evidence on the impact of open surgery on aortic stiffness. Like stent-grafts, the biomechanical properties of surgical grafts (e.g., Dacron®) and the native aorta differ as well, potentially leading to complications in the longer term.[16,17] Indeed, one prior study[18] found increases in aortic PWV after open graft replacement of aortic arch aneurysms, whereas another study[19] found aortic PWV to be similar after surgical replacement of the ascending aorta. Nevertheless, and in contrast to TEVAR, evidence remains scarce after open repair of thoracic aortic segments, nor a direct comparison of changes in aortic PWV after open and endovascular repair of the descending aorta has ever been performed.

Therefore, we aimed to investigate the impact of open surgical interposition grafting of the descending aorta on aortic PWV and blood pressure in an *ex vivo* porcine model. Given the evidence available in literature that found increased arch angulation (i.e., type III arch) to lead to higher aortic PWV and blood pressure[20], its role in the setting of open surgery was investigated as well. Additionally, this study compared data on aortic PWV after open surgery to previously published data after TEVAR.[20]

MATERIALS AND METHODS

The experimental set-up of this study has been utilised to perform multiple previous *ex vivo* analyses on the biomechanical coupling between fresh porcine thoracic aortic samples and thoracic aortic stent grafts.[13,14,20–23] The aortic samples (i.e., thoracic aortas from young and healthy pigs, 10 – 12 months, 160 – 180 kg), experimental set-up and its components (e.g., custom-made pulsatile pump with ventricular compliance and biomorphic mechanical heart valves[24], aortic arch guides, pressure sensor, flowmeter), and the method to calculate aortic PWV (i.e., mechanical transit-time computation with the cross-correlation method[25], manual centerline length measurements) were identical as described in detail in a previous study by our group.[20]

Below we describe the specific experimental workflow and methodological steps of the present study in detail. Ethical approval by the local animal ethics committee was waived since the pigs were solely raised for commercial purposes and not sacrificed for this study. All experiments were performed at the experimental β-lab of the University of Pavia in Pavia, Italy.

Experimental Workflow

The aortas were surgically prepared (TM, JK) by removing excess connective and cardiac tissue, allowing for ligation of the two supra-aortic trunks, spinal arteries, and attachment of connectors to the aortic root and to the descending aorta at the level of the celiac trunk.

Subsequently, the aorta was mounted in a type I arch configuration[20] and pressurised with continuous steady-state flow. Planar images were taken at arterial pressure levels of 80, 100, and 120 mmHg with a digital camera parallel to the aortic plane to consequently measure centerline length.[20] At 100 mmHg mean arterial pressure (MAP), baseline antero-posterior aortic diameters were measured using ultrasound (Medison Accuvix XQ, Seoul, South-Korea) by two operators (TM, JK) with an inner-to-inner caliper placement. Diameters were measured at four predefined locations: 1) ascending aorta just distal to the proximal connector; 2) just distal to the second supra-aortic trunk (site of proximal anastomosis); 3) 10 cm distal to point 2 (site of distal anastomosis); 4) descending aorta just before the distal connector. In parallel, locations 2 and 3 were marked with a water-resistant marker as the locations for proximal and distal anastomosis, to ensure adequate recognition of these points after depressurization, during interposition grafting (**Figure 1**).

After baseline measurements, pulsatile flow was introduced and peripheral resistance and ventricular and peripheral compliance were tuned to obtain physiologic baseline cardiac output of 4.5 – 5.5 Liters per minute (L/min), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and MAP values of 75 – 85, 115 – 125, 40 – 50, and 90 – 100 mmHg, respectively. Heart rate was fixed at 75 beats per minute. PP was defined as the difference between SBP and DBP.[26] MAP was defined as DBP plus one third of PP.[26] Pressure values (at the level of the second supra-aortic trunk) and aortic flow curves (at the level of the ascending aorta and celiac trunk) were then acquired for at least 25 consecutive cardiac cycles.

The same aorta was then disconnected and reconfigured into the type III arch configuration (**Figure 1**).[20] Planar images at the same three MAP levels were retaken under continuous pressurisation as under the type I arch configuration, as described above. Then, flow regime was changed to pulsatile and the pump stroke was adjusted to achieve an equal cardiac output (quantified as flow [L/min]) as in the type I arch configuration if a flow reduction was noted. This allowed us to mimic physiologic compensation mechanisms of the heart with varying pre- and/or afterload conditions.[27] Then, pressure values and proximal and distal aortic flow curves were acquired in the type III arch configuration.

Surgical interposition grafting with Dacron®

As the next step, the porcine thoracic aorta was disconnected, and 10 cm proximal descending aorta was excised (delimited by locations 2 and 3, as explained above). This segment was surgically replaced (TM, JK) by 10 cm Intergard Silver Knitted (IGK0018-40S) Dacron® graft (Getinge AB, Gothenborg, Sweden) with Prolene 4-0 (Ethicon, Inc., NJ, U.S.A.). After surgical interposition grafting, the aorta was reconnected to the set-up and planar images, blood pressures, and flow curves were acquired again for both arch configurations, as described above before surgical repair (**Figure 1**).

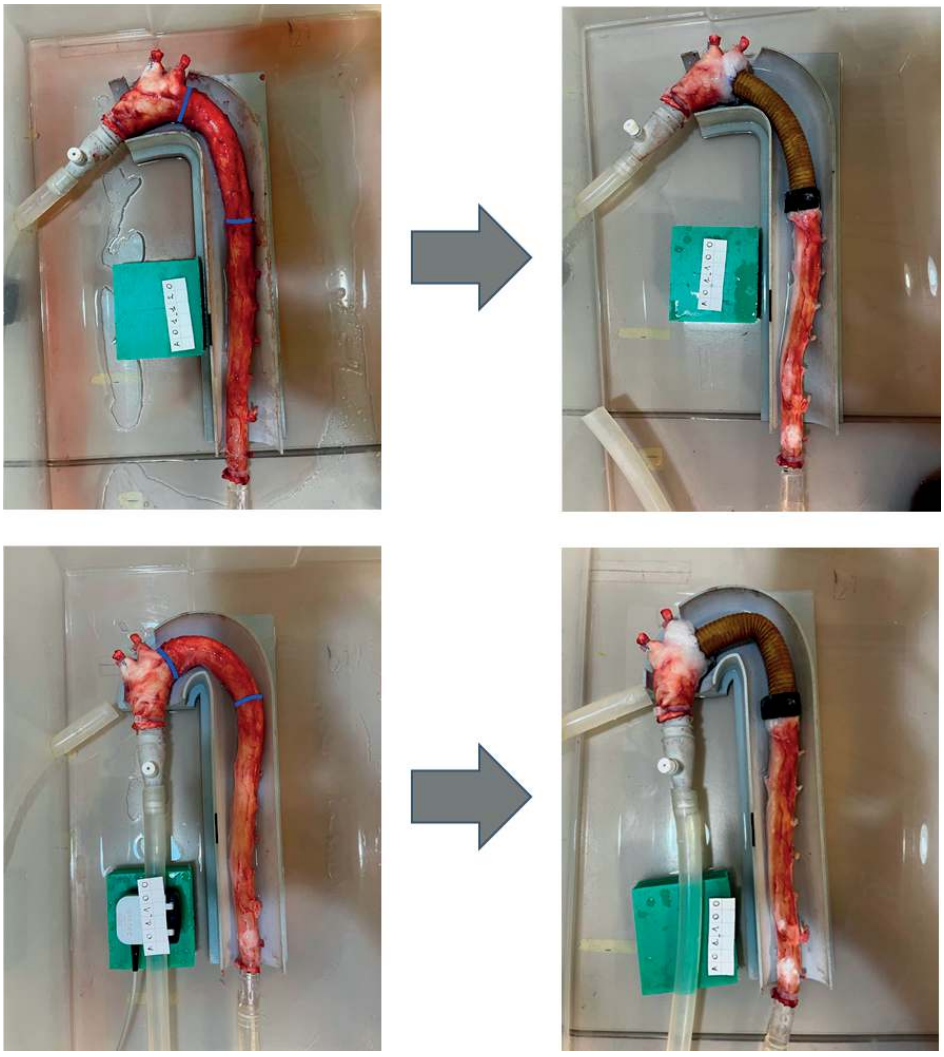

Figure 1. Thoracic porcine aortic samples before (left) and after (right) open surgical interposition grafting of the proximal descending aorta from the distal border of the second supra-aortic trunk to 10 cm more distal, in a type I (top) and type III arch (bottom) configuration.

Outcomes

The primary outcome was aortic PWV (in metres per seconds [m/s]) before and after surgical interposition grafting, in both arch configurations. As a secondary outcome, we assessed changes in DBP, SBP, PP, and MAP after interposition grafting, in both arch configurations. Additionally, we performed a comparative analysis with TEVAR-induced aortic stiffening as described in detail below, and we assessed changes in aortic PWV with changing arch angulation (Type I *vs* III arch), both before and after surgery.

Sample size calculation

Given the lack of available literature providing appropriate data on changes in aortic stiffness after open surgical proximal descending aortic repair, we were unable to perform an a priori power analysis for this study. Therefore, based on our previous study[20] that had accounted for a potential margin of error with n = 15 experiments to assess changes in aortic PWV with increased arch angulation and after TEVAR (with a significance level $\alpha = .050$ and power of 80%, the required sample size was n = 7), we opted to align and set the current sample size at a minimum of n = 15 experiments as well.

Comparison with TEVAR-induced aortic stiffening

This study compared the obtained data on aortic PWV after open surgery to previously collected data after TEVAR, to assess similarities and differences between these surgical treatment modalities.[20] In the referenced study, TEVAR deployment with the Valiant™ thoracic aortic stent-graft with the Captivia™ delivery system (Medtronic, Inc., MN, U.S.A.) was performed at exactly the same aortic location (proximal descending aorta, 10 cm long). Moreover, the study was performed with similar aortic samples and the same experimental set-up and components, aortic arch guides, and methodology to calculate aortic PWV, as mentioned above.

Statistical analysis

Data were analysed using Microsoft Excel (Microsoft, Redmond, WA, U.S.A.), Matlab version R2020b (Mathworks, Natick, MA, U.S.A.), and IBM SPSS Statistics version 28 (SPSS Inc., Chicago, IL, U.S.A.). Data was reported as number (n) and percentage (%) or mean ± standard deviation. Shapiro-Wilk test was performed to test for normality on all studied variables. Paired samples t-test was performed to compare the means of two groups of paired measurements, if the differences between pairs were normally distributed. In case of non-normal distribution of the paired differences, we performed the non-parametric alternative Wilcoxon signed rank test. For our comparison with TEVAR-induced aortic stiffening, the non-parametric Wilcoxon rank sum test was performed to compare differences between both independent treatment groups. Two-sided p-values $< .05$ were considered statistically significant. Regarding the operator-dependent centerline length measurements included in the calculation of aortic PWV, we previously demonstrated adequate intra- and interobserver repeatability.[20]

RESULTS

Baseline characteristics of the porcine thoracic aortic samples

Between March and September 2023, a total of 15 aortas were harvested, surgically prepared, and mounted to the experimental set-up. Following the predefined experimental workflow, baseline calibre measurements, pressure values, and flow curves were acquired before and after surgical interposition grafting with Dacron®, in both a type I and type III arch configuration. Baseline diameters and centerline lengths are reported in Table 1. The aortas were tapered from proximal to distal and centreline length was similar with both arch configurations (Table 1).

Table 1. Baseline diameters and centerline length of the 15 thoracic aortic samples.

	n = 15
Diameter point 1*, mm	26.7 ± 2.3
Diameter point 2*, mm	23.4 ± 2.1
Diameter point 3*, mm	17.6 ± 1.1
Diameter point 4*, mm	15.9 ± 0.9
Centreline length, type I arch, cm	38.0 ± 1.4
Centreline length, type III arch, cm	38.2 ± 1.5

Values are presented as mean ± SD. *Point 1: just distal to the proximal connector at the level of the aortic root; point 2: just distal to the offspring of the second supra-aortic trunk (corresponding to the left subclavian artery in humans); point 3: 10 cm more distal in the descending aorta; point 4: just proximal to the distal connector at the level of the celiac trunk. Data are reported as mean ± SD. Abbreviations: n = number, mm = millimetre, cm = centimetre.

Table 2 reports the aortic flow (cardiac output), aortic PWV and DBP, SBP, PP, and MAP at baseline and after surgery, in both the type I and type III arch configurations. Compared to baseline values before surgery, aortic PWV was higher after surgery in a type I arch configuration (3.46 ± 0.47 *vs* 3.84 ± 0.75 m/s (+10.7%), $p < .001$) and in a type III arch configuration (3.61 ± 0.50 *vs* 3.98 ± 0.63 m/s (+10.4%), $p < .001$). Figure 2 visualises the changes in aortic PWV after surgery, for both arch configurations.

Compared to baseline values before surgery and in a type I arch configuration, DBP was lower (73 ± 3 *vs* 65 ± 6 mmHg, $p < .001$) and SBP was stable (121 ± 3 *vs* 124 ± 7 mmHg, $p = .26$) after surgery. Consequently, PP was higher (49 ± 4 *vs* 59 ± 5 mmHg, $p < .001$) and MAP was lower (89 ± 2 *vs* 85 ± 6 mmHg, $p = .039$) after surgery. Similarly, after surgery and with a type III arch configuration, aortic PWV and PP increased while DBP and MAP decreased, and SBP remained stable (Table 2). Figure 3 shows the changes in DBP, SBP, and MAP after surgery, in both arch configurations.

Table 2. Aortic flow (cardiac output), pulse wave velocity, and blood pressures for the 15 thoracic aortic samples and in both arch configurations.

Variable	Type I			Type III		
	Baseline	After surgery	P-value	Baseline	After surgery	P-value
Cardiac output, L/min	4.83 ± 0.31	4.86 ± 0.34	.15	4.88 ± 0.33	4.91 ± 0.37	.37
Pulse wave velocity, m/s	3.46 ± 0.47	3.84 ± 0.75	**< .001***	3.61 ± 0.50	3.98 ± 0.63	**< .001**
Diastolic blood pressure, mmHg	73 ± 3	65 ± 6	**< .001**	75 ± 5	66 ± 8	**< .001**
Systolic blood pressure, mmHg	121 ± 3	124 ± 7	.26*	124 ± 7	124 ± 11	.85
Pulse pressure, mmHg	49 ± 4	59 ± 5	**< .001**	49 ± 4	58 ± 6	**< .001**
Mean arterial pressure, mmHg	89 ± 2	85 ± 6	**.039**	92 ± 5	85 ± 9	**< .001**

Values are presented as mean ± SD. *Wilcoxon sign rank test instead of paired samples t-test. Data are reported as mean ± SD. Abbreviations: n = number, cm = centimetre, mm = millimetre, L/min = litres per minute, m/s = meters per second.

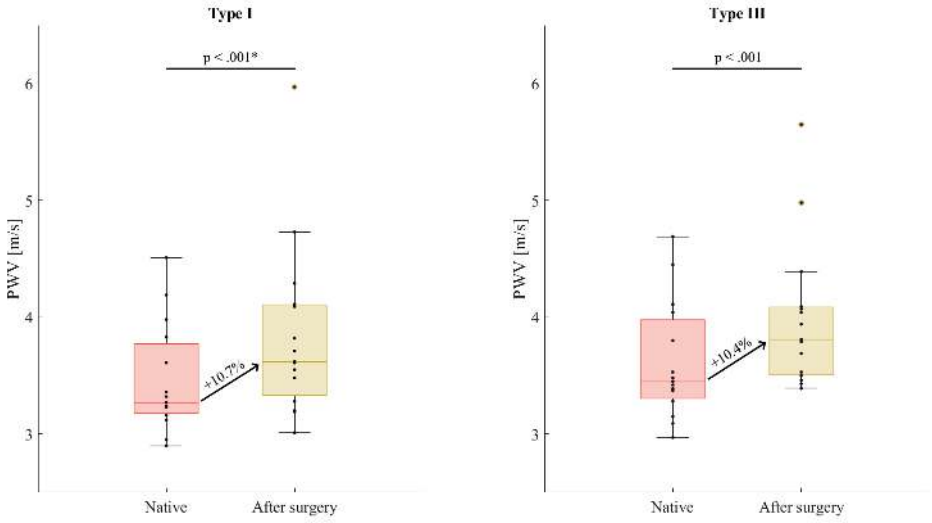

Figure 2. Boxplots and comparison of aortic pulse wave velocity (PWV) for the 15 porcine thoracic aortic samples before and after open surgery, in a type I and type III arch configuration. Asterisk indicates that p-value is derived from the Wilcoxon sign rank test. Lower and upper borders of the box represent the 25th and 75th percentile (interquartile range), respectively. Lower and upper whiskers represent the minimum and maximum values of non-outliers, respectively. Points represent individual data points and positive or negative outliers.

Comparative analysis with TEVAR-induced aortic stiffening

Compared with another 15 porcine thoracic aortic samples in which a thoracic aortic stent graft was deployed, there was no significant difference between the increased mean aortic PWV after surgery or after TEVAR (Type I: 3.84 ± 0.75 *vs* 3.81 ± 0.44 m/s, p = .63); Type III: 3.98 ± 0.63 *vs* 4.03 ± 0.46, p = .53). Figure 4 visualizes the comparison of aortic PWV after surgery and after TEVAR, in both arch configurations. While the absolute

median PWV value after TEVAR seems slightly higher as compared to the absolute median PWV value after surgery, absolute baseline PWV values were slightly higher in the TEVAR group as well. Specifically, baseline aortic PWV between the 15 aortas in the open surgery group and the 15 aortas in the TEVAR group were not statistically significantly different in both a type I (3.46 ± 0.47 *vs* 3.55 ± 0.39 m/s, p = .74) and type III arch configuration (3.61 ± 0.50 *vs* 3.86 ± 0.42 m/s, p = .48).

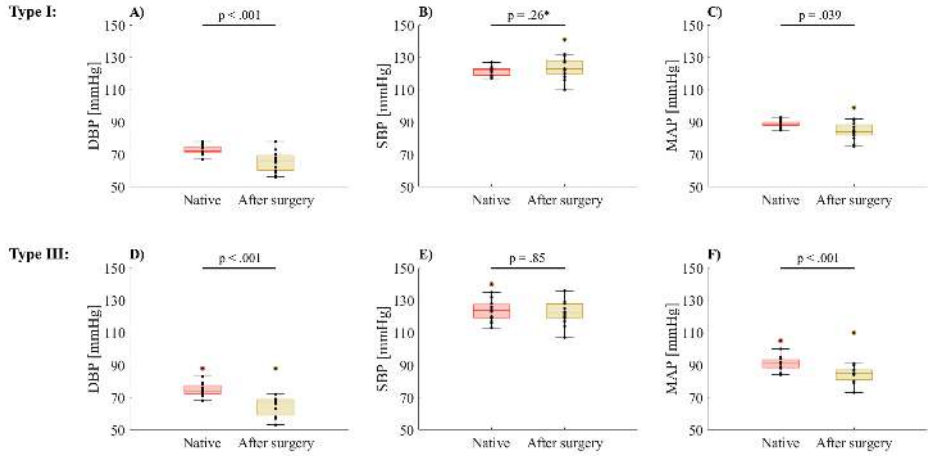

Figure 3. Boxplots and comparisons of diastolic (A), systolic (B), and mean (C) arterial pressure for the 15 thoracic aortic samples before and after surgery in a type I arch configuration, and diastolic (D), systolic (E), and mean (F) arterial pressure for the same 15 thoracic aortic samples before and after surgery in a type III arch configuration. Asterisk indicates that p-value is derived from the Wilcoxon sign rank test. Lower and upper borders of the box represent the 25th and 75th percentile (interquartile range), respectively. Lower and upper whiskers represent the minimum and maximum values of non-outliers, respectively. Points represent individual data points and positive or negative outliers.

Comparison of aortic PWV in a type I and III arch before and after surgery

Before surgery, there was an increase in baseline aortic PWV with a change from the type I to the type III arch configuration (3.46 ± 0.47 *vs* 3.61 ± 0.50 m/s, p = .004). After surgery, and compared with a type I arch configuration, aortic PWV was higher in a type III arch configuration, although not statistically significant (3.84 ± 0.75 *vs* 3.98 ± 0.63 m/s, p = .11).

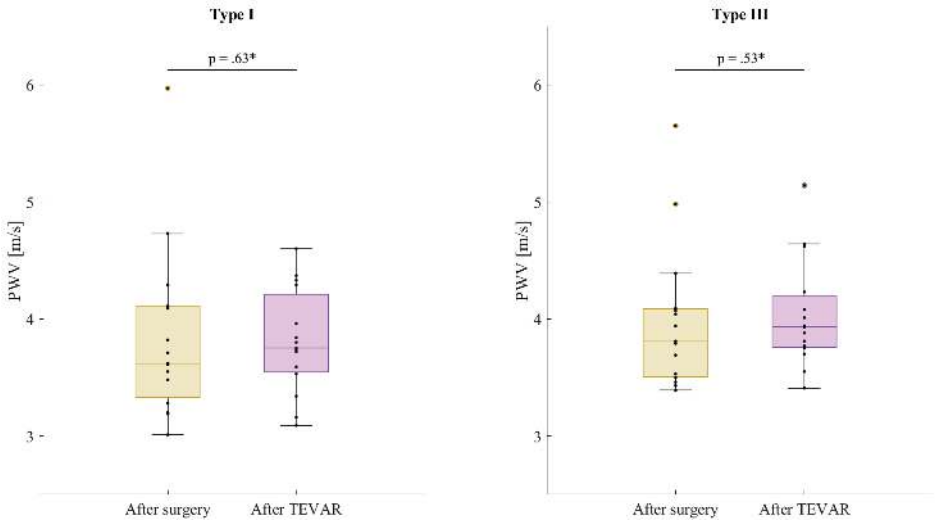

Figure 4. Boxplots and comparison of aortic pulse wave velocity (PWV) values after open surgery and after thoracic endovascular aortic repair (TEVAR) for the 15 porcine thoracic aortic samples, in a type I and type III arch configuration. Asterisk indicates that p-values are derived from the Wilcoxon rank sum test. Lower and upper borders of the box represent the 25th and 75th percentile (interquartile range), respectively. Lower and upper whiskers represent the minimum and maximum values of non-outliers, respectively. Points represent individual data points and positive or negative outliers.

DISCUSSION

This experimental study has shown that open surgical interposition grafting of the proximal descending aorta increases aortic PWV and thus aortic stiffness, regardless of aortic arch angulation utilising a porcine *ex vivo* circulatory mock loop. Moreover, it has shown that after surgery, DBP decreases and SBP remains stable, leading to higher PP and lower MAP. Interestingly, compared with aortic PWV values after TEVAR[20], the absolute mean values of aortic PWV following increases after both surgery and TEVAR were similar. Thus, this study provides mechanistic evidence highlighting that open surgical interposition grafting of the proximal descending aorta stiffens the native aorta, comparable to TEVAR-induced aortic stiffening in the same setting. Since aortic PWV is a well-established surrogate for aortic stiffness and has independently been associated with future adverse cardiovascular events, all-cause mortality, and cardiovascular mortality, these findings may play an important role in determining patients' cardiovascular health.[7–10]

As described for thoracic aortic stent-grafts, the biomechanical properties of Dacron® differ from those of the native aorta.[16,17] One might expect that the absence of nitinol in

surgical interposition grafts and their easily deformable character when depressurized, might render them less stiff compared to stent-grafts. However, our study suggests that this is not true after interposition grafting and intraluminal pressurisation, based on the observed increase in aortic PWV after surgery, which are comparable to the PWV values observed after TEVAR. During the experiments, we anecdotally observed that with pressurisation, the surgical grafts expanded mainly in the longitudinal direction, while there seemed to be less radial expansion. During the cardiac cycle, with pulsatile flow and at physiological blood pressures, the surgical grafts did not distend and recoil as the adjacent native aortic segments. This visual reduction of the aortic Windkessel effect in the surgically replaced aortic segment might explain our findings of increased PWV over the porcine aorta, as well as the specific changes in diastolic blood pressures after surgery. Compared to open surgery, the treated aortic segment remains in place after TEVAR, potentially still contributing to the total arterial compliance of the aorta. Moreover, a stent-graft consists of oversized nitinol rings that are crimped and attached to the fabric.[28] This might leave some capacity for the stent-graft to expand radially in contrast to a surgical graft, or (more probably) this already induces a maximum stretch of the stent-graft fabric that impairs further Windkessel function in this segment. However, these anecdotal observations and this reasoning remains to be further verified and quantified in future dedicated studies. Moreover, future studies could better quantify the change in extensibility and distensibility of the aortic segments adjacent to surgical repairs, to evaluate differences in elastic behaviour of the native aorta before and after surgery or endovascular repair.

Regarding the specific changes in blood pressures after open surgery, there was an increase in PP. Compared with blood pressure changes after TEVAR, this was caused by different changes in SBP and DBP.[13,23] After TEVAR, prior *ex vivo* studies[13,23] by our group and utilising the same set-up, highlighted an increased PP driven by an increase in SBP and stable DBP. In this study however, we found an increase in PP driven by a decrease in DBP and stable SBP which has also driven the significant decrease in MAP, while MAP remained stable after TEVAR in prior studies.[13,23] These observations differ from another *ex vivo* study by our group that found increases in both SBP and DBP after TEVAR, but to a greater extent for SBP, leading to an increased PP, while MAP increased as well.[20] Altogether, there thus seems to be a clear difference in blood pressure response after surgical interposition grafting and TEVAR based on these *ex vivo* analyses.

With a higher PWV due to an increased aortic stiffness, wave reflections typically return during mid-to-late systole as opposed to diastole in young and more compliant aortas, theoretically augmenting SBP and reducing DBP, leading to a wider PP.[8] Our findings after surgery and TEVAR however, reflect that these procedures induce different and

non-physiological blood pressure responses. While higher PP, as an indirect measure of aortic stiffness, has been linked to increased cardiovascular risk by prior studies, recent interest has focused on more direct measures of aortic stiffness and central pulsatile hemodynamic load, like aortic PWV.[29] Moreover, the relationship between PP and PWV is not completely clear[30] and specific blood pressure responses both after surgery and TEVAR deserve investigation and validation by future *in vivo* studies, as human compensation mechanisms could potentially influence these findings, and patient-specific cardiovascular prevention could benefit from those results.

In general, there is a paucity of available data on changes in aortic flow dynamics after open surgical repair of the aorta. This contrasts the availability of data on aortic stiffening after both thoracic and abdominal endovascular repairs[7,11–14,21–23], which might seem odd given the later adoption of endovascular repair as an alternative to open surgery. Nevertheless, in the abdominal region, two prior studies[31,32] found an increase in aortic PWV after open AAA repair, and one of them found a larger increase after endovascular repair.[31] However, a recent meta-analysis[7] pooled the data from three studies [31,33,34] and concluded that open abdominal aortic surgical interposition grafting does not increase aortic PWV. In the thoracic region, Hori *et al.*[18] evaluated changes in aortic PWV after surgical repair of aortic arch aneurysms. After prosthetic graft replacement, aortic PWV increased, but to a lesser extent compared to frozen elephant trunk or hybrid surgery.[18] For the ascending aorta, even more proximally located with respect to the heart and most extensible and distensible compared to more distal thoracic aortic segments[35], the scarce prior literature remains heterogeneous. In contrast to Hori *et al.*[18] and our *ex vivo* findings, Salvi *et al.*[19] did not find increases in aortic PWV in the short to mid-term after surgical replacement of the ascending aorta in 30 patients. On the other hand, Scharfschwerdt *et al.*[36] did not evaluate aortic PWV but found increased systolic blood pressures and maximum aortic diameters in their *ex vivo* study utilising porcine thoracic aortas and a pulsatile flow simulator as well. Thus, data remain limited and heterogenous, paving the way for future *ex vivo*, *in silico*, and *in vivo* studies evaluating the biomechanical and hemodynamical impact of each open and/or endovascular surgical treatment modality for different aortic segments (e.g., ascending aorta, arch) or different treatment lengths. In this way, we and device manufacturers may strive to further improve device materials and designs, ultimately improving the surgical outcomes of patients with aortic disease.

Limitations

This experimental study has limitations related to its design, the use of thoracic porcine aortic samples, and thus the translational value to humans, as elaborated in detail by numerous previous studies utilising this set-up (e.g., water as perfusion fluid).[13,14,20–23]

The absence of pertinent prior literature precluded an a priori power analysis, so a potential type II error for the similar SBP before and after surgery cannot be ruled out. The additional comparative analysis could be limited by the slightly larger absolute diameters of the aortas in the open surgery group, although not significant. However, the aortas and baseline aortic PWV values between both groups were similar, as demonstrated in both arch configurations.

CONCLUSIONS

This experimental porcine *ex vivo* study has shown that compared with baseline values and regardless of arch angulation, open surgical interposition grafting of the proximal descending aorta increases aortic PWV and PP, decreases DBP and MAP, while SBP remains stable. The study has shown that both open surgery and TEVAR stiffen the proximal descending aorta similarly. These findings are important for the long-term results of patients undergoing surgical treatment of aortic diseases, as aortic stiffness increases cardiovascular risk, and may stimulate device manufacturers to further improve both open and endovascular device materials and designs regarding device compliance.

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Comparison of Two Generations of Thoracic Aortic Stent Grafts and Their Impact on Aortic Stiffness in an *Ex Vivo* Porcine Model☆

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☆ This work was invited for the EJVES Vascular Forum bimonthly online Disqus chat on July 26, 2023. Comments can be viewed at: https://www.ejvesreports.com/article/S2666-688X(23)00046-1/fulltext#comments-heading.

WHAT THIS PAPER ADDS

This experimental study investigates intergenerational differences in thoracic aortic stent graft induced aortic stiffening in an ex vivo porcine model. It confirms that TEVAR increases aortic pulse wave velocity (PWV, m/s) – as a marker of aortic stiffness – and shows that potential improvements in device design do not necessarily result in lower aortic PWV values and higher aortic compliance. This may aid device manufacturers in focusing more on improving future device compliance to prevent potential cardiovascular complications in the long term.

ABSTRACT

Objective: Little is known regarding the cardiovascular changes after TEVAR and regarding the impact on aortic stiffness for different stent graft generations specifically, following changes in device design. The present study evaluates the stent graft induced aortic stiffening of two generations of the Valiant thoracic aortic stent graft.

Methods: This was an ex vivo porcine investigation using an experimental mock circulatory loop. Thoracic aortas of young healthy pigs were harvested and connected to the mock circulatory loop. At a 60 bpm heart rate and stable mean arterial pressure, baseline aortic characteristics were obtained. Consequently, pulse wave velocity (PWV) was calculated before and after stent graft deployment. Paired and independent samples t tests or their non-parametric alternatives were performed to test for differences where appropriate.

Results: Twenty porcine thoracic aortas were divided into two equal subgroups, in which a Valiant Captivia or a Valiant Navion stent graft was deployed. Both stent grafts were similar in diameter and length. Baseline aortic characteristics did not differ between the subgroups. Mean arterial pressure values did not change after both stent grafts, while pulse pressures increased statistically significantly after Captivia (mean 44 ± 10 mmHg to 51 ± 13 mmHg, $p = .002$) but not after Navion. Mean baseline PWV increased after both Captivia (4.4 ± 0.6 m/s to 4.8 ± 0.7 m/s, $p = .007$) and Navion (4.6 ± 0.7 m/s to 4.9 ± 0.7 m/s, $p = .002$). There was no statistically significant difference in the mean percentage increase in PWV for both subgroups (8 ± 4% vs. 6 ± 4%, $p = .25$).

Conclusion: These experimental findings showed no statistically significant difference in the percentage increase of aortic PWV after both stent graft generations and confirm that TEVAR increases aortic PWV. As a surrogate for aortic stiffness, this calls for further improvements in future thoracic aortic stent graft designs regarding device compliance.

INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) is currently the first choice treatment option for most thoracic aortic diseases according to the most recent clinical practice guidelines of the European and American societies for vascular surgery, and is increasingly being adopted to treat more proximal aortic zones.[1–5]

In parallel with these advances, the clinical outcomes of TEVAR are still impaired by several drawbacks of currently available stent grafts, ranging from device related complications, such as endoleak or migration, to limited structural durability in the long term.[6,7] Moreover, TEVAR has been shown to alter cardiovascular haemodynamics by increasing aortic stiffness8 and inducing cardiovascular remodelling over time.[9,10] Increased aortic stiffness, normally occurring with age[11] and quantified by aortic pulse wave velocity (PWV),[12] is acknowledged to have an important impact on cardiovascular health.[13]

To improve these aspects that may impact the long term outcomes of TEVAR, device manufacturers are constantly developing newer generation stent grafts with improvements in delivery systems, proximal device configurations, or conformability, compared with previous stent graft generations.[14–17]

Little is known regarding the cardiovascular changes after TEVAR and regarding its impact on aortic stiffness for different stent graft generations specifically, following changes in device design. The aim of the present study is to narrow this gap, by investigating changes in aortic PWV for two generations of the Valiant thoracic aortic stent graft by quantifying their impact on aortic stiffness in an ex vivo porcine model. It was hypothesised that a newer generation with improved conformability would have less impact on the stent graft induced aortic stiffening.

MATERIALS AND METHODS

Aortic specimens

Aortas of young healthy pigs (commercial hybrid, 10 – 12 months, 160 – 180 kg) were collected from a local slaughterhouse and evaluated by a veterinary physician to discover eventual disorders. The aortas were procured from the aortic valve to the renal arteries. No pigs were sacrificed solely for the purpose of this study but were raised for commercial purposes. Therefore, ethical approval by the local animal ethics committee was waived. Preservation and transportation took place in 0.9% saline solution at 4°C and the experiments were conducted within 48 hours of harvesting to ensure the freshness

of the specimens. Before the experiment, each aortic specimen was surgically prepared from the aortic root to the celiac trunk at room temperature, by removing excess connective and cardiac tissue. Side branches (e.g., spinal arteries, the two supra-aortic trunks) were ligated. In the case of a small iatrogenic transmural lesion during preparation, this was sutured with Prolene 4-0.

Experimental set up

The aortas were connected to a circulatory mock loop, which allowed for intraluminal pressurisation under continuous steady state or pulsatile flow in a controlled manner (Fig. 1A). Steady state flow was obtained with a centrifugal pump (Medtronic Biomedicus 550, Minneapolis, MN, USA), while pulsatile flow was obtained with a custom made pulsatile pump containing both mechanical heart valves.[18] The pulsatile pump was set at a heart rate of 60 beats per minute and cardiac output of 4.5 litres per minute. Peripheral resistance was set to obtain a mean arterial pressure (MAP) between 80 and 100 mmHg within the aortic specimens of every experiment. A 3D printed case guided the aortic specimens to approximate the movement of the thoracic aorta within the thoracic cavity, as shown in Figure 1B. Water was kept at body temperature with a liquid heater (Schego 542 Heizer Titan [100 Watt], Offenbach am Main, Germany) and was used for perfusion to preserve the biomechanical characteristics of nitinol stents and to prevent tissue dehydration. Intraluminal pressures were constantly recorded using two pressure sensors (Honeywell pressure sensor 40pc015g series, Morristown, NJ, USA) located at the ascending aorta and just above the celiac trunk, at 1 cm distance from

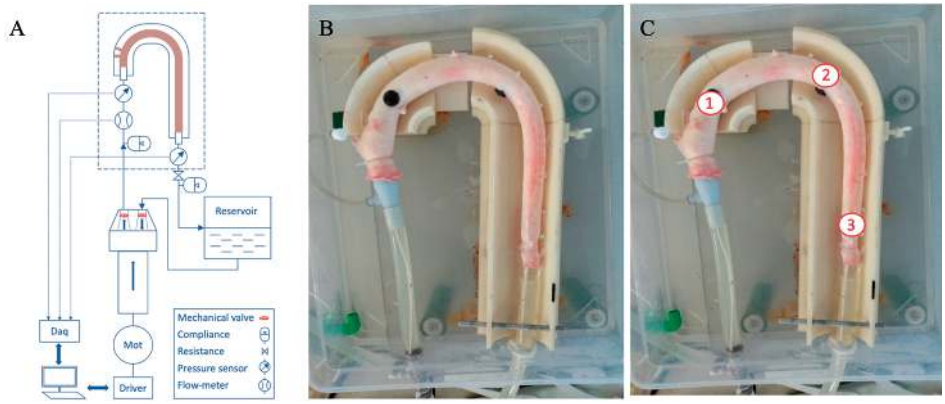

Figure 1. (A) Schematic representation of the circulatory mock loop and its components. Daq = data acquisition; Mot = motor. (B) Porcine aorta connected to the circulatory mock loop. (C) Schematic representation of the three predefined points where the aortic diameters were measured. 1. just distal to the second porcine supra-aortic trunk; 2. 10 cm distal to point 1; 3. Just before the distal tube connector. The proximal stent graft edge was deployed just distal to the second porcine supra-aortic trunk, from point 1 to point 2. Table 1 provides the corresponding aortic diameters.

the connection of the aorta to the silicone tubes. Pressures were recorded for at least 10 consecutive cardiac cycles, after stable values were obtained.

Aortic measurements

Prior to pressure measurement under pulsatile flow, the specimens were pressurised up to a MAP of 80 – 100 mmHg by steady state flow, to repair secondary leakage and to measure luminal calibres. Pulse pressure (PP) was measured, defined as the difference between systolic and diastolic blood pressures. Baseline diameters were manually measured using an echographic probe (Medison Accuvix XQ, Seoul, South Korea) and by two skilled operators (S.A., D.B.). Measurements were performed from adventitia to adventitia. The plastic box in which the 3D printed case, the porcine aorta, and the silicone connecting tubes are positioned, was filled with water to act as echocontrast media. Diameters were collected at three predefined points, the first at the proximal landing zone just distal to the second porcine supra-aortic trunk, the second 10 cm distal to point 1, and the third just before the distal tube connector (Fig. 1C). Aortic centreline length measurements were performed using open source image processing and measurement software (ImageJ, U.S. National Institutes of Health, Bethesda, MD, USA). A planar image of the aortic specimen, taken with a digital camera parallel to the aortic plane, was imported to the ImageJ software. Pixels were scaled in millimetres using a reference of 2 cm in the image (Fig. 1B). Following calibre measurements, steady state flow was replaced by pulsatile flow and aortic PWV measurements were performed, as a surrogate for aortic stiffness.

Stent graft devices and implantation

Two different stent graft types were deployed in the present study, the earlier generation (second) Captivia (Medtronic, Minneapolis, MN, USA) and the newer generation (third) Navion (Medtronic, Minneapolis, MN, USA). Stent graft size for Captivia used in the present study was 26-26-100, and 25-25-96 for Navion. This study started before the global device recall for Navion, and the decision to continue the analysis was taken to better understand the potential improvements of newer generation stent grafts in terms of device compliance.

After distal disconnection of the aorta from the circulatory mock loop, stent grafts were deployed using a custom made delivery system (Appendix A). The proximal stent graft edge was deployed just distal to the second porcine supra-aortic trunk from point 1 to point 2 (Figure 1C). After deployment and reconnection of the aorta to the loop, the proximal and distal landing zones were confirmed manually. Intraluminal pressures were recorded at the level of the ascending aorta and just above the celiac trunk. Aortic PWV (in metres per second [m/s]) was calculated by dividing the distance between the

tips of the proximal (ascending aorta) and distal (just above the celiac trunk) pressure sensors, by the time between the two minima of the proximal and distal pressure signals (transit time [TT]), following the foot to foot method. The same stent graft was reloaded into the custom made delivery system and used for the next experiment (Appendix A).

Data analysis

Boxplots were created to graphically summarise results. Exclusion criteria were adopted: (1) a conservation time of more than 48 hours between harvesting of the aorta and the experiment; (2) aortic specimens with severe aortic leakage during continuous flow pressurisation; (3) initial technical issues that resulted in unstable pressure values during continuous and/or pulsatile pressurisation; (4) experiments with a decline in PWV after stent graft deployment were not considered for statistical analysis as the impact of a stent graft on aortic PWV can be zero at minimum from a theoretical biomechanical point of view;[8,9,19–22] (5) extreme PWV increase outliers (> Q3 + 3 * interquartile range) after stent graft deployment. Data were analysed using Matlab version R2022b (Mathworks, Natick, MA, USA), Microsoft Excel (Microsoft, Redmond, WA, USA), and IBM SPSS Statistics versions 27 and 28 (SPSS Inc., Chicago, IL, USA). Data are reported as number (n) and percentage (%), or as mean ± standard deviation (SD). The Shapiro- Wilk test was performed to test for normality. Independent samples t test and paired student t test were performed to compare independent and paired groups of normally distributed measurements, respectively. In the case of non-normally distributed data, non-parametric alternatives Wilcoxon rank sum and Wilcoxon signed rank tests were performed. Two sided p values < .050 were considered to be statistically significant. Intra-observer, interobserver agreement, and repeatability coefficients (RC, reported as number and percentage of the mean of all measurements) were assessed for the centreline length (TM, DB) and (manually adjusted) transit time (TT) measurements (MC, DB), according to the Bland-Altman method (see Appendix B for a detailed explanation).[23]

RESULTS

In total, 31 porcine aortas were harvested and connected to the pulsatile mock circulatory loop between July 2020 and November 2021. Captivia was deployed in 16 aortas (52%), while in another 14 aortas (45%) Navion was deployed. One aorta (3%) was excluded before stent graft deployment due to excessive leakage during pressurisation. Four initial samples (13%) were excluded due to technical issues, and one (3%) due to a conservation time > 48 hours. Exclusion criteria 4 and 5 led to an inclusion range of PWV changes after stent graft deployment from 0% to 21.8% (for the Captivia subgroup). In the remaining 25 experiments (81%), this led to four (13%) exclusions due to a decline

in PWV after stent graft deployment (Captivia subgroup: n = 3, Navion subgroup: n = 1), while one (3%) was an extreme PWV increase outlier (Captivia subgroup).

Consequently, 20 experiments were found to be eligible for the present analysis, and the Captivia subgroup (n = 10) was compared with the Navion subgroup (n = 10). Baseline aortic specimen characteristics are shown in Table 1. The porcine thoracic aortas were tapered from proximal to distal (Table 1). Therefore, oversizing at the proximal landing zone (PLZ) in the Captivia subgroup was 6% ± 8%, gradually increasing to a distal landing zone (DLZ) oversizing of 34% ± 9%. Similarly, in the Navion subgroup, PLZ oversizing was 6% ± 7%, gradually increasing to a DLZ oversizing of 32% ± 11%. There was no statistically significant difference regarding the oversizing at the PLZ and DLZ between both stent grafts (PLZ: p = .96, DLZ: p = .66). In 17 (85%) specimens, experiments were conducted within 24 hours from harvesting and in the remaining three (15%) within 48 hours.

Table 1. Baseline aortic specimen characteristics and differences between the Captivia and Navion subgroups.

	Captivia subgroup (n = 10)	Navion subgroup (n = 10)	p-value
Diameter point 1*, mean ± SD, cm	2.5 ± 0.2	2.4 ± 0.2	.243
Diameter point 2*, mean ± SD, cm	2.0 ± 0.1	1.9 ± 0.2	.538
Diameter point 3*, mean ± SD, cm	1.7 ± 0.1	1.7 ± 0.2	.292
Centreline length, mean ± SD, cm	31.2 ± 3.3	33.0 ± 3.6	.251
Conservation time, days	1.20 ± 0.42	1.10 ± 0.32	.739

Data are presented as mean ± SD.
*See Figure 1C for a schematic specification of the locations of porcine aortic diameter measurements.

In both subgroups, MAP values did not significantly change after Captivia (mean MAP from 92 ± 7 mmHg to 90 ± 10 mmHg, p = .62) and Navion (mean MAP from 97 ± 4 mmHg to 97 ± 6 mmHg, p = .87) deployment. A statistically significant increase was found in PP after Captivia (mean PP from 44 ± 10 mmHg to 51 ± 13 mmHg, p = .002) but not after Navion (mean PP from 68 ± 20 mmHg to 74 ± 22 mmHg, p = .100) deployment. Figure 2 visualises MAP and PP changes for both subgroups.

Baseline aortic PWV did not differ between the Captivia and Navion subgroups (Table 2). Boxplots of the PWV values before and after stent graft deployment are shown in Figure 3, and a substantial increase was found in PWV in both subgroups. A boxplot of the % increase in PWV for both subgroups is shown in Figure 4. A lower mean % increase was found in PWV after Navion compared with Captivia; however, this finding was not statistically significant (Table 2).

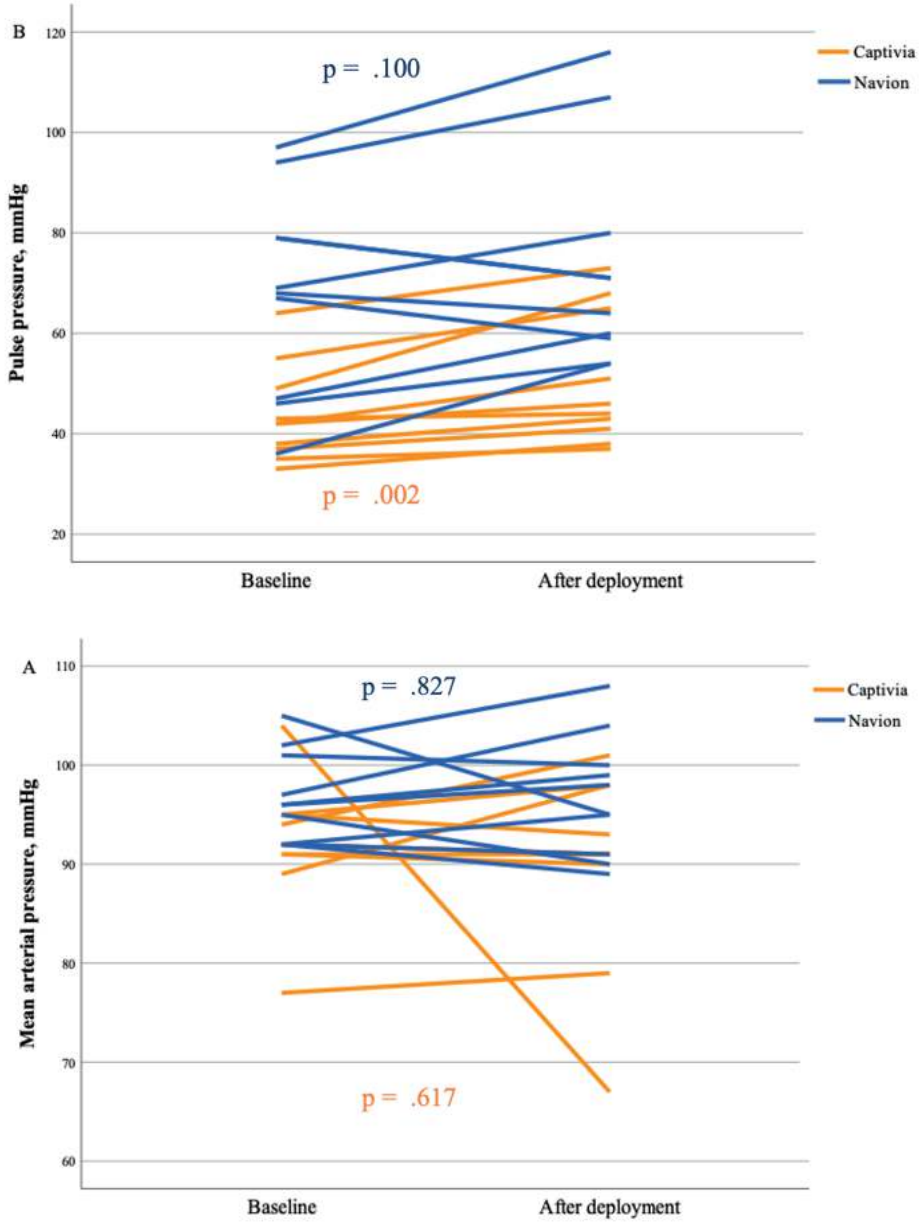

Figure 2. Spaghetti plots of the changes in mean arterial pressure (A) and pulse pressure (B) before and after stent graft deployment.

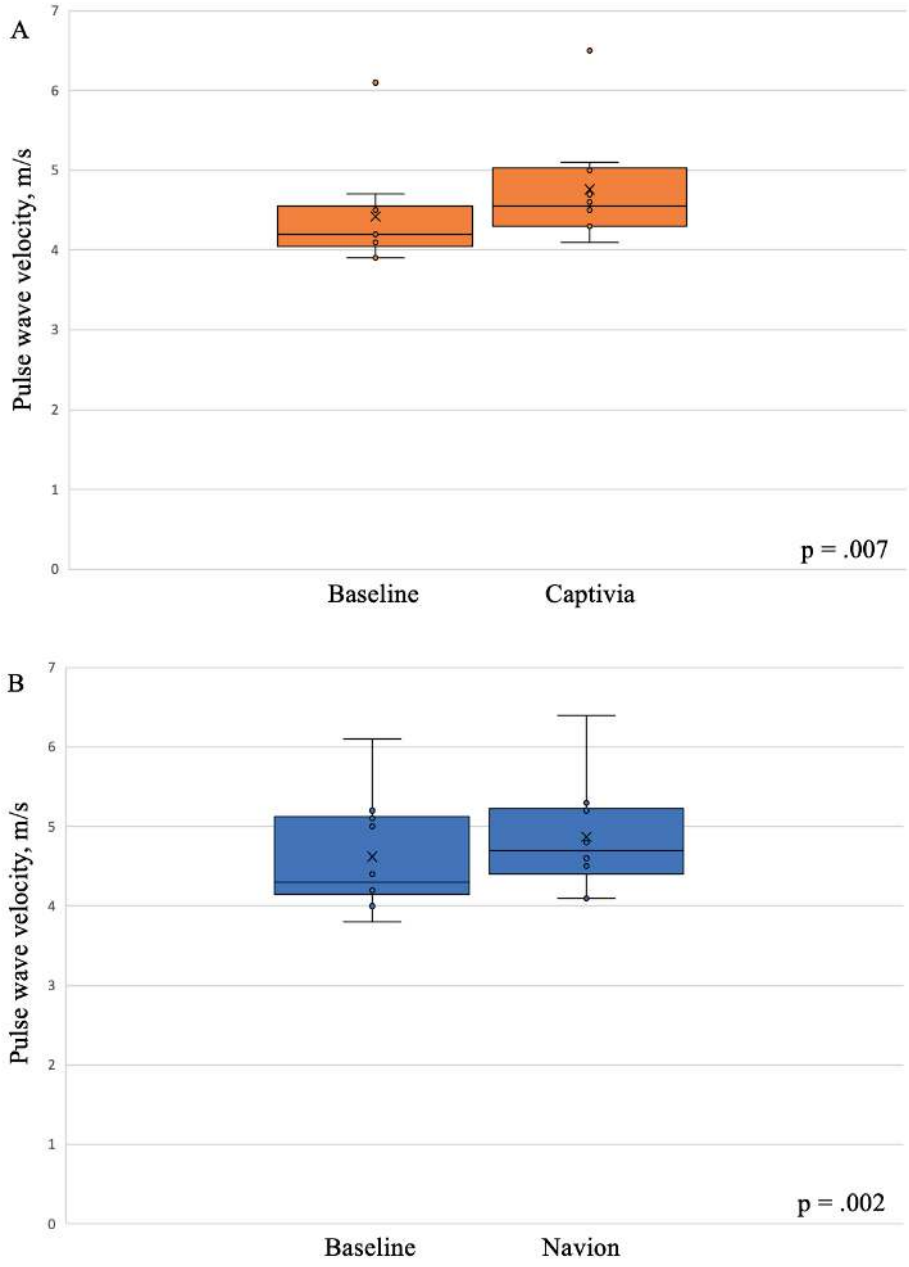

Figure 3. Spaghetti plots of the changes in mean arterial pressure (A) and pulse pressure (B) before and after stent graft deployment.

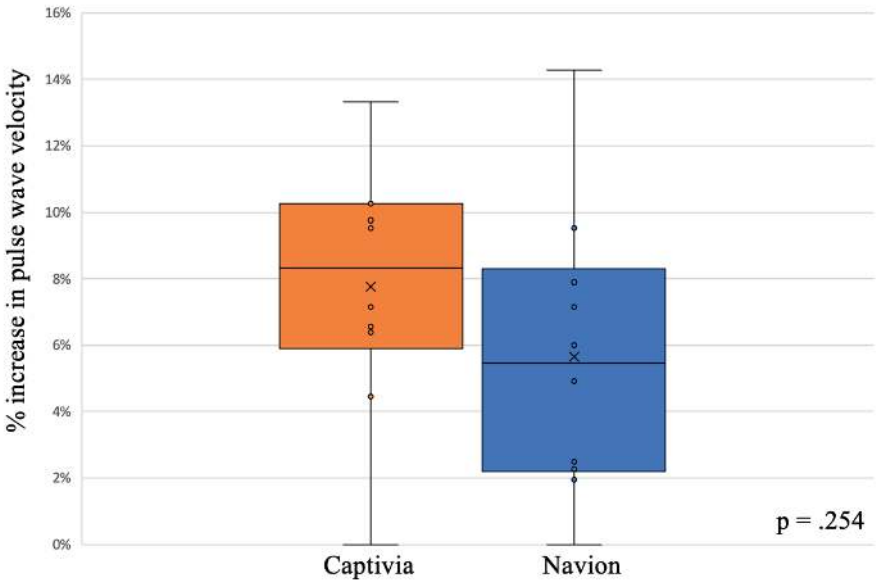

Figure 4. Spaghetti plots of the changes in mean arterial pressure (A) and pulse pressure (B) before and after stent graft deployment.

Intra-observer and interobserver agreement for the centreline length measurements (n = 20) and TT measurements (n = 5) was adequate (Appendix B). For the centreline length measurements, the intra-observer RC was .86 cm (3%) and interobserver RC was .68 cm (2%).

Table 2. Differences between the Captivia and Navion subgroups regarding baseline pulse wave velocity and the pulse wave velocity after stent graft deployment.

	Captivia subgroup (n = 10)	Navion subgroup (n = 10)	p-value
Baseline PWV, m/s	4.4 ± 0.6	4.6 ± 0.7	.481
PWV after stent graft deployment, m/s	4.8 ± 0.7	4.9 ± 0.7	-
% increase in PWV after stent graft deployment, m/s	8 ± 4	6 ± 4	.254

Data are presented as mean ± SD.

DISCUSSION

This ex vivo study evaluated changes in aortic PWV – a marker of aortic stiffness – after deployment of two generations of Valiant thoracic aortic stent grafts in thoracic porcine aortas connected to a circulatory mock loop. To the present authors' knowledge, this is the first study that investigates differences in stent graft induced aortic stiffening between two generations of thoracic aortic stent grafts in an experimental setting, following improvements in device conformability. The main finding is no statistically significant difference in the percentage increase of aortic PWV after deployment of both stent grafts (Fig. 4). Moreover, it is confirmed that aortic PWV increases after TEVAR with both devices (Fig. 3).

Potential improvements in device design may reduce the impact of thoracic aortic stent grafts on aortic stiffness and prevent future cardiovascular events.[8,9,13,24] This may improve the long term outcomes of endovascular aortic treatment modalities by reducing a patient's cardiovascular risk. On the other hand, caution and lifelong surveillance remain crucial, as this may also negatively impact clinical outcomes or cause device failure.[7] Reasons for the global device recall of Navion were 11 structural failures at one to four years of follow up (e.g., type IIIb endoleaks, fractures and loss of seam integrity, stent ring enlargement).[7]

The present findings are comparable with previous porcine ex vivo studies and show a similar order of magnitude in mean PWV increase (range 4 – 9%).[21,22] One of these studies only found a statistically significant increase in PWV after distal extension of a single stent graft (length 100 mm), suggesting that the increase in PWV might be dependent on the amount of aortic coverage by TEVAR.21 In contrast to this, the main findings of the present study and of another study that compares four different stent graft brands show an increase in aortic PWV after deployment of a single stent graft with 96 – 100 mm aortic coverage.22 However, in the same study it was concluded that the increase in aortic PWV was dependent on the extent of stent graft coverage.[22]

After Captivia deployment, a statistically significant increase was found in PP, while this was not found after Navion deployment (Fig. 2B). This may raise attention to the fact that different devices could impact cardiovascular haemodynamics in different ways. In humans, certain physiological compensation mechanisms may mitigate these effects. Increases in systolic blood pressure or PP following increases in aortic stiffness causes increased pulsatile damage to target organs, especially those that operate at high arterial flow and low vascular resistance (e.g., kidneys, brain).[13,25,26] Here, it seems important to note that natural aortic stiffening occurring with aging and an acutely induced aortic

stiffness mismatch after stent graft deployment are two different things. Nevertheless, they both increase aortic PWV, and the haemodynamic impact seems comparable from a conceptual point of view. Moreover, due to increased aortic stiffness, cardiac afterload increases, and coronary perfusion pressure reduces. This has been shown to induce adverse cardiac and aortic remodelling over time by several clinical, experimental, and computational investigations.[9,10,19,20,27]

Altogether, there is a growing interest in evaluating the long term outcomes of TEVAR for different aortic diseases. Adverse outcomes may be of specific importance in young patients without comorbidities, typically treated with TEVAR for blunt thoracic aortic injury (without questioning the application of TEVAR to treat this life threatening disease).[9] Research regarding this topic need to be advocated as it can provide useful insights for physicians to improve the clinical outcomes of TEVAR, while it could aid medical device manufacturers with future stent graft development. Moreover, as the general treatment trend is shifting towards the endovascular management of arterial and venous disease, related issues such as aortic stiffening or more widely vascular stiffening, request knowledge, attention, and a specific approach.

Limitations

Ex vivo studies investigating the biomechanical coupling between TEVAR and porcine aortic tissue have inherent limitations. The circulatory mock loop aims at eliminating factors that could influence the results, such as variations in blood pressure, as PWV is known to be dependent on MAP.[12,28] Future development of the set up would aim to integrate the control of both baseline MAP and PP. On the one hand, this experimental setting allows for control, isolation, and analysis of certain parameters, while there is variability in other parameters at the same time (e.g., aortic specimens). This is the main reason for the relatively high number of exclusions in which a PWV decline after stent graft deployment (n = 4) or extreme PWV increase (n = 1) was found, compared with the other experiments. Moreover, sample size calculation was not performed for the primary outcome, which might have led to a false acceptance of the null hypothesis (type II error). Next, the use of thoracic porcine aortic tissue is most comparable with human aortic tissue < 60 years old, and the results of the present study might thus be less translatable to patients > 60 years old.[29] A single stent graft size was used in both subgroups, and this stent graft was not gradually tapered to have an equal amount of oversizing at the PLZ and DLZ. The slight difference in diameter (1 mm) and length (4 mm) between both stent grafts may theoretically have introduced a bias on the results. As mentioned by previous authors, water is known to have a lower viscosity than blood but is a commonly used perfusion fluid in ex vivo porcine models.[30] The influence on PWV measurements is expected to be low due to the high speed of travel of water in a

pulsatile environment.[31] Another possible limitation might be that the porcine aortas had no surrounding connective tissues as in humans, and this might influence movement or passive biomechanics.[32]

Conclusions

This porcine ex vivo study did not find a statistically significant difference in the percentage increase of aortic PWV of both generations of Valiant thoracic aortic stent grafts; however, both stent grafts did increase aortic PWV, as a surrogate for aortic stiffness.

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Part III

Computational and imaging perspectives

6

Thoracic Stent Graft Numerical Models To Virtually Simulate Thoracic Endovascular Aortic Repair: A Scoping Review☆

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WHAT THIS PAPER ADDS

This scoping review identified 14 currently available virtual thoracic endovascular aortic repair simulation models. Severe heterogeneity exists in study characteristics, methodological aspects, and outcomes. Before a wider application to clinical practice during pre-procedural planning and follow up of patients with aortic disease, the need to further increase the credibility and reliability of such tools is emphasised. This review may serve as an initial step in that direction. Collaborative medical and engineering efforts are of primary importance and should be further stimulated to better understand complex cardiovascular haemodynamics and to improve patient outcomes.

ABSTRACT

Objective: Pre-procedural planning of thoracic endovascular aortic repair (TEVAR) may implement computational adjuncts to predict technical and clinical outcomes. The aim of this scoping review was to explore the currently available TEVAR procedure and stent graft modelling options.

Data sources: PubMed (MEDLINE), Scopus, and Web of Science were systematically searched (English language, up to 9 December 2022) for studies presenting a virtual thoracic stent graft model or TEVAR simulation.

Review methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) was followed. Qualitative and quantitative data were extracted, compared, grouped, and described. Quality assessment was performed using a 16 item rating rubric.

Results: Fourteen studies were included. Among the currently available *in silico* simulations of TEVAR, severe heterogeneity exists in study characteristics, methodological details, and evaluated outcomes. Ten studies (71.4%) were published during the last five years. Eleven studies (78.6%) included heterogeneous clinical data to reconstruct patient specific aortic anatomy and disease (e.g., type B aortic dissection, thoracic aortic aneurysm) from computed tomography angiography imaging. Three studies (21.4%) constructed idealised aortic models with literature input. The applied numerical methods consisted of computational fluid dynamics analysing aortic haemodynamics in three studies (21.4%) and finite element analysis analysing structural mechanics in the others (78.6%), including or excluding aortic wall mechanical properties. The thoracic stent graft was modelled as two separate components (e.g., graft, nitinol) in 10 studies

(71.4%), as a one component homogenised approximation (*n* = 3, 21.4%), or including nitinol rings only (*n* = 1, 7.1%). Other simulation components included the catheter for virtual TEVAR deployment and numerous outcomes (e.g., Von Mises stresses, stent graft apposition, drag forces) were evaluated.

Conclusions: This scoping review identified 14 severely heterogeneous TEVAR simulation models, mostly of intermediate quality. The review concludes there is a need for continuous collaborative efforts to improve the homogeneity, credibility, and reliability of TEVAR simulations.

INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) is now the first choice to treat thoracic aortic aneurysms (TAA) and acute aortic syndromes (AAS) in the descending thoracic aorta and distal aortic arch (zone 2 – 5). As a hybrid adjunct or alternative to open surgical repair it is also increasingly considered for treatment of the diseased proximal aortic arch or ascending aorta (zone 0 – 1) if open surgical repair is contraindicated.[1-4]

Favourable technical TEVAR results largely depend on the anatomical suitability of the aortic region of interest for endovascular repair. Meticulous pre-operative assessment of vessel diameter, morphology, and the presence of atherosclerosis, thrombus, or calcifications is of primary importance. Conventional imaging techniques to assess this consist of computed tomography angiography (CTA) and magnetic resonance imaging (MRI) with three dimensional (3D) reconstructions.[5,6]

Over recent years, there has been a rise in the development and application of *in silico* computational tools to evaluate haemodynamic parameters and to help pre-procedural planning by simulating the TEVAR procedure and predicting technical and clinical results.[7-10] There are different computational methods to model the complex dynamic interplay between the aortic wall, blood, and stent graft. Computational fluid dynamics (CFD) simulates the aortic haemodynamics (i.e., blood flow) in an aorta with a rigid wall, while finite element analysis (FEA) allows for modelling the structural mechanics of the aorta and the stent graft. As a third, fluid structure interaction (FSI) combines both methods and allows for an evaluation of blood induced wall motion and deformation, combining both aortic haemodynamics and structural mechanics of the aortic wall (Figure 1).[11]

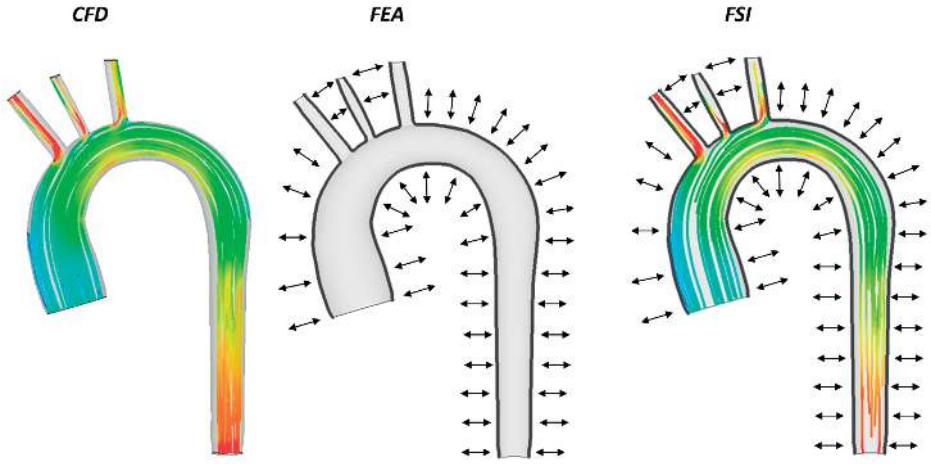

Figure 1. Illustration of (A) computational fluid dynamics (CFD) simulating aortic haemodynamics in a rigid aorta, (B) finite element analysis (FEA) simulating structural mechanics of the aortic wall, and (C) fluid structure interaction (FSI) integrating both methods allowing for a computational evaluation of blood induced wall motion and deformation.

The aim of this scoping review was to explore the currently available TEVAR procedure and stent graft modelling options, assessing, and comparing different study characteristics, methodological numerical details, and outcomes. In contrast to a systematic review aiming to answer a specific and clearly defined research question, a scoping review scopes the body of literature on a certain topic in a similar robust and systematic manner.[12]

MATERIALS AND METHODS

Review design

The conduct of this scoping review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review (PRISMA-ScR) and initial methodological frameworks to perform scoping reviews.[13-15] The protocol was registered and made publicly available on the Open Science Framework (https://osf.io/brzaj/).[16] Critical appraisal of the individual sources of evidence was deemed optional following the PRISMA-ScR.[13]

Objectives

The main objective of this study was to assess, compare, and describe the different available thoracic aortic stent graft models to simulate the TEVAR procedure. Specifi-

cally, studies were assessed and compared regarding the similarities and differences in baseline characteristics, methodological details, details of the numerical methods applied, and qualitative or quantitative outcomes.

Literature sources and search strategy

The search process was performed independently by two authors (T.M., A.R.) with a medical and bioengineering background. This process included the systematic search, study selection with application of inclusion and exclusion criteria, data acquisition, and data management. A third and or fourth senior author (F.M., S.T.) was consulted to provide consensus in case of discrepancies.

The systematic search was conducted on 9 December 2022. The PubMed (MEDLINE), Scopus, and Web of Science databases were queried. No filters except for English language articles were applied. The search strategy was developed following a similar strategy to the Patient, Intervention, Comparison, Outcome (PICO) framework[17]; however, there were only two categories included in the search string consisting of multiple entry terms and or Medical Subject Headings (MeSH) related to computational simulation (e.g., virtual, simulation*, Finite Element Analysis) and TEVAR (e.g., thoracic endovascular aortic repair, thoracic stent graft, aortic endograft). In this way, all relevant studies that could potentially serve the review topic were broadly examined. Per category, relevant entry terms and MeSH terms were combined with OR, while both categories were combined with AND. The satisfactory search string for PubMed was consequently translated to a comparable search for Scopus and Web of Science. Full detailed search strings for the three databases can be found in Supplementary Table S1.

Study selection

Rayyan software[18] was used to facilitate the selection process and consisted of duplicate removal, screening on title and abstract, and assessment for eligibility of the remaining studies based on their full text. Reference lists of eligible studies were screened for additional eligible studies not included in the search results. No automation tools were used. The study selection process was finalised on 16 December 2022.

Inclusion and exclusion criteria

English language original articles presenting a virtual thoracic stent graft or TEVAR simulation model irrespective of the type of clinical data included in the study, the input for segmentation, or the numerical method, were included. Exclusion criteria were: (1) review article; (2) referral to the same methodology of another study that initially developed the TEVAR simulation model; (3) studies presenting real life simulations for clinical training purposes (i.e., non-numerical simulations).

Data acquisition

Relevant data from eligible studies were extracted and summarised on pre-defined tables in Microsoft Word (Microsoft Corp, Redmond, WA). Columns of tables were created with the aim to group data from studies in a concise manner. Data regarding study characteristics (e.g., first author, publication year, journal, journal focus, article type, study location, involved departments [i.e., medical doctors and or engineers], study aim, any specific discriminating aspects), methodological details including clinical data if present (e.g., patients, type and zone of aortic disease, stent graft type, dimensions, and oversizing) or numerical data (e.g., input for segmentation, method, aortic model, stent graft model, other simulation components), and qualitative and quantitative clinical, numerical, or comparative outcomes (between the clinical and numerical results).

Quality assessment

Quality assessment was performed independently by two authors using a 16 item rating rubric (T.M., A.R.) and final consensus was provided by a senior author (F.M.) in case of discrepancies.[19] As the rubric was originally developed as a tool to evaluate research addressing simulations as a teaching methodology for physicians and or nurses, the questions were applied to the numerical studies included in this review and interpreted as such. A final score < 50% was considered low, between 50% and 70% intermediate, and > 70% high quality.

Data presentation

Data were reported in textual form, as number (*n*) and percentage (%), as mean ± standard deviation (SD) or median (range or interquartile range [IQR]) where appropriate. Missing data were reported as (-).

RESULTS

Study selection

Figure 2 provides the detailed PRISMA-ScR flow diagram of study selection. The initial search identified 417 studies. After duplicate removal, the remaining 184 studies were screened on title and abstract. Forty-five studies were assessed based on their full text. Finally, 14 studies met the eligibility criteria and were included.[20-33] One study was included based on reference screening during full text assessment. The most important reasons for exclusion at this stage were the lack of (a detailed description of) the stent graft model and or TEVAR simulation (*n* = 22), or referral to an already included TEVAR simulation model (*n* = 5).

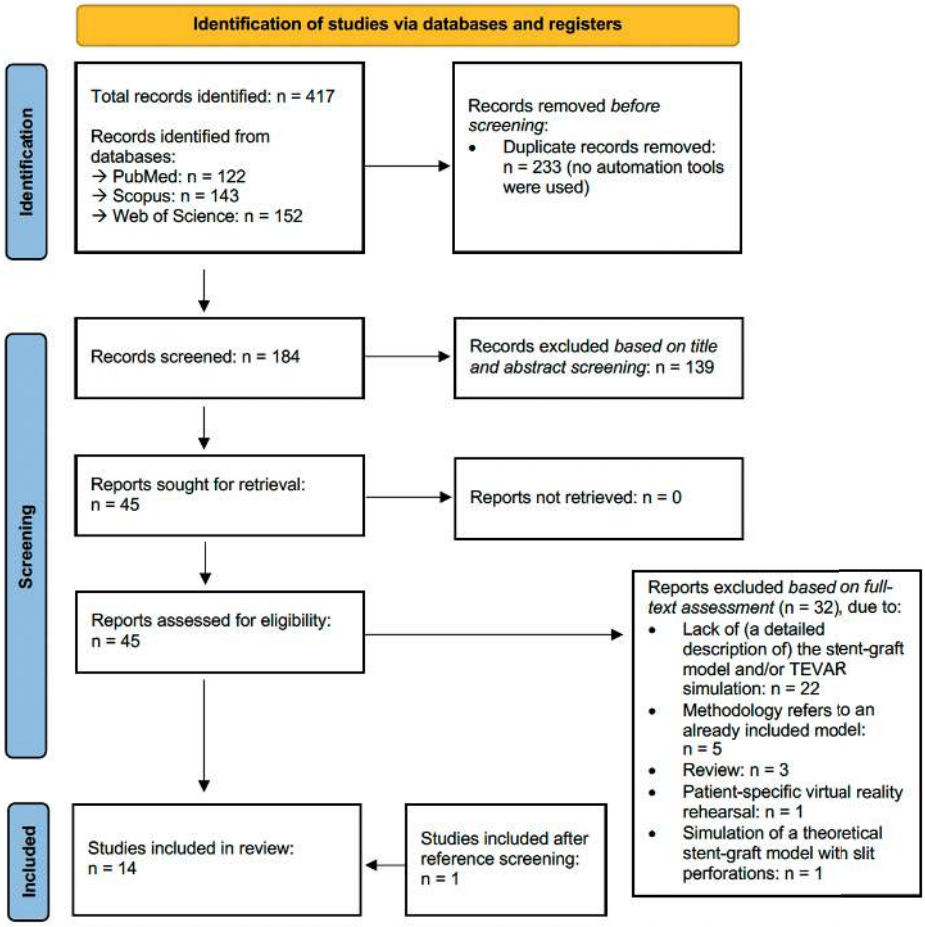

Figure 2. Study selection flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) to identify studies presenting a virtual thoracic endovascular aortic repair simulation model.

Study characteristics

Table 1 presents the detailed characteristics of the studies included in this review including the study aim and specific discriminating aspects of respective studies. The first TEVAR simulation model was presented in 2008 by Cheng *et al.* from Hong Kong, China, and was published in the *Journal of Vascular Surgery*.[20] Ten of 14 studies (71.4%)[24-33] were published during the past five years, which might demonstrate the increased interest in computational tools to serve the medical community over the last decade, together with technological advances to support this. Three studies (21.4%)[20,21,25] were published in a surgical journal, while the remaining 11 studies were published in journals with a biomechanical, biomedical engineering, biophysics, or physiology background (78.6%).

Most of these studies were collaborative efforts of surgeons or other physicians and engineers (*n* = 11, 78.6%) originating from China (*n* = 4, 21.4%), Italy, France, United States of America, or a collaboration between the United Kingdom and China (*n* = 2 per group, 14.3%).

Quality assessment

Three studies (21.4%)[20,23,26] obtained a total score indicating low quality, nine studies (64.3%)[21,22,24,25,27-29,31,32] were of intermediate quality, while two studies (14.3%)[30,33] were considered high quality (Table 1). The scores for each of the 16 items for the single studies can be found in Supplementary Table S2.

Methodological details

Table 2 (clinical data) and Table 3 (simulation model) provide a detailed overview of the methodological details of the included studies.

Clinical data

Eleven studies (78.6%)[20-27,29-31] used clinical patient data in their study with corresponding CTAs that either served as input for the segmentation of the aortic model and comparison with the simulation results (n = 5, 45.5%),[22,24,27,30,31] as a basis to evaluate haemodynamic parameters such as drag or displacement forces using CFD (n = 2, 18.2%),[20,21] or as a basis to evaluate structural mechanical parameters such as Von Mises stress or apposition using FEA (n = 4, 36.4%).[23,25,26,29] Eight of these studies (72.7%)[22,23,25-27,29-31] included one specific patient to reconstruct the aortic model, most frequently resembling type B aortic dissections (TBAD, n = 4, 50%),[25,29-31] thoracic aortic aneurysm (TAA) located in the descending aorta or aortic arch (n = 2, 25%),23,27 or pseudoaneurysms of the ascending aorta (n = 2, 25%).[22,26] The remaining three studies that included clinical data (n = 11) evaluated more than one patient (range 2 – 58) and investigated specific haemodynamic parameters using CFD in TBAD (n = 2, 66.6%) or descending TAA (n = 1, 33.3%). Stent graft details and dimensions of these patients are reported in Table 2.

Table 1. Study characteristics of the 14 including studies presenting a virtual thoracic endovascular aortic repair simulation model

First author, year	Journal	Journal focus	Study location	Investigators focus	Aim of the study	Specific aspects	Quality assessment score*
1. Cheng, 2008	J Vasc Surg	Medical, surgical	Hong Kong (China)	Surgery – Mechanical engineering – Electrical and electronic engineering	1. To study the forces acting on thoracic stent-grafts and their relationship to geometry and flow using CFD 2. To determine the changes in drag forces associated with stent-graft remodelling using 3D reconstructed flow models from actual patients	Relationship of drag force with geometry, flow, and stent-graft remodelling	39%
2. Figueroa, 2009	J Endovasc Ther	Medical, surgical	Stanford (United States of America)	Bioengineering – Surgery	To assess 3D pulsatile displacement forces acting on thoracic aortic stent-grafts	Relationship of displacement force with stent-graft location, size, and elevated pressure	50%
3. Auricchio, 2013	Comput Biol Med	Biomedical engineering	Pavia, Milan (Italy)	Civil engineering and architecture – Thoracic aorta research center	To evaluate the capability of patient-specific structural FEA to predict apposition of a patient-tailored stent-graft	-	64%
4. Altnji, 2013	Comp Methods Biomech Biomed Engin	Biomechanical, biomedical engineering	Lyon (France)	-	To develop a numerical simulation of a complete stenting system in complex aortic morphology	Positional stability, mechanical-related migration factors, proximal neck angulation	21%
5. Chen, 2018	Theranostics	Biomedical	Beijing, Kunming (China)	Diagnostic and interventional (neuro)radiology – Vascular and endovascular surgery	To develop and validate a fast virtual stent-graft deployment algorithm to provide functional predictions	-	52%
6. Ma, 2018	J Vasc Surg	Medical, surgical	Shanghai (China)	Vascular surgery – Aeronautics and astronautics – Radiology	To evaluate and quantify the stent-graft to aorta interaction and to analyse the risk factors for injury through computational simulation	Stent-graft related stress	50%

Table 1. Study characteristics of the 14 including studies presenting a virtual thoracic endovascular aortic repair simulation model (*continued*)

First author, year	Journal	Journal focus	Study location	Investigators focus	Aim of the study	Specific aspects	Quality assessment score*
7. Romarowski, 2018	Comput Biol Med	Biomedical engineering	Pavia, Milan (Italy)	3D and computer simulation laboratory – Civil engineering and architecture – Electrical, computer, and biomedical engineering	To propose a computational framework for choosing and deploying stent-grafts via FEA	-	46%
8. Derycke, 2019	Ann Biomed Eng	Biomedical engineering	Saint-Étienne, Créteil, Saint-Priez-en-Jarez (France)	Vascular surgery	To develop a computational tool able to predict stent-graft deployment in complex aortic arch pathology	Sensitivity analyses for different young moduli and friction coefficients	50%
9. Desyatova, 2020	Biomech Model Mechanobiol	Biophysics	Omaha (United States of America)	Surgery	To develop a method that allows accounting for the longitudinal pre-stretch of the thoracic aorta and its main branches before and after TEVAR	Longitudinal pre-stretch	56%
10. Meng, 2020	Artif Organs	Biomedical	Shanghai (China)	Cardiology and aortic centre – National heart and lung institute – Chemical engineering	To investigate the biomechanical mechanism of stent-graft induced new lesions	To compare and analyse the difference between radial force and spring-back force in the causation of peak stress on the aorta for different oversizing ratios	52%
11. Kan, 2021	Biomech Model Mechanobiol	Biophysics	London (United Kingdom), Shanghai (China)	Chemical engineering – Vascular surgery	To develop a virtual stent-graft deployment framework	-	71%

Table 1. Study characteristics of the 14 including studies presenting a virtual thoracic endovascular aortic repair simulation model (*continued*)

First author, year	Journal	Journal focus	Study location	Investigators focus	Aim of the study	Specific aspects	Quality assessment score*
12. Kan, 2021	Front Physiol	Physiology	London (United Kingdom), Shanghai (China)	Chemical engineering – Vascular surgery – Key laboratory of textile science and technology	To investigate the influence of stent-graft length and local biomechanical changes before and after TEVAR using a virtual stent-graft deployment simulation model	Stent-graft length	66%
13. Shahbazian, 2022	Int J Numer Meth Biomed Eng	Biomedical engineering	Toronto (Canada)	Mechanical and industrial engineering – Vascular surgery – Institute of biomedical engineering	To propose a novel modelling framework for creating realistic population-based computational models of TEVAR	-	52%
14. Ramella, 2022	Ann Biomed Eng	Biomedical engineering	Milan (Italy), Mulhouse (France)	Computational biomechanics laboratory-Chemistry, Materials, and Chemical engineering – Laboratory of physics and textile mechanics – Civil engineering and architecture – Vascular surgery	To develop high-fidelity FE simulations to virtually reproduce the TEVAR procedure	Stent-graft material calibration (not literature parameters)	75%

*Quality assessment was performed using a 16-item rating rubric: a quality score < 50% was considered low, 50% – 70% intermediate, and > 70% high. Abbreviations: CFD: Computational fluid dynamics, FEA: Finite element analysis; FE: Finite element 3D: three-dimensional, TEVAR: Thoracic endovascular aortic repair.

Table 2. Methodological details of the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model – focus on clinical data

First author, year	Clinical data				
	Patients, n	**Aortic pathology**	**Aortic zone**[4]	**Stent-graft type**	**Stent-graft dimensions and oversizing, mm and %**
1. Cheng, 2008	12	Uncomplicated TBAD	2 – 3	Zenith TX2 proximal endograft components	D: 32.8 (28 – 38) L: 153 (-) OS: 12.8 (5 – 31)
2. Figueroa, 2009	2	TAA	3, 4 – 5	-	-
3. Auricchio, 2013	1	Pseudoaneurysm	0	Custom-made (Bolton)	D: 38 (proximal), 48 mm (distal) L: 70 OS: 10
4. Altnji, 2013	1	TAA	5	-	-
5. Chen, 2018	58	Acute TBAD	-	cTAG, Valiant, Zenith, Hercules, Ankura, Grimed	-
6. Ma, 2018	1	Complicated acute TBAD	3	Valiant	-
7. Romarowski, 2018	1	Pseudoaneurysm	0	-	-
8. Derycke, 2019	1	Arch aneurysm	0 – 2	RelayBranch	-
9. Desyatova, 2020	-	-	-	-	-
10. Meng, 2020	1	TBAD	2	-	-
11. Kan, 2021	1	Complicated subacute TBAD	-	Valiant	D: 28 L: 150 Proximal bare stent
12. Kan, 2021	1	TBAD	-	Zenith 2PT	D: 42 (proximal, 38 (distal) L: 158
13. Shahbazian, 2022	-	-	-	-	-
14. Ramella, 2022	-	-	-	-	-

Data reported as mean (range). Abbreviations: TAA: thoracic aortic aneurysm, TBAD: type B aortic dissection; cTAG: Conformable GORE® TAG® Thoracic Endoprosthesis; D: diameter, L: length, OS: oversizing, CT(A): computed tomography (angiography), DTA: Descending Thoracic Aorta.

Numerical method

Three studies[20,21,24] applied CFD to evaluate aortic haemodynamics, while the remaining 11 studies applied the FEA method.[22,23,25-33]

Aortic model

The aortic model was mostly reconstructed from CTA imaging in the 11 studies that included clinical data and was patient specific in this case.[20-27,29-31] Three studies (21.4%)[28,32,33] obtained the input for their segmentation from the literature leading to parametric or idealised aortic models. One study[28] also performed mechanical characterisation of fresh human descending thoracic aorta for different age groups and added these details to the aortic model as additional longitudinal pre-stretch. The aortic wall was reported as rigid in four studies[22,24,26,33] and two studies included pre-stress of the aorta.[30,31]

Stent graft model

Ten studies[22,25-33] simulated the graft material and nitinol stent rings as two separate components, three studies[20,21,24] created a homogenised stent graft by approximating the stent graft as a single component (with in between mechanical properties), while one study[23] only modelled the nitinol stent rings disregarding the graft material. Specific stent graft model parameters (e.g., dimensions, oversizing) are reported in Table 3 and five studies[25,28,29,32,33] followed the designs of specific stent graft brands. Thirteen studies modelled standard TEVAR, except for one study[27] that modelled a double branched (i.e., RelayBranch) stent graft design including bridging stents to simulate the TEVAR procedure of an aortic arch aneurysm from zone 0 – 2. Two studies included pre-stress of the nitinol rings.[27,33]

Other simulation components

Ten studies[22,23,25,26,28-33] additionally modelled a catheter over which the stent graft was crimped, morphed to the correct anatomical position, and consequently deployed (virtual catheter method), while one study[33] added a specific tracking method to this deployment sequence by advancing the stent graft to the desired landing zone within a catheter and then gradually releasing it. Another study[27] applied the virtual shell method in which a virtual shell is placed around the stent graft followed by a morphing algorithm that maps the stent graft and shell into the desired geometry before deployment. The three studies that used a homogenised stent graft model and applied CFD, disregarded a specific deployment method and virtually added the stent graft to the specific aortic model.

Table 3. Methodological details of the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model – focus on simulation model

First author, year	Simulation					
	Input for segmentation	Numerical method	Aortic model	Stent-graft model	Stent-graft model parameters	Other simulation components
1. Cheng, 2008	CT	CFD	Aim 1: idealized, Aim 2: patient-specific	Homogenized graft and stent rings	D: 26 – 42 mm Starting position: 90 – 180° Aortic arch curvature: 70 – 130°	Blood flow, pressure, and density
2. Figueroa, 2009	Cardiac gated CTAs	CFD	Patient-specific	Homogenized graft and stent rings	D: 30 mm (zone 3) and 36 mm (zone 4 – 5) L: not specified (zone 3), twice the first length (zone 4 – 5) OS: 10%	Blood flow and pressure, vessel wall dynamics
3. Auricchio, 2013	CTA	FEA	Patient-specific, rigid vessel wall	Graft and stent rings as different components	D: 38 mm (proximal), 48 mm (distal) L: 70 mm OS: 10%	Catheter model (“virtual catheter method”)
4. Altnji, 2013	CTA	FEA	Patient-specific	Stent rings only	L: “standard-length” (n = 2), “optimized length” (n = 1) OS: 15% PASL: 15, 23, 35 mm Proximal neck angulation: 60° Tangential behavior	Catheter model (“virtual catheter method”)
5. Chen, 2018	CTA	Simplex mesh method + CFD	Patient-specific, rigid vessel wall	Homogenized graft and stent rings	OS: 10%, value of the stent-graft radial force	Blood flow and pressure, wall-shear stress

Table 3. Methodological details of the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model – focus on simulation model (*continued*)

First author, year	Simulation					
	Input for segmentation	Numerical method	Aortic model	Stent-graft model	Stent-graft model parameters	Other simulation components
6. Ma, 2018	CTA	FEA	Patient-specific	Graft and stent rings as different component (Talent, Valiant)	Six groups: D: 33, 38 mm L: 130, 140, 172,5 mm With and without connecting bar OS: 0 – 15% Valiant or Talent design	Catheter model ("virtual catheter method")
7. Romarowski, 2018	CT	FEA	Patient-specific, rigid	Graft and stent rings	L: 60, 70, 75 mm	Catheter model ("virtual catheter method")
8. Derycke, 2019	CT	FEA	Patient-specific	Graft and stent rings as different components, bridging stents, stent pre-stress included	Double-branched design: Large single window harbouring two internal tunnels Four kinds of stent rings (Z, half, crown, and flattened stent) Torsion effect	Deployment ("virtual shell method")
9. Desyatova, 2020	Literature (geometry, longitudinal pre-stretch), fresh human DTA per age group (mechanical characterization)	FEA	Idealized parametric model (six age groups), longitudinal pre-stretch	Graft and stent rings (cTAG)	D: 21, 26 mm L: 94.9, 97.6 mm	Catheter model ("virtual catheter method")
10. Meng, 2020	CTA	FEA	Straight and elbow vessel (patient-specific)	Graft and stent rings as different components, with proximal bare stent (Valiant)	D: 33, 34, 35, 36, 37, 38 mm L: 172.5 mm OS: 0 – 3 – 6 – 9 – 12 – 15%	Catheter model ("virtual catheter method")

Table 3. Methodological details of the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model – focus on simulation model (*continued*)

First author, year	Simulation					
	Input for segmentation	Numerical method	Aortic model	Stent-graft model	Stent-graft model parameters	Other simulation components
11. Kan, 2021	CTA	FEA	Patient-specific, dissection flap, pre-stress of the aorta	Graft and stent rings	D: 28 mm L: 150 mm Proximal bare stent	Catheter model, action of internal pressure on stent-graft ("virtual catheter method")
12. Kan, 2021	CTA	FEA	Patient-specific, dissection flap, pre-stress of the aorta	Graft and stent rings as different components	D: 42 mm (proximal), 38 mm (distal) L: 158, 183, 208 mm	Catheter model, action of internal pressure on stent-graft ("virtual catheter method")
13. Shahbazian, 2022	Literature	FEA	Parametric model (four cases), with and without aneurysm	Graft and stent rings as different component (Zenith Alpha)	D: 28 mm L: 109 mm OS: 12%	Catheter model
14. Ramella, 2022	Literature	FEA	Idealized model, rigid wall	Graft and stent rings as different components, including pre-stress of the nitinol (Valiant)	D: 30, 46, 34 mm L: 150, 200 mm Proximal configuration: Closed-Web and Free-Flo	Catheter model ("tracking method")

Data reported as mean (range). Abbreviations: D: diameter, L: length, OS: oversizing, CT(A): computed tomography (angiography, DTA: Descending Thoracic Aorta; CFD: computational fluid dynamics (with blood), FEA: finite-element analysis (structural), FSI: fluid-structure interaction (with blood), PASL: proximal stent-graft attachment length.

Outcomes of the respective studies

Table 4 summarises the clinical, numerical, and comparative outcomes (between the simulation and CTA) of the included studies. In summary, two[20,21] of the three studies applying CFD evaluated the drag or displacement forces acting on the thoracic aortic stent grafts, while the third study[24] calculated differences in cross sectional areas and curvatures, time averaged wall shear stress (TAWSS), oscillatory shear index (OSI), and relative residence time (RRT). The remaining 11 studies applying FEA mainly investigated Von Mises stresses[23,25,28,29,31,32] and stent graft apposition to the aortic wall.[22,26]

DISCUSSION

This scoping review identified 14 severely heterogeneous TEVAR simulation models, mainly developed by surgeons and engineers over the last five years using different methodological approaches. It emphasises different ways to model the aorta (e.g., idealised, patient specific, rigid, or deformable), the stent graft (e.g., graft and stent materials, nitinol rings, with or without stent pre-stress), and the presence of other simulation components (e.g., crimping catheter). The information to model these aspects may originate from the literature, experimental mechanical tests, or by segmentation of imaging techniques. Clinical data may be included or not to provide patient specific aortic models. Moreover, regarding the simulation of the aortic haemodynamics, there are different numerical approaches: rigid wall CFD, structural mechanics using FEA, or a combination of both using FSI (Fig. 1). To date, there are no available TEVAR simulations that include blood induced wall motion and deformation using FSI which demands an increased computational workload and time to perform such analyses. Following quality assessment, most studies (64.3%) were found to be of intermediate quality. Given the absence of a validated and accepted tool for the specific studies included in this review, the results should be interpreted cautiously. This also highlights the need for the development of a tool specifically designed to assess the quality of studies presenting a virtual numerical model that mimics and evaluates the performance of medical devices and or endovascular surgical procedures.

The heterogeneity among these studies and summary of the several specific aspects of the different TEVAR simulations in this review may help to homogenise future TEVAR simulations and thoracic aortic stent graft models. To achieve this, research groups might consider including additional methodological aspects in future models and simulations, outlined in this review (grouped regarding, e.g., clinical data, numerical method, aortic model, stent graft model, other simulation components). Specifically, future models should preferably adhere to the verification and validation process for

Table 4. Quantitative clinical, numerical, and comparative outcomes (between the clinical and numerical results) from the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model

Author, year	Clinical outcomes (unit)	Numerical outcomes (unit)	Comparative outcomes between simulation and CT(A) (unit)
1. Cheng, 2008	Aim 2: Inlet and outlet graft area at initial and postoperative CTs (mm^2)	Aim 1: Drag force (N), Aim 2: Drag forces at initial and follow-up CTs (N)	-
2. Figueroa, 2009	-	Flow waveforms at DTA, LCCA, LSA, 3D displacement force (including wall shear and pressure stresses)	-
3. Auricchio, 2013	Cross-sectional variation of the aorta: radius (mm)	Difference between pre- and postoperative vascular anatomy: distance (mm)	Apposition: distance (mm), Cross-sectional graft radius at 3 locations (mm)
4. Altnji, 2013	-	Von Mises stress (MPa), normal contact forces (N), tangential drag forces (N)	-
5. Chen, 2018	Distal SINE	Differences in cross-sectional areas and curvatures (%), TAWSS (Pa), OSI, RRT (s/Pa), deformation (mm)	CFD related indexes TAWSS (Pa), OSI, RRT (s/Pa)
6. Ma, 2018	-	Von Mises stress (MPa)	-
7. Romarowski, 2018	-	Apposition: distance (mm), kinetic energy (ALLKE) and internal energy (ALLIE) along the expansion phase	-
8. Derycke, 2019	-	Sensitivity analyses for different young moduli (MPa) and friction coefficients	Relative diameter deviation, longitudinal deviation along the arterial centreline, transverse deviation in the cross section
9. Desyatova, 2020	-	Von Mises stress (MPa, stress-strain fields)	-
10. Meng, 2020	-	Von Mises stress (MPa), radial force (N), spring-back force (N)	-
11. Kan, 2021	Stress-stretch curves from TBAD aortic tissue (n = 12 samples)	Maximal principal stress (kPa)	Local opening area at the end of each strut (mm^2)

Table 4. Quantitative clinical, numerical, and comparative outcomes (between the clinical and numerical results) from the 14 included studies presenting a virtual thoracic endovascular aortic repair simulation model (*continued*)

Author, year	Clinical outcomes (unit)	Numerical outcomes (unit)	Comparative outcomes between simulation and CT(A) (unit)
12. Kan, 2021	-	Von Mises stress on the intimal flap and aortic wall (kPa)	Relative diameter deviation, longitudinal deviation along the arterial centreline, transverse deviation in the cross section (adapted from Derycke, 2019)
13. Shahbazian, 2022	-	Bird-beak length and angle (mm, %), Von Mises stress (GPa), residual displacement (mm)	-
14. Ramella, 2022	-	Simulation correctly running (positive or negative)	Opening area (mm^2), error (%)

Abbreviations: CT(A): computed tomography (angiography), N: Newton, DTA: descending thoracic aorta, LCCA: left common carotid artery, LSA: left subclavian artery, 3D: three-dimensional; SINE: stent-graft induced new entry, TAWSS: time-averaged wall shear stress, OSI: oscillatory shear index, RRT: relative residence time, CFD: computational fluid dynamics.

medical devices developed by the American Society of Mechanical Engineers (ASME)[34] as described below (e.g., include pre-stress of the nitinol if present, calibration of stent graft materials), and authors should consider evaluating additional clinical and numerical outcomes summarised in Table 4. Combining such methodological aspects and evaluated outcomes from different studies could help in the development of more credible and realistic TEVAR simulations, to eventually improve the outcomes of patients treated with TEVAR, and to which this review may serve as a basis.

Due to the different methodological approaches, the credibility and reliability of these models change as well. Nowadays, the main challenges in applying these models to clinical practice persist, given the difficulties in accurately correlating numerical results with technical and clinical outcomes. For this purpose, evaluating and reporting the application of recently developed models to patient specific aortic anatomies as case report or series could be useful to demonstrate applicability during the pre- or post-operative phase.[35,36] The implementation of these computational tools during follow up of patients with aortic diseases might also help predicting longer term clinical outcomes, for example, correlation of numerical results with certain imaging parameters.

No clinical guidelines or consensus documents exist that guide clinicians in the application of such tools to clinical practice as these tools are not widely available and rely on close, usually academic, collaborations between medical doctors and engineers. However, in 2018, the American Society of Mechanical Engineers (ASME) provided a framework to assess the credibility of a computational model for medical devices specifically.[34] Ten of the TEVAR simulations have been published since this release, but only the most recent TEVAR simulation model proposed by Ramella *et al.*[33] implemented this validation and verification process. The credibility and reliability of this *in silico* validated TEVAR methodology has been further assessed by performing an applicability assessment to justify the specific context of use and it was demonstrated that this methodology is trustworthy for replicating TEVAR in virtual patients.[37-40] This can be considered as a step in the right direction towards clinical application of these computational tools by following rigorous methodological validation.

Qualitative and quantitative comparisons of the results of different TEVAR simulations are limited given the heterogeneity in study design as emphasised in Table 4. However, as an example, Kan *et al.*[30] and Ramella *et al.*[33] both qualitatively evaluated and quantified the local opening area at the different stent graft struts in mm^2. Qualitatively there was a clearly visible better overlap between the TEVAR simulation and stent graft position as reconstructed from post-operative CTA in the study by Ramella *et al.*[33] This was reflected in an opening area error below < 2.5% for every nitinol stent ring (strut), as

compared with the study by Kan *et al.*[30] in which this error was between 10 – 25% at the proximal struts and around 10% at the distal struts. The reasons for these improved results are related to the idealised rigid aortic model used compared with the patient specific TBAD model of Kan *et al.*[30] On the one hand, patient specific aortic models more realistically depict a clinical scenario, but this may complicate the validation process. Ramella *et al.*[33] designed (computer aided) an idealised model using literature input and 3D printed this model. The exact mechanical characteristics of this model were thus known and could consequently be used for the aortic model in the simulation. Opening area errors increased by applying the TEVAR simulation methodology to a patient specific case[37] in which the aortic wall deformability is considered, but the errors remained < 10% at every strut, compared with the 10 – 25% of the proximal struts in the study by Kan *et al.*[30] Clearly, reduction of these errors demands further optimisation of the TEVAR simulations. Moreover, further validation may be expected by including other comparative outcomes such as apposition (distance, mm), cross sectional graft radius at multiple locations, relative diameter deviations, longitudinal deviations along the arterial centreline, and transverse deviations in the cross sections, as reported by other authors.[22,27]

Computational modelling of stent graft deployment has also been extensively studied in endovascular abdominal aortic aneurysm repair (EVAR), transcatheter aortic valve implantation (TAVI), and thrombectomy procedures with similar challenges remaining.[41-43] The need to cover or endovascularly revascularise additional side branches during both EVAR and/or TEVAR using fenestrations or branches complicates the simulation. The study by Derycke *et al.* is the only one that modelled a double branched aortic arch stent graft, as compared with standard TEVAR in the other studies.[27] Another study has performed a haemodynamic analysis using CFD of different aortic arch stent graft designs with different branch shapes and orientations for zone 0 endovascular aortic repair.[44]

Collaborations between medical doctors, engineers, and device manufacturers may provide unique insights into the complex dynamic interplay between thoracic aortic stent grafts and the diseased aorta, with the goal of improving patient outcomes.

Future perspectives

Further implementation of advanced numerical methods such as FSI could lead to increased application of these computational tools by integrating aortic wall dynamics and blood flow. The quantification of compliance mismatches and cardiovascular remodelling post TEVAR including the calculation of aortic pulse wave velocity, as a surrogate for aortic stiffness, could be a possibility.[45,46] One of the advantages of computational modelling is that it can be designed specifically to analyse individual

or confined aspects of the aortic pathologies with or without TEVAR, which is not feasible with *in vivo* analyses and more difficult with *ex vivo* analyses, and such analyses might thus be reduced with a parallel increase in computational simulations. *In silico* clinical trials could be designed if a population of patient specific aortic anatomies and specific diseases can be created, in which multiple commercially available medical devices could be tested to check for differences or to choose the most desired device for a specific patient's anatomy and disease. Computational tools may provide additional numerical data that could functionally guide clinicians in choosing the right treatment strategy for their patients.[47,48] Further technological advances and implementation of artificial intelligence data processing techniques like machine or deep learning might reduce the time to perform computational calculations and make them more readily available to surgeons, eventually in the form of a web or mobile application. Moreover, the segmentation process to reconstruct patient specific aortic anatomies from pre- or post-operative CTA imaging may be sped up by using these techniques.

Limitations

Inherent to the design of scoping reviews is the descriptive presentation of the results that maps the available literature in the field of interest. The lack of a validated quality assessment tool for the specific studies in this scoping review has been acknowledged. A potential selection bias during study selection or incomplete capture of all available evidence may have occurred given the absence of a specific and clearly defined research question in scoping reviews; however, the scope of the systematic literature search was wide and the topic specific. Moreover, the severe heterogeneity among studies regarding their specific aims, methodology, and qualitative and quantitative outcomes prevented the pooling of data.

Conclusions

This scoping review assessed and described the body of literature presenting a virtual TEVAR simulation method, mimicking the real world clinical TEVAR procedure. It highlighted the severe heterogeneity of included studies regarding the different simulation components and applied methodologies. To be able to implement these tools in clinical practice and aid surgeons during pre-procedural planning or follow up, additional efforts to improve their credibility and reliability are required. This review is an initial attempt in the direction towards improving the fidelity of these tools and homogenising the methodology of future models by implementing additional methodological steps, techniques, and outcome analyses.

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7

Utilizing numerical simulations to prevent stent graft kinking during thoracic endovascular aortic repair

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ABSTRACT

Numerical simulations of thoracic endovascular aortic repair (TEVAR) may be implemented in the preoperative workflow if credible and reliable. We present the application of a TEVAR simulation methodology to an 82-year-old woman with a penetrating atherosclerotic ulcer in the left hemiarch, that underwent a left common carotid artery to left subclavian artery bypass and consequent TEVAR in zone 2. During the intervention, kinking of the distal thoracic stent graft occurred and the simulation was able to reproduce this event. This report highlights the potential and reliability of TEVAR simulations to predict perioperative adverse events and short-term postoperative technical results.

INTRODUCTION

Numerical simulations that virtually reproduce thoracic endovascular aortic repair (TEVAR) represent innovative computational adjuncts that may potentially aid the preprocedural planning phase in the future by predicting perioperative or short-term postoperative technical events and results.[1] Such tools could be further optimized regarding their credibility and reliability by providing evidence of their effectiveness and workflow, as illustrated in this study that applied a recently developed TEVAR simulation methodology to a patient-specific case with preoperative distal thoracic aortic stent graft kinking. The patient provided informed consent for the publication of this case report and related imaging.

CASE REPORT

An 82-year-old woman with hypertension and a history of heavy smoking (approximately 20 cigarettes per day) presented with a penetrating atherosclerotic ulcer (PAU) in the left hemiarch with maximum axial diameters of 38 × 37 mm on computed tomography angiography (CTA). There were no further relevant cardiovascular diseases or interventions in her medical history. Additionally, an intraluminal floating thrombus located at the outer curvature of the proximal descending aorta (approximately 18 mm length, 15 × 8 mm diameter) was identified on CTA, that seemed to be connected to the intraluminal thrombus of the PAU anteriorly (Fig 1, A).

First, a left common carotid artery (LCCA) to left subclavian artery (LSA) bypass was performed, to obtain an adequate proximal landing zone in zone 2 for TEVAR. During the same intervention, a Valiant thoracic aortic stent graft with the Captivia delivery system (Valiant Captivia, VAMF3232C100TU) (Medtronic Inc., Minneapolis, MN) was deployed followed by a plug at the LSA origin to prevent retrograde type II endoleak. Interestingly, during the intervention, a kinking of the thoracic stent graft occurred between the fifth and sixth nitinol stent rings at the distal portion of the thoracic stent graft in zone 4, which was resolved after ballooning this portion of the stent graft (Fig 1, B).

The postoperative course was regular, without any adverse events, including neurological and peripheral thromboembolic. Postoperative CTA after 8 days showed adequate exclusion of the PAU and intraluminal thrombus, without endoleak and patency of the Valiant Captivia and LCCA to LSA bypass (Fig 1, C). Discharge was on postoperative day 11. During follow-up, color Doppler ultrasound examination showed adequate patency

and flow over the LCCA-LSA bypass. No further follow-up diagnostic imaging has been performed to date.

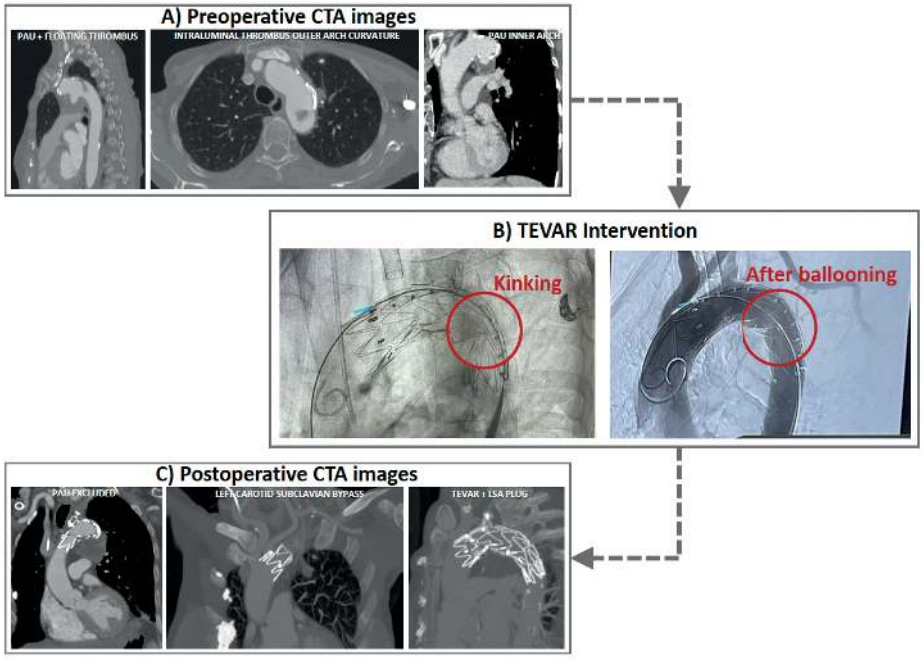

Figure 1. (A) Preoperative computed tomography angiography (*CTA*) imaging. (B) Fluoroscopy illustrating the distal stent graft kinking, resolved by ballooning as shown on the final angiogram. (C) Technical results as seen on postoperative CTA after 8 days. *LSA*, left subclavian artery; *PAU*, penetrating atherosclerotic ulcer; *TEVAR*, thoracic endovascular aortic repair.

The patient-specific ascending, arch, and descending aortic anatomy were reconstructed from preoperative CTA images, including the intraluminal thrombus in zone 3. A recently developed high-fidelity numerical methodology[2,3] was adopted to simulate Valiant Captivia deployment in the reconstructed patient-specific anatomy. Simulations were carried out using the commercial finite element LsDyna software (Ansys Inc., Canonsburg, PA) on 28 CPUs and 250 GB of RAM memory. The device model incorporated nitinol stent prestress and underwent complete mechanical characterization.[2] As during the intervention, a Valiant Captivia was deployed at the distal border of the LCCA. The numerical method was able to reproduce the kinking of the thoracic stent graft between the fifth and sixth nitinol rings. Ballooning of the stent graft was virtually replicated as well, to resolve the kinking (Fig 2, Supplementary Video, online only). The reliability of the simulation was evaluated by qualitatively comparing the stent graft configuration segmented from postoperative CTA images with the numerical results obtained by the simulation: there was a satisfactory overlap (Fig 2). In terms of quantitative assessment,

the opening area at each nitinol stent ring (expressed as a percentage error between the simulation and CTA segmentation in square millimeters) remained <10%, with higher values in the region of the thrombus at the outer arch curvature (Fig 2).

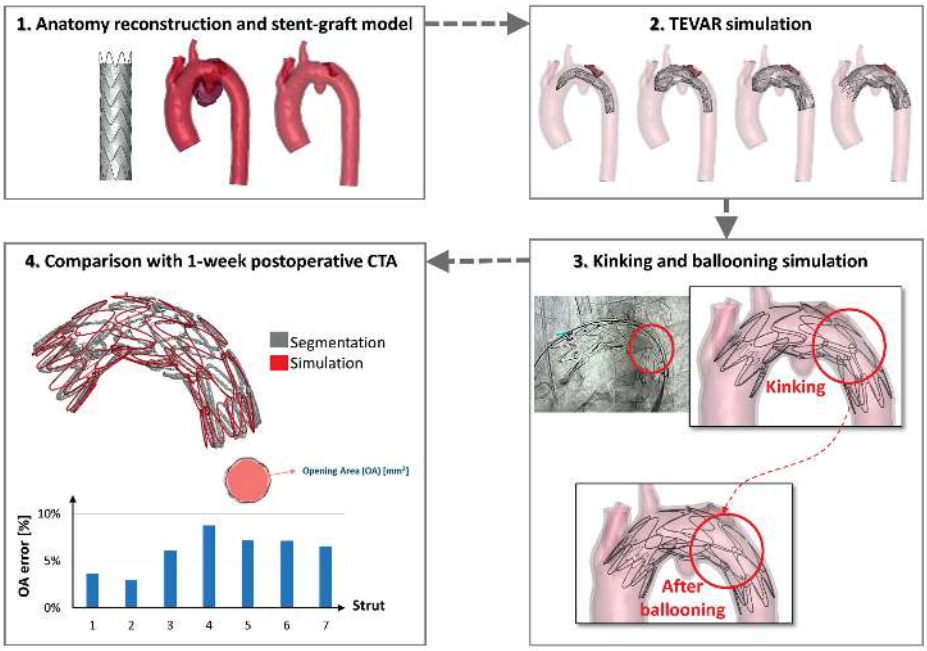

Figure 2. Workflow of the numerical simulation and comparison of the simulation results with postoperative computed tomography angiography (*CTA*) image segmentation. *TEVAR*, thoracic endovascular aortic repair.

DISCUSSION

The potential impact of applying this methodological TEVAR simulation model with Valiant Captivia to patient-specific cases could be of significant value during preprocedural planning given the ability to predict both perioperative adverse events (such as kinking for the illustrated case) and short-term postoperative technical results. As an additional tool, it may serve physicians in choosing the optimal proximal and/or distal sealing zones in specific cases with challenging aortic anatomy. In fact, as depicted in Fig 3, a simulation was performed to evaluate the stent graft apposition and kinking with a more distal landing zone. In this scenario, we noted that the distal kinking disappeared and that the third nitinol stent ring bulged into the PAU. However, this configuration might not be optimal, not only because of proximal landing zone reduction, but also because of the increased distance between the aorta and stent graft.

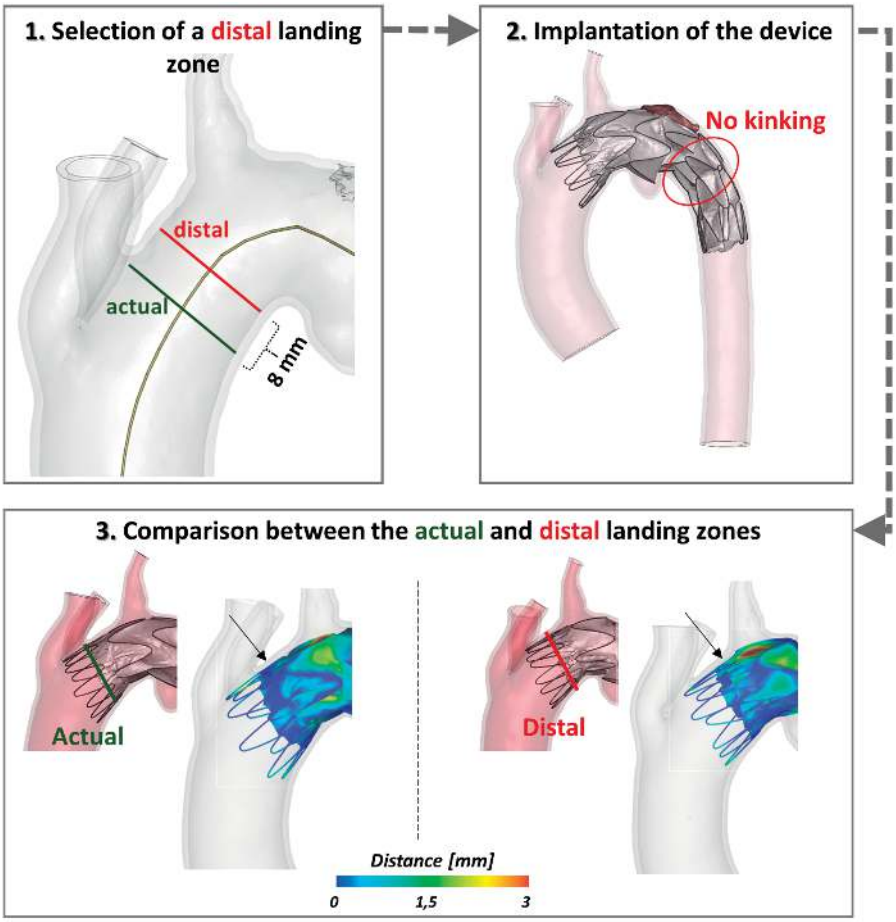

Figure 3. Virtual scenario of a more distal landing zone and comparison to the actual one in terms of distance between the stent graft and the aortic wall.

The time to obtain virtual results is compatible with the time needed to plan elective TEVAR; this procedure can be performed in 1 day. Furthermore, other patient-specific components such as the presence of intraluminal thrombus (as for this case) or calcifications, can be included in the simulation, to evaluate their impact on the stent graft deployment. Virtual deployment of different thoracic aortic stent grafts of different manufacturers, if verified and validated,[4] may also help to find the most suitable device with optimal sealing for different patient-specific aortic anatomies that vary according to geometrical characteristics (eg, diameter, length, angulation, and tortuosity).

Similar to the present case, another illustrative case by Derycke et al[5] has previously demonstrated the potential of a FE custom-made double branch Relay (Terumo Aortic, Sunrise, FL) TEVAR simulation for an aortic arch aneurysm, to reliably find stent graft collapse that led to postoperative complications. This TEVAR simulation found the deformation of the three nitinol stent rings at the same location as seen on postoperative CTA. Also in our case, the simulation was performed after the clinical procedure to verify if the numerical model was able to predict the perioperative stent graft kinking during the intervention. In our patient-specific case, the event was managed promptly by using a balloon without clinical and technical consequences.

CONCLUSIONS

This study further highlights the potential and reliability of TEVAR simulations to be adopted in and facilitate preprocedural planning in the future. For example, they could investigate optimal proximal landing and stent graft apposition or the ideal stent graft model in demanding aortic anatomies. One of the challenges before a wider implementation of such tools in daily clinical cardiovascular practice, remains the need to further enhance simulations regarding their reliability and credibility, by providing evidence of their effectiveness and workflow, as illustrated by this case.

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8

Sex-specific Morphometric Analysis of Ascending Aorta and Aortic Arch for Planning Thoracic Endovascular Aortic Repair: A Retrospective Cohort Study

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CLINICAL IMPACT

Men had 7.4% greater ascending aorta and arch diameters than women in a retrospective cohort, gated computed tomography-based study of 116 patients. Sex-specific differences in ascending aortic and arch size should be considered by aortic endovascular device manufacturers and physicians when developing ascending and arch endografts and planning aortic interventions.

ABSTRACT

Objective: In many studies on aortic disease, women are underrepresented. The present study aims to assess sex-specific morphometric differences and gain more insight into endovascular treatment of the ascending aorta (AA) and arch.

Methods: Electrocardiogram-gated cardiac computed tomography scans of 116 consecutive patients who were evaluated for transcatheter aortic valve replacement were retrospectively reviewed. Measurements of the AA and aortic arch were made in multiplanar views, perpendicular to the semi-automatic centerline. Multiple linear regression analysis was performed to identify predictors affecting AA and aortic arch diameter in men and women. Propensity score matching was used to investigate whether sex influences aortic morphology.

Results: In both sexes, body surface area (BSA) was identified as a positive predictor and diabetes as a negative predictor for aortic diameters. In men, age was identified as a positive predictor and smoking as a negative predictor for aortic diameters. Propensity score matching identified 40 pairs. Systolic and diastolic mean diameters and AA length were significantly wider in men. On average, male aortas were 7.4% wider than female aortas, both in systole and diastole.

Conclusions: The present analysis demonstrates that, in women, increased BSA is associated with increased aortic arch diameters, while diabetes is associated with decreased AA and arch diameters. In men, increased BSA and age are associated with increased AA and arch diameters, while smoking and diabetes are associated with decreased AA and arch diameters. Men were confirmed to have 7.4% greater AA and arch diameters than women.

INTRODUCTION

Aneurysmatic disease of the ascending aorta (AA) and aortic arch is a potentially lethal but treatable condition. In the current era of endovascular aortic repairs, accurate assessment of aortic size is crucial for diagnosis, treatment, and follow-up. The first ascending thoracic endovascular aortic repair (aTEVAR) for type A aortic dissection (TAAD) was reported in 2000.[1–3] Nowadays, it is more commonly employed in expert aortic centers, mostly to treat patients otherwise not fit for open surgical repair.[4,5] Endovascular repair of the AA and arch is a valuable alternative to open surgery, providing acceptable early and mid-term outcomes[4] in patients who would otherwise face mortality rates of up to 95% when left untreated.[6]

Aortic disease, being largely associated with atherosclerosis, is more common in males. However, more women are being treated nowadays due to an increasing aging population, and a change of social habits, such as smoking, making it increasingly important to understand how sex differences might impact disease pathophysiology, prognosis, and treatment.[7–9] Women have been traditionally underrepresented in many of the landmark studies that form the basis for guidelines recommendations, but contemporary research is increasingly focusing on sex-specific differences in aortic disease.[7–9] The aim of the present study was to assess morphometric differences and identify different variables that might be associated with increased aortic size in the AA and aortic arch segments in the 2 sexes.

METHODS

Study Population

This retrospective study was conducted after approval by an institutional review board. A total of 116 consecutive patients who underwent trans-catheter aortic valve replacement (TAVR) at our institution between September 2016 and February 2017 and had a preoperative, electrocardiography-gated computed tomography angiography (ECG-gated CTA) scans were selected for morphometric analysis. Patients with aortic dissection, TEVAR, left ventricular ejection fraction <40%, and those without ECG-gated CTAs were excluded.

Data Collection

Demographic data were collected for each patient, including sex, age, race, body mass index (BMI), body surface area (BSA), smoking habits, aortic gradient, left ventricular ejection fraction, and aortic arch type with retrospective chart review. Comorbidities,

including chronic kidney disease, diabetes mellitus, hypertension, coronary artery disease, cardiac heart failure, atrial fibrillation, chronic obstructive pulmonary disease, hyperlipidemia, connective tissue disease (CTD), and history of coronary interventions were also assessed. History of aortic disease (arteritis and aneurysm) and prior aortic surgery were investigated as well.

Measurement Protocol

The initial 10 measurements were taken by 2 individual vascular surgeons (M.Z, A.S.) according to a previously published protocol,[10] to ensure inter-observer and intra-observer consistency. The rest was measured by a single vascular surgeon (M.Z.). Measurements were taken on multiplanar views perpendicular to a semi-automatically created aortic centerline on a single post-processing software workstation (Syngo.Via, Siemens Healthcare GmbH, Germany). R-R interval between 30% and 40%, and 70% and 80% dictated the systolic and diastolic phases, respectively. Inner aortic wall diameters were measured at the sinotubular junction (STJ), mid-AA (at 4 cm proximal to the innominate artery [IA] ostium), proximally to the IA, left common carotid (referred to as Ishimaru zone 1) and left subclavian (referred to as Ishimaru zone 2) ostium levels. Total ascending aortic length was measured from the STJ to the IA ostium.

Circumferential and arterial strain at each measuring point was calculated using the following equations:

1. Circumferential arterial strain (%)=(systolic diameter−diastolic diameter)/diastolic diameter×100
2. Longitudinal arterial strain (%)=(systolic length−diastolic length)/diastolic length×100

Statistical analysis

The primary outcome of this study was to identify sex-specific variables associated with AA and arch size. The secondary outcome was to determine sex-specific morphometric differences and provide baseline measurements.

Multiple linear regression analysis was performed to identify variables potentially affecting ascending aortic and arch diameter in the male and female sex. The analysis was performed on the total initial cohort of patients. Age, BSA, smoking, diabetes, and hypertension were chosen as potential clinical predictors for aortic diameter. In particular, BSA, age, and diabetes have been previously identified as predictors for ascending aortic size.[11] Body surface area has been identified to have a stronger correlation with aortic size than BMI,[12] and therefore, it was chosen as the most relevant variable to assess body size.

To mitigate sex-related biases, propensity score matching techniques were employed. Variables, including age, BSA, BMI, CTD, hypertension, coronary artery disease, chronic heart failure, aortic arch type, aortic gradient, history of aortic disease, and history of aortic surgery were utilized in the matching processes. A logistic regression was then performed to achieve similar baseline characteristics between the 2 groups using a 1:1 nearest neighbor matching technique with a 0.2 standard deviation caliper.

Numeric variables are expressed as means with standard deviation and compared through 2-sample *t* test or Mann-Whitney *U* test. Nominal variables are expressed as number and percentages, and compared with chi-square test or Fisher's exact test.

In all analyses, *p* values <0.050 were considered statistically significant. Statistical analysis was conducted using IBM SPSS 28 (Chicago, IL, USA).

RESULTS

Inter-observer and Intra-observer Variability

Inter-observer and intra-observer variability was reported in our previous work;[2] Intra-class correlation coefficient (ICC) and Bland-Altman analysis were performed. Inter-observer analysis showed good correlation for aortic diameter (ICC=0.99, mean difference=–0.001±0.52 mm) and aortic length (ICC=0.99, mean difference=–0.03±0.62 mm). Inter-observer analysis showed good correlation as well for aortic size (ICC=0.97, mean difference=0.14±1.08 mm) and aortic length (ICC=0.99, mean difference=–0.21±3.01 mm).

Baseline Characteristics

Baseline demographics and comorbidities before and after propensity score matching are reported in Table 1. Significant differences in demographics before matching were seen in race, BSA, smoking habits, and left ventricular ejection fraction. Our propensity score analysis yielded 40 matched pairs. The patients were well matched for age, race, BMI, smoking habits, aortic gradient and aortic arch type (normal or bovine). Significant differences were observed in BSA only (1.71±0.21 vs 2.05±0.16, p=0.02). The 2 groups were well matched also for all comorbidities (Supplemental Table 1).

Table 1. Baseline Demographic Characteristics

	Total cohort			1:1 ratio		
	Women (n=55)	**Men (n=61)**	**p**	**Women (n=40)**	**Men (n=40)**	**p**
Age	77.31±11.83	77.46±9.71	0.71	77.97±11.26	76.68±10.41	0.49
Race			.01			1.0
Caucasian	36 (65.5)	53 (86.9)		26 (65)	34 (85)	
Black	8 (14.5)	3 (4.9)		5 (12.5)	1 (2.5)	
Hispanic	11 (20)	3 (4.9)		9 (22.5)	3 (7.5)	
Other	0 (0)	2 (3.3)		0 (0)	2 (5)	
BMI	29.01±7.23	27.75±4.86	0.72	27.67±5.69	27.37±4.74	0.76
BSA	1.74±0.21	2.03±0.20	<0.001	1.71±0.21	2.05±0.16	0.02
Smoking			0.01			0.85
Never	38 (69.1)	25 (41)		24 (60)	24 (60)	
Active	3 (5.5)	5 (8.2)		2 (5)	3 (7.5)	
Ex-smoker	14 (25.5)	31 (50.8)		14 (35)	13 (32.5)	
LVEF (%)	65.36±11.37	58.46±11.71	0.002	65.85±10.96	58.33±10.96	0.94
Aortic gradient	41.6±18.25	40.82±12.93	0.855	43.83±20.18	40.53±13.94	0.77
Arch type			0.61			0.77
1	43 (78.2)	50 (82)		31 (77.5)	33 (82.5)	
2	12 (21.8)	11 (18)		9 (22.5)	7 (17.5)	

Data are presented as n (%).
Abbreviations: BMI, body mass index; BSA, body surface area; LVEF: left ventricular ejection fraction.

Multiple Linear Regression Analysis

In men, multiple linear regression analysis identified BSA as a positive predictor for aortic diameter from mid AA to zone 2 (mag.=6.45, p=0.004; mag.=4.22, p=0.022; mag.=4.42, p=0.026; mag.=5.69, p=0.001) (Figure 1) and age as a positive predictor for zone 2 diameter (mag.=0.104, p=0.005). The presence of diabetes mellitus was a negative predictor for diameter from the STJ to zone 1 (mag=–2.99, p=0.002; mag.= –2.54, p=0.005; mag.=–1.66, p=0.023; mag.=–1.62, p=0.04), and smoking was a negative predictor in mid AA (mag.=–0.97, p=0.033). In women, the presence of diabetes in the distal AA and zone 1 (mag.=–2.75, p=0.017; mag.=–2.18, p=0.03) was a negative predictor for diameter and BSA in zone 2 (mag.=5.34, p=0.01) was a positive predictor. The multiple linear regression analysis is presented in Table 2.

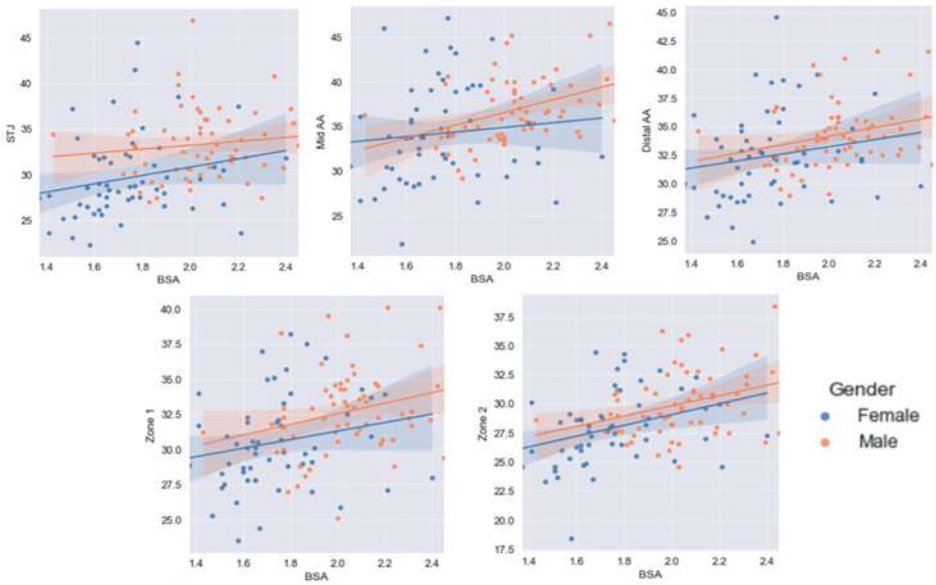

Figure 1. Linear regression scatter plots demonstrating the interaction between body surface area and aortic diameter (mm) for male and female sex. Male sex had a significant correlation with body surface area (m2) at mid and distal ascending aorta, zones 1 and 2 (p=.004, .022, .026, .001), while female sex showed correlation in zone 2 (p=.012) (STJ, SinoTubular Junction; AA, Ascending Aorta; BSA, Body Surface Area).

Table 2. Multiple Linear Regression Analysis for Predictors Affecting Ascending Aortic Size in Men and Women.

	STJ		Mid AA		Distal AA		Zone 1		Zone 2	
	Magnitude	**p**	**Magnitude**	**p**	**Magnitude**	**p**	**Magnitude**	**p**	**Magnitude**	**p**
Men (n=61)										
Age	0.004	0.939	−0.02	0.677	0.048	0.204	−0.052	0.207	0.104	0.005
BSA	1.65	0.484	6.45	0.004	4.22	0.022	4.42	0.026	5.69	0.001
Smoking	−1.19	0.018	−0.97	0.033	−0.59	0.113	−0.49	0.227	−0.488	0.170
DM	−2.99	0.002	−2.54	0.004	−1.66	0.023	−1.62	0.040	−0.713	0.294
HTN	3.39	0.082	2.20	0.21	−0.57	0.696	−1.20	0.449	−2.56	0.068
Women (n=55)										
Age	−0.07	0.181	−0.059	0.410	−0.02	0.670	0.005	0.893	0.016	0.685
BSA	3.84	0.207	2.63	0.490	4.10	0.100	4.06	0.064	5.34	0.012
Smoking	−0.48	0.505	−0.82	0.367	−0.46	0.429	−0.007	0.989	−0.17	0.718
DM	−0.80	0.561	−1.77	0.307	−2.75	0.017	−2.18	0.030	−1.00	0.238
HTN	0.21	0.916	1.42	0.573	1.67	0.309	2.48	0.088	−0.006	0.996

Abbreviations: AA, ascending aorta; BSA, body surface area; DM, diabetes mellitus; HTN, hypertension; STJ, sinotubular junction.

Differences in Diameters and Lengths and Arterial Strain

Differences in aortic measurements before and after propensity score matching are reported in Table 3. Considering the total cohort, before propensity score matching, systolic and diastolic diameters in the AA, aortic arch, and AA length were significantly different between women and men. In both men and women, the largest diameters were observed for the mid AA (36.81±3.66 vs 34.23±3.70, p=0.004). All diameters progressively decreased when going distally from mid AA to zone 2. The percent difference in systolic diameters between men and women were 10.9% at the STJ, 7% in mid AA, 5.4% in distal AA, 6.5% in zone 1, 7% in zone 2, and 8.8% for AA length. Those differences remained similar for the diastolic measurements (10.4%, 6.9%, 5.8%, 6.1%, 7.9%, 9.2%, respectively). All diameters and AA length were greater in systole than in diastole. Diameters are illustrated in Figures 2 and 3.

Table 3. Ascending Aorta and Aortic Arch Measurements.

	Total cohort			**1:1 ratio**		
	Women (n=55)	**Men (n=61)**	**p**	**Women (n=40)**	**Men (n=40)**	**p**
Systolic measurements						
STJ	29.66±4.55	33.3±3.79	<0.001	29.67±4.74	33.92±3.86	0.001
Mid AA	34.23±3.70	36.81±3.66	0.004	34.17±5.76	37.48±3.42	0.01
Distal AA	32.44±3.85	34.29±2.86	<0.001	32.78±4.08	34.76±2.85	0.03
Length	64.35±10.05	70.6±8.48	<0.001	64.86±10.42	71.60±8.55	0.01
Zone 1	30.52±3.33	32.66±3.06	0.001	30.97±3.53	33.07±2.97	0.004
Zone 2	27.88±3.14	29.97±2.85	0.001	28.29±3.34	30.41±2.69	0.006
Diastolic measurements						
STJ diameter	28.35±4.5	31.64±3.65	<0.001	28.29±4.62	32.06±3.78	0.001
Mid AA	33.49±5.53	35.99±3.44	0.002	33.29±5.69	36.70±3.27	0.008
Distal AA	31.56±3.61	33.52±2.84	0.001	31.84±3.77	34.09±2.93	0.012
Length	61.73±10.02	67.98±8.51	<0.001	62.18±10.38	69.16±8.62	0.004
Zone 1	29.92±3.34	31.85±2.99	0.001	30.26±3.43	32.25±3.01	0.016
Zone 2	27.18±3.24	29.51±2.78	0.001	27.57±3.37	29.81±2.86	0.003
Change between systole-diastole						
STJ diameter	1.30±0.88	1.65±0.95	0.049	1.38±0.93	1.85±0.97	0.042
Mid AA	0.80±0.61	0.82±1.11	0.201	0.88±0.62	0.78±1.20	0.627
Distal AA	0.87±0.95	0.76±0.87	0.401	0.93±1.06	0.67±0.79	0.189
Length	2.61±1.94	2.61±1.91	3.66	2.67±1.95	2.44±1.70	0.542
Zone 1	0.60±0.71	0.80±0.95	0.197	0.71±0.65	0.82±0.90	0.542
Zone 2	0.70±0.94	0.45±1.10	0.204	0.72±0.97	0.60±0.87	0.601

Table 3. Ascending Aorta and Aortic Arch Measurements. (*continued*)

	Total cohort			1:1 ratio		
	Arterial strain (%)					
STJ circ.	4.72±3.28	5.29±3.14	0.954	4.96±3.46	5.89±3.20	0.252
Mid AA circ.	2.46±2.07	2.33±3.16	0.280	2.71±2.10	2.16±3.45	0.381
Distal AA circ.	2.77±2.76	2.33±2.61	0.124	2.92±3.02	2.02±2.42	0.121
AA longitudinal	4.40±3.41	3.92±2.22	0.275	4.48±3.48	3.61±2.14	0.182
Zone 1 circ.	2.08±2.47	2.58±3.10	0.340	2.38±2.18	2.62±2.87	0.675
Zone 2 circ.	2.71±3.67	1.62±3.75	0.116	2.72±3.66	2.16±3.12	0.480

Data are presented as mean±standard deviation (SD).
Abbreviations: AA, ascending aorta; circ., circumferential; STJ, sinotubular junction.

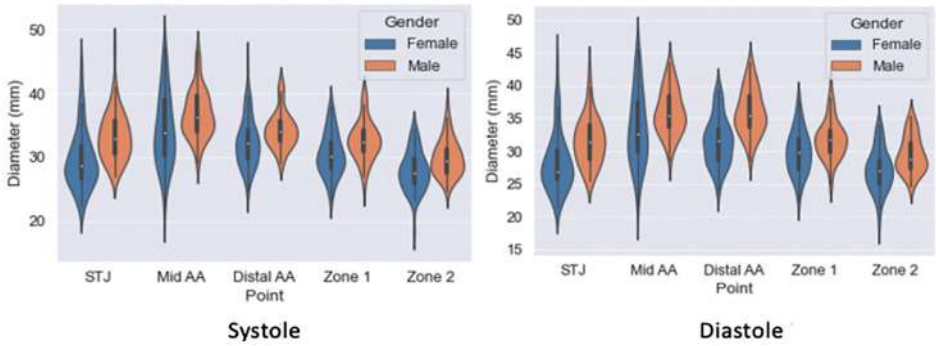

Figure 2. Violin plots comparing aortic diameters between women and men in systole and diastole. Mean diameter (white dot) in men is consistently larger across all the aortic points that were measured. Systolic diameters are higher than the diastolic counterpart in both genders. Largest diameters were measured at mid-AA and smallest at zone 2.

Arterial circumferential strain was more pronounced at the STJ (4.72±3.28 for men vs 5.29±3.14 for women, p=0.95) and least pronounced at zone 1 for women (2.08±0.2.47) and zone 2 for men (1.62±3.75), progressively decreasing from proximally to distally. Longitudinal strain in the AA was 4.40±3.41 vs 3.92±2.2, p=0.27. These values did not differ significantly between the 2 sexes.

When considering the group of matched patients, systolic and diastolic diameters, and AA length also differed significantly at every point along the AA and arch. The percent differences in systolic diameters and AA length between the 2 sexes were 12.5% in the STJ, 8.8% in mid AA, 5.7% in distal AA, 6.3% in zone 1, 6.9% in zone 2, and 9.4% for AA length. On average, aortas in men were 8% larger. The differences for the diastolic measure-

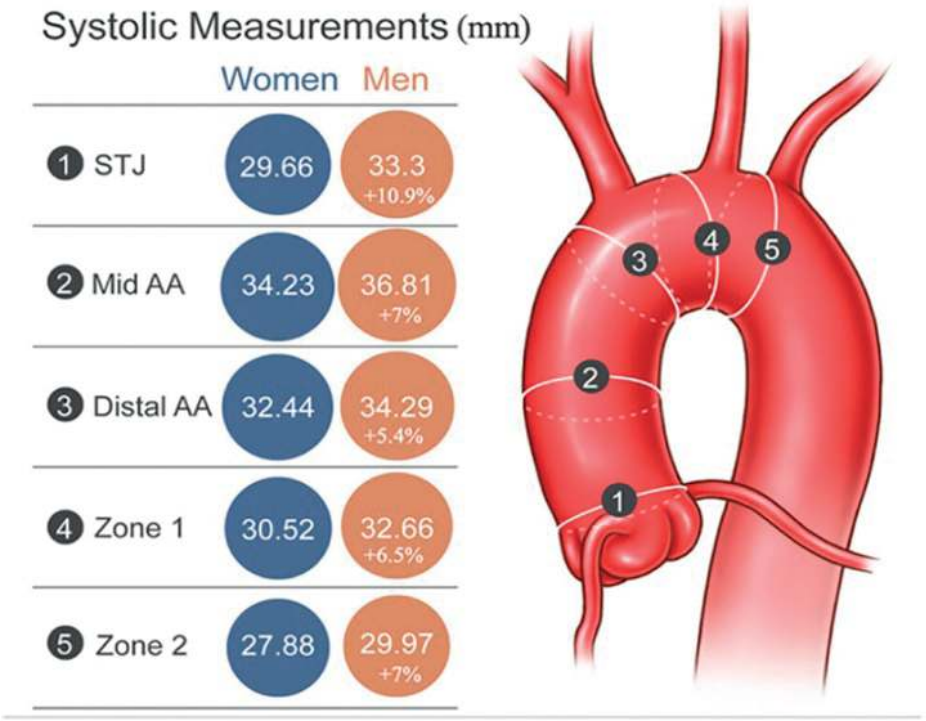

Figure 3. Graphical representation depicting the location where measurements were taken in the aorta, from sinotubular junction (STJ) to mid-ascending aorta (AA), distal AA, zones 1 and 2. On the left, cross-sections representing the diameter (mm) and % differences between men and women at each measurement point.

ments were 11.7%, 9.3%, 6.6%, 6.2%, 7.5%, 10%, respectively. Arterial circumferential and longitudinal strain values did not differ significantly between the 2 sexes.

DISCUSSION

As women are increasingly being treated for aortic diseases, research focuses on sex-based differences for disease pathology, treatment, and outcome. Women are currently underrepresented in studies on TEVAR,[13] especially aTEVAR,[4,14–16] and have been shown to have more complications and worse surgical outcomes.[7,9] In this study, we attempted to gain more insight into AA and arch size and geometry between the 2 sexes. The demographic characteristics, comorbidities, and measurements of our cohort are consistent with the current literature.[17–19] Our analysis provided baseline measurements for the AA in systole and diastole in both sexes, showing that diameters in the AA, aortic arch, and

AA length were significantly different between women and men. On average, AA and aortic arch were 7.4% larger in men.

Our primary endpoint was to determine whether there are any variables affecting AA and arch size in both men and women. In this context, multiple linear regression analysis revealed that increased age and BSA were positively associated with AA and arch diameters in men and BSA was positively associated arch diameters in women. Diabetes was negatively associated in both sexes, and smoking was negatively associated in men. Mori et al[20] recently proposed a predictive model to identify patients with AA aneurysm, and they concluded that female sex and diabetes are associated with lower risk of AA aneurysm, whereas older age, higher BSA, hypertension, and family history of aortic aneurysm were associated with an increased risk of an AA aneurysm. Wolak et al[11] also confirmed the association between BSA, diabetes, and aortic size.[12] The authors also suggest that male sex is a significant predictor only when interacting with age, meaning that older men have larger aortas than women of a similar age, but the difference is smaller for younger men and women. In our cohort, age was a positive predictor in zone 2 of men only, but this finding could be due to the decreased range of age among the patients evaluated. Smoking is traditionally considered as a risk factor for aneurysmal dilatation, but it was not found to be strongly correlated with aortic diameter. However, this could be inherent to the fact that ascending and descending aortic aneurysms have different etiopathogenic mechanisms.

Women generally have smaller and shorter arteries than men.[18,19,21] With the advent of endovascular treatment of aortic arch pathologies, it is fair to question whether arterial size would impact endovascular treatment in women, or if they would need different endografts as compared with men. This should also be viewed in the light of the differences in diameter in zone 0 during the cardiac cycle, which might affect endograft size planning.[22]

When considering the total cohort before propensity score matching, systolic and diastolic diameters and lengths were significantly different between both male and female participants in the AA. Men were found to have larger and longer AAs and arches. This finding is consistent with the work of Boufi et al[19] who concluded that the mean difference in AA and arch diameter between men and women was 2.4 mm. In our cohort, the biggest difference was documented at the STJ with a mean difference of 3.5 mm, or 10.9%. Boufi also demonstrated that men have longer zone 0. We found that AA in men was, on average, 6 mm longer in both systole and diastole (8.8% and 9.19%, respectively). Interestingly, the change in length during the cardiac cycle was identical between the 2 sexes, averaging at 2.6 mm.

To mitigate potential bias related to sex, a propensity score matching was performed. Among the variables that we considered for the propensity score calculation was age, which has been shown to have a linear relationship with aortic measurements, mostly length.[18,19,23] Rylski et al[24] reported that women display a significantly greater increase in the size of the ascending and aortic arch segments with age than men. We also corrected for BSA which is also correlated with aortic morphology and has been shown to be more reliable than BMI for aortic dimensions.[11] After correcting for BSA, Rylski et al[24] found that AA and aortic arch diameters were greater in women.

One of the main challenges with aTEVAR is correct sizing. Excessive oversizing might lead to aortic valve dysfunction or retrograde dissection while under sizing might lead to stent graft migration and possible flow disruption into the supra-aortic trunks. Even though the former holds true for most aortic endovascular interventions, it is even more important when treating the AA due to its natural hemodynamic and anatomical characteristics. Calculation of proximal landing zone diameter, most usually commonly at the STJ, is therefore essential when choosing a stent graft. ECG-gated CTA provides high-resolution images and eliminates motion artifacts thus allowing for precise 3D measurements. In our cohort, change in STJ diameter between systole and diastole varied on average from 4.4% in women to 4.9% in men. Moreover, our mean population age was 77 years, so that, we can assume that pulsatile changes might be even more pronounced in younger patients with less aortic stiffening.[25] Csobay-Novák et al[26] demonstrated that the largest diameter throughout the aorta is observed at 30% of the cardiac cycle. In our practice, the systolic phase at 40% of the cardiac cycle is used for planning measurements to avoid underestimation of oversizing.

Electrocardiography-gated CTA is the most common imaging modality used for studying the AA due to superior spatial resolution. However, several authors report morphometric data using alternative imaging modalities like trans-esophageal echocardiography (TEE) and magnetic resonance (MR).[27-29] Magnetic resonance lacks spatial resolution but offers the advantage of decreased radiation exposure. Trans-esophageal echocardiography allows for simultaneous functional cardiac evaluation, which can be useful in the preoperative setting. Rodríguez-Palomares et al[29] evaluated the AAs of 140 patients with TEE, CTA, and MR. The authors concluded that aortic root and AA diameters measured by TEE using the leading edge-to-leading edge convention showed accurate and reproducible values compared with internal diameters assessed by CTA or MR. The good correlation between the 3 most common modalities permits multi-modality follow-up of patients with aortic disease without any impact on aortic measurement accuracy. Although future studies with larger sample sizes are needed to better understand sex-specific morphological variations and their potential impact on endovascular aortic

repair, our findings are of importance, both for physicians and device manufacturers, for clarifying some of the current gaps in endovascular programs' development of AA and arch. Using body surface indexed measurements may decrease sex-related anatomic disparities. In addition, setting different morphometric limits for treating aortic disease, or simply for imaging follow-up should take into consideration factors, such as sex, BSA, and the presence of established risk factors for arterial disease. Increased awareness and knowledge about sex-specific differences in aortic disease are important to improve patient outcomes and tailor endovascular procedures and materials to female needs.

Limitations

One of the limitations of this study is the limited number of patients included in the study cohort and the retrospective, single-center nature of study design. Moreover, patients with aneurysms or dissections were excluded from the study, so that, the values collected may not be representative in patients with those diseases. Data were drawn from a selected cohort of patients who underwent TAVR for aortic stenosis, which could introduce a selection bias. However, this study provides insight into healthy aortas, thus eligible proximal landing zones for endovascular procedures. Considering the older age of the cohort, conclusions might not be drawn for younger populations, but most aortic interventions interest older patients. Another limitation is that measurements were performed mostly by a single operator, but the intra-observer and inter-observer variability cohort analysis identified small differences of under 1 mm. Small changes in size can be simply identified on ECG-gated CTA because of the high spatial resolution. However, out-of-plane aortic movement might have caused minimal miscalculations, which is inherent to imaging studies.

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9

Editor's Choice – Comparison of the Reproducibility of Ultrasound Calliper Placement Methods in Abdominal Aortic Diameter Measurements: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies☆

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WHAT THIS PAPER ADDS

This systematic review and meta-analysis of diagnostic test accuracy studies shows that the outer to outer and inner to inner calliper placements in ultrasound measurements of anteroposterior abdominal aortic diameter could be considered more reproducible than a leading edge to leading edge calliper placement. There are however no statistically significant differences between these three methods. When considering studies published in 2010 and later, the leading edge to leading edge calliper placement turned out to be the most reproducible, without statistically significant differences between the methods. Additional data are required to provide robust recommendations regarding the preferred calliper placement in anteroposterior ultrasound measurements of maximum abdominal aortic diameter.

ABSTRACT

Objective: To assess which ultrasound (US) method of maximum anteroposterior (AP) abdominal aortic diameter measurement can be considered most reproducible.

Data Sources: MEDLINE, Scopus, and Web of Science were searched (PROSPERO ID: 276694). Eligible studies reported intra- and or interobserver agreement according to Bland–Altman analysis (mean ± standard deviation [SD]) for abdominal aortic diameter AP US evaluations with an outer to outer (OTO), inner to inner (ITI), and or leading edge to leading edge (LELE) calliper placement.

Review Methods: The Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies statement was followed. The QUADAS-2 tool and QUADAS-C extension were used for risk of bias assessment and the GRADE framework to rate the certainty of evidence. Pooled estimates (fixed effects meta-analysis, after a test of homogeneity of means) for each US method were compared with pairwise one sided *t* tests. Sensitivity analyses (for studies published in 2010 or later) and meta-regression were also performed.

Results: 21 studies were included in the qualitative analysis. Twelve were eligible for quantitative analysis. Studies showed heterogeneity in the US model and transducer used, sex of participants, and observer professions, expertise, and training. Included studies shared a common mean for each US method (OTO: $p = 1.0$, ITI: $p = 1.0$, and LELE: $p = 1.0$). A pooled estimate of interobserver reproducibility for each US method was obtained, combining the mean ± SD (Bland–Altman analysis) from each study: OTO: 0.182

± 0.440; ITI: 0.170 ± 0.554; and LELE: 0.437 ± 0.419. There were no statistically significant differences between the methods (OTO vs. ITI: $p = .52$, OTO vs. LELE: $p = .069$, ITI vs. LELE: $p = .17$). Considering studies published in 2010 and later, the pooled estimate for LELE was the smallest, without statistically significant differences between the methods. Despite the low risk of bias, the certainty of the evidence for both meta-analysed outcomes remained low.

Conclusion: The interobserver reproducibility for OTO and ITI was 2.5 times smaller (indicating better reproducibility) than LELE; however, without statistically significant differences between the methods and low GRADE evidence certainty. Additional data are needed to validate these findings, while inherent differences between the methods need to be emphasised.

INTRODUCTION

The identification of abdominal aortic aneurysms (AAAs) in the general population can be reached through several imaging modalities such as ultrasound (US), computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Among these, US is a well established tool to adopt during screening programmes,[1] outpatient visits and or bedside evaluation,[2] as well as in the emergency setting[3] due to its feasibility, safety, and reliability. Furthermore, US, and contrast enhanced US (CEUS) in particular, can also be employed as the diagnostic method of choice for post-operative surveillance and endoleak detection after endovascular procedures.[4-6] In fact, US and CEUS maintain acceptable accuracy in both pre-operative and post-operative settings,[7] if compared with CTA, and reach a pooled sensitivity and specificity of 81% and 91%, respectively, if compared with digital subtraction angiography.[8]

Despite the widespread application of US worldwide, no recommendations have been published regarding the preferred method of maximum abdominal aortic diameter measurement that obtains the most reproducible aortic dimensions. This method varies according to the plane of acquisition, axis of measurement, selected diameter, and most of all, calliper placements. The acquisition plane can be coronal or sagittal, the axis of measurement can be longitudinal or orthogonal, diameter can be measured in an anteroposterior (AP) or laterolateral (LL) or transverse direction, and US callipers can be placed according to the outer to outer (OTO), inner to inner (ITI), or leading edge to leading edge (LELE, also known as outer to inner) method (Fig. 1).[9] Inherently, different US methods result in some variation in the measured abdominal aortic diameter, with the ITI method resulting in the smallest diameters, while the OTO method results in 4 – 7 mm larger diameters than ITI.[10,11]

The aim of the present systematic review was to evaluate all published studies that address intra- and interobserver reproducibility of different US methods to measure maximum abdominal aortic diameters, to assess which method may be considered most reproducible, and to determine whether there is enough evidence to recommend its use in daily clinical practice.

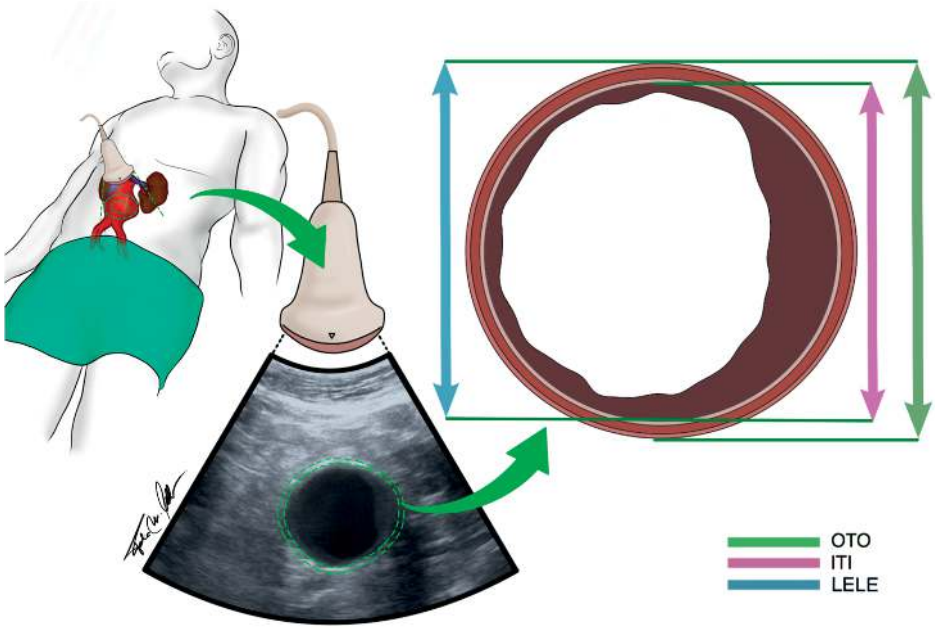

Figure 1. Graphical clarification of the three methods for calliper placement during abdominal aortic diameter measurements using ultrasound. OTO = outer to outer; ITI = inner to inner; LELE = leading edge to leading edge.

METHODS

Design

The Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement[12] was followed (completed checklists can be found in Supplementary Material) and suggestions offered by Koelemay and Vermeulen were also considered.[13] The study protocol is available on the International Prospective Register of Systematic Reviews database (PROSPERO, registration number 276694). The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was adopted for evidence certainty assessment.[14]

Literature sources and research strategy

Two authors (D.B. and T.M.) independently and systematically performed the research process. In case of disputes or discrepancies between researchers, a third author (S.T.) was consulted to give the final judgement and provide consensus. The systematic search was performed on 10 November 2021. Study selection was performed between

25 November 2021 and 22 November 2022. The entire literature search strategy process is presented in detail below.

The research was conducted on MEDLINE, Scopus, and Web of Science. Keywords were selected using medical subject headings (MeSH) for PubMed and MeSH/EMTREE for Scopus. The keywords ultrasound, measurement, intra-observer, and interobserver were combined with abdominal aortic aneurysm and aortic diameter to obtain the first publications cluster (see Supplementary Appendix, part I). When possible, the [MeSH terms] modality was used during query composition, to avoid redundant results. The Boolean operators AND and OR were used to connect keywords with each other. Moreover, the reference lists of selected studies were screened for additional relevant publications. Finally, the Article in press sections of vascular journals were revised to detect articles not yet indexed in scientific databases (see Supplementary Appendix, part II). The EndNote 20 software (Clarivate Analytics, London, UK) was used to collect, remove duplicates, and screen selected documents.

Data extraction

An Excel spreadsheet (Microsoft Corp, Redmond, WA) was used to note the following data deriving from selected papers when available: (1) baseline data: US scanner used, transducer type, cohort size, characteristics, and recruitment (i.e., invitation, selection, consecutive, randomised), mean age and sex of participants, calliper placement method, mean maximum diameter of the infrarenal aorta; (2) observers' characteristics: number, professional type, training, and expertise, time between observations; (3) methods and outcomes: maximum aortic diameter measurement method, exact calliper placement position, Bland–Altman analysis metrics (mean ± standard deviation [SD]) regarding intra-observer agreement (i.e., variation in repeated measurements made on the same subject by the same observer and under identical conditions), interobserver agreement (i.e., variation in measurements made between different observers on the same subject or under changing conditions). In particular, the mean difference between two measurements (the bias) and 95% limits of agreement were extracted and reported as mean ± SD. Given the heterogeneity among studies in the referral to these metrics (e.g., coefficient of repeatability, accuracy of ultrasonographers, interobserver variability), in case of difficulties, a statistician (L.S., F.I.) was consulted to reach consensus.

Inclusion and exclusion criteria

All original articles published in English and between 1 January 1990 and 31 December 2021 that addressed the use of US in human maximum abdominal aortic diameter measurement were included. Other inclusion criteria to obtain eligible articles were (1) analysis on > 10 patients; (2) intra- and interobserver agreement assessed by Bland–Altman

analysis or primary data to enable limits of agreement and reproducibility to be derived, or regression modelling with generalised estimating equations. Exclusion criteria were the following: (1) reviews (both systematic and non-systematic); (2) *in vitro* or *ex vivo* animal or *in silico* studies; (3) computational studies; (4) analysis performed on patients who underwent previous endovascular, hybrid, or open surgical aortic treatments; (5) studies evaluating maximum abdominal aortic diameter only using CTA or MRA; and (6) letters, comments and editorials on small scale and or incomplete experiences.

Quality assessment

Following PRISMA-DTA, the methodological quality of each study was assessed independently by two authors (D.B., T.M.) with the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[15] This tool comprises four domains: (1) patient selection; (2) index text; (3) reference standard; and (4) flow and timing. These four domains were assessed regarding risk of bias and the first three in terms of concerns regarding applicability. The recently developed QUADAS-C tool (extension of QUADAS-2)[16] for comparative diagnostic accuracy studies was then applied since six studies performed comparisons of different US methods (i.e., US OTO, ITI, and or LELE, Table 1). Possible answers for the different domains were yes, no, unclear, or not applicable and risk of bias was scored high, low, or unclear.

Objectives

Objectives were identified and described using the PICO framework methodology, in which the intervention group was changed to index test following the PRISMA-DTA.[17] This PICO framework was also used to combine keywords of interest during the establishment of the systematic search and the research process. The aim of this systematic review was to assess which US method of maximum abdominal aortic diameter measurement can be considered most reproducible. Consequently, another objective was to determine whether there is enough evidence to recommend the use of one US method (e.g., calliper placement) over the other(s) in daily clinical practice.

Statistical analysis

Data were reported in textual form as number (%), mean ± SD, median (interquartile range [IQR]), mean (range) or range, depending on the study. Missing data were flagged as such (–) during data extraction. Intra- and interobserver agreement according to Bland–Altman analysis were reported as mean ± SD to create homogeneity in tables and allow for consequent meta-analysis. A test of homogeneity of means was performed to check if the included studies shared a common mean of interobserver reproducibility, to evaluate whether a fixed or random effects model was preferred (see Supplementary Appendix, part III).[18] Then, the meta-analysis (fixed effects model) allowed obtaining a

pooled estimate for each US method, combining the mean and SD from each study (i.e., OTO, ITI, LELE). A smaller pooled estimate indicates better reproducibility, as the mean of the paired differences are closer to zero, following Bland–Altman analysis. Pooled estimates for each US method were compared with pairwise one sided *t* tests. A p value < .050 was considered to be statistically significant.

Sensitivity and meta-regression analyses

A sensitivity analysis was performed that considered studies published in or after 2010, aiming to account for advances in more recent clinical practice and technological performance (e.g., CEUS machine and probe).

Finally, meta-regression models were used to identify potential time related heterogeneity in the results. In particular, the publication year of a study was examined to see whether it could be used to predict a part of the heterogeneity observed in the pooled estimates.

RESULTS

Study selection

A total of 1 532 studies were identified through primary database searching (Fig. 2). After the removal of duplicates, 1 120 studies were screened. Of these, 1 075 were deleted based on screening of the title and abstract due to an unmatched topic. Consequently, 43 articles were retrieved and assessed for eligibility based on the full text. Main reasons for exclusion at this stage were failure to match the inclusion and exclusion criteria (n = 9), a review or systematic review (n = 6), only 3D or 4D colour doppler US (n = 2), or a post-endovascular abdominal aneurysm repair (EVAR) analysis (n = 2). Two studies were added from reference lists. Finally, 21 studies[10,11,19-37] were included in the qualitative analysis. Of these, 12 studies[10,11,23-25,29-32,34-36] were included in the quantitative analysis as they provided useful data for an interobserver reproducibility comparison between the OTO,[10,11,24,29,31,35] ITI,[10,11,23,34,35] and LELE[10,25,30,32,35,36] methods. Here, respective studies were excluded when maximum aortic diameters were not measured in the AP direction[28] (n = 1) when the exact calliper placement method was not stated,[20,21,26] or comparable[22] (n = 4) when only SDs of Bland–Altman intra- and or interobserver agreement were reported without mean value[37] (n = 1), or when neither the mean nor SD of Bland–Altman intra- and or interobserver agreement could be derived from the study[19,27,33] (n = 3).

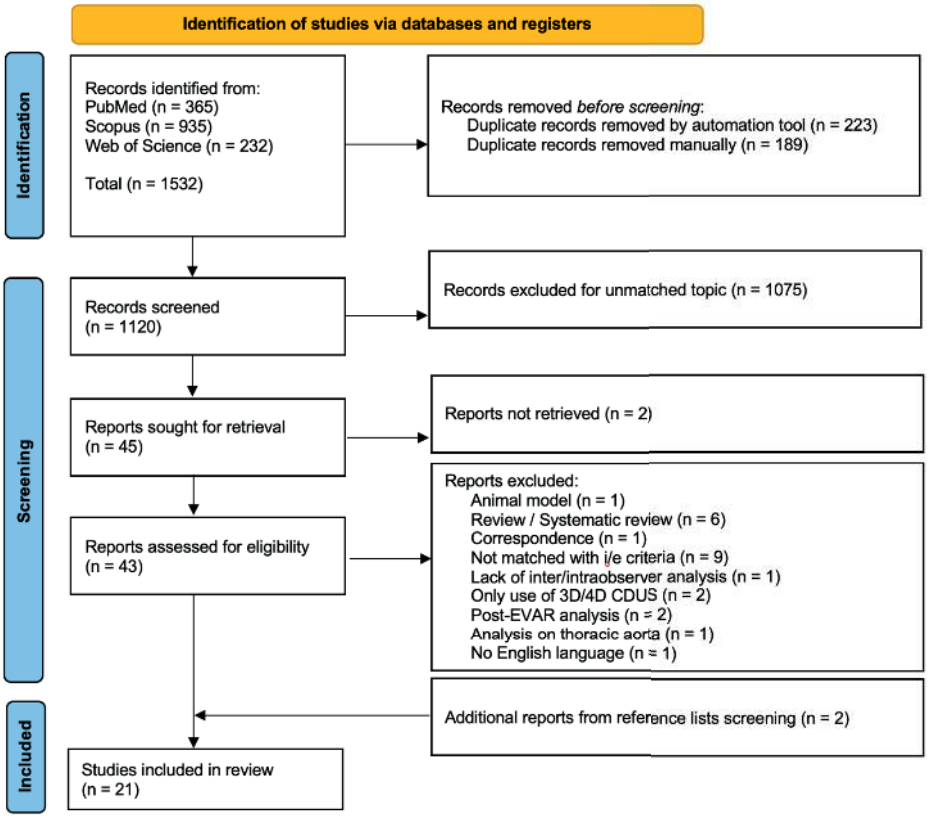

Figure 2. Study selection flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement for new systematic reviews to identify studies that address intra- and interobserver repeatability and reproducibility of ultrasound methods to measure maximum abdominal aortic diameters. EVAR = endovascular abdominal aneurysm repair; CDUS = colour Doppler ultrasound.

Characteristics of studies and participants

Table 1 provides a detailed overview of study characteristics. Included studies were published between 1991 and 2021 and showed important heterogeneity in the US machine and probes used for abdominal aortic measurements. The median study size was 52 participants (range 10 – 215). Participants consisted of both men and women in nine studies[21,24,25,28,29,31,32,36,37] (43%), of only men in four studies[26,27,34,35] (19%), while eight studies[10,11,19,20,22,23,30,33] (38%) did not report the sex of the participants. The median age of participants was 72 years (range 6.5 – 105) among the 13 studies[21,23-26,27,28,31,32,34-37] (62%) that reported the age of participants. Among included studies, authors defined calliper placement as external, middle point of the wall echoes, OTO, ITI, or LELE. Six studies[19,21,30,31,35,36] (29%) did not report the mean maximum diameter of the infrarenal aorta measured using US.

Table 1. Baseline study characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter.

Nr.	Author, year	Ultrasound scan	Ultrasound transducer	Cohort size, characteristics, and recruitment	Sex and age of participants, y	Calliper placement method	Maximum diameter of infrarenal aorta, mean, mm
1.	Ellis, 1991 [19]	Acuson 128 Colour Duplex (Acuson, Stevenage, UK) Siemens Sonoline 2 (Siemens, Sunbury-on-Thames, UK) Acuson 128 Duplex (Siemens Medical Solutions)	3-5 MHz probe (linear array) 3-5 MHz probe (mechanical sector) 3-5 MHz probe (linear array)	10, clinical evidence of infrarenal aortic dilatation, invitation	-	OTO ("external diameter")	-
2.	Akkersdijk, 1994 [20]	-	5 MHz transducer	100, infrarenal AAA, consecutive	-	-	AP 39 (24-84)* TS 38 (23-84)*
3.	Thomas, 1994 [21]	SL1 scanner (Siemens, Sunbury-on-Thames, UK)	3.5 MHz probe (linear array)	29 – 30, AAA, recall and invitation	Men and women, 73.7 (65-80)	-	-
4.	Jaakkola, 1996 [22]	Aloka 650 (Tokyo, Japan)	3-5 MHz convex	33, normal aorta or AAA, invitation	-	"From- to middle point of wall echos"	Normal: AP 17 (12-27)* TS 19 (14-29)* AAA: AP 39 (24-64)* TS 42 (26-70)*
5.	Lanne, 1997 [23]	Diamove echo-tracking ultrasonic equipment (Teltec AB, Lund, Sweden)	3-5 MHz B mode (real-time linear array)	18 – 36, aortic dilatation or (small) AAA	-, 42-82	ITI ("inner surface of the aortic walls")	ITI AP 37 (21–51)*
6.	Pleumeekers, 1998 [24]	Toshiba SHH 60A (Toshiba Medical Systems, Crawley, UK)	3-5 MHz (linear array)	135, different aortic ammeters, selection	Men and women, ≥ 55	OTO ("the two most outer wall echo"	OTO AP 19.6 (12–82)*

Table 1. Baseline study characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter. (*continued*)

Nr.	Author, year	Ultrasound scan	Ultrasound transducer	Cohort size, characteristics, and recruitment	Sex and age of participants, y	Calliper placement method	Maximum diameter of infrarenal aorta, mean, mm
7.	Singh, 1998 [25]	Acuson 128-XP (Siemens Medical Solutions)	3-5 MHz sector probe	112, general population, random selection	Men and women, ≥ 24	LELE	LELE AP 19.8 (3.3)† LELE TS 21.1 (3.2)†
8.	Lindholt, 1999 [26]	Philips SDR 1550 (Philips Healthcare)	4 MHz linear transducer	50, normal aorta, consecutive	Men, 65–73	-	Distal infrarenal AP 17.9 (2.9)† Proximal infrarenal AP 18.4 (2.45)†
9.	Thapar, 2010 [11]	Philips HDI 5000 (Philips Bothel, USA)	3-5 MHz probe	50, small AAA, consecutive	-	OTO, ITI	OTO 32–78‡
10.	Hartshorne, 2011 [27]	LOGIQ (GE Healthcare, Little Chalfont, UK)	2.5-5 MHz curvilinear transducer	60, normal to AAA, random selection	Men, 65	OTO, ITI	OTO AP 41.8 (16.3-70.9)* ITI AP 39.1 (13.9-68)*
11.	Dijos, 2012 [28]	IE33 (Philips Medical System, Boston, MA, USA)	-	52, normal aorta, consecutive	Men and women, 6.5 ± 12.8	OTO	OTO TS 19.3 ± 7.1
		VSCAN (General Electric Medical Systems, Milwaukee, WI, USA)	1.7-3.8 MHz probe (phased array)				OTO TS 19.0 ± 7.0
12.	Bonnafy, 2013 [29]	VSCAN (GE Healthcare, Wauwatosa, WI, USA)	1.7-3.8 MHz probe (phased array)	56, history of cardiovascular disease, invitation	Men and women, -	OTO	OTO AP 19.0 (5.8)† by expert sonographer OTO AP 18.2 (5.8)† by novice operator
		iE33 (Philips Healthcare, Boston,MA, USA)	5 MHz probe (phased array)				OTO AP 18.9 (5.8)† by expert sonographer OTO AP 19.0 (6.0)† by expert sonographer

Table 1. Baseline study characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter. (*continued*)

Nr.	Author, year	Ultrasound scan	Ultrasound transducer	Cohort size, characteristics, and recruitment	Sex and age of participants, y	Calliper placement method	Maximum diameter of infrarenal aorta, mean, mm
13.	Bredahl, 2013 [30]	ECG-gated CX-50 US system (Philips, Bothell, Washington, USA)	5 MHz probe (curved array, C5-1)	27, small asymptomatic AAA, random selection	-	A: LE adventitia anterior – LE adventitia posterior, B: LE adventitia anterior – LE intima posterior (LELE)	A: LE adventitia – LE adventitia AP 45.1 (39.9 – 57.6)*
14.	Nguyen, 2013 [31]	Terason (-)	3.5 MHz probe (curved array)	215 max., normal to AAA, invitation	Men and women, 50-105	OTO	-
		Antares (-)	3.5 MHz probe (curved array)				
15.	Gurtelschmid, 2014 [10]	Philips iU22 (Philips Health Care, Best, The Netherlands)	3 – 5 MHz probe	127, small AAA, consecutive	-	OTO, ITI, LELE	OTO AP 41.9 (24.5-83.0)* ITI AP 37.8 (21.5-77.5)* LELE AP 39.6 (24.0-81.5)*
		Siemens S2000 (Siemens, Erlangen, Germany)	3 – 5 MHz probe				
16.	Bredahl, 2015 [32]	X6-1 xMATRIX (Philips Health Care, Bothwell, WA, USA)	3D matrix transducer	100, small asymptomatic AAA, consecutive	Men and women, 73 ± 7	-	-
		Philips iU22 (Philips Health Care, Bothwell, WA, USA)	-			A: LE adventitia anterior – LE adventitia posterior	LELE AP median 46 (31-55)

Table 1. Baseline study characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter. (*continued*)

Nr.	Author, year	Ultrasound scan	Ultrasound transducer	Cohort size, characteristics, and recruitment	Sex and age of participants, y	Calliper placement method	Maximum diameter of infrarenal aorta, mean, mm
17.	Chiu, 2015 [33]	Philips HD9 (Philips, Bothel, USA) Toshiba Aplio 300 (Toshiba Medical Systems, Crawley, UK)	3-5 MHz probe (curvilinear) 2-5 MHz probe (curvilinear)	50, five aortic diameter groups, random selection	-	OTO, ITI, LELE	OTO AP 39.9 (16.8-115.7)* ITI AP 35.9 (13.9-108.4)* LELE AP 37.7 (15.5-111.6)*
18.	Crilly, 2016 [34]	General Electric LOGIQe	1.5-4.6 MHz with 4C curvilinear probe	63, normal aorta, consecutive	Men, 65.5	ITI	ITI AP 18 (13-25)*
19.	Borgbjerg, 2017 [35]	Logiq E ultrasound systems (GE Fairfield, CT, USA)	4 MHz curved transducer	50, normal aorta, random selection	Men, 70 ± 2.8	OTO, ITI, LELE	OTO AP 23 (-) ITI AP 18 (-) LELE AP 20 (-)
20.	Ghulam, 2019 [36]	Philips EPIQ 7G US-system (Philips Healthcare, Bothell, USA) Philips EPIQ 7G US-system (Philips Healthcare, Bothell, USA)	C5-1 curved array transducer (2D) X6-1 xMATRIX transducer (3D)	90, asymptomatic infrarenal AAA, consecutive	Men and women, median 74	LE adventitia anterior – LE adventitia posterior	- - AP 37.9 ± 6.7 (observer 1), 38 ± 6.6 (observer 2)
21.	Matthews, 2021 [37]	Phillips iu22 machine (Phillips Medical Systems, USA)	C5-1 MHz general purpose curvilinear transducer	50, small infrarenal AAA, invitation	Men and women, 72 (68-77)	OTO, ITI, LELE	-

Data are reported as mean (range), mean ± standard deviation, and range. (–) = missing data. UK = United Kingdom; AAA = abdominal aortic aneurysm; AP = anteroposterior; TS = transverse; OTO = outer to outer; ITI = inner to inner; LE = leading edge; max = maximum.

Observer characteristics

Table 2 provides a detailed overview of observer characteristics. The median number of observers among studies was three (range 2 – 24). There was significant heterogeneity among the professions, experience, and training of observers. Professions were novice operator, sonographer, vascular technician or scientist, radiologist or radiology resident, nurse, cardiologist, interventional radiology fellow, or medical student. Lengths of experience ranged from novice, less than one year to more than 10 years, 16 years, expert, or extensive. Training differed extensively among observers and ranged from one day to two years using different theoretical and practical methods. Fifteen studies[10,11,19,21-27,29-32,35] (71%) were not completely transparent about the length of experience or training of the observers, while one study[26] (5%) did not provide any observer information.

Ultrasound methods of abdominal aortic diameter measurement

Table 3 summarises sample size and mean ± SD) for the intra- and interobserver agreement according to Bland–Altman analysis[10,11,23-25,29-32,34-37] providing information on US abdominal aortic measurements in the AP direction and using OTO, ITI, or LELE calliper placements. Over the last decade, more studies have started to apply at least one of the last three methods and provide direct comparisons between two or three methods.

Outcomes of methods comparison

The comparison of US methods regarding intra-observer agreement (expressed as mean ± SD) was not performed due to a lack of available data to combine during meta-analysis (Table 3). A test of homogeneity of means of the interobserver agreement showed that the included studies share a common and comparable mean for each US calliper placement method (OTO: $p = 1.0$, ITI: $p = 1.0$, and LELE: $p = 1.0$). The pooled estimate of interobserver reproducibility was 0.182 ± 0.440 for OTO and 0.170 ± 0.554 for ITI. For LELE, the pooled estimate was 0.437 ± 0.419. As can be emphasised, the pooled estimates for OTO and ITI were 2.4 – 2.6 times smaller than the pooled estimate for LELE, indicating better reproducibility. However, there were no significant differences between each of the three US methods (OTO *vs.* ITI: $p = .52$, OTO *vs.* LELE: $p = .069$, ITI *vs.* LELE: $p = .17$).

Table 2. Baseline observer characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter.

Nr.	Author, year	Observers, n	Professional type, (n)	Experience in measuring ultrasound aortic diameters, y, (n)	Training (standard measurement technique)	Time between measurements
1.	Ellis, 1991 [19]	3	Ultrasonographers (2)	-	-	3 weeks
			Experienced vascular technician (1)	-	-	
2.	Akkersdijk, 1994 [20]	4	Experienced radiologists (2)	-	Yes; in the 2 months before the study the 4 radiologists measured aneurysms in one another's presence for standardization	-
			Senior trainee radiologists (2)	< 1		
3.	Thomas, 1994 [21]	3	Experienced vascular ultrasonographer (2)	-	-	3 months
			Experienced vascular radiologist (1)	-	-	
4.	Jaakkola, 1996 [22]	3	Experienced radiologists (3)	-	-	"At least some days"
5.	Lanne, 1997 [23]	2	Experienced technicians (2)	-	-	-
6.	Pleumeekers, 1998 [24]	3	Experienced sonographers (3)	-	"Well-trained"	"As shorts as possible to minimize biological variation over time"
7.	Singh, 1998 [25]	4	Registered and assistant nurses (2)	< 1	Yes; 40 h theoretical and practical training over 2 weeks and then surveillance in imaging the aorta for 2 months	1 – 3 weeks
			Radiographer (1)	< 1	Yes; 60 h theoretical and practical training in imaging the aorta	
			Experienced radiologist (1)	-	-	
8.	Lindholt, 1999 [26]	2	-	-	-	-

Table 2. Baseline observer characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter. (*continued*)

Nr.	Author, year	Observers, n	Professional type, (n)	Experience in measuring ultrasound aortic diameters, y, (n)	Training (standard measurement technique)	Time between measurements
9.	Thapar, 2010 [11]	2	Vascular scientists (2)	> 3	-	"During one appointment"
10.	Hartshorne, 2011 [27]	24	Qualified AAA screening technicians (13)	> 10 (2) 1 – 4 (6) < 1 (5)	Yes; 3 months' NAAASP training programme	-
			Vascular sonographers (11)	> 10 (6) 1 – 4 (4) < 1 (1)	Yes; minimum of 2 years' ultrasound training, which included imaging the aorta	
11.	Dijos, 2012 [28]	3	Cardiologist (2)	-	-	-
			Blinded observer for variability assessment (1)	-	-	
12.	Bonnafy, 2013 [29]	-	Novice operators (medical students) (-)	0	Yes; 3 times 3 hours training sessions	-
			Expert sonographers (9)	-	-	
13.	Bredahl, 2013 [30]	2	Experienced sonographers (2)	> 10 (2)	-	"Both morning and afternoon"
14.	Nguyen, 2013 [31]	10	Novice operators (5)	0	Yes; 15-day training course	-
			Experienced technologists (5)	- (4) 16 (1)	-	

Table 2. Baseline observer characteristics of the 21 studies included in this systematic review, comparing ultrasound methods to measure aortic diameter. (*continued*)

Nr.	Author, year	Observers, n	Professional type, (n)	Experience in measuring ultrasound aortic diameters, y, (n)	Training (standard measurement technique)	Time between measurements
15.	Gurtelschmid, 2014 [10]	13	Experienced sonographers (13)	-	-	-
16.	Bredahl, 2015 [32]	2	Experienced sonographers (2)	-	-	-
17.	Chiu, 2015 [33]	6	Vascular radiologists (2)	> 4	Yes; trained in peripheral vascular imaging	6 weeks
			Interventional radiology fellows (2)	> 4	Yes; trained in peripheral vascular imaging	
			Sonographers (2)	> 4	Yes; trained in peripheral vascular imaging	
18.	Crilly, 2016 [34]	4	Nurses (4)	1.5	Yes; nationally accredited 2-day classroom-based educational course	-
19.	Borgbjerg, 2017 [35]	18	Radiology consultants (11)	> 3	-	1 – 210 days
			Radiology residents (7)	> 3	-	
20.	Ghulam, 2019 [36]	2	Vascular technologists (2)	8 (1) 10 (1)	Yes; a single day of supervised standardized training (for the 3D measurements)	"During the same examination"
21.	Matthews, 2021 [37]	3	Vascular sonographer (1)	Extensive	Yes; trained using a predefined protocol	1 week
			Medical student (1)	0	Yes; trained using a predefined protocol	
			Research worker and exercise physiologist (1)	Extensive	Yes; trained using a predefined protocol	

NAAASP = National Health Service Abdominal Aortic Aneurysm Screening Programme. (–) = missing data.

Table 3. Intra- and interobserver agreement according to Bland–Altman analysis for the outer to outer (OTO), inner to inner (ITI), and leading edge to leading edge (LELE) ultrasound methods of maximum anteroposterior abdominal aortic diameter measurement, derived from 13 studies included in this systematic review that provided these data

Nr.	Author, year	Sample size, n	OTO		ITI		LELE	
			Intra, mean (SD)	Inter, mean (SD)	Intra, mean (SD)	Inter, mean (SD)	Intra, mean (SD)	Inter, mean (SD)
5.	Lanne, 1997 [23]	36/18 (intra/inter)	-	-	0 (0.78)	0 (0.93)	-	-
6.	Pleumeekers, 1998 [24]	50, distal diameter	-	0.06 (1.42)	-	-	-	-
		38, distal diameter	-	0.08 (1.02)	-	-	-	-
		47, distal diameter	-	0.06 (1.02)	-	-	-	-
7.	Singh, 1998 [25]	99/106 (intra/inter), max. infrarenal level	-	-	-	-	-0.6 (2.0)	-1.5 (2.2)
		-/77 (intra/inter), max. infrarenal level	-	-	-	-	-	-1.1 (1.7)
		-/77 (intra/inter), max. infrarenal level	-	-	-	-	-	-0.0 (1.8)
		88/30 (intra/inter), max. infrarenal level	-	-	-	-	-0.1 (2.0)	-2.4 (1.6)
		75/30 (intra/inter), max. infrarenal level	-	-	-	-	-0.7 (1.5)	0.3 (1.4)
		26/29 (intra/inter), max. infrarenal level	-	-	-	-	-0.8 (1.7)	0.3 (1.3)
9.	Thapar, 2010 [11]	50	-	-0.22 (1.5)	-	-0.46 (3.0)	-	-
12.	Bonnafy, 2013 [29]	56	-	-0.1 (1.55)	-	-	-	-
			-	0.7 (2.2)	-	-	-	-
			-	0.0 (2.0)	-	-	-	-
			-	0.75 (2.275)	-	-	-	-

Table 3. Intra- and interobserver agreement according to Bland–Altman analysis for the outer to outer (OTO), inner to inner (ITI), and leading edge to leading edge (LELE) ultrasound methods of maximum anteroposterior abdominal aortic diameter measurement, derived from 13 studies included in this systematic review that provided these data (*continued*)

Nr.	Author, year	Sample size, n	OTO		ITI		LELE	
			Intra, mean (SD)	Inter, mean (SD)	Intra, mean (SD)	Inter, mean (SD)	Intra, mean (SD)	Inter, mean (SD)
13.	Bredahl, 2013 [30]	27	-	-	-	-	-	0.3 (1.5)
			-	-	-	-	-	0.4 (1.6)
			-	-	-	-	-	0.02 (1.6)*
			-	-	-	-	-	0.03 (1.7)*
14.	Nguyen, 2013 [31]	209, max. coronal	-	-0.7 (2.35)	-	-	-	-
		194, max. coronal	-	-0.5 (2.5)	-	-	-	-
		167, max. coronal	-	0.5 (2.4)	-	-	-	-
15.	Gurtelschmid, 2014 [10]	127	-	-0.42 (2.7)	-	-0.38 (2.3)	-	-0.40 (2.0)
16.	Bredahl, 2015 [32]	79	-	-	-	-	-	0.04 (1.9)*
18.	Crilly, 2016 [34]	63	-	-	-	0.5 (1.15), pooled	-	-
19.	Borgbjerg, 2017 [35]	50	0 (1.0)	0 (1.3)	0 (0.80)	0.05 (0.975)	0 (0.75)	0 (0.95)
20.	Ghulam, 2019 [36]	90	-	-	-	-	-	0.14 (2.46)*
21.	Matthews, 2021† [37]	50	- (1.33)	- (2.46)	- (1.20)	- (2.28)	- (1.10)	- (2.34)

Data are expressed as mean of the paired differences of two measurements ± standard deviation. intra = intra-observer repeatability; inter = interobserver reproducibility; max.: maximum.
* From the leading edge of the adventitia anterior wall to the leading edge of the adventitia posterior wall (other studies defined LELE from the leading edge of the adventitia anterior wall to the leading edge of the intima on the posterior wall).
† Not included in the quantitative analysis due to the absence of the mean value in this study.

Sensitivity analysis

A sensitivity analysis was performed that considered studies published in or after 2010 (n = 9[10,11,29-32,34-36]). There were no studies included in this systematic review that were published between 2000 and 2010. A test of homogeneity of means of the interobserver agreement showed that the included studies in the sensitivity analysis shared a common and comparable mean for each US calliper placement method (OTO: $p = 1.0$, ITI: $p = 1.0$, and LELE: $p = 1.0$). Here, the pooled estimate was 0.283 ± 0.603 for OTO and 0.264 ± 0.690 for ITI. For LELE, the pooled estimate was 0.131 ± 0.545. In contrast to the main analysis, the pooled estimates for OTO and ITI increased, while the pooled estimate for LELE was lowest, indicating better reproducibility. SDs increased compared with the main analysis, probably due to the reduction in sample size. Also here, there were no significant differences between each method (OTO vs. ITI: $p = .52$, OTO vs. LELE: $p = .48$, ITI vs. LELE: $p = .79$).

Meta-regression analysis

Through the meta-regression time dependent analysis, no significant differences were obtained in the pooled estimates.

Quality assessment

The results of the quality assessment are presented in the Supplementary Appendix, part IV. The main limitation and source of concern was the lack of a reference standard to measure the true maximum abdominal aortic diameter (i.e., CTA). For this reason, answers for domains 3 and 4 were not applicable in both QUADAS-2 and QUADAS-C evaluations. The index test was ultrasound for all studies and when more than one US method (i.e., OTO, ITI, and/or LELE) was assessed in one study (n = 6[10,11,27,33,35,37]), these were considered as separate index tests. In this case, the QUADAS-C extension was applied for evaluation of the comparison. The comparisons did not introduce further risk of bias.

The results risk of bias and applicability for domain 1 was low for 13 studies[10,11,20,25-28,30,32-36] (consecutive or random patient selection), high for seven studies[19,21,22,24,29,31,37] (patients selected based on invitation), while one study[23] was unclear on this aspect. The conduction of, and the conditions during ultrasound measurements in the respective studies were judged adequate, as well as their interpretation. This led to a low risk of bias and applicability in domain 2.

GRADE certainty of evidence

The GRADE evidence certainty assessment for the main and sensitivity analyses are presented in Table 4. The certainty of the evidence remained low for both the meta-analysed outcomes due to serious inconsistency and very serious indirectness, despite the low risk of bias.

Table 4. Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) assessment for selected studies

Quality assessment							Patients, n			Effect		Quality	Importance
Studies, n	**Design**	**Risk of bias***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OTO**	**ITI**	**LELE**	**Pooled interobserver reproducibility coefficient, *mean ± SD***	**Comparisons between methods**		
Reproducibility of abdominal aortic ultrasound measurements													
12	DTA studies	Low	Serious†	Very serious‡	Not serious	-	988	308	722	OTO: 0.182 ± 0.440 ITI: 0.170 ± 0.554 LELE: 0.437 ± 0.419	OTO *vs* ITI: p = .518 OTO *vs* LELE: p = .069 ITI *vs* LELE: p = .170	⨁⨁◯◯ Low	Important
Reproducibility of abdominal aortic ultrasound measurements (studies published ≥ 2010)													
9	DTA studies	Low	Serious†	Very serious‡	Not serious	-	853	290	373	OTO: 0.283 ± 0.603 ITI: 0.264 ± 0.690 LELE: 0.131 ± 0.545	OTO vs ITI: p = .519 OTO vs LELE: p = .481 ITI vs LELE: p = .709	⨁⨁◯◯ Low	Important

Data are shown as *n*, mean ± standard deviation. DTA = diagnostic test accuracy studies; OTO = outer to outer; ITI = inner to inner; LELE = leading edge to leading edge.

* Deriving from the QUADAS-2 tool and QUADAS-C tool extension.

† Serious heterogeneity present regarding baseline study and observer characteristics as can be emphasised in Table 1 and 2.

‡ Comparisons between OTO, ITI, and/or LELE are indirect and not always within the same study.

DISCUSSION

US may be considered a simple, non-invasive, and safe method to measure abdominal aortic diameters. Due to these characteristics, US is largely proposed as the first line diagnostic tool in the general population to detect or monitor abdominal aortic dimensions. Despite these advantages, a clear measuring protocol is missing, particularly regarding calliper placement. The method used to acquire the real aneurysm sac dimensions with the most accurate and reproducible US method is crucial for several reasons: to identify patients with AAA (e.g., during screening programmes); to detect a significant (> 50 – 55 mm) AAA and define a threshold for invasive correction; to compare different measurements and detect abdominal aortic growth rates; to analyse AAA shrinkage after EVAR (e.g., during the post-operative follow up period); and to increase homogeneity and consensus in the scientific community regarding calliper placements.

The recent European Society of Vascular and Endovascular Surgery (ESVS) guidelines remains unable to recommend a detailed preferred maximum US abdominal aortic diameter measurement method, but AP diameter seems to be considered the preferred one.[38] The Society for Vascular Surgery practice guidelines recommend the use of US for screening and surveillance without specifying the details of the measurement method.[39] However, the NICE guidelines reported that the ITI measured using the AP diameter should be used in accordance with the National Abdominal Aortic Aneurysm Screening Programme (NAAASP), which enrols patients with an AAA > 30 mm.[40] Despite this, the suggested threshold for surgical intervention (for AAA > 55 mm) is based on the UK Small Aneurysm (UKSAT)41 and Aneurysm Detection and Management Veterans Affairs Cooperative Study (ADAM)42 trials, using the OTO AP diameter. Meecham et al.[43] demonstrated a consistent and significant 4 mm difference between ITI and OTO diameters, underlining an aortic diameter underestimation using the ITI AP method and, therefore, more difficulties to match the NAAASP criterion for AAA repair using this method. On the other hand, using OTO AP diameters increases the sensitivity of detecting any AAA in screening programmes, as diameters are consistently larger. In contrast with the NAAASP, the LELE method is adopted in the Swedish AAA screening programme,[44] based on the study by Gürtelschmid et al.[10] that found the lowest variability using the LELE method, compared with ITI and OTO, also confirming a 4 mm difference between the ITI and OTO AP methods. Furthermore, maximum AAA diameter measurements can vary during the cardiac cycle, with a reported systole to diastole difference of 2 mm.[45]

Beales et al.[46] tried to analyse evidence derived from nine studies (published between 1991 and 2011)[11,19,20,22-27] more than 10 years ago. The authors came to vague conclusions, due to heterogeneity in selected papers and the lack of an indirect comparison between

OTO, ITI, and LELE. Despite this, their analysis offered the first attempt to highlight the disparity between the widespread and daily use of US and the lack of precise recommendations about abdominal aortic diameter measurement.

The current systematic review conducted to obtain the most reproducible method to measure abdominal aortic diameters using US, reveals some thought provoking results. At first, there is a significant heterogeneity in patients, US technicians, patient enrolment, measurement protocols and outcomes among studies. The analysis showed a 2.5 times smaller pooled estimate (mean ± SD) of interobserver agreement for both OTO and ITI (indicating better reproducibility), compared with LELE; however, this difference was not statistically significant. This could be influenced by the fact that the absolute differences are small, together with the limited amount of available data in the current literature. Furthermore, the publication date range of included studies spanned 30 years, and the changes in US machine performance and resolution over that period could have influenced the results in such a way that the sensitivity analyses found increased pooled estimates for OTO and ITI, while the pooled estimate for LELE decreased. Also here, there were no statistically significant differences between the methods, but the LELE method was the most reproducible looking at the absolute value of the pooled estimate of interobserver agreement. These discrepancies might explain the superiority of LELE,[10] or similar results between ITI and OTO,[43] found in some studies. There were no studies included that were published between 2000 and 2010, so an additional sensitivity analysis considering a wider timespan was not possible.

Due to the thickness of the aortic wall, differences between ITI and OTO may vary significantly (up to 7 mm).[11] Variations between sex, age groups, hypertension, and the presence of atherosclerosis have also been reported.[47] Hence, it is of primary importance to decide how abdominal aortic diameters should be measured exactly (e.g., an AAA of 49 mm using the ITI method may be measured as 56 mm using the OTO method). These differences between US methods may have a significant impact on the prevalence of AAAs detected by screening programmes. This aspect deserves to be underlined regardless of the presented reproducibility results of the different US methods.

Based on the results of this study, the quality assessment of the included studies, and the low grade evidence demonstrated by the GRADE analysis (Table 4), it remains challenging to draw robust conclusions and recommend one US method over the other. Nevertheless, both well established and AAA screening programmes under development, that use either of these AP US methods, need to be aware of the inherent differences between calliper positioning and should consider the reproducibility of these methods, as presented in this study.

Despite all this reasoning, using modern technologies and following recommendations, exact calliper position may still be difficult under some specific circumstances (e.g., obese patients, inadequate bowel preparation, vessel tortuosity, endoluminal thrombus), making its location not always easily recognisable. Besides calliper position, the level of maximum aortic plane acquisition and the AP diameter seem to be the most used, even though these choices did not derive from strong evidence.

Limitations

This systematic review has some limitations that should be acknowledged. The different quality of selected studies, particularly concerning single arm without control index test studies compared with those comparing two or three methods, as well as heterogeneity in baseline characteristics, settings, and operator expertise may have influenced the results. The GRADE report reflects the quality of the selected studies, which nonetheless highlight substantial differences in interobserver agreement between the different methods, though not statistically different. Nevertheless, future original investigations and consensus documents should explain their methods of abdominal aortic diameter measurement in detail and compare two or three methods rigorously.

Conclusion

In measuring maximum abdominal aortic diameters using US, an AP OTO and ITI calliper placement could be considered more reproducible than the LELE method. If studies published in 2010 or later are considered, LELE seems to be the most reproducible. Nevertheless, given the low certainty of evidence (GRADE) and the absence of statistically significant differences between the three methods, no robust recommendations can be provided regarding the superiority of one method over the other. While inherent differences between the methods need to be emphasised, further studies are needed to increase the certainty of the evidence and provide useful insight for future guideline recommendations, improving daily clinical practice.

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Part IV

Clinical perspectives on thoracic aortic disease

10

Five-year sex-related outcomes of thoracic endovascular aortic repair in the Global Registry for Endovascular Aortic Treatment☆

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ARTICLE HIGHLIGHTS

- **Type of research:** Multicenter, retrospective, observational cohort study of real-world data from the Global Registry for Endovascular Aortic Treatment
- **Key Findings:** Estimated freedom from 5-year sex-specific all-cause mortality is similar for 535 male (67.0%) and 270 female (65.9%) patients treated with thoracic endovascular aortic repair (TEVAR), irrespective of aortic disease type (P = .847).
- **Take Home Message:** Debate remains regarding the impact of sex on outcomes after thoracic endovascular aortic repair, and this study highlights no differences in the short- to long-term mortality and complication rates for males and females.

ABSTRACT

Objective: The impact of sex on outcomes of thoracic endovascular aortic repair (TEVAR) represents an area of increased interest over the last decade, and long-term data are lacking. The aim of the present study was to investigate sex-related differences in long-term outcomes after TEVAR using real-world data from the Global Registry for Endovascular Aortic Treatment.

Methods: Data were obtained retrospectively after querying the multicenter, sponsored Global Registry for Endovascular Aortic Treatment. Patients treated with TEVAR between December 2010 and January 2021 were selected regardless of the type of thoracic aortic disease. The primary outcome was sex-specific all-cause mortality at 5 years and maximum follow-up. Secondary outcomes were sex-specific all-cause mortality at 30 days and 1 year, and aorta-related mortality, major adverse cardiac events, neurological complications, and device-related complications or reinterventions at 30 days, 1 year, 5 years, and maximum follow-up.

Results: A total of 805 patients were analyzed; 535 (66.5%) were males. Females were older (median, 66 years [interquartile range (IQR), 57-75 years] vs 69 years [IQR, 59-78 years], P < .001). Males had more frequently a history of coronary artery bypass grafting and renal insufficiency (8.7% vs 3.7% [P = .010] and 22.4% vs 11.6% [P < .001]). The median follow-up was 3.46 years (IQR, 1.49-4.99 years) for males and 3.18 years (IQR, 1.29-4.86 years) for females. Indications for TEVAR were mostly descending thoracic aortic aneurysms (n = 307 [38.1%]) type B aortic dissections (n = 250 [31.1%]) or others (n = 248 [30.8%]). Freedom from 5-year all-cause mortality was similar for males and females (67% [95% CI, 62.1-72.2] vs 65.9% [95% CI, 58.5-74.2]; P = .847), and there were no differences in secondary outcomes. Multivariable Cox regression showed females to

have lower all-cause mortality rates; however, this difference did not reach statistical significance (hazard ratio, 0.97; 95% CI, 0.72-1.30; P = .834). Additional subgroup analyses based on the indication for TEVAR did not identify differences between both sexes for the primary and secondary outcomes except more endoleak type II in females with complicated type B aortic dissection (1.8% vs 12.1%; P = .023).

Conclusions: The present analysis suggests that long-term outcomes of TEVAR performed irrespective of the type of aortic disease are similar for males and females. Further studies are needed to clarify existing controversies regarding the impact of sex on outcomes of TEVAR.

INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) has become the first-line treatment for most thoracic aortic diseases according to the most recent European and Northern American clinical practice guidelines for cardiovascular surgery.[1-4] Over the last decade, there is a growing interest in evaluating sex-specific differences in in-hospital and longer term outcomes after endovascular aortic interventions.[5-7] Continuous research evaluating the outcomes of TEVAR for specific patient subgroups (eg, males, females) is important to identify characteristics that could be associated with increased morbidity and/or mortality.

Although earlier reports found similar short-, mid-, and longer-term mortality rates for both males and females,[8-11] more recent studies have reported higher short- and longer-term mortality rates in females after TEVAR.[12,13] When interpreting these studies, notable differences in study design should be emphasized. The analyses differ regarding the indications for TEVAR that are mostly intact descending thoracic aortic aneurysms (dTAAs)[9-13] or irrespective of the aortic disease.[8] Studies are performed as single-center or multicenter investigations with differing number of patients, using different stent graft types or generations. Three studies address short-term mortality rates (eg, 30 days, 1 year),[9,10,12] and another three studies report sex-specific outcomes up to the mid- and longer-term (eg, 2-5 years).[8,11,13] In general, there are few data reporting sex-specific outcomes of TEVAR in the long term.

The aim of the present study was to contribute to the existing evidence by reporting the sex-specific short- to long-term morbidity and mortality rates of patients treated with TEVAR and included in the Global Registry for Endovascular Aortic Treatment (GREAT), irrespective of the indication for intervention.

METHODS

Study design

This multicenter, retrospective, observational cohort study analyzed data obtained by the GREAT. The prospective, sponsored, multicenter, and observational GREAT cohort database was designed to obtain real-world data on performance and clinical outcomes of patients treated with W. L. Gore & Associates (Flagstaff, AZ) endovascular aortic products (Clinicaltrials.gov identifier number: NCT01658787). The objectives and design containing the precise inclusion and exclusion criteria of GREAT have been reported previously.[14]

In brief, data originate from the 114 participating centers (low- or high-volume, non-academic or academic) in Europe, Northern and Southern America, Australia, and New Zealand. Patients included in the registry are treated with Gore aortic stent grafts. Before participation, each local center must obtain institutional review board or ethics committee approval. Enrollment started in December 2010 and was finalized in October 2016. The target follow-up duration is aimed at 10 years. Local treating physicians decide on the indication for endovascular aortic repair, and patients treated with aortic stent grafts that are deployed outside the instructions for use, off-label, and for nonstandard indications, are included in the GREAT.

After signed informed consent for each patient, data are collected using an electronic case report form containing data on demographics, prior vascular interventions and imaging, indication for treatment, aortic stent graft(s) used, adverse events, and survival. Consequently, an internet-based electronic data capture system (Medidata Solutions Worldwide, New York, NY) is used to manage the data forms.

Patient selection

The GREAT database was queried retrospectively to obtain data on all patients included in the database and treated with TEVAR, irrespective of the type of aortic disease. Next, patients were divided in a male and female subgroup and analyzed as such. Patients were treated with one or multiple Gore TAG (TAG) thoracic endoprostheses or Conformable Gore TAG (CTAG) thoracic endoprostheses (W. L. Gore & Associates, Inc., Newark, DE). Data regarding demographics, medical history, details regarding the aortic indication for intervention, chronicity of the aortic pathology, follow-up, procedural details, and outcomes were collected.

Outcomes

The primary outcome was sex-specific all-cause mortality at 5 years and maximum follow-up. Secondary outcomes were sex-specific all-cause mortality at 30 days and 1 year, and aorta-related mortality, major adverse cardiac events, neurological complications (eg, cerebrovascular accident [CVA]; transient ischemic attack [TIA]; paraplegia, paraparesis, or spinal cord ischemia as one group), device- or procedure-related severe adverse event14 (eg, endoleak [type I-IV], migration, fracture, compression), or device-related reinterventions (eg, conversion to open repair) at 30 days, 1 year, 5 years, or maximum follow-up.

Follow-up was divided into 30-day, 1-year, 5-year, and maximum follow-up. During the analysis of the primary and secondary outcomes, no distinction was made between elective or emergent treatments and complicated or uncomplicated pathology. The

focus of the analysis was on overall differences between males and females. Ultimately, we performed stratified subgroup analyses based on the indication for TEVAR if there was a minimum cohort size of >50 (ie, dTAA, complicated and uncomplicated type B aortic dissection, penetrating atherosclerotic ulcer, and traumatic aortic transection). All primary and secondary outcomes were evaluated to check for eventual sex-specific differences for single thoracic aortic disease subgroups.

Statistical analysis

The GREAT database is managed by the Gore Clinical Research Department, and therefore, not accessible to the authors. After this specific project proposal and corresponding analysis requests, data were made available to the authors. Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) where appropriate. Normality checks were performed by visual inspection of the histograms. Categorical variables are presented as number (%). Comparisons between the male and female cohorts for the different variables were performed using Fisher's exact test, Wilcoxon rank-sum test, or Pearson's $\chi 2$ test where appropriate. Survival analysis was applied for the sex-specific follow-up outcomes. Multivariable Cox regression was performed to investigate the effect of sex on all-cause mortality after adjusting for covariates. Predefined covariates included age, race, history of smoking, diabetes, and renal insufficiency. Overfitting was prevented by avoiding covariates with low numbers. Multivariable Cox regression was also performed for the mentioned disease-specific subgroups based on the indication for TEVAR. Two-sided P values of <.050 were considered statistically significant.

RESULTS

Patient characteristics

Eight-hundred five eligible patients were identified after querying the GREAT database; 535 patients were male (66.5%) and 270 patients were female (33.5%). Females were older than males at intervention (median, 66 years [IQR, 57-75 years] vs 69 years [IQR, 59-78 years]; P < .001). There were no statistically significant differences in body mass index, race, or smoking between males and females. Males had more coronary artery bypass grafting and renal insufficiency in their medical history (male, 8.7% vs female, 3.7% [P = .010] and male, 22.4% vs female, 11.6% [P < .001]). The remaining medical history variables were equally distributed between the sexes (Table I). The median maximum follow-up was 3.46 years (IQR, 1.49-4.99 years) for males and 3.18 years (IQR, 1.29-4.86 years) for females.

Table I. Baseline characteristics of 805 patients treated with thoracic endovascular aortic repair (TEVAR), irrespective of specific aortic disease type and stratified for sex

Variable	Male (n = 535)	Female (n = 270)	*P* value[a]
Age, years	66 (55-73)	69 (59-78)	**<.001**
BMI, kg/m^2	27.0 (24.6-30.4)	26.4 (23.4-30.7)	.061
Race			.189
White or Caucasian	384/535 (71.8)	202/270 (74.8)	
Black or African American	78/535 (14.6)	42/270 (15.6)	
Asian/Oriental	9/535 (1.7)	6/270 (2.2)	
American Indian or Alaskan Native	1/535 (0.2)	3/270 (1.1)	
Other	28/535 (5.2)	6/270 (2.2)	
Unknown	29/535 (5.4)	10/270 (3.7)	
Days to last contact	1315 (651-1826)	1195 (604-1741)	.244
Tobacco use	258/499 (51.7)	119/257 (46.3)	.160
Medical history			
Hypertension	447/531 (84.2)	218/268 (81.3)	.311
Hypercholesterolemia	228/518 (44.0)	119/260 (45.8)	.642
Stroke	40/530 (7.5)	18/266 (6.8)	.690
Transient ischemia attack	18/528 (3.4)	12/263 (4.6)	.424
Carotid disease	39/509 (7.7)	18/261 (6.9)	.701
Coronary artery disease	128/525 (24.4)	54/265 (20.4)	.207
Congestive heart failure	45/525 (8.6)	20/267 (7.5)	.600
Coronary artery bypass graft	46/529 (8.7)	10/268 (3.7)	**.010**
Chronic obstructive pulmonary disease	92/529 (17.4)	54/266 (20.3)	.317
Diabetes mellitus	67/532 (12.6)	37/266 (13.9)	.603
Renal insufficiency	119/531 (22.4)	31/267 (11.6)	**<.001**
Renal dialysis	14/529 (2.6)	5/267 (1.9)	.499
Peripheral vascular disease	64/525 (12.2)	30/265 (11.3)	.721
Valvular heart disease	52/527 (9.9)	32/266 (12.0)	.350
Cardiac arrhythmia	93/530 (17.5)	44/267 (16.5)	.706
Thromboembolic event	23/525 (4.4)	13/267 (4.9)	.755
Paraplegia	5/529 (0.9)	2/268 (0.7)	>.999
Paraparesis	4/531 (0.7)	1/268 (0.4)	.669
Erectile dysfunction (male only)	15/306 (4.9)	NA	NA
Cancer	52/527 (9.9)	32/266 (12.0)	.686
Degenerative connective tissue disease	10/522 (1.9)	10/265 (3.8)	.118

BMI, Body mass index; *NA*, not applicable.

Boldface entries indicate statistical significance.

[a] Fisher's exact test, Wilcoxon rank-sum test, or Pearson's $\chi 2$ test. Data reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables.

Indications for TEVAR

Most indications for TEVAR were for dTAAs (n = 307 [38.1%]), complicated type B (n = 147 [18.2%]), and uncomplicated type B aortic dissections (n = 103 [12.8%]). There were significantly more dTAAs among females (male, 34.8% vs female, 48.9%; P < .001), whereas complicated and uncomplicated type B aortic dissections were more present among males (male, 21.3% vs female, 12.2% [P < .001] and male, 15.3% vs female, 8.5% [P = .002]), as well as traumatic aortic transections (male, 7.5% vs female, 3.7%; P = .036). The maximum diameters of the aortic aneurysm and changes in lesion size over time were not statistically different between the sexes, except for larger dTAAs in males at 5 years of follow-up (male, 56.5 [range, 33.0-104] vs female, 45.0 [range, 33.0-98]). Further detailed information regarding the specific aortic indications for TEVAR and distribution by aortic segment are summarized in Table II.

Table II. Indications for thoracic endovascular aortic repair (TEVAR) of 805 patients irrespective of specific aortic disease type and stratified for sex

Variable	Male (n = 535)	Female (n = 270)	*P* value[a]
Indication for surgery (treated pathology)			
dTAA	175 (34.8)	132 (48.9)	**<.001**
Complicated type B aortic dissection	114 (21.3)	33 (12.2)	**.002**
Uncomplicated type B aortic dissection	82 (15.3)	21 (7.8)	**.002**
Penetrating aortic ulcer	47 (8.8)	30 (11.1)	.3
Traumatic aortic transection	40 (7.5)	10 (3.7)	**.036**
Multiple pathologies	18 (3.4)	8 (3.0)	.8
Aortic arch aneurysm	18 (3.4)	7 (2.6)	.6
Pseudoaneurysm	13 (2.4)	4 (1.5)	.4
dTAA rupture	7 (1.3)	9 (3.3)	.052
Intramural hematoma	6 (1.1)	7 (2.6)	.14
Aortic coarctation	3 (0.6)	5 (1.9)	.6
Descending aortic dissection rupture	6 (1.1)	1 (0.4)	.4
Aortic arch aneurysm rupture	3 (0.6)	1 (0.4)	>.9
Aortobronchial fistula	1 (0.2)	1 (0.4)	>.9
Traumatic aortic dissection	2 (0.4)	0 (0)	.6
Aortoesophageal fistula	0 (0)	1 (0.37)	.3
Aortic segment			.671
Ascending	2 (0.4)	0 (0)	
Arch	40 (7.5)	23 (8.5)	
Descending	493 (92.1)	247 (91.5)	

dTAA, Descending thoracic aortic aneurysm.
Boldface entries indicate statistical significance.
[a] Fisher's exact test or Pearson's $\chi 2$ test. Data reported as number (%) for categorical variables.

Table III. Stent graft and procedure details of 805 patients treated with thoracic endovascular aortic repair (TEVAR) irrespective of specific aortic disease type and stratified for sex

Variable	Male	Female	*P* value[a]
Device group			.923
TAG device	53 (9.9)	24 (8.9)	
CTAG device	475 (88.8)	243 (90.0)	
Other device combination	7 (1.3)	3 (1.1)	
Chimney proc	13 (2.4)	6 (2.2)	.855
Off-label use[b]	268 (50.1)	133 (49.3)	.823
Off indication[b]	131 (25.6)	71 (26.3)	.576
Off direction[b]	137 (25.6)	62 (23.0)	.412
Incorrect proximal diameter	66 (12.3)	31 (11.5)	.725
Incorrect distal diameter	113 (21.1)	54 (20.0)	.711
Insufficient PLZ[c]	100 (18.7)	47 (17.4)	.656
Extremely insufficient PLZ[c]	40 (7.5)	17 (6.3)	.538
Unapproved pathology[d]	21 (3.9)	9 (3.3)	.676
Procedure to discharge, days	7 ± 8	8 ± 10	.763
Access site(s)			
Femoral	518 (96.8)	249 (92.2)	**.004**
Iliac	518 (2.4)	23 (8.5)	**<.001**
Infrarenal	0 (0)	2 (0.7)	.112
Brachial	28 (96.8)	15 (5.6)	.848
Other	18 (96.8)	13 (4.8)	.313
Access method(s)			
Percutaneous	235 (43.9)	137 (50.7)	.067
Cut down	357 (66.7)	173 (64.1)	.453
Surgical conduit	19 (3.6)	23 (8.5)	**.003**
Endovascular conduit	19 (3.6)	23 (8.5)	**.003**

CTAG, Conformable Gore TAG; *PLZ*, proximal landing zone; *TAG*, Gore TAG.

Data reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables.

[a] Fisher's exact test, Wilcoxon rank-sum test, or Pearson's $\chi 2$ test.

[b] Unapproved pathology or location refers to deployment outside of the instructions for use.

[c] Subjects are considered treated off-label if there is device sizing not matching directions for use (ie, off direction) or there is device usage outside of instructions for use (ie, off indication), which includes improper anatomy or vessel measurements outside device treatable range, improper device placement, treatment of an unapproved pathology, a lack of necessary and compatible pieces, revision of a previously placed stent, chimney procedures, or evidence of significant calcification or thrombus.

[d] Insufficient: <2 cm landing zone; extremely insufficient: <1.5 cm landing zone.

Stent graft and procedure details

Table III summarizes the stent graft and procedure details stratified for sex. The use of one or multiple TAG, CTAG devices, and/or chimney procedures was equally distributed among males and females. In total, almost one-half of TEVAR device deployments (n = 401 [49.8%]) were performed off-label, and 30 of those patients (3.7%) were performed on unapproved pathologies. Off-label (ie, off-indication, off-direction) (Table III) uses were equally distributed among males and females (P = .576 and P = .412). Access sites were more frequently femoral for males (male, 96.8% vs female, 92.2%; P = .004) and iliac for females (male, 2.4% vs female, 8.5%; P < .001). Regarding access method, percutaneous access was more frequently used in females, however, without a significant difference between the sexes (male, 43.9% vs female, 50.7%; P = .067). Surgical and endovascular conduits were also more frequently used in females (surgical: male, 3.6% vs 8.5% [P = .003]; endovascular: male, 3.6% vs female, 8.5% [P = .003]).

Table IV summarizes the primary and secondary outcomes for both sexes. Estimated freedom from all-cause mortality for males at 1-year and 5-years follow-up was 86.9% (95% CI, 84.0-89.9) and 67.0% (95% CI, 62.1-72.2), respectively (Fig 1). For females, the estimated freedom from all-cause mortality at 1 year and 5 years of follow-up was 89.9% (95% CI, 86.2-93.6) and 65.9% (95% CI, 58.5-74.2), respectively (Fig 1). There was no significant difference in all-cause mortality rates between males and females (P = .847) (Fig 1). Multivariable Cox regression showed females to have lower all-cause mortality rates; however, this difference was not statistically significant (HR, 0.97; 95% CI, 0.72-1.30; P = .834). At the same time, patients at older age, with Black race, or with renal insufficiency did have significantly higher all-cause mortality rates (HR, 1.05 [95% CI, 1.04-1.07; P < .001]; HR, 1.56 [95% CI, 1.08-2.26; P = .017]; and HR, 1.70 [95% CI, 1.25-2.31; P < 001], respectively). Supplementary Table (online only) summarizes the results of multivariable Cox regression for all-cause mortality.

Estimated freedom from aorta related mortality for males at 1 year and 5 years of follow-up was 96.9% (95% CI, 95.4-98.4) and 94.0% (95% CI, 91.3-96.7), respectively (Fig 2). For females, the estimated freedom from aorta related mortality at 1 year and 5 years of follow-up was 96.2% (95% CI, 93.9-98.5) and 93.6% (95% CI, 89.6-97.6), respectively. There was no significant difference in aorta related mortality rates between males and females (P = .549) (Fig 2).

Regarding the secondary outcomes, there were no significant differences between the sexes for aortic rupture (P = .760), major adverse cardiac events (P = .865), CVA/TIA (P = .698), device- or procedure-related severe adverse events (P = .134), device-related reintervention (P = .400), paraplegia, paraparesis, or spinal cord ischemia (P = .569), conversion to open repair and/or explant (P = .238), any endoleak (P = .615), type Ia en-

Table IV. Outcomes of 805 patients treated with thoracic endovascular aortic repair (TEVAR), irrespective of specific aortic disease type and stratified for sex

Variable	Male	Female	*P* value[a]
All-cause mortality	141 (26.4)	70 (25.9)	.896
30-Day aorta related mortality[b]	9 (1.7)	7 (2.6)	.382
1-Month aorta related mortality[b]	12 (2.2)	8 (3.0)	.536
365-Day aorta related mortality[b]	16 (3.0)	10 (3.7)	.589
1-Year aorta related mortality[b]	16 (3.0)	10 (3.7)	.589
Aortic rupture	9 (1.7)	3 (1.1)	.760
MACE (no TIA)	34 (6.4)	18 (6.7)	.865
Stroke/TIA	25 (4.7)	11 (4.1)	.698
Paraplegia/paraparesis/spinal cord ischemia	8 (1.5)	6 (2.2)	.569
All reinterventions	85 (15.9)	49 (18.1)	.416
Conversion to open repair and/or explant	11 (2.1)	2 (0.7)	.238
Additional graft	27 (5.0)	13 (4.8)	.886
Other procedure/surgery	60 (11.2)	35 (13.0)	.468
Device/procedure-related SAE	88 (16.4)	56 (20.7)	.134
Device/procedure-related reintervention	85 (15.9)	49 (18.1)	.416
Device-related reintervention	62 (11.6)	26 (9.6)	.400
Any endoleak	43 (8.0)	19 (7.0)	.615
Endoleak I[a]	13 (2.4)	5 (1.9)	.600
Endoleak I[b]	15 (2.8)	5 (1.9)	.413
Endoleak II	12 (2.2)	7 (2.6)	.758
Endoleak III	2 (0.4)	1 (0.4)	>.999
Endoleak IV	0 (0)	0 (0)	N/A
Migration	2 (0.4)	0 (0)	.554
Fracture	0 (0)	0 (0)	N/A
Compression	1 (0.2)	0 (0)	>.999

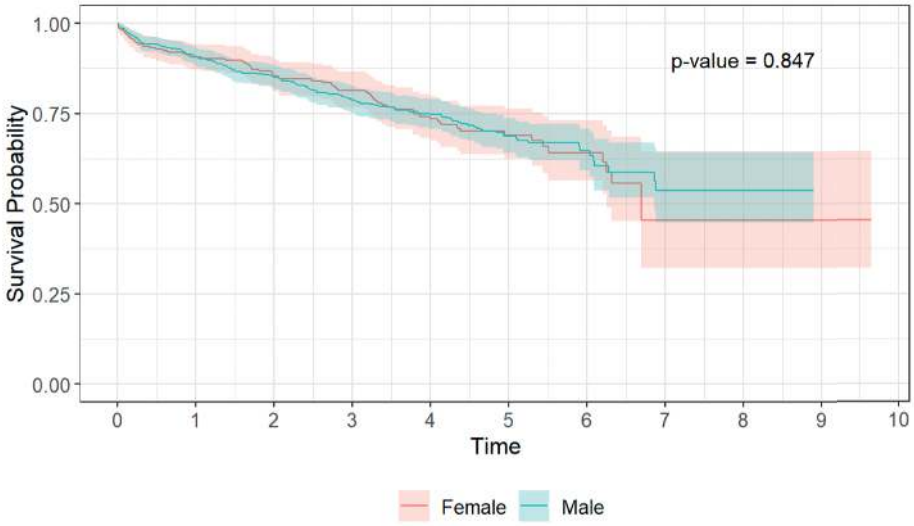
MACE, Major adverse cardiac event; *SAE*, severe adverse event; *TIA*, transient ischemic attack.

Data reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables.

[a] Fisher's exact test or Pearson's $\chi 2$ test.

[b] Unapproved pathology or location refers to deployment outside of the instructions for use.

[c] GREAT Reporting windows by days since procedure: 1 month, 0-59; 6 months, 60-240; 1 year, 241-545; 2 years, 546-910; 3 years, 911-1276; 4 years, 1277-1641; 5 years, 1642-2006; 6 years, 2007-2371; 7 years, 2372-2736; 8 years, 2737-3101; 9 years, 3102-3466; and 10 years, 3467-3831.

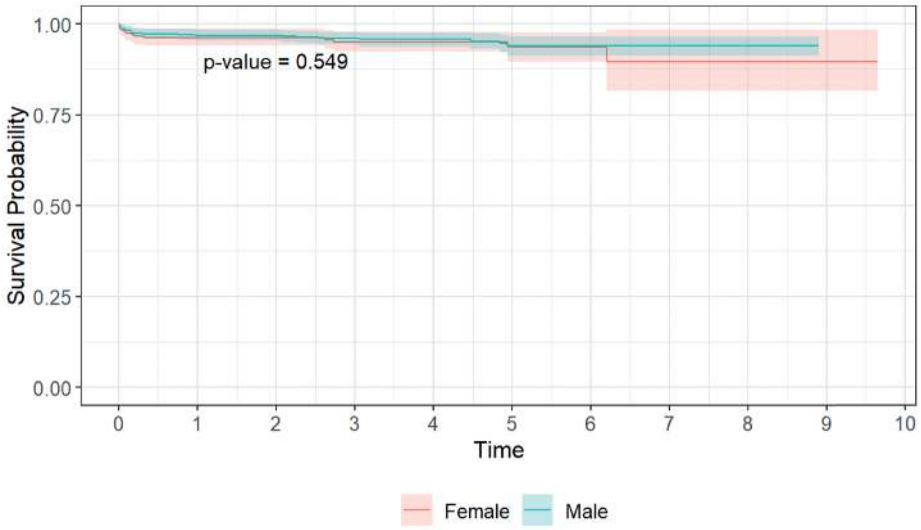


Female											
At Risk	270	220	187	151	101	56	26	5	3	2	0
Events	0	24	36	44	57	62	65	70	70	70	70
Male											
At Risk	535	442	385	309	235	134	47	16	6	0	0
Events	1	46	73	100	115	130	135	141	141	141	141

Figure 1. Kaplan-Meier graph showing freedom from all-cause mortality over time of the 805 patients treated with thoracic endovascular aortic repair (TEVAR), irrespective of specific aortic disease type and stratified for sex.

doleak (P = .600), type Ib endoleak (P = .413), type II endoleak (P = .758), type III endoleak (P = 1), type IV endoleak (P = 1), or migration, fracture, or compression (P = .554, P = 1, or P = 1) (Table IV). Kaplan-Meier graphs showing the estimated freedom from aortic rupture, major adverse cardiac events, and CVA/TIA can be found in the Supplementary Fig 1 (online only), Supplementary Fig 2 (online only), Supplementary Fig 3 (online only) (online only).

The results of the thoracic aortic disease-specific subgroup analyses did not reveal significant differences between both sexes for the primary outcome and disease-specific multivariable Cox regression found females to have lower all-cause mortality rates; however, this difference was not statistically significant. For the secondary outcomes, there were only more endoleak type II in females with complicated type B aortic dissection (male, 2/114 [1.8%], female, 4/33 [12.1%]; P = .023). There were no differences in secondary outcomes in any of the other disease-specific subgroup analyses between the sexes.



Female											
At Risk	270	220	187	151	102	56	26	5	3	2	0
Events	0	10	10	12	12	13	13	14	14	14	14
Male											
At Risk	535	443	386	310	235	134	47	16	6	0	0
Events	1	16	16	19	20	23	23	23	23	23	23

Figure 2. Kaplan-Meier graph showing freedom from aortic related mortality over time of the 805 patients treated with thoracic endovascular aortic repair (TEVAR), irrespective of specific aortic disease type and stratified for sex.

DISCUSSION

The present study used real-world data from patients enrolled in the GREAT database who underwent TEVAR to investigate potential differences in the short- and long-term clinical outcomes between males and females. The main findings showed no differences in the short- and long-term regarding all-cause mortality, aorta-related mortality, or the remaining secondary outcomes between both sexes, even though females were older. The cohort included patients who underwent TEVAR, irrespective of the type of aortic disease; disease-specific subgroup analyses could not identify differences in the primary and secondary outcomes between the sexes, except that there were more endoleak type II in females with complicated type B aortic dissection.

The present registry observed a higher percentage of dTAAs among females (male, 34.8 vs female, 48.9%; P < .001), whereas a previous population-based study found

a male:female ratio of 1.7:1.0 in the occurrence of TAAs.[15] In contrast, complicated, uncomplicated type B aortic dissections, and traumatic aortic transections were more common in males (complicated: male, 21.3 vs female, 12.2% [P < .001]; uncomplicated: male, 15.3% vs female, 7.8% [P = .002]; traumatic aortic transection: male, 7.5% vs female, 3.7% [P = .036]). The age of occurrence of the thoracic aortic diseases included in this study was higher for females (median, 66 years [IQR, 57-75 years] vs 69 years [IQR, 59-78 years]; P < .001), and this finding does concur with the higher age of dTAA occurrence in females as observed in the previously mentioned population-based study (median 65 years [males] vs median 77 years [females]).[15]

Given that the incidence of thoracic aortic diseases is higher in males than females in general,[16] it remains challenging to analyze large cohorts of female patients who undergo TEVAR. Regarding abdominal aortic disease, abdominal aortic aneurysm (AAA) or abdominal aortic dissection, the prevalence is also higher in males as compared with females.[17,18] This aspect is also reflected by the higher percentage of males (66.5%) undergoing TEVAR in the present study. In this regard, the importance of national or international collaborative registries like GREAT and International Registry of Acute Aortic Dissection needs to be underlined, because they can gather data from larger cohorts of patients with thoracic aortic diseases and provide insight into these diseases that have a low incidence in general. A report from the International Registry of Acute Aortic Dissection[19] already highlighted an increased in-hospital mortality after type A aortic dissection in females, potentially owing to a differing clinical presentation and later recognition. Fewer females received surgical management of their type A aortic dissection, as compared with males.[19]

In this study, females had more frequent iliac access sites (male, 2.4% vs female, 8.5%; *P* < .001) and conduits were more frequently used (surgical: male, 3.6% vs female, 8.5% [*P* = .003]; endovascular: male, 3.6% vs female, 8.5%; *P* = .003). A previous sex-specific outcome analysis using data from patients enrolled in GREAT that underwent TEVAR (largely the same cohort as in the present study) highlighted a potential increased risk of access complications in females, irrespective of aortic disease type, clinical setting, or device size (eg, TAG or CTAG).[20] This factor has also been observed in females undergoing EVAR.[10,13] Another recent sex-specific GREAT analysis using data from patients who underwent EVAR with the Gore Excluder endograft (W. L. Gore & Associates, Inc., Newark, DE) found that females more often had more complex morphological aneurysm characteristics as compared with males.[21] This factor led to higher rates of reinterventions without increases in mortality.[21] A sex-specific analysis in a large cohort of patients with an AAA from the Vascular Quality Initiative that underwent either open surgical repair or EVAR has also highlighted unfavorable neck characteristics and an increased

risk of major complications in females, together with a 50% increased risk of 30-day mortality.[22] In contrast, single-center analyses of patients who underwent elective EVAR found similar longer term mortality rates in males and females, although females did present with more postoperative complications as well.[23,24] Nevertheless, two recent meta-analyses, one combining the sex-specific results of open surgical AAA repair and EVAR[6] and one comparing the sex-specific results of complex EVAR,[7] found consistently more adverse events in females accompanied by higher short-term mortality rates.

There are also studies evaluating sex-specific differences in outcomes after other cardiovascular interventions such as percutaneous coronary interventions or coronary artery bypass grafting. A meta-analysis published in 2007 reported greater in-hospital mortality and more complications for females after both interventions.[25]

Theoretically, potential explanations of differences between males and females in outcomes of cardiovascular disease may be explained by differences in aortic diameter or access vessel sizes between males and females, that are generally smaller for females, as well as the older age of thoracic aortic disease occurrence observed in females.[13,20] Changes in hormonal status with advancing age in females may cause an increased aortic stiffening in females,[26] which has also been associated with an increased thoracic aneurysm growth in females.[27] A previous experimental study in a rodent model has highlighted sex-specific differences in AAA development mediated by hormonal changes that may lead to alterations in macrophages and matrix metalloproteinases.[28] Altogether, such sex-specific differences are most likely multifactorial. As discussed elsewhere in this article, our results contrast with the results of previous analyses that found increased short- and longer-term mortality rates for females,[12,13] although they are in line with other studies evaluating short-, mid-, and longer-term TEVAR outcomes stratified by sex.[8-11]

Future perspectives

To smoothen the existing controversies regarding the sex-specific outcomes after TEVAR, future studies are needed on large cohorts of patients, especially females. A meta-analysis of the available studies regarding TEVAR outcomes stratified by sex may provide a combined estimate for specific outcomes. Obtaining larger number of patients to analyze TEVAR outcomes stratified by sex and specific aortic diseases, as attempted in the present study, remains challenging given the lower incidence of thoracic aortic disease for females. Nevertheless, studies with larger patient cohorts in the disease-specific subgroups are needed to provide more definitive concluding statements for these aortic diseases.

Limitations

Some limitations are inherent to the retrospective, observational nature of the GREAT. The relatively large number of patients as compared with other studies evaluating TEVAR outcomes between both sexes did not persist in the disease-specific subgroup analyses, because incidences are low and these specific sample sizes and event rates may have been too low to detect potential differences between both sexes. Moreover, GREAT analyzes patients treated with only two thoracic aortic stent grafts, TAG and CTAG. Such aspects challenge the comparison of the present outcomes with the literature, given the heterogeneity in study designs and outcomes between studies.

CONCLUSIONS

The present multicenter, retrospective, observational cohort study analyzed data from patients who underwent TEVAR, irrespective of the type of aortic disease, and enrolled in GREAT. The sex-specific outcome analysis showed that males and females have similar all-cause mortality rates at 5 years of follow-up. Moreover, short-term all-cause mortality, aorta-related mortality, major adverse cardiac events, neurological complications, and device-related complications or reinterventions were similar between both sexes at both short- and longer-term follow-up intervals. Except for more type II endoleaks in females with complicated type B aortic dissection, thoracic aortic disease-specific subgroup analyses based on the indication for TEVAR did not identify differences between both sexes regarding the primary and secondary outcomes.

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Surgeon volume and outcomes following thoracic endovascular aortic repair for blunt thoracic aortic injury☆

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ARTICLE HIGHLIGHTS

- **Type of research:** Multicenter, retrospective, observational cohort study of real-world data in the Vascular Quality Initiative (VQI).
- **Key Findings:** In 1,321 patients undergoing TEVAR for BTAI, higher surgeon volume was independently associated with lower perioperative mortality and postoperative stroke, the latter persisting in non-ruptured BTAI alone, and regardless of hospital volume.
- **Take Home Message:** In patients undergoing TEVAR for BTAI, higher surgeon volume is independently associated with lower perioperative mortality and postoperative stroke, the latter persisting in non-ruptured BTAI alone, and regardless of hospital volume.

ABSTRACT

Objective: Thoracic endovascular aortic repair (TEVAR) for blunt thoracic aortic injury (BTAI) at high-volume hospitals has previously been associated with lower perioperative mortality, but the impact of annual surgeon volume on outcomes following TEVAR for BTAI remains unknown.

Methods: We analyzed Vascular Quality Initiative (VQI) data from patients with BTAI that underwent TEVAR between 2013-2023. Annual surgeon volumes were computed as the number of TEVARs (for any pathology) performed over a one-year period preceding each procedure and were further categorized into quintiles. Surgeons in the first volume quintile were categorized as low-volume (LV), the highest quintile as high-volume (HV), and the middle three quintiles as medium-volume (MV). TEVAR procedures performed by surgeons with less than one-year enrollment in the VQI were excluded. Using multi-level logistic regression models, we evaluated associations between surgeon volume and perioperative outcomes, accounting for annual center volumes and adjusting for potential confounders including aortic injury grade and severity of coexisting injuries. Multilevel models accounted for the nested clustering of patients and surgeons within the same center. Sensitivity analysis excluding Grade IV BTAI patients was performed.

Results: We studied 1,321 patients who underwent TEVAR for BTAI (28% by LV surgeons [0-1 procedures per year], 52% by MV surgeons [2-8 procedures per year], 20% by HV surgeons [≥9 procedures per year]). With higher surgeon volume, TEVAR was delayed more (in <4 hours: LV: 68%, MV: 54%, HV: 46%, p<.001; elective (>24 hours): LV: 5.1%; MV: 8.9%: HV: 14%), heparin administered more (LV: 80%, MV: 81%, HV: 87%, p=.007),

perioperative mortality appears lower (LV: 11%, MV: 7.3%, HV: 6.5%,p=.095), and ischemic/hemorrhagic stroke was lower (LV: 6.5%, MV: 3.6%, HV: 1.5%,p=.006). After adjustment, compared with LV surgeons, higher volume surgeons had lower odds of perioperative mortality (MV: 0.49[95%C.I.:0.25–0.97],p=.039; HV: 0.45[0.16–1.22],p=.12; MV/HV: 0.50[0.26-0.96],p=.038) and ischemic/hemorrhagic stroke (MV: 0.38[0.18–0.81],p=.011; HV: 0.16[0.04–0.61],p=.008). Sensitivity analysis found lower adjusted odds for perioperative mortality (although not significant) and ischemic/hemorrhagic stroke for higher volume surgeons.

Conclusions: In patients undergoing TEVAR for BTAI, higher surgeon volume is independently associated with lower perioperative mortality and postoperative stroke, regardless of hospital volume. Future studies could elucidate if TEVAR for non-ruptured BTAI might be delayed and allow stabilization, heparinization, and involvement of a higher TEVAR volume surgeon.

INTRODUCTION

Previous studies have highlighted inverse relationships between hospital volume and surgical mortality, which supported the centralization of cardiovascular surgical care to higher volume hospitals.[1,2] It has however been shown that annual surgeon volume largely mediated the lower mortality rates observed in higher volume hospitals.[3]

Prior studies analyzing hospital and vascular surgeon volume related outcomes have largely focused on abdominal aortic aneurysm (AAA) repairs, both open and endovascular. While many of these studies have focused on either hospital[4-7] or surgeon volumes[8-11], a combination of both has been considered in more recent studies[12-16] as well. Fewer studies have focused on thoracic aortic diseases, but the impact of hospital and/or surgeon volume on surgical outcomes has also been investigated in the context of intact open thoracoabdominal aneurysm repairs (lower in-hospital mortality with higher volume hospitals and surgeons)[17], open and thoracic endovascular repair (TEVAR) of descending thoracic aortic aneurysm (open: lower 30-day mortality and 6-year survival with higher volume hospitals; TEVAR: no association)[18], open repair and TEVAR of aortic dissection (open: lower in-hospital mortality with higher volume hospitals; TEVAR: no association)[19], and aortic root replacements (lower 30-day mortality with higher volume hospitals and surgeons).[20]

With TEVAR now being the primary treatment option for most thoracic aortic diseases[21], only a small number of studies have investigated hospital and surgeon volume related outcomes after TEVAR.[18,19,22-26] Two of these studies investigated surgeon volume related outcomes after TEVAR for aortic dissections and thoracic aortic aneurysms, and did not find it to be associated with perioperative and 5-year mortality.[22,26]

In the setting of TEVAR for blunt thoracic aortic injury (BTAI) specifically, striving to achieve optimal clinical outcomes by insights from such analyses seems of the utmost importance, given the often life-threatening nature of BTAI and its occurrence in young and healthy patients. A previous study found lower perioperative mortality after TEVAR for traumatic aortic injuries in higher volume centers and found trauma specific TEVAR center volumes to be more relevant than overall TEVAR center volumes.[24] However, the impact of surgeon volumes has not yet been studied in this context. In this study, we analyzed perioperative outcomes of TEVAR for BTAI, stratified by annual surgeon volume and accounting for center volumes.

METHODS

Study design and data source

This is a retrospective observational cohort study using prospectively collected data from the TEVAR/Complex EVAR module of the Society for Vascular Surgery Vascular Quality Initiative (SVS-VQI) registry (http://www.vqi.org/). The module includes 199 centers and variables pertaining to patient demographics, anatomical characteristics, procedural characteristics, in-hospital outcomes, and long-term mortality data obtained by linkage with the Social Security Death Index. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[27] and has been approved by the Beth Israel Deaconess Medical Center Institutional Review Board (2021P000131). Patients' informed consent was waived due to the retrospective and de-identified nature of the data utilized for this study.

Surgeon and center volumes

For computing surgeon and center volumes, we merged the TEVAR/Complex EVAR module with the EVAR module of the SVS-VQI. Of all procedures in the merged dataset, we identified 17,043 repairs that involved the thoracic aorta (proximal landing zone ≤5) during the period 2013-2023, after exclusion of 3,933 repairs with missing data for proximal landing zone. These repairs were included in computing annual surgeon volumes, and thus included endovascular repairs extending into the abdominal aorta (distal landing zone >5). All pathologies and urgency categories were included in this computation, and surgeons were identified using the unique identification numbers that are consistent across the dataset. Surgeon volume was assessed for the 365 days prior to each procedure and when data for the 365 days prior to procedure were not available, we excluded the procedures from the analysis. Thus, surgeons had to be enrolled in at least one of the modules for a minimum of one year before their TEVAR procedure for BTAI to be included in the analyses. Merging both modules allowed us to include procedures performed by surgeons without one year enrollment in the TEVAR/Complex EVAR module, but with enrollment in the EVAR module for more than one year.

Center volumes were calculated in a similar fashion and were analyzed for overall TEVAR cases (for any pathology, proximal landing zone ≤5) as well. Since prior literature has suggested that the thoracic aortic trauma volume at a center was more predictive than the overall TEVAR volume of the center for perioperative mortality after TEVAR for BTAI, we tested for this (also for trauma-TEVAR specific surgeon volume) but we did not find an association between trauma-TEVAR volumes and outcomes in our cohort.[24] Therefore, we included overall TEVAR center (and surgeon) volumes in our final models.

Study cohort

Of all procedures in the TEVAR/Complex EVAR module as of May 2023 (n = 25,862), we identified those patients with BTAI who underwent TEVAR (n = 1,769). Patients with a proximal or distal landing zone <2 or >5 (n = 89), <18 years (n = 41), with missing data for SVS aortic injury grade (n = 67), and without adequate data (i.e., 365 days enrollment in either the TEVAR/Complex EVAR or EVAR module) to compute annual surgeon volume (n = 251), were excluded from the analyses (**Figure S1**).

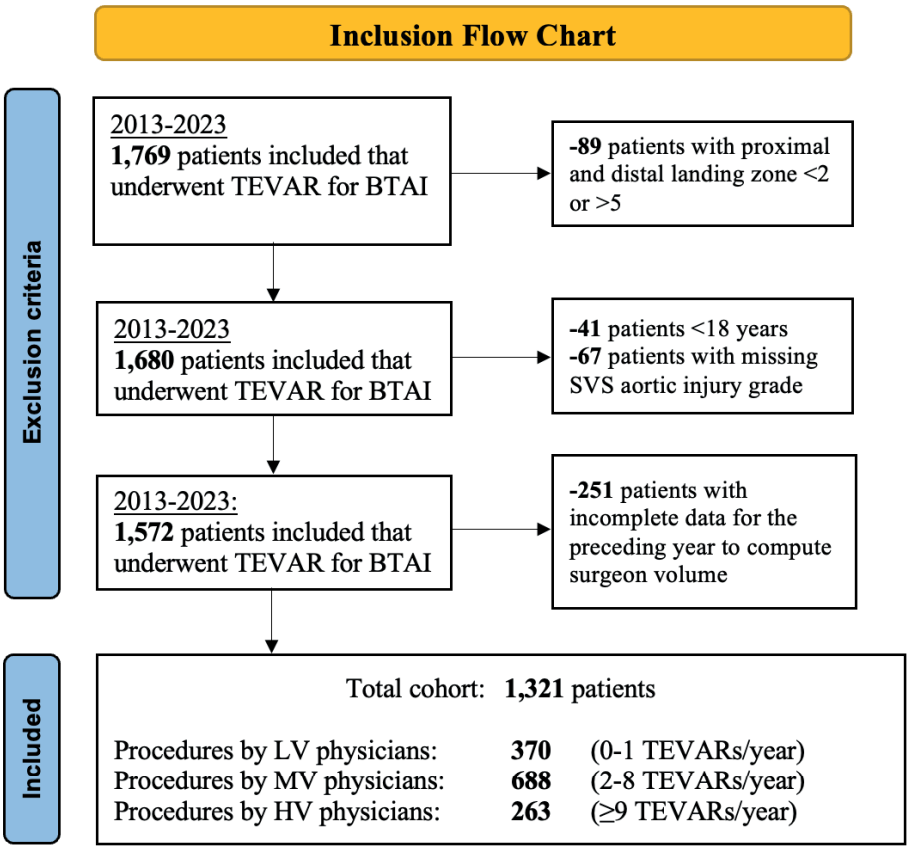

Figure S1. Flow chart of patient inclusion form the TEVAR/Complex EVAR module of the Vascular Qualitative Initiative (VQI) Registry.

Surgeon and center volumes categorization

Volumes were divided into quintiles for ease of interpretation.[14] To maximize the observed differences and minimize type I errors from multiple comparisons, we further grouped the quintiles into low volume (LV), medium volume (MV), and high volume (HV).

Surgeons in the first volume quintile were considered as LV (0-1 TEVAR procedures) and the highest quintile as HV (≥9 procedures), with the middle three quintiles categorized as MV (2-8 procedures) (**Figure S1**). Similarly, centers in the first volume quintile were considered as LV (0-9 procedures) and the highest quintile as HV (≥43 procedures), with the middle three quintiles categorized as MV (10-42 procedures).

Variables and definitions

We identified baseline patient characteristics (i.e., demographics, comorbidities), coexistent injuries, procedural and anatomical characteristics, and perioperative outcomes (i.e., overall mortality, aortic related mortality, major complications during index hospitalization). Perioperative mortality was defined as death due to any cause occurring within 30 days or during index hospitalization if the primary admission exceeded 30 days. Within the in-hospital deaths, aortic related mortality was defined by the VQI as deaths related to the disease or treatment or any complication occurring during the in-hospital period. New postoperative stroke was categorized into ischemic/hemorrhagic events and ischemic events alone. LSA management was categorized into covered/occluded, endovascular or open revascularization (surgical bypass) for zone 2 TEVAR procedures. Acute Kidney Injury (AKI) was defined according to the guidelines of the Kidney Guidelines Improving Global Outcomes (KDIGO)-criteria 17, as a ≥1.5 times increase from baseline serum creatinine or an increase of >0.3 mg/dL from baseline.[28] A composite variable for any in-hospital postoperative complication was created and defined as the occurrence of postoperative ischemic/hemorrhagic stroke, AKI, new-onset postoperative dialysis, spinal cord ischemia, bowel ischemia, leg ischemia, pulmonary complication, cardiac complication, or treatment-related reintervention during index hospitalization.

Outcomes

The primary outcome was perioperative mortality. Secondary outcomes included postoperative complications during index hospitalization.

Statistical analysis

We compared baseline characteristics, coexistent injuries, procedural characteristics, and outcomes after stratifying the cohort by surgeon volume. Continuous variables were presented as medians and interquartile range (IQR) and compared with the Kruskal-Wallis test. Categorical variables were presented as numbers and proportions and were compared using the Pearson's chi-squared test. We performed multilevel logistic regression analyses to examine the independent association between surgeon volume and perioperative outcomes, accounting for annual center volumes (LV/MV/HV categories) and adjusting for potential confounders (i.e., age (continuous/year), sex (male/female),

SVS aortic injury severity (Grade I-IV)[29], LSA revascularization[30] (zone >2 TEVAR/zone 2 TEVAR without LSA revascularization/zone 2 TEVAR with LSA revascularization), anemia (Hb >10g/dl/Hb <10g/dl), Injury Severity Score (ISS, 25-75), renal dysfunction (eGFR <30 or dialysis, eGFR 30-45, eGFR 45-60, eGFR >60), traumatic brain injury severity (mild: Glasgow Coma Score [GCS] 13-15, moderate: GCS 9-12, severe: GCS ≤8), heparin [only in the model with stroke as outcome]). We selected adjustment variables based on clinical relevance a priori and added variables based on statistical significance at univariable analysis. The multilevel models accounted for the nested clustering of patients and surgeons within the same center. All statistical analyses were performed using R version 4.2.2 (http://www.r-project.org).

Sensitivity analysis for Grade I-III BTAI patients alone

Since Grade IV BTAI patients should undergo emergency treatment and are thus unlikely to be transferred to a MV or HV surgeon, we performed a sensitivity analysis after excluding Grade IV (ruptured) BTAI patients (n = 215). Volumes were divided into quintiles, and then further grouped into LV, MV, and HV surgeons as done in the primary analysis. Surgeons in the first volume quintile were considered as LV (0-1 TEVAR procedures) and the highest quintile as HV (≥9 procedures), with the middle three quintiles categorized as MV (2-8 procedures). In this cohort, centers in the first volume quintile were considered as LV (0-10 procedures) and the highest quintile as HV (≥44 procedures), with the middle three quintiles categorized as MV (11-43 procedures).

RESULTS

Patient characteristics

Table I presents baseline characteristics of our cohort stratified by surgeon volume. Of the 1,321 patients, 370 (28%) were treated by LV surgeons, 688 (52%) by MV surgeons, and 263 (20%) by HV surgeons (**Figure S1**), while 266 (20%) were treated in a LV center, 784 (60%) in a MV center, and 264 (20%) in a HV center (**Table I**). Demographics and comorbidities were similar between the LV, MV, and HV subgroups, except for higher rates of preoperative anemia for higher volume surgeons (LV: 19%, MV: 26%, HV: 29%, p=.008), more betablocker use for higher volume surgeons (LV: 26%, MV: 34%, HV: 37%, p=.007), and more transferred admissions for higher volume surgeons (LV: 30%, MV: 42%, HV: 38%, p<.001).

Table I. Baseline characteristics of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume.

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
SVS aortic injury grade				**.003**
Grade I	28 (7.6%)	47 (6.8%)	20 (7.6%)	
Grade II	73 (20%)	123 (18%)	44 (17%)	
Grade III	118 (51%)	411 (60%)	172 (65%)	
Grade IV	81 (22%)	107 (16%)	27 (10%)	
SVS aortic injury grade (sensitivity analysis)				.261
Grade I	27 (9.5%)	47 (8.6%)	19 (8.4%)	
Grade II	72 (25%)	116 (21%)	40 (18%)	
Grade III	184 (65%)	385 (70%)	166 (74%)	
GCS	14 [10-15]	14 [7-15]	14 [8-15]	.88
Head and neck injury (AIS>3)	59 (16%)	103 (15%)	27 (10%)	.15
Face injury (AIS>3)	21 (5.7%)	36 (5.2%)	11 (4.2%)	.76
Chest injury (AIS>3)	163 (44%)	388 (56%)	146 (56%)	**< .001**
Abdominal injury (AIS>3)	92 (25%)	136 (20%)	49 (19%)	.15
Extremity injury (AIS>3)	79 (21%)	150 (22%)	54 (21%)	.90
External injury (AIS>3)	39 (11%)	50 (7.3%)	15 (5.7%)	.075
Traumatic brain injury				.18
Mild (GCS 13-15)	238 (64%)	433 (63%)	167 (64%)	
Moderate (GCS 9-12)	43 (12%)	61 (8.9%)	24 (9.1%)	
Severe (GCS ≤8)	74 (20%)	183 (27%)	68 (26%)	
Injury severity score categories				**.021**
Not assignable	20 (5.4%)	18 (2.6%)	6 (2.3%)	
Minor (ISS ≤8)	30 (8.1%)	37 (5.4%)	16 (6.1%)	
Moderate (ISS 9-15)	49 (13%)	58 (8.4%)	24 (9.1%)	
Severe (ISS 16-24)	49 (13%)	120 (17%)	46 (18%)	
Very severe (ISS 25-75)	191 (52%)	374 (54%)	137 (52%)	

*Pearson's chi-squared test or Kruskal-Wallis test. Data reported as median (interquartile range) for continuous variables and n (%) for categorical variables. Abbreviations: SVS: Society for Vascular Surgery; GCS: Glasgow Coma Scale; AIS: Abbreviated Injury Scale; ISS: Injury Severity Score.

Coexisting injuries at admission

Table II presents the coexistent injuries at presentation of our cohort stratified by surgeon volume. There were heterogeneous differences in proportions for SVS aortic injury grade, ISS categories, and traumatic brain injury groups between the LV, MV, and HV subgroups. There were no differences in GCS between the subgroups (**Table II**).

Table II. Coexistent injuries of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume.

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
Age, years	38 [28-56]	40 [28-58]	42 [30-57]	.63
Gender				.76
Male	271 (73%)	505 (73%)	199 (76%)	
Female	99 (27%)	183 (27%)	64 (24%)	
Race/ethnicity				.51
White	232 (63%)	407 (59%)	139 (53%)	
Black/African American	62 (17%)	128 (19%)	54 (21%)	
Asian	11 (3.0%)	20 (2.9%)	6 (2.3%)	
Hispanic	15 (4.1%)	28 (4.1%)	13 (4.9%)	
Other	48 (13%)	103 (15%)	48 (18%)	
Hypertension	104 (28%)	173 (25%)	74 (28%)	.63
Diabetes	26 (7.0%)	45 (6.5%)	20 (7.6%)	.89
Prior MI	6 (1.6%)	25 (3.6%)	6 (2.3%)	.12
Congestive heart failure				.18
Asymptomatic/mild	13 (3.5%)	14 (2.0%)	9 (3.4%)	
Moderate/severe	0 (0%)	4 (0.6%)	0 (0%)	
Ever smoking	157 (42%)	285 (41%)	95 (36%)	.17
Prior COPD	14 (3.8%)	17 (2.5%)	6 (2.3%)	.45
Prior stroke	6 (1.6%)	18 (2.6%)	10 (3.8%)	.22
Obesity	145 (39%)	267 (39%)	102 (39%)	.98
Renal dysfunction				.30
eGFR >60 mL/min/1.73m^2	263 (71%)	484 (70%)	180 (68%)	
eGFR 45-60 mL/min/1.73m^2	54 (15%)	110 (16%)	34 (13%)	
eGFR 30-45 mL/min/1.73m^2	33 (8.9%)	60 (8.7%)	31 (12%)	
eGFR <30 mL/min/1.73m^2 or dialysis	15 (4.1%)	20 (2.9%)	15 (5.7%)	
Anemia (Hb < 10g/dl)	70 (19%)	178 (26%)	75 (29%)	**.008**
Aspirin use	37 (10%)	69 (10%)	37 (14%)	.20
Statin use	32 (8.6%)	68 (9.9%)	32 (12%)	.37
Betablocker use	96 (26%)	233 (34%)	97 (37%)	**.007**

Table II. Coexistent injuries of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume. (*continued*)

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
ACE-I/ARB use	38 (10%)	75 (11%)	38 (14%)	.24
Prior aortic surgery	1 (0.3%)	4 (0.6%)	2 (0.8%)	.70
Center volume				**< .001**
Low-volume center	156 (42%)	110 (16%)	0 (0.0%)	
Medium-volume center	177 (48%)	462 (67%)	145 (55%)	
High-volume center	34 (9.2%)	115 (17%)	115 (44%)	
Transferred admission	112 (30%)	291 (42%)	100 (38%)	**< .001**

*Pearson's chi-squared test or Kruskal-Wallis test. Data reported as median (interquartile range) for continuous variables and n (%) for categorical variables. Abbreviations: MI: Myocardial Infarction; COPD: Chronic Obstructive Pulmonary Disease; Hb: Hemoglobin; ACE-I: Angiotensin-converting enzyme-inhibitor; ARB: Angiotensin receptor blocker.

Procedural and anatomical characteristics

Table III presents the procedural characteristics of our cohort stratified by surgeon volume. Procedural times were shorter with higher surgeon volume (LV: median 72 min. [IQR 50-120], MV: 70 [47-98], HV: 60 [43-90], p<.001) and contrast volume was lower for the HV surgeons (LV: median 70 ml [IQR 45-110], MV: 70 [45-100], HV: 60 [40-94], p=.011). There was more frequent heparin use in HV surgeons (LV: 80%, MV: 81%, HV: 87%, p=.007), and with higher surgeon volume, there were significantly more elective TEVARs (LV: 5.1%, MV: 8.9%, HV: 14%), more urgent TEVARs (<24 hours) (LV: 27%, MV: 37%, HV: 41%), and fewer TEVARs performed in an emergency setting (<4 hours) (LV: 68%, MV: 54%, HV: 46%) (**Table III**). No other differences were observed regarding proximal and distal landing zone extent, aortic coverage, management of the left subclavian artery, or conversion to open repair (**Table III**).

Perioperative outcomes

Table IV presents the unadjusted perioperative outcomes of our cohort stratified by surgeon volume. Compared with LV surgeons, MV and HV surgeons had lower – although not significant – rates of perioperative mortality (LV: 11%, MV: 7.3%, HV: 6.5%, p=.095), had significantly lower ischemic/hemorrhagic stroke rates (LV: 6.5%, MV: 3.6%, HV: 1.5%, p=.006), ischemic stroke rates (LV: 4.7%, MV: 2.8%, HV: 1.1%, p=.034), and in-hospital reinterventions related to the aortic disease or treatment (LV: 4.7%, MV: 1.8%, HV: 1.9%, p<.001). We observed no other differences regarding perioperative outcomes between the LV, MV, and HV surgeon subgroups. In patients undergoing TEVAR starting in zone 2, ischemic/hemorrhagic stroke rates were similar for patients with and without LSA revascularization (4.7% *vs.* 4.9%, p=.96).

Table III. Procedural and anatomical characteristics of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume.

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
Total procedure time, min	72 [50-120]	70 [48-104]	60 [43-90]	**< .001**
Contrast volume, ml	70 [45-110]	70 [45-100]	60 [40-94]	**.011**
Heparin use	295 (80%)	557 (81%)	233 (87%)	**.007**
Grade I-III alone	230 (80%)	475 (82%)	215 (91%)	**< .001**
Urgency				**< .001**
Elective	19 (5.1%)	61 (8.9%)	36 (14%)	
Urgent (<24 hours)	100 (27%)	255 (37%)	107 (41%)	
Emergency (<4 hours)	250 (68%)	370 (54%)	120 (46%)	
Urgency (Grade I-III alone)				**< .001**
Elective	18 (6.2%)	58 (10%)	34 (14%)	
Urgent (<24 hours)	89 (31%)	241 (42%)	100 (42%)	
Emergency (<4 hours)	181 (63%)	280 (48%)	102 (43%)	
Proximal landing zone				.33
Zone 2	137 (37%)	270 (39%)	102 (39%)	
Zone 3	199 (54%)	383 (56%)	142 (54%)	
Zone 4	27 (7.3%)	27 (3.9%)	15 (5.7%)	
Zone 5	7 (1.9%)	8 (1.2%)	4 (1.5%)	
Distal landing zone				.061
Zone 3	28 (7.6%)	66 (9.6%)	17 (6.5%)	
Zone 4	274 (74%)	509 (74%)	183 (70%)	
Zone 5	68 (18%)	113 (16%)	63 (24%)	
Total number of zones covered	2 [2-3]	2 [2-3]	2 [2-3]	.19
Proximal disease zone				.55
Zone 0	0 (0%)	1 (0.1%)	1 (0.4%)	
Zone 1	2 (0.5%)	5 (0.7%)	2 (0.8%)	
Zone 2	65 (18%)	103 (15%)	42 (16%)	
Zone 3	235 (64%)	482 (70%)	184 (70%)	
Zone 4	57 (15%)	76 (11%)	28 (11%)	
Zone 5	8 (2.2%)	14 (2.0%)	5 (1.9%)	
Distal disease zone				**.006**
Zone 1	1 (0.3%)	0 (0%)	0 (0%)	
Zone 2	8 (2.2%)	13 (1.9%)	5 (1.9%)	
Zone 3	83 (22%)	213 (31%)	87 (33%)	
Zone 4	219 (59%)	353 (51%)	125 (48%)	
Zone 5	51 (14%)	93 (14%)	38 (14%)	
Zone >5	4 (1.0%)	8 (1.2%)	7 (2.7%)	

Table III. Procedural and anatomical characteristics of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume. (*continued*)

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
LSA management (zone 2 TEVAR procedures)				.38
Covered/occluded	127 (93%)	250 (93%)	89 (87%)	
Endovascular	6 (4.4%)	8 (3.0%)	7 (6.9%)	
Surgical bypass	4 (2.9%)	12 (4.4%)	6 (5.9%)	
Conversion to open repair	3 (0.8%)	2 (0.3%)	1 (0.4%)	.55

*Pearson's chi-squared test or Kruskal-Wallis test. Data reported as median (interquartile range) for continuous variables and n (%) for categorical variables. Abbreviations: LSA: Left Subclavian Artery.

Table IV. Perioperative outcomes of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume.

Variable	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)	P-value*
Perioperative mortality	39 (11%)	50 (7.3%)	17 (6.5%)	.095
Aortic related mortality	25 (6.8%)	27 (3.9%)	13 (4.9%)	.11
Any complication	132 (36%)	223 (32%)	78 (30%)	.31
Ischemic/hemorrhagic stroke	24 (6.5%)	25 (3.6%)	4 (1.5%)	**.006**
Ischemic stroke	17 (4.7%)	19 (2.8%)	3 (1.1%)	**.034**
Acute kidney injury	72 (20%)	124 (18%)	44 (17%)	.70
Postoperative dialysis	15 (4.1%)	18 (2.6%)	9 (3.4%)	.48
Spinal Cord Ischemia	6 (1.6%)	5 (0.7%)	3 (1.1%)	.37
Bowel Ischemia	5 (1.4%)	8 (1.2%)	7 (2.7%)	.22
Leg Ischemia	4 (1.1%)	9 (1.3%)	5 (1.9%)	.70
Pulmonary Complications	75 (20%)	123 (18%)	45 (17%)	.55
Cardiac Complication	10 (2.7%)	21 (3.1%)	2 (0.8%)	.12
Reintervention during index admission				**< .001**
Related to disease/treatment	17 (4.7%)	12 (1.8%)	5 (1.9%)	
Unrelated to disease/treatment	75 (21%)	202 (30%)	104 (40%)	

*Pearson's chi-squared test. Data reported as median (interquartile range) for continuous variables and n (%) for categorical variables.

Table V presents the adjusted perioperative outcomes of our cohort stratified by surgeon volume. After adjustment, overall surgeon TEVAR volume was independently associated with lower odds of perioperative mortality (0.62 [0.39-1.00], p=.049) and compared with LV surgeons, MV surgeons had lower odds of perioperative mortality (MV: 0.49 [0.25-0.97], p=.039), while HV surgeons had lower odds (similar to MV) although not statistically significant (HV: 0.45 [0.16-1.22], p=.12), and both MV and HV surgeons together (deemed appropriate given the similar OR) had lower odds of perioperative mortality (MV/HV: 0.50[0.26-0.96],p=.038). After adjustment and compared with LV surgeons, both MV and HV surgeons had lower odds of postoperative ischemic/hemorrhagic stroke (MV: 0.38 [0.18-0.81], p=.011; HV: 0.16 [0.04-0.61], p=.008), ischemic stroke (MV: 0.42 [0.17-1.00], p=.050; HV: 0.19 [0.05-0.76], p=.019), and in-hospital reinterventions related to the aortic disease or treatment (MV: 0.31 [0.12-0.77], p=.011; HV: 0.17 [0.03-0.89], p=.036). After adjustment and compared with MV surgeons, HV surgeons had lower odds of ischemic/hemorrhagic stroke, although not statistically significant (HV: 0.38 [0.11-1.35], p=.13). Additionally, heparin administration was associated with lower odds of hemorrhagic stroke (OR 0.07 [0.02-0.25], p<.001).

Sensitivity analysis for Grade I-III BTAI patients alone

Of 1,106 patients undergoing TEVAR and presenting with Grade I-III BTAI, 289 (26%) were treated by LV surgeons, 581 (23%) by MV surgeons, and 236 (21%) by HV surgeons. Heterogeneous differences in proportions for SVS aortic injury grade persisted, but there were slightly higher rates of Grade I-II BTAI lesions and slightly lower rates of Grade III BTAI lesions treated by LV surgeons, compared with MV and HV surgeons (Grade I: LV: 9.5%, MV: 8.6%, HV: 8.4%; Grade II: LV: 25%, MV: 21%, HV: 18%; Grade III: LV: 65%, MV: 70%, HV: 74%, p=.261) (**Table II**). More frequent heparin administration in HV surgeons persisted (LV: 80%, MV: 82%, HV: 91%, p<.001), as well as the distribution of treatment urgency (**Table III**).

Table VI presents the unadjusted and adjusted perioperative outcomes of our cohort stratified by surgeon volume. After adjustment, compared with LV surgeons, MV and HV surgeons had lower odds of perioperative mortality, although not significant (MV *vs* LV: 6.5% *vs* 8.0%; 0.57 [0.24-1.31], p=.18, HV *vs* LV: 5.1% *vs* 8.0%; 0.32 [0.09-1.14], p=.079, MV/HV *vs* LV: 0.52 [0.25-1.17], p=.12), and lower odds of ischemic/hemorrhagic stroke (MV *vs* LV: 3.1 *vs* 6.2%; 0.36 [0.15-0.91], p=.030, HV *vs* LV: 1.7% *vs* 6.2%; 0.26 [0.07-0.96], p=.044).

Table V. Multilevel logistic regression models for perioperative outcomes of 1,321 patients that underwent TEVAR for BTAI stratified by annual surgeon volume.

Outcome	Low-volume surgeon (n = 370)	Medium-volume surgeon (n = 688)	High-volume surgeon (n = 263)
Perioperative mortality	Ref.	**0.49 [0.25-0.97]**	0.45 [0.16-1.22]
Aortic related mortality	Ref.	**0.39 [0.16-0.92]**	0.75 [0.25-2.31]
Any Complication	Ref.	0.80 [0.56-1.14]	0.64 [0.39-1.05]
Ischemic/hemorrhagic stroke	Ref.	**0.38 [0.18-0.81]**	**0.16 [0.04-0.61]**
Ischemic stroke	Ref.	0.42 [0.17-1.00]	**0.19 [0.05-0.76]**
Acute Kidney Injury	Ref.	0.89 [0.60-1.32]	0.71 [0.41-1.23]
Postoperative Dialysis	Ref.	0.56 [0.25-1.24]	0.56 [0.19-1.62]
Spinal Cord Ischemia	Ref.	0.72 [0.07-6.97]	1.64 [0.08-34.1]
Bowel Ischemia	Ref.	0.61 [0.14-2.66]	2.30 [0.45-11.8]
Leg Ischemia	Ref.	1.45 [0.41-5.11]	2.29 [0.46-11.3]
Pulmonary Complications	Ref.	0.79 [0.52-1.19]	0.82 [0.46-1.45]
Cardiac Complications	Ref.	0.52 [0.03-10.0]	0.05 [0.00-1.65]
Reintervention during index admission, related to aortic disease/ treatment	Ref.	**0.31 [0.12-0.77]**	**0.17 [0.03-0.89]**
Reintervention during index admission, unrelated to aortic disease/ treatment	Ref.	1.08 [0.69-1.68]	1.53 [0.86-2.73]

Data are presented as adjusted odds ratios with [95% Confidence Intervals]. This model was adjusted for overall TEVAR center volume, age (continuous/year), sex (male/female), SVS aortic injury grade (Grade I-IV), left subclavian revascularization (zone 3-5 TEVAR/zone 2 TEVAR without revascularization/zone 2 TEVAR and open or endovascular revascularization), anemia (Hb >10g/dl/Hb <10g/dl), Very Severe Injury Severity Score (25-75), renal function (eGFR <30 or dialysis, eGFR 30-45, eGFR 45-60, eGFR >60), Traumatic Brain Injury (mild/moderate/severe), Heparin (only in the model with Stroke as outcome). Abbreviation: Ref.: reference.

Table VI. Unadjusted and adjusted perioperative outcomes of 1,106 patients undergoing TEVAR for Grade I-III BTAI stratified by annual surgeon volumes (sensitivity analysis).

	Unadjusted				Adjusted*	
Outcome	**Low volume surgeon (0-1) (n = 289)**	**Medium-volume surgeon (2-8) (n = 581)**	**High volume surgeon (≥9) (n = 236)**	**P-value****	**MV vs LV aOR (95%CI)**	**HV vs LV aOR (95%CI)**
Perioperative mortality	23 (8.0%)	38 (6.5%)	12 (5.1%)	.43	0.57 [0.24-1.31]	0.32 [0.09-1.14]
Aortic related mortality	13 (4.5%)	18 (3.1%)	8 (3.4%)	.57	0.35 [0.10-1.15]	0.38 [0.08-1.83]
Any Complication	96 (33%)	182 (31%)	67 (28%)	.53	0.83 [0.56-1.22]	0.71 [0.42-1.21]
Ischemic/hemorrhagic stroke	18 (6.2%)	18 (3.1%)	4 (1.7%)	**.013**	**0.36 [0.15-0.91]**	**0.26 [0.07-0.96]**
Ischemic Stroke	12 (4.2%)	14 (2.4%)	3 (1.3%)	.10	0.42 [0.14-1.27]	0.24 [0.05-1.18]
Acute Kidney Injury	52 (18%)	101 (17%)	36 (15%)	.68	0.93 [0.59-1.47]	0.71 [0.38-1.32]
Postoperative Dialysis	11 (3.8%)	15 (2.6%)	8 (3.4%)	.64	0.56 [0.22-1.42]	0.63 [0.19-2.10]
Spinal Cord Ischemia	3 (1.0%)	2 (0.3%)	3 (1.3%)	.27	0.26 [0.02-3.70]	1.19 [0.08-16.8]
Bowel Ischemia	4 (1.4%)	6 (1.0%)	4 (1.7%)	.77	0.25 [0.04-1.49]	1.18 [0.18-7.86]
Leg Ischemia	3 (1.0%)	6 (1.0%)	4 (1.7%)	.73	1.11 [0.26-4.80]	1.82 [0.30-11.2]
Pulmonary Complications	53 (18%)	100 (17%)	39 (17%)	.87	0.74 [0.46-1.19]	0.84 [0.45-1.55]
Cardiac Complications	6 (2.1%)	16 (2.8%)	2 (0.8%)	.24	0.85 [0.11-6.64]	0.17 [0.01-4.58]
Reintervention during index admission				**<.001**		
Related to disease/treatment	10 (3.5%)	8 (1.4%)	4 (1.7%)		0.53 [0.13-2.11]	0.30 [0.04-2.44]
Unrelated to disease/treatment	52 (18%)	169 (29%)	93 (39%)		1.14 [0.68-1.91]	1.65 [0.86-3.17]

*This model was adjusted for overall TEVAR center volume, age (continuous/year), sex (male/female), SVS aortic injury grade (Grade I-IV), left subclavian revascularization (zone 3-5 TEVAR/zone 2 TEVAR without revascularization/zone 2 TEVAR and open or endovascular revascularization), anemia (Hb >10g/dl/Hb <10g/dl), Very Severe Injury Severity Score (25-75), renal function (eGFR <30 or dialysis, eGFR 30-45, eGFR 45-60, eGFR >60), Traumatic Brain Injury (mild/moderate/severe), Heparin (only in the model with Stroke as outcome). **Pearson's chi-squared test.

DISCUSSION

This study utilized real-world data from the multicenter VQI registry to retrospectively evaluate the impact of annual surgeon volume on perioperative outcomes of patients undergoing TEVAR for BTAI. In adjusted analyses, MV surgeons were independently associated with lower perioperative mortality, while HV surgeons had lower adjusted odds of perioperative mortality although not statistically significant, potentially related to a

smaller sub cohort size.[31] MV and HV surgeons grouped together were independently associated with lower perioperative mortality as well, supporting the importance of the lower adjusted odds for perioperative mortality observed for HV surgeons, although this did not reach statistical significance.[31] Most notably, MV and HV surgeons were independently associated with lower postoperative stroke rates, persisting in our sensitivity analysis. For BTAI patients specifically, postoperative complications like stroke may be more directly related to the TEVAR procedure compared with perioperative mortality, as this might be determined more by injuries concomitant to the aortic injury. Our findings suggest that a surgeon's annual overall TEVAR volume may be more influential than the annual overall TEVAR volume of a specific center in achieving favorable outcomes. Altogether, this may form the basis for a recommendation stating that when feasible, MV or HV surgeons should be included in the treatment of BTAI.

Several studies have examined hospital and/or surgeon volume-outcome relationships in aortic surgery. Specifically, we identified 13 studies[4-16] that evaluated these relationships in open and/or endovascular AAA repair, and 9 studies[17-20,22-26] that evaluated these relationships in thoracic aortic diseases. We have summarized the differences and similarities of these hospital and surgeon volume aortic outcome relationship analyses in detail in supplemental **Table SI**. Of note, over 75% of these studies have been published during the last five years, and six studies utilizing the SVS-VQI have been published since 2020[10,11,16,24-26]. Scali *et al.*[11] also incorporated a surgeon's cumulative years of experience in addition to annual surgeon volumes to evaluate short-term mortality after open AAA repair but found that annual case volume was more strongly associated than a surgeon's cumulative years of experience.

Five studies addressed surgeon volume alone, of which four focused on open and endovascular AAA repairs[8-11] while the remaining study by Cooke *et al.*[26] focused on patients treated with TEVAR for aortic dissection specifically (**Table SI**). Cooke *et al.*[26] did not find higher surgeon volume to impact 30-day mortality while MV and HV surgeons were associated with lower complication rates on univariable analysis, which did not persist after adjustment.

Table SI. Summary of previous literature focusing on volume-outcome relationships in aortic surgery.

Author, year	Journal	Number of patients (time-span)	Data source	Disease type	Treatment	Investigated volume-outcome relationship	Outcomes
Abdominal aortic disease							
Dimick JB, 2008[4]	J Vasc Surg	81,052 (2001-2003)	Medicare	Intact AAA	Open surgery, EVAR	Hospital-volume	Lower perioperative mortality with HV
Landon BE, 2010[5]	Circulation	230,736 (2001-2006)	Medicare	Intact and ruptured AAA	Open surgery, EVAR	Hospital-volume	Open: lower perioperative mortality with HV; EVAR: early threshold
McPhee, 2011[12]	J Vasc Surg	14,093 (2003-2007)	Nationwide Inpatient Sample	Intact AAA	Open surgery, EVAR	Hospital- and surgeon volume	Open: lower in-hospital mortality for HV surgeons; EVAR: no association for both
Zettervall SL, 2017[14]	J Vasc Surg	122,495 (2001-2008)	Medicare	Intact AAA	Open surgery, EVAR	Hospital- and surgeon-volume	Open: lower perioperative mortality with HV for both; EVAR: minimal association with HV hospitals
Meltzer AJ, 2017[13]	J Vasc Surg	18,842 (2000-2011)	New York Statewide Planning and Research Cooperative System data	Intact and ruptured AAA	Open surgery, EVAR	Hospital- and surgeon-volume	Intact AAA/open: lower in-hospital mortality for HV surgeons; Intact AAA/EVAR: lower mortality for HV surgeons; rAAA/open: lower mortality for HV surgeons; rAAA/EVAR: no association
Dubois L, 2018[8]	J Vasc Surg	7,211 (2005-2014)	Population-based, prospectively collected health administrative database	Intact AAA	Open surgery	Surgeon-volume	No association for perioperative mortality but HV had lower postoperative complication and reoperation rates

Table SI. Summary of previous literature focusing on volume-outcome relationships in aortic surgery. (*continued*)

Author, year	Journal	Number of patients (time-span)	Data source	Disease type	Treatment	Investigated volume-outcome relationship	Outcomes
Esce A, 2018[9]	Ann Vasc Surg	1,526 (2000-2010)	New York Statewide Planning and Research Cooperative System data	Intact AAA	Open surgery, EVAR	Surgeon-volume	Lower 30-day, and 3-year mortality with HV
Scali ST, 2019[6]	Circulation	178,860 (2010-2016)	Eleven international registries	Intact and ruptured AAA	Open surgery, EVAR	Hospital-volume	Open: lower perioperative mortality with HV; EVAR: no association
Arnaoutakis DJ, 2020[10]	J Vasc Surg	11,900 (2003-2019)	SVS-VQI	Intact and ruptured AAA	Open surgery	Surgeon-volume (and years of experience)	Intact AAA: lower 30-day mortality with greater experience; rAAA: no association; 1-year mortality: no association
Sawang M, 2020[15]	Eur J Vasc Endovasc Surg	14,262 (2010-2016)	Australasian Vascular Audit	Ruptured AAA	Open surgery, EVAR	Hospital- and surgeon volume	Lower perioperative mortality for HV hospitals
Scali ST, 2021[11]	J Vasc Surg	11,900 (2003-2019)	SVS-VQI	Intact and ruptured AAA	Open surgery	Surgeon-volume (and years of experience)	Lower 30-day, and 1-year mortality for HV surgeons, not with greater experience
Tong T, 2021[7]	Br J Surg	(2006-2018)	Hospital Episode Statistics	Intact and ruptured AAA	Open surgery, EVAR	Hospital-volume	Open: lower in-hospital mortality with HV; EVAR: no association
Mehta A, 2023[16]	J Vasc Surg	14,110 (2012-2019)	SVS-VQI	Intact and ruptured AAA	Open surgery	Hospital- and surgeon volume	Lower 30-day mortality if LV surgeon operates at HV hospital

Table SI. Summary of previous literature focusing on volume-outcome relationships in aortic surgery. (*continued*)

Author, year	Journal	Number of patients (time-span)	Data source	Disease type	Treatment	Investigated volume-outcome relationship	Outcomes
Thoracic aortic disease							
Cowan JA Jr, 2003[17]	J Vasc Surg	1,542 (1988-1998)	Nationwide Inpatient Sample	Intact TAAA	Open surgery	Hospital- and surgeon volume	Lower in-hospital mortality with HV for both
Patel VI, 2013[18]	J Vasc Surg	7,071 (2004-2007)	Medicare Provider Analysis and Review data set	Descending TAA	Open surgery, TEVAR	Hospital volume	Open: lower 30-day mortality, and 6-year survival with HV; TEVAR: no association
Stern JR, 2019[22]	Ann Vasc Surg	1,838 (2005-2014)	New York Statewide Planning and Research Cooperative System data	AD, intact and ruptured TAA	TEVAR	Hospital- and surgeon volume	No associations with in-hospital mortality
Brescia AA, 2019[19]	Ann Thorac Surg	6,650 (2010-2014)	Seven all-payer state inpatient administrative databases	Type A, type B AD	Open surgery, TEVAR	Hospital volume	Open: lower in-hospital mortality with HV; TEVAR: no association
Iyengar A, 2020[23]	Eur J Cardiothorac Surg	24,983 (2010-2014)	National Readmissions Database	Intact or ruptured TAA or TAAA, AD, or trauma	TEVAR	Hospital volume	No associations with index LOS, costs, or 30-day readmissions
Mohapatra A, 2021[24]	J Vasc Surg	619 (2011-2017)	SVS-VQI	BTAI	TEVAR	Hospital volume	Lower perioperative mortality with HV
Brown C, 2021[20]	J Card Surg	4,629 (2014-2019)	Medicare	Aortic root aneurysm	Open surgery (root replacement)	Hospital- and surgeon volume	Lower 30-day mortality with HV for both
Alhajri N, 2022[25]	J Vasc Surg	3,584 (2015-2019)	SVS-VQI	AD, TAA, trauma	TEVAR	Hospital volume	No association with 30-day mortality

Table SI. Summary of previous literature focusing on volume-outcome relationships in aortic surgery. (*continued*)

Author, year	Journal	Number of patients (time-span)	Data source	Disease type	Treatment	Investigated volume-outcome relationship	Outcomes
Cooke PV, 2022[26]	J Vasc Surg	1,217 (2014-2021)	SVS-VQI	AD	TEVAR	Surgeon volume	No association with 30-day, 5-year mortality but lower overall complications with HV

Abbreviations: AAA: Abdominal Aortic Aneurysm, EVAR: EndoVascular Aneurysm Repair, SVS-VQI: Society for Vascular Surgery Vascular Quality Initiative, TAAA: ThoracoAbdominal Aortic Aneurysm, BTAI: Blunt Thoracic Aortic Injury, AD: Aortic Dissection, TEVAR: Thoracic Endovascular Aortic Repair, HV: high volume, LOS: Length of stay, rAAA: ruptured AAA.

Regarding TEVAR for BTAI, a prior study by Mohapatra *et al.*[24] evaluated the effect of hospital volume on perioperative mortality after stratifying their 619 patients, though they did not account for annual surgeon volumes. They showed HV hospitals to be independently associated with lower perioperative mortality following TEVAR for BTAI, particularly true when considering trauma specific hospital TEVAR volumes. As mentioned before, we tested for this association but were unable to confirm this in our cohort.[24]

Besides lower perioperative mortality for MV/HV surgeons and lower stroke rates for MV and even more so HV volume surgeons, we found procedural times to be shorter for higher volume surgeons, along with lower contrast use. Such aspects may as well provide additional benefits in terms of radiation exposure to the patient and the operating team or in patients with renal failure. Moreover, we showed that HV surgeons are more likely to administer heparin and perform TEVAR in a more delayed fashion. This persisted in our sensitivity analysis (**Table III**). Thus, part of the benefit of a HV surgeon may involve the judgement to defer surgery for BTAI without rupture until the patient is stabilized enough to tolerate heparin. Simply deferring surgery would likely improve the mortality rate of intervention by not operating on those who would die soon after admission from concomitant injuries. In addition, there were more transferred admissions for higher volume surgeons which might also have driven this observed treatment delay (**Table I**).[32] However, higher volume surgeons might be considered a surrogate for better functioning trauma systems in these HV surgeon's hospitals, and although we accounted for center volume and other factors linked with higher surgeon volume, this may need additional study to better understand this relationship.

We also observed lower reintervention rates for MV and HV surgeons on both univariable and multivariable analysis. Unfortunately, we cannot determine the exact indication or type of reintervention. We could hypothesize that lower reinterventions with higher surgeon volume may be attributed to technical expertise. However, more delayed TEVAR (and heparin administration) may also have led to lower rates of aortic or procedure-related reinterventions as TEVAR is then likely to be performed in a less acute setting.

Given that grade IV BTAI requires emergent intervention, it would be challenging to centralize care of these patients and ensure availability of MV or HV surgeons for emergent intervention. Nevertheless, for the majority of patients who present with non-ruptured BTAI and require TEVAR, deferral should be possible to involve a MV or HV surgeon. Of note, our results do not suggest that every MV surgeon should involve a HV surgeon, but rather that LV surgeons might involve MV or HV surgeons. Our sensitivity analysis of Grade I-III patients found that higher surgeon volume is independently associated with lower stroke rates after TEVAR, and while mortality was no longer significantly lower, the

adjusted odds ratios still suggest a potential benefit, but with smaller numbers statistical significance was lost.

Limitations

Besides strengths of this study like merging the TEVAR/Complex EVAR and EVAR modules to reduce the number of excluded procedures based on missing preceding year data to compute annual surgeon volume and multilevel models accounting for the nested clustering of our data, this retrospective cohort study is limited by its design to use data from the TEVAR/Complex EVAR module of the SVS-VQI. We do not have information regarding how patients were selected for intervention as we have no data for BTAI managed without TEVAR, nor can we comment on patients that died before undergoing TEVAR. The usual limitations of retrospective registry data are present including potential miscoding, under-diagnosis of complications such as stroke. The VQI does not specify the specific amount of heparin that was administered. There is limited information regarding concomitant injuries and their management. Compared with trauma specific databases, the VQI focuses on data related to vascular surgery. However, data on access vessel size, thrombus, stent graft details, and procedures for other injuries are not included. Moreover, the VQI does not include all centers in the United States, potentially limiting the generalizability of these findings, especially to other healthcare systems in other countries.

CONCLUSIONS

This study showed that higher surgeon volume was independently associated with lower perioperative mortality and postoperative stroke in BTAI patients undergoing TEVAR. The impact of surgeon volume seems to weigh more than hospital volume in achieving favorable outcomes. Future studies could elucidate if TEVAR for non-ruptured BTAI might be delayed and allow patient stabilization, heparinization, and involvement of MV or HV surgeons, as our study suggests there may be a benefit.

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Long-term patency of surgical left subclavian artery revascularization

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ARTICLE HIGHLIGHTS

- **Type of research:** Single-center retrospective cohort study
- **Key Findings:** At 10-year follow-up, surgical left subclavian artery (LSA) revascularization is associated with high patency rates, with an estimated 97% freedom from occlusion and 90% freedom from severe stenosis.
- **Take Home Message:** Surgical LSA revascularization in the context of thoracic endovascular aneurysm repair may still be considered the gold standard to preserve antegrade LSA flow in the current endovascular era, as it is associated with high patency rates.

ABSTRACT

Objective: Little is known regarding the long-term patency rates of surgical left subclavian artery (LSA) revascularization, especially when performed concomitant to thoracic endovascular aortic repair and without arterial occlusive disease. Our aim is to contribute to the existing evidence by reporting the patency rates at mid- and long-term follow-up after surgical LSA revascularization.

Methods: This observational, retrospective, single-center cohort study included 90 eligible patients who underwent a left common carotid artery to LSA bypass (72%) or transposition (28%) from December 31, 2017 to January 1, 2000. Data regarding demographics, medical history, intraoperative characteristics, and outcomes regarding bypass graft or transposition patency, severe stenosis, or occlusion were assessed at discharge, 3 months, 1 year, and maximum follow-up using consecutive follow-up computed tomography scans.

Results: In our predominantly male (74%) cohort with a mean age of 66 years (standard deviation, ±12 years), LSA revascularization was mostly performed concomitant to or adjacent to thoracic endovascular aneurysm repair procedures (98%) with the primary indication for surgery being degenerative or saccular aneurysmatic aortic disease (50%), subacute or acute type B aortic dissection (17%), post-dissection aortic aneurysm (16%), type B intramural hematoma (6%), and other indications (11%). Ninety-seven percent of our left common carotid artery to LSA bypasses were performed using a central, supraclavicular approach, and the other 3% were performed using an infraclavicular approach to the LSA. Median diameter of the bypass was 6 mm (range, 6-12 mm). We found two occlusions at 7.7 and 12.9 months follow-up and four severe stenoses at 21.2, 35.4, 38.3, and 46.7 months follow-up, respectively. Estimated freedom

from occlusion was 97% ± 2% and freedom from severe stenosis was 90% ± 4% at both midterm (5 years) and long-term (10 years) follow-up, with a median follow-up duration of 42.2 months for occlusion (25th-75th percentile, 15.4-67.4 months) and 41.9 months (25th-75th percentile, 15.4-67.4 months) for severe stenosis.

Conclusions: Open surgical LSA revascularization may be considered the gold standard to preserve antegrade LSA flow in the context of debranching for thoracic endovascular aneurysm repair or open surgical aortic arch repair, with excellent patency rates at mid-term and long-term follow-up.

INTRODUCTION

Left subclavian artery (LSA) revascularization has become increasingly important as thoracic endovascular aortic repair (TEVAR) is now the treatment of choice for both acute aortic syndromes as well as for thoracic aortic aneurysms in certain clinical situations.[1-4]

Several recommendations are made by the Society for Vascular Surgery guidelines regarding the management of the LSA in patients with TEVAR. In patients who need elective TEVAR treatment with a landing zone in zone 2 for adequate sealing and thus need coverage of the LSA, routine preoperative revascularization of the LSA is recommended.[2,5,6] Revascularization and preservation of antegrade LSA flow can be done by open surgical means using a bypass or transposition, or more recently also by endovascular techniques with single-branched, chimney graft, (in situ) fenestrations, or scalloped endografts in highly selected patients using custom-made devices.[7-11] Concerns exist regarding the safety of these alternative procedures, and long-term follow-up data is lacking.[9]

Perioperative and postoperative complications of surgical LSA revascularization have been widely investigated and described before by several authors and meta-analyses.[12-29] However, little is known about patency rates of these surgical LSA revascularizations in the long-term, with only several authors reporting patency rates from LSA to left common carotid artery (LCCA) transpositions or LCCA to LSA bypass at short-term and mid-term follow-up.[12-22]

Our aim is to contribute to the existing evidence by reporting our single-center results regarding the mid-term and long-term patency after open surgical LSA revascularization. Together with the well-known operative morbidity of open surgical revascularization, these long-term patency rates may aid in the sometimes complex decision-making process with regards to the rapidly expanding alternative options in the current endovascular era.

METHODS

Study design and data collection

This is an observational, retrospective cohort study including all surgical LSA revascularizations performed from December 21, 2017 to January 1, 2000 at the St. Antonius Hospital, Nieuwegein, the Netherlands, either isolated or concomitant to or adjacent to a TEVAR procedure. Eligible patients were found after querying a local database register-

ing all surgical supra-aortic debranching procedures. The study protocol was approved by the local ethical committee, and the need for informed consent was waived due to the retrospective nature of the study.

Medical records were retrospectively consulted for data regarding demographics, medical history, intraoperative characteristics, and outcomes regarding bypass graft or transposition patency at discharge, patency at first follow-up computed tomography (CT) scan after 3 months, patency at follow-up CT scan after 1 year, patency at last available follow-up CT scan, mortality, and any reinterventions.

Data collection was performed by the first author (T.M.). CT scans were evaluated in all available planes: axial, sagittal, and coronal. Interpretation regarding patency, stenosis, or occlusion was always compared with the report of the radiologist, who did not always report on the bypass or transposition mainly due to a specific focus on the aorta. All CT scans were reported by an experienced, board-certified cardiovascular or interventional radiologist. In case of any discrepancies between the findings of the first author (T.M.) and the report of the radiologist, this was discussed with the second author (H.B.) and a final decision was made.

The datasheet was analyzed by the first and second author (T.M. and H.B.), and all patients with a different type of supra-aortic revascularization than a LSA revascularization were excluded to create homogeneity. Also, patients without at least one available follow-up CT scan or without visualization of their LSA revascularization on CT needed to be excluded from the analysis.

Definitions

A patent LSA revascularization was defined as visible contrast in both the carotid and subclavian vessels and/or bypass graft without narrowing of the lumen of more than 50% on consecutive follow-up CT scans. Occlusion of a LSA revascularization was defined as a lack of visible contrast in at least the proximal LSA or the bypass graft. Stenosis of a LSA revascularization was defined at first as a visible severe narrowing of the lumen of the bypass graft. When severe narrowing was noticed, the reduction in endoluminal diameter was measured, and a reduction of at least 70% was considered a severe stenosis in line with the reports of our radiology department. Our observations were always compared with the description of the radiologist who mostly described a stenosis as being present, severely stenosed, tapered, or sometimes expressed the amount of stenosis in a percentage.

Mid-term outcome was defined at 5 years postoperatively and long-term outcome as at least 10 years postoperatively. Freedom from occlusion and freedom from severe stenosis for the entire cohort was calculated at the mid-term and at the long-term level. Freedom from occlusion was defined as the primary outcome. An event in this group was defined as an occlusion. Secondary outcome was defined as freedom from severe stenosis, with an event being a severe stenosis or occlusion. We did not include patients operated after December 31, 2017 due to our specific focus on patency at the mid-term and long-term level.

Preoperative workup, operative procedure, and follow-up protocol

Our institutional approach to patients undergoing LSA revascularization, including preoperative workup, operative procedure, and follow-up protocol, have been described in detail in previous publications.[23,30-33] In short, all procedures were performed under transcranial Doppler and electroencephalography monitoring. Either a central or infraclavicular approach to the LSA was used for the patients included in this study, based on preoperative imaging.[31,32]

In the central, supraclavicular approach, central is referring to the centrally located proximal part of the LSA. In this approach, one small supraclavicular incision makes it possible to dissect between the two heads of the sternocleidomastoid muscle using deep wound spreaders, and to expose the internal jugular vein, LCCA, parallel vagal nerve, and usually around 1 cm deeper in the neck, the central part of the LSA and its side branches.31 Both LCCA to LSA bypass and LSA to LCCA transposition can be performed using the same supraclavicular incision and exposure. When LCCA to LSA bypass grafting is performed using the infraclavicular approach, two small transverse incisions are made. The first is equal to the incision described above; the second is located more laterally and infraclavicular. This infraclavicular incision is located medial to the deltopectoral groove. Using deep wound spreaders, the region lateral to the major pectoral muscle and medial to the minor pectoral muscle is exposed. In this way, the distal anastomosis can be performed on a more distal part of the LSA, in close relationship to the brachial plexus.[32]

Patients postoperatively routinely receive lifelong mono antiplatelet therapy with acetylsalicylic acid unless other indications for anticoagulation or antiplatelet therapy coexist. Postoperative CT scan is routinely performed after 3 months, initially followed by annual CT scans that can be altered to longer intervals depending on the clinical characteristics of the patient and radiological characteristics of the LSA revascularization.

Statistical analysis

Continuous variables are reported as standard mean ± standard deviation (SD). Categorical variables are reported as number (n) and percentage (%). The mid-term and long-term data regarding patency were analyzed using Survival analysis, using IBM SPSS Statistics version 26. Freedom from occlusion, freedom from severe stenosis, overall mortality, and aorta-related mortality are reported using Kaplan-Meier graphs.

RESULTS

Study selection

A local database registering all surgical supra-aortic debranching procedures, provided 110 postprocedural patients during the study period, of which 90 were found eligible for inclusion in our study. Eighty-eight of these patients (98%) underwent LSA revascularization concomitant or adjacent to TEVAR, and two (2%) underwent LSA revascularization in preparation for open surgical aortic arch repair. Seven patients were excluded because they underwent a different revascularization than LSA revascularization. This group consisted of right common carotid artery (RCCA) to right subclavian artery (RSA) bypass or transposition (n = 5), RCCA to RSA bypass with a pretracheal course (n = 1), or RSA to LSA bypass with a presternal course (n = 1). Another seven patients were excluded due to inadequate visualization of the supra-aortic vessels on consecutive follow-up CT scans. Among these exclusions, two were LCCA to LSA bypasses and five were LSA to LCCA transpositions. Another six patients were excluded due to lack of a single available follow-up CT. Reasons were postoperative referral to the referring center and follow-up by their cardiologist (n = 3), no available images or report about patency by the radiologist (n = 1), or unknown (n = 2). Among these exclusions, three were LCCA to LSA bypasses, and three were LSA to LCCA transpositions. Except for the presternal RSA to LSA bypass that occluded at 23 months follow-up, we found no occlusions or severe stenosis in our excluded patients.

Table I provides a detailed overview of baseline patient characteristics. Our cohort was mostly male (74%) with a mean age at revascularization of 66 years (SD, ±12 years). Most common comorbidities in the medical history were arterial hypertension (40%), history of aortic surgery (27%), and hypercholesterolemia (19%). Most included patients were treated for aortic diseases such as a degenerative or saccular thoracic aortic aneurysm (50%), subacute Stanford type B aortic dissection (17%), post-dissection aneurysmatic dilatation of the aorta (16%), acute or symptomatic intramural hematoma of the proximal descending aorta or distal aortic arch (6%), blunt thoracic aortic injury (2%), penetrating aortic ulceration (1%), or others (8%).

Table I. Baseline patient characteristics

Characteristic	Value
Male	67 (74)
Age at revascularization, years	66 ± 12
Medical history	
Hypertension	36 (40)
Hypercholesterolemia	17 (19)
Diabetes	8 (9)
History of stroke (transient or ischemic)	13 (14)
Chronic obstructive pulmonary disease	14 (16)
Renal insufficiency	14 (16)
History of aortic surgery	24 (27)
Peripheral arterial disease	10 (11)
Coronary artery disease	13 (14)
Coronary artery bypass grafting	4 (4)
Indications for surgery	
Degenerative or saccular aortic aneurysm	45 (50)
Type B aortic dissection	15 (17)
Post-dissection aortic aneurysm	14 (16)
Intramural hematoma	5 (6)
Blunt thoracic aortic injury	2 (2)
Pseudoaneurysm after previous open surgical aortic repair	2 (2)
Progression aortic diameters after TEVAR	2 (2)
Penetrating aortic ulceration	1 (1)
Aortic aneurysm contained rupture	1 (1)
Endoleak type Ia	1 (1)
Proximal SINE with aortic growth	1 (1)
Dysphagia lusoria after previous RSA transposition	1 (1)
Type of surgery besides LSA revascularization	
Thoracic endovascular aortic repair	88 (98)
Open surgical aortic arch repair	2 (2)

LSA, left subclavian artery; *RSA*, right subclavian artery; *SINE*, stent graft induced new entry; *TEVAR*, thoracic endovascular aneurysm repair.
Data are presented as number (%) or mean ± standard deviation.

Table II provides a detailed overview of operative characteristics. Regarding the LSA revascularization specifically, a LCCA to LSA bypass was performed in most cases (72%). Almost all bypasses were performed using a central, supraclavicular approach (97%); only two bypasses were performed using an infraclavicular approach to the LSA (3%).[31,32] Median diameter of the bypass was 6 mm (range, 6-12 mm), and all but one vascular graft consisted of polyester (98%). Remaining LSA revascularizations were performed by LSA transposition to the LCCA (28%).

Table II. Operative characteristics

Characteristic	Value
Transposition	25 (28)
Bypass	65 (72)
Central approach	63 (97)
Infraclavicular approach	2 (3)
Diameter bypass	6 (6-12)
Bypass graft type	
Dacron (polyester)	59 (91)
Ringed PTFE	1 (2)
Intergard (polyester)	4 (6)
AlboGraft (polyester)	1 (2)
Significant TCD changes or asymmetric EEG peroperatively	16 (18)
Postoperative complications	
Ischemic stroke	2 (2)
Permanent sympathetic chain nerve palsy	3 (3)
Permanent phrenic nerve palsy	3 (3)
Permanent recurrent laryngeal nerve palsy	1 (1)
Reinterventions, cause	5 (6)
LSA stump bleeding	1 (1)
LVA bleeding	1 (1)
Chyle leakage	3 (3)
Plug placement for retrograde type II endoleak via LSA	1 (1)
Embolization for retrograde type II endoleak via LSA	1 (1)
Chyle leakage treated with medium-chain triglyceride diet	2 (2)
Overall mortality, cause	28 (31)
Aorta related mortality	2 (7)
Non-aorta related mortality	5 (18)
Unknown	21 (75)

EEG, Electroencephalography; LSA, left subclavian artery; LVA, left vertebral artery; PTFE, polytetrafluoroethylene; TCD, transcranial Doppler.
Data are presented as number (%) or median (range).

Postoperative complications were two ischemic strokes (2%), both in patients who underwent LSA to LCCA transposition concomitant to TEVAR. One was a posterior circulation stroke after planned TEVAR coverage of the orifice of the left vertebral artery arising from the aortic arch, which ended as a posterior inferior cerebellar artery. This was not visible on preoperative imaging. The second was a central stroke located in the left hemisphere. During TEVAR and scallop manipulation in the LCCA, micro-embolic events were noted on transcranial Doppler. No permanent spinal cord ischemia was found. Remaining postoperative complications are presented in Table II.

Two late occlusions occurred; the first at 7.7 months and the second at 12.9 months follow-up. Median follow-up was 42.4 months (25th-75th percentile, 15.4-67.4 months) for freedom from occlusion. Primary indications for surgery were a post-dissection dilatation of the distal aortic arch and proximal LSA (type B aortic dissection) for the first, and a subacute type B aortic dissection with the primary entry tear localized at the origin of the LSA for the second occlusion. Both were incidental findings at follow-up without clinical signs of left arm claudication. Both were LCCA to LSA bypasses performed using a 6-mm diameter bypass graft. The first according to an infraclavicular approach to the LSA, whereas the second was performed using a central, supraclavicular approach. Survival analysis showed a 97% ± 2% Kaplan-Meier estimate for freedom from occlusion at mid-term (5 years) and long-term (10 years) follow-up. Fig 1 shows the Kaplan-Meier curve for freedom from occlusion.

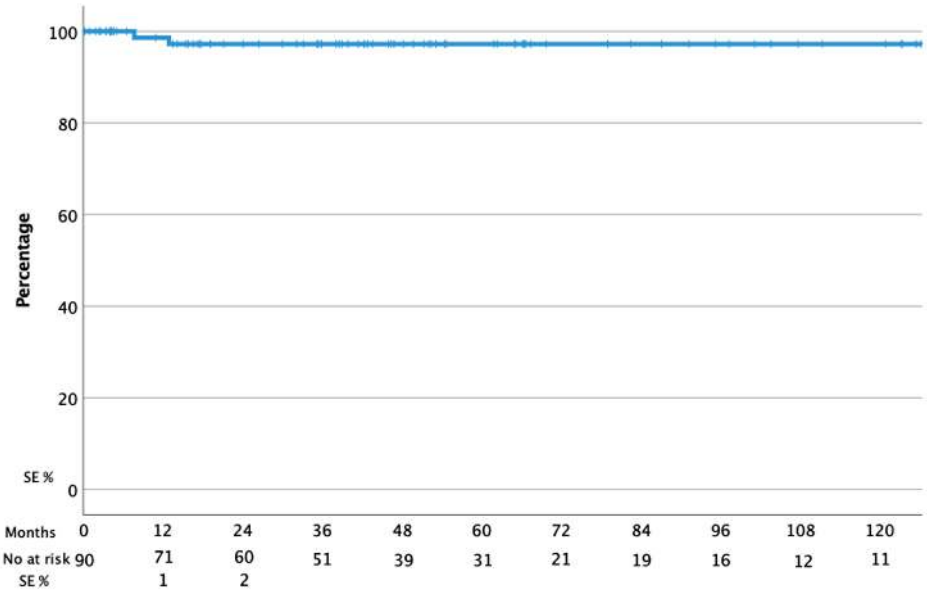

Figure 1. Freedom from occlusion over time. Number of events = 2. *SE*, Standard error.

Four severe stenoses occurred at 21.2 months, 35.4 months, 38.3 months, and 46.7 months, respectively. Median follow-up was 41.9 months (25th-75th percentile, 15.4-67.4 months) for freedom from severe stenosis. Primary indications for surgery were a saccular aneurysm of the distal aortic arch for the first two, one distal malperfusion of the left lower limb 5 months after a Stanford type B aortic dissection for the third, and one penetrating atherosclerotic ulcer of the distal aortic arch for the fourth severe stenosis. All stenoses were incidental findings at regular follow-up CT scans without clinical signs of arm claudic ation. All four were LCCA to LSA bypasses using a central, supraclavicular approach. The bypass with a stenosis at 21.2 months was performed using a 7-mm diameter bypass graft, whereas the remaining three were performed using a 6-mm diameter bypass graft. Survival analysis showed a 90% ± 4% Kaplan-Meier estimate for freedom from severe stenosis at mid-term (5 years) and long-term (10 years) follow-up. Fig 2 shows the Kaplan-Meier curve for freedom from severe stenosis.

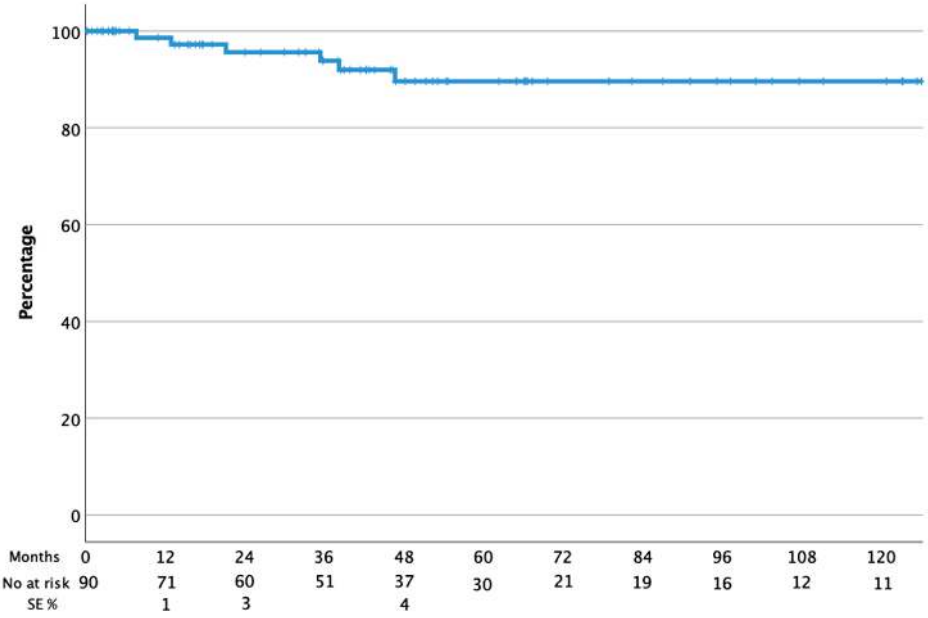

Figure 2. Freedom from severe stenosis over time. Number of events = 6. *SE*, Standard error.

During follow-up, 28 patients (31%) died. Median follow-up was 49.0 months (25th-75th percentile, 26.9-81.9 months). Two deaths (7%) were aorta-related, five deaths (18%) were non-aorta related; the remaining 21 causes were unknown (75%). One patient (4%) died in-hospital at 0.4 months due to hypoxic cardiac arrest. For the entire cohort, the estimated survival rates at 1, 5, and 10 years were 98% ± 2%, 77% ± 5%, and 55% ± 8%, respectively. Supplementary Fig 1 (online only) and Supplementary Fig 2 (online only)

show the Kaplan-Meier curves for freedom from overall mortality and freedom from aorta-related mortality.

DISCUSSION

It is becoming increasingly important to manage the supra-aortic vessels by either conventional surgical debranching techniques or newer endovascular options, including custom-made stent graft devices, as TEVAR is moving more and more to the proximal aorta in specific clinical situations. Often, when endografts land in zone 2 of the aortic arch, antegrade flow to the LSA needs to be preserved. Our results show that surgical LSA revascularization is associated with a low risk of complications and high patency rates in the long-term, with an estimated 97% of patients free from occlusion and 90% free from severe stenosis at 10-year follow-up.

Our patency rates are comparable to the findings of several recent (<10 years) reports on LCCA to LSA bypass and transposition short- and mid-term patency rates in the context of TEVAR. Table III provides a detailed overview of the reported patency rates in the literature according to the type of disease, type of revascularization, and follow-up duration. In brief, Zamor et al[12] reported 100% primary patency rates for 60 revascularizations with less than 5 years of follow-up, Scali et al[14] reported 94% primary patency rates at 3 years of follow-up, whereas Voigt et al[22] found 97% primary patency at 5 years, all three in the context of TEVAR. Moreover, Protack et al[15] stratified their patency rates according to the type of revascularization in the context of TEVAR, and found high primary patency rates (98%) for a large number of LCCA to LSA bypasses (n = 269) and even higher (100%) for their transposition subgroup (n = 19).

Two authors compared a LCCA to LSA bypass subgroup with a chimney graft subgroup.[16,21] Piffaretti et al[16] reported 100% primary patency for both subgroups at a mean follow-up of 24 ± 21 months, whereas Xiang et al[21] also found 100% primary patency in the bypass subgroup compared with a lower primary patency rate (96%) in the chimney subgroup at a median follow-up duration of 26.2 months.

It is important to take the indications for surgery into account when comparing several studies reporting their outcomes of LSA revascularization. When performed concomitant or adjacent to TEVAR for a type B aortic dissection for example, the expected success rate regarding patency might be higher as compared with a LSA revascularization being performed in the context of arterial occlusive disease (AOD) with a significant LSA stenosis or occlusion. This is reflected by the lower LSA revascularization patency rates

Table III. Summary of reported patency rates in literature

Author, year	Revascularizations, n	Type of disease, n (%)	Type of revascularization, n (%)	Mean follow-up duration, months	Reported patency rates	At n months, for n patients
Zamor, 2015[12]	60	Debranching for TEVAR: 60 (100)	CSB, 22 (37) SCT, 38 (63)	24.9 ± –	Primary patency: 100%	At <60 months, for 47 patients
Gombert, 2018[13]	107	AOD: 46 (43) Debranching for TEVAR: 61 (57)	CSB, 63 (58.8) CCB, – (–) CCSB, – (–)	42 ± 34.1	Primary patency: 95% (SE 2.6%) Secondary patency: 98% (SE 1.8%)	At 36 months, for 96 patients
Scali, 2013[14]	139	AOD: 38 (27) Debranching for TEVAR: 101 (73)	CSB, 132 (95) SCT, 7 (5)	16 ± 24.8	Primary patency (AOD): 73% (SE >10% after 30 months) Primary patency (TEVAR): 94% (SE >10% after 30 months)	At 36 months, for - patients
Protack, 2020[15]	288	Debranching for TEVAR: 288 (100)	CSB, 269 (93%) SCT, 19 (7)	50.4 ± –	Primary patency (CSB): 98% (–) Primary patency (SCT): 100% (–)	At 60 months, for – patients
Piffaretti, 2018[16]	73	Debranching for TEVAR: 73 (100)	CSB, 42 (58) CG, 31 (42)	24 ± 21	Primary patency: 100%	At – months, for 73 patients
Cinà, 2002[17]	23	AOD: 23 (100)	SCT, 23 (100)	25 ± 21	Primary patency: 100%	At – months, for 23 patients
Woo, 2008[18]	42	Debranching for TEVAR: 42 (100)	CSB, 37 (88) SCT, 5 (12)	11 ± –	Primary patency: 100%	At – months, for 42 patients
Peterson, 2006[19]	23	Debranching for TEVAR: 23 (100)	CSB, 2 (9) SCT, 21 (91)	18 ± –	Primary patency: 100%	At – months, for 23 patients
Edwards, 1994[20]	186	AOD: 186 (100)	CSB, 9 (5) SSB, 1 (0.5) CBB, 1 (0.5) SCT, 175 (94)	46 ± –	Primary patency: >99%	At >24 months, for 114 patients
Xiang, 2018[21]	38	Debranching for TEVAR: 38 (100)	CSB, 14 (37) CG, 24 (63)	Median 26.2 (–)	Primary patency (CSB): 100% Primary patency (CG): 96%	At – months, for 38 patients
Voigt, 2019[22]	112	Debranching for TEVAR: 88 (79)	CSB, 112 (100)	27 ± 26	Primary patency: 97%	At 60 months, for 92 patients

AOD, Arterial occlusive disease; *CBB,* carotid-brachial bypass; *CCB,* carotid-carotid bypass; *CCSB,* carotid-carotid-subclavian bypass; *CG,* chimney graft; *CSB,* carotid-subclavian bypass; *SCT,* subclavian-carotid transposition; *SE,* standard error; *SSB,* subclavian-subclavian bypass; *TEVAR,* thoracic endovascular aneurysm repair.
Data reported as n (%), median (range) or mean ± standard deviation.
– denotes missing data.

in the context of AOD reported by Scali et al.[14] They performed 38 revascularizations in this context and reported 73% primary patency rates at 3 years of follow-up. In contrast to these findings, Gombert et al[13] found a 95% primary patency rate at 3 years of follow-up; however, these revascularizations were performed in both contexts of TEVAR and AOD. After treatment for one occlusion and three stenoses, a secondary patency rate of 98% was reported. Moreover, an older report by Edwards et al[20] reported one occlusion (0.6%) at 26 months of follow-up for 178 LSA transpositions performed in the context of AOD with a mean follow-up duration of 42 ± 34.1 months.

An overview of the revascularization specifications and indications for surgery for the observed occlusions and stenoses in our cohort can be found in Table IV. In the occlusion that occurred at 7.7 months, we opted to revascularize the LSA using an infraclavicular approach to the LSA because there were dense adhesions present at the medial and centrally located part of the LSA and because the LSA was also dissected. Moreover, the follow-up CT scan was performed earlier than usual because the second follow-up CT scan at 0.7 months showed a kink in the bypass course caudal to the clavicle.

Table IV. Revascularization specifications and indications for surgery for the observed occlusions and severe stenoses

Event at n months follow-up	Indication for surgery	Specification of revascularization	Surgical approach
Occlusion at 7.7 months	Post-dissection aortic aneurysm	Bypass, 6-millimeter, Dacron graft	Infraclavicular approach
Occlusion at 12.9 months	Type B aortic dissection	Bypass, 6-millimeter, ringed PTFE graft	Central, supraclavicular approach
Severe stenosis at 21.2 months	Saccular aortic aneurysm	Bypass, 7-millimeter, Dacron graft	Central, supraclavicular approach
Severe stenosis at 35.4 months	Saccular aortic aneurysm	Bypass, 6-millimeter, Dacron graft	Central, supraclavicular approach
Severe stenosis at 38.3 months	Type B aortic dissection	Bypass, 6-millimeter, Dacron graft	Central, supraclavicular approach
Severe stenosis at 46.7 months	Penetrating aortic ulceration	Bypass, 6-millimeter, Dacron graft	Central, supraclavicular approach

PTFE, Polytetrafluoroethylene.

Interestingly, all revascularizations showing later occlusion or severe stenosis were LCCA to LSA bypasses. We found no occlusions or stenoses in the LSA to LCCA transposition subgroup (n = 25; 28%), and this corresponds with most findings in literature as shown in Table III.[13,17,20] No bypass in this study was performed as isolated procedure for AOD of the LSA. Unfortunately, the numbers were too small to investigate a correlation between

patient's risk factors, medical history, bypass graft type, anticoagulation use, or indications for surgery and the occurrence of a severe stenosis, occlusion, or the absence of those. Thus, they can rather be declared as coincidental findings. However, one highlight and a possible explanation for the occlusion using the infraclavicular approach might be the kink in the bypass caudal to the clavicle. Using this approach, the bypass stretches over a longer distance and passes under the clavicle, which might be posed as a risk factor for later occlusion, as we report one occlusion in two LCCA to LSA bypass using the infraclavicular approach. Moreover, the fact that the LSA was dissected up until the infraclavicular part might also be a partial explanation for the occurred occlusion due to the altered flow patterns in the dissected LSA. We opt for the infraclavicular approach if the most preferred central, supraclavicular approach is technically not feasible, due to the presence of dense adhesions at the proximal and most medial LSA, a functional left internal mammary artery coronary artery bypass graft is present, or this part of the LSA is dissected. A third option is the supraclavicular approach in which the distal anastomosis of the LCCA to LSA bypass is made posterior to the anterior scalene muscle, which is thus at a more laterally located part of the LSA.[33] Using this approach, the supraclavicular incision used in the central, supraclavicular approach is extended laterally, and specific attention must be paid to the nearby brachial plexus in this region.

In the severely stenosed subgroup, patients did not show any sign of clinical left arm malperfusion such as left arm claudication or spinal cord ischemia and they were managed conservatively with regular follow-up intervals. The occlusion that occurred at 12.9 months did not present with clinical signs of left arm claudication, but this occlusion was found on consecutive follow-up CT scans. After thorough clinical examination and multidisciplinary consultation, we decided to perform a redo-operation using the supraclavicular approach. This bypass also occluded at 1.2 months follow-up, and the patient showed signs of left arm claudication for which an extra-anatomical bypass from the descending aorta to the left subclavian artery through left thoracotomy was performed. This bypass was patent at most recent follow-up CT scan at 117 months of follow-up. The occlusion that occurred at 7.7 months was managed conservatively, as this patient showed no clinical signs of left arm claudication up until the last follow-up at 60.6 months.

Limitations of this study include the retrospective collection of data and the relatively small patient population with a low event rate, which did not allow for analysis of risk factors for occlusion or severe stenoses.

In the current endovascular era, alternative endovascular techniques to preserve antegrade LSA flow are rapidly expanding. This data on long-term patency of open surgical

LSA revascularization may serve as a benchmark with which alternative approaches can be compared. Together with the previously well-described operative risks associated with this procedure, this can aid in providing the safest treatment option for our patients.

CONCLUSIONS

Open surgical LSA revascularization is associated with excellent patency rates at mid-term and long-term follow-up, and may be considered the gold standard to preserve antegrade LSA flow in the context of aortic arch debranching prior to TEVAR or open surgical repair without AOD.

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Comparison of open and endovascular left subclavian artery revascularization for zone 2 thoracic endovascular aortic repair ☆

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ARTICLE HIGHLIGHTS

- **Type of research:** Multicenter, retrospective, observational cohort study of real-world data in the Vascular Quality Initiative (VQI).
- **Key Findings:** In 2,489 patients undergoing zone 2 TEVAR and LSA revascularization stratified by revascularization type (74% open *vs.* 26% any endovascular), endovascular patients experienced lower stroke rates but had comparable rates of spinal cord ischemia and perioperative mortality.
- **Take Home Message:** In patients undergoing zone 2 TEVAR and LSA revascularization, endovascular revascularization had lower rates of postoperative stroke and overall composite in-hospital complications, but similar spinal cord ischemia, perioperative and 5-year mortality rates compared with open LSA revascularization.

ABSTRACT

Objective: In patients undergoing elective thoracic endovascular aortic repair (TEVAR) and left subclavian artery (LSA) coverage, routine preoperative LSA revascularization is recommended. However, in the current endovascular era, the optimal surgical approach is debated. We compared baseline characteristics, procedural details, and perioperative outcomes of patients undergoing open or endovascular LSA revascularization in the setting of TEVAR.

Methods: Adult patients undergoing TEVAR with zone 2 proximal landing and LSA revascularization between 2013-2023 were identified in the Vascular Quality Initiative. We excluded patients with traumatic aortic injury, aortic thrombus, or ruptured presentations, and stratified based on revascularization type (open *vs.* any endovascular). Open LSA revascularization included surgical bypass or transposition. Endovascular LSA revascularization included single-branch, fenestration, or parallel stent grafting. Primary outcomes were stroke, spinal cord ischemia, and perioperative mortality (Pearson's χ^2-test). Multivariable logistic regression was used to evaluate associations between revascularization type and primary outcomes. Secondarily, we studied other in-hospital complications and 5-year mortality (Kaplan-Meier, multivariable Cox-regression). Sensitivity analysis was performed in patients undergoing concomitant LSA revascularization to TEVAR alone.

Results: Of 2,489 patients, 1,842 (74%) underwent open and 647 (26%) received endovascular LSA revascularization. Demographics and comorbidities were similar between open and endovascular cohorts. Compared with open, endovascular revascularization

had shorter procedure times (median 135 *vs.* 174min, p<.001), longer fluoroscopy time (median 23 *vs.* 16min, p<.001), lower estimated blood loss (median 100 *vs.* 123ml, p<.001), and less preoperative spinal drain use (40% *vs.* 49%, p<.001). Patients undergoing endovascular revascularization were more likely to present urgently (24% *vs.* 19%) or emergently (7.4% *vs.* 3.4%) (p<.001). Compared with open, endovascular patients experienced lower stroke rates (2.6% *vs.* 4.8%, p=.026; aOR 0.50[95%C.I., 0.25-0.90]), but had comparable spinal cord ischemia (2.9% *vs.* 3.5%, p=.60; 0.64[0.31-1.22]) and perioperative mortality (3.1% *vs.* 3.3%, p=.94; 0.71[0.34-1.37]). Compared with open, endovascular LSA revascularization had lower rates of overall composite in-hospital complications (20% *vs.* 27%, p<.001; 0.64[0.49-0.84]) and shorter overall hospital stay (7 *vs.* 8 days, p<.001). After adjustment, 5-year mortality was similar among groups (aHR 0.85[0.64-1.13]). Sensitivity analysis supported the primary analysis with similar outcomes.

Conclusions: In patients undergoing TEVAR starting in zone 2, endovascular LSA revascularization had lower rates of postoperative stroke and overall composite in-hospital complications, but similar spinal cord ischemia, perioperative and 5-year mortality rates compared with open LSA revascularization. Future comparative studies are needed to evaluate the mid- to long-term safety of endovascular LSA revascularization and assess differences between specific endovascular techniques.

INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) has become the primary treatment option for thoracic aortic disease involving the distal aortic arch and descending aorta (Ishimaru zones 2 – 5).[1–3] For proximal aortic arch disease or pathology involving the ascending aorta (zone 0 – 1), TEVAR provides a feasible hybrid adjunct as an alternative to open repair among high-risk patients.[1–3]

In contrast to TEVAR of descending thoracic aortic disease, involvement of the aortic arch necessitates supra-aortic branch management.[2,4,5] With zone 2 coverage, preserving antegrade left subclavian artery (LSA) flow by performing revascularization is recommended based on a reduced risk of perioperative neurological events such as stroke and spinal cord ischemia (SCI).[2,3,6–12] Open surgical LSA revascularization with bypass or transposition has traditionally been performed and favorable long-term patency has been demonstrated.[13,14] More recent endovascular alternatives like chimney grafts, single-branched, fenestrated (e.g., in-situ laser), scalloped, or physician-modified devices are rapidly emerging, and have shown to be technically feasible with acceptable short- to mid-term results.[15–19]

Based on this, open surgical LSA revascularization has traditionally been considered the gold standard, so endovascular alternatives have been compared to this historical benchmark. Notably, two recent meta-analyses compared open and endovascular LSA revascularization techniques and found similar perioperative complication and mortality rates in both groups, based on low-grade evidence from heterogeneous studies.[20,21] Therefore, the need for additional well-designed (comparative) studies with large sample sizes was highlighted by these authors and others.[20] In this study, we aimed to contribute to the existing evidence by comparing the perioperative outcomes of open surgical to any endovascular LSA revascularization in the setting of TEVAR starting in zone 2.

MATERIALS AND METHODS

Study design and data source

This is a retrospective observational cohort study utilizing prospectively collected data from the Society for Vascular Surgery Vascular Quality Initiative (SVS-VQI) registry (http://www.vqi.org/). This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[22] and has been approved by the Beth Israel Deaconess Medical Center Institutional Review Board (2021P000131). Patients'

informed consent was waived due to the retrospective and de-identified nature of the data.

Study cohort and stratification

Of all procedures in the TEVAR/Complex EVAR module as of May 2023 (n=25,862), we identified those patients who underwent TEVAR with a proximal landing in zone 2 and underwent LSA revascularization (n=2,489). We did not restrict the cohort based on distal landing zone. Patients with traumatic aortic injury (n=2,128), aortic thrombus (n=171), proximal landing zone other than zone 2 (n=18,786), aortic rupture (n=258), or missing data were excluded from the analyses (**Figure 1**). We then stratified the final cohort (n=2,489) based on either open (i.e., surgical bypass or transposition) or endovascular LSA revascularization.

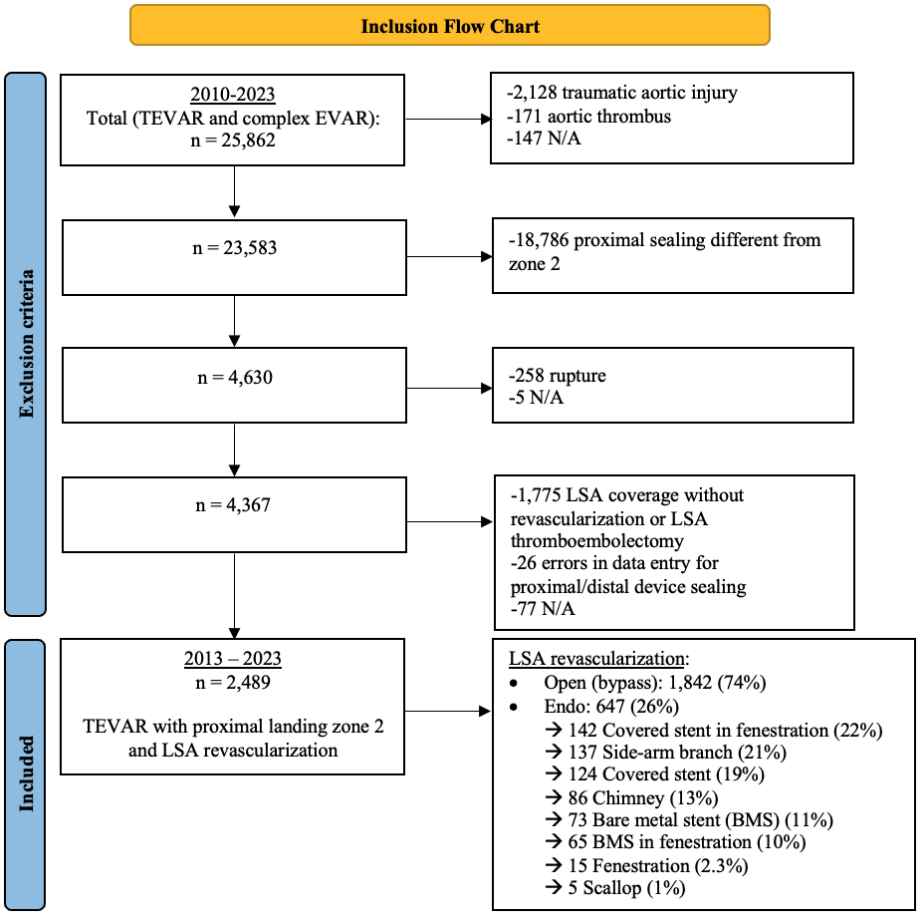

Figure 1. Flow chart of patient selection.

Variables and definitions

We identified baseline patient characteristics (i.e., demographics, comorbidities), pathology and anatomic details, procedural details, and perioperative outcomes (i.e., major complications during index hospitalization, perioperative mortality, length of intensive care [ICU] and hospital stay). The VQI data dictionary stipulates nine groups to specify endovascular LSA revascularization techniques (Supplementary Table SI). Bare metal stent (BMS) or covered stent groups are specified as not through a graft fenestration or branch nor as chimney, unless otherwise specified. Chimney referral includes parallel stent grafting like chimney, snorkel, periscope, and sandwich configurations. Side-arm branch descriptions in the registry include internal or external directional graft branches with a bridging covered stent in the LSA.

Body mass index (BMI) was categorized as five categories (i.e., underweight: <18.5kg/m^2, normal: 18.5-25kg/m^2, overweight 25-30kg/ m^2, obese 30-40kg/m^2, morbidly obese ≥40kg/m^2 and obesity as BMI ≥30kg/m^2). Renal function was categorized as four categories (i.e., estimated glomerular filtration rate [eGFR] >60ml/min/1.73m^2, eGFR 45-60ml/min/1.73m^2, eGFR 30-45ml/min/1.73m^2, eGFR <30ml/min/1.73m^2).[23] Anemia was defined as a preoperative hemoglobin level <10 g/dL. Aortic diameter was defined as the maximum diameter within the treated aortic segment.

Annual hospital and surgeon volumes were computed as the number of TEVARs (for any pathology) with a proximal landing zone ≤5 performed over a one-year period preceding each procedure and were further categorized into quintiles.[24] Hospitals and surgeons in the first volume quintile were categorized as low-volume (LV), the highest quintile as high-volume (HV), and the middle three quintiles as medium-volume (MV).[24]

A composite variable for any in-hospital postoperative complication was defined as the occurrence of either stroke, SCI, acute kidney injury (AKI), reintubation, pneumonia, new dialysis (temporary or permanent), bowel ischemia, leg ischemia, myocardial infarction, congestive heart failure, or reintervention during index hospitalization. New postoperative stroke included both ischemic and hemorrhagic events. AKI was defined according to the guidelines of the Kidney Guidelines Improving Global Outcomes (KDIGO)-criteria as a ≥1.5 times increase from baseline serum creatinine.[25] Perioperative mortality was defined as death due to any cause occurring within 30 days or during index hospitalization if the primary admission exceeded 30 days.

Outcomes

The primary outcomes were in-hospital stroke, SCI, and perioperative mortality. Secondarily, we studied other in-hospital complications and 5-year mortality.

Table SI. Variable of the TEVAR/Complex EVAR module of the VQI stipulating the specific LSA branch treatment performed concomitant or adjacent to zone 2 TEVAR.

BRANCH_LSUB_TRT variable	Help text
1. Purposely covered	Intentionally covered by a stent graft without embolization
2. Unintentionally covered	Covered by a stent graft without planning to do so, can be due to device malfunction or mal-deployment
3. Occluded-coil	Occlusion of branch vessel using coil embolization methods
4. Occluded-plug	Occlusion of branch vessel using plug devices such as the Amplatzer
5. Occluded-open	Occlusion of branch by open surgical technique
6. Stent	Bare metal stent without graft material placed in a vessel NOT through a graft fenestration or branch, and NOT in chimney configuration
7. Stent graft	Covered stent placed in a vessel NOT through a graft fenestration or branch and NOT in chimney configuration
8. Chimney	Branch vessel stent or stent graft placed in parallel stent configuration alongside an aortic stent graft. Includes "chimney, snorkel, periscope, and sandwich" configurations
9. Scallop	Opening in the grafted portion of the aortic stent graft at the proximal or distal edge of the aortic graft (such that graft material surrounds only a portion of the opening) with no stent/stent graft through the scallop
10. Stented Scallop	Scallop WITH a stent/stent graft into the branch vessel through the scallop
11. Fenestration	Opening in the grafted portion of the aortic stent graft with graft material on all sides, NO stent/stent graft placed through the opening
12. Stented-fen	Fenestration with a bare metal stent through the graft opening
13. Fen-branch	Fenestration with a covered stent through the fenestration
14. Side-arm branch	Directional graft branch (can be internal or external) with a bridging stent graft placed into the branch vessel
15. Surgical bypass	Bypass graft or transposition, a so-called de-branching procedure
16. Thromboembolectomy	Removal of thrombus or embolus to restore patency;
17. Iliac device	Any device intended as a modular component of an endovascular aortic aneurysm repair (EVAR); Excludes bare stents, and stent grafts not primarily intended to be used with EVAR such as Gore Viabahn or Atrium iCAST devices

Statistical analysis

Continuous variables were presented as median [interquartile range (IQR): 25^{th}-75^{th} percentile] and compared with the Wilcoxon rank-sum test. Normality was evaluated with the Shapiro-Wilk test. Categorical variables were presented as numbers and percentages and were compared with Pearson's χ^2-test. Multivariable logistic regression was used to evaluate the association between type of revascularization and in-hospital complications and perioperative mortality. The following clinically relevant or statistically significant adjustment variables were selected: age (continuous/year), sex (male/female), race

(white/black/Asian/Hispanic/other), aortic diameter (continuous/mm), renal function (eGFR>60, 45-59, 30-44, <30), overall TEVAR hospital volume (LV: ≤13/year, MV: 14-80/year, HV: ≥81/year), treatment urgency (elective/urgent/emergent), aortic coverage length (i.e., number of aortic zones covered), and surgery year. We estimated 5-year mortality using survival analysis (Kaplan-Meier) and Cox proportional-hazard modeling. Cohorts were compared using the log-rank test. For 5-year mortality, we adjusted for the variables mentioned above and for BMI, history of smoking, type of pathology, treatment length, diabetes categories, prior percutaneous coronary intervention, and chronic obstructive pulmonary disease. Aortic diameter, treatment urgency, and surgery year were not included in the Cox-regression. Additionally, we studied monotonic upward or downward trends in the proportions of surgical approaches over the study period with the Mann-Kendall test. Statistical significance level was set at 5% (α=.050). All statistical analyses were performed using R version 4.3.2 (http://www.r-project.org).

Sensitivity analysis for TEVAR procedures and concomitant LSA revascularization alone

In our cohort, we identified those patients who underwent LSA revascularization on the same day as their TEVAR procedure (n=1,717). Patients with missing data on the days between LSA revascularization and TEVAR variable were considered to have undergone same day LSA revascularization (n=1,609, open: n=1,024 [92%], endo: n=585 [97%]). For these patients, we verified with another dedicated variable which specified that no staged LSA branch treatment was performed and excluded five additional patients (staged LSA treatment: n=4, missing data: n=1, final cohort: n=1,712). As in the primary analysis, we stratified based on either open or endovascular LSA revascularization and evaluated primary and secondary outcomes accordingly.

RESULTS

Of 2,489 patients that underwent zone 2 TEVAR and LSA revascularization between 2013-2023, 1,842 (74%) underwent open and 647 (26%) received endovascular LSA revascularization. Endovascular procedures included covered stent within fenestration (22%), side-arm branch (21%), covered stent (19%), chimney (13%), BMS (11%), BMS in fenestration (10%), fenestration (2.3%), or scallop (0.8%). Procedures were performed at 148 hospitals, of which 86 (58%) performed both open and endovascular LSA revascularization.

Table I presents demographics and comorbidities. Between cohorts, there were no differences regarding age, sex, BMI, or any of the other baseline characteristics except in

the endovascular group there was lower pre-hospital aspirin use (49% *vs.* 54%, p=.049), higher P2Y12-inhibitor use (8.8% *vs.* 5.0%, p<.001), and lower anticoagulation exposure (14% *vs.* 17%, p=.031).

Table I. Baseline characteristics of 2,489 patients undergoing zone 2 TEVAR stratified by open surgical or endovascular LSA revascularization.

Variable	Open LSA (n = 1,842)	Endo LSA (n = 647)	P-value*
Age, years	65 [56-73]	66 [56-74]	.061
Sex, male	1,236 (67%)	438 (68%)	.78
Race			**.018**
White	1,034 (56%)	344 (53%)	
Black	506 (28%)	162 (25%)	
Asian	84 (4.6%)	36 (5.6%)	
Hispanic	39 (2.1%)	23 (3.6%)	
Other	18 (1.0%)	14 (2.2%)	
BMI, kg/m^2			.49
Underweight	53 (2.9%)	18 (2.8%)	
Normal	460 (25%)	165 (26%)	
Overweight	672 (37%)	236 (37%)	
Obese	573 (31%)	188 (29%)	
Morbidly Obese	83 (4.5%)	40 (6.2%)	
Smoking			.17
Prior	688 (37%)	226 (35%)	
Current	535 (29%)	178 (28%)	
Hypertension	1,680 (91%)	595 (92%)	1
Diabetes mellitus			.97
On diet	65 (3.5%)	24 (3.7%)	
Non-insulin dependent	144 (7.8%)	50 (7.7%)	
Insulin dependent	53 (2.9%)	18 (2.8%)	
Renal function			.057
eGFR >60	1,265 (69%)	411 (64%)	
eGFR 45-60	315 (17%)	133 (21%)	
eGFR 30-45	142 (7.7%)	51 (7.9%)	
eGFR <30	70 (3.8%)	34 (5.3%)	
On dialysis	50 (2.7%)	18 (2.8%)	.78
Anemia, Hb <10g/dl	354 (19%)	117 (18%)	.56
COPD			.44

Table I. Baseline characteristics of 2,489 patients undergoing zone 2 TEVAR stratified by open surgical or endovascular LSA revascularization. (*continued*)

Variable	Open LSA (n = 1,842)	Endo LSA (n = 647)	P-value*
No treatment	95 (5.2%)	41 (6.3%)	
On medication	239 (13%)	83 (13%)	
On home oxygen	42 (2.3%)	20 (3.1%)	
Congestive heart failure			.44
NYHA I-II	182 (9.9%)	74 (11%)	
NYHA III-IV	23 (1.2%)	10 (1.5%)	
Prior myocardial infarction	202 (11%)	67 (10%)	.71
Prior CABG	138 (7.5%)	40 (6.2%)	.31
Prior PCI	163 (8.8%)	71 (11%)	.13
Medication use			
Aspirin	991 (54%)	318 (49%)	**.049**
P2Y12-inhibitor	92 (5.0%)	57 (8.8%)	**< .001**
Anticoagulant	320 (17%)	88 (14%)	**.031**
Statin	1,034 (56%)	364 (56%)	.98
Betablocker	1,464 (80%)	509 (79%)	.74
ACE-I/ARB	957 (52%)	319 (49%)	.28
Antiplatelet therapy			**.038**
No antiplatelet therapy	824 (45%)	306 (47%)	
Single antiplatelet therapy	951 (52%)	305 (47%)	
Dual antiplatelet therapy	66 (3.6%)	35 (5.4%)	
Genetic aortopathy			.48
Marfan	30 (1.6%)	9 (1.4%)	
Ehlers-Danlos	2 (0.1%)	0 (0%)	
Loeys-Dietz	1 (0.1%)	2 (0.3%)	
Non-specific	50 (2.7%)	17 (2.6%)	
Prior aortic surgery			.64
Open surgery	322 (18%)	120 (19%)	
Endovascular surgery	137 (7.4%)	52 (8.0%)	
Both	41 (2.2%)	10 (1.5%)	

*Independent samples t-test, Wilcoxon rank sum test, or Pearson's χ^2-test where appropriate. Data are reported as median [interquartile range] for continuous variables and as number (percentage) for categorical variables. Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention.

Table II presents pathology and presentation details. In both cohorts, the most frequent indications for repair were aortic dissection (open: 46%; endo: 45%) and aneurysm (open: 30%; endo: 27%), without significant differences in proportions between cohorts (p=.51). Compared with the open cohort, the endovascular revascularization cohort had smaller maximum aortic diameters (48 [39-58] *vs.* 50 [40-60] mm, p=.002). The presentation was similar between cohorts (asymptomatic: 50% *vs.* 47%, symptomatic: 50% *vs.* 53%, p=.21).

Table II. Pathology and presentation details of 2,489 patients undergoing zone 2 TEVAR stratified by open surgical or endovascular LSA revascularization.

Variable	Open LSA (n = 1,842)	Endo LSA (n = 647)	P-value*
Indication for surgery			.51
Aneurysm	554 (30%)	175 (27%)	
Dissection	838 (46%)	293 (45%)	
Post-dissection aneurysm	233 (13%)	89 (14%)	
PAU	121 (6.6%)	47 (7.3%)	
IMH	53 (2.9%)	22 (3.4%)	
PAU and IMH	43 (2.3%)	21 (3.2%)	
Other	18 (1.0%)	14 (2.2%)	
Aortic diameter, mm	50 [40-60]	48 [39-58]	**.002**
Presentation			.21
Asymptomatic	859 (47%)	321 (50%)	
Symptomatic	983 (53%)	326 (50%)	
Presentation (in sensitivity analysis**)			**.004**
Asymptomatic	458 (41%)	293 (49%)	
Symptomatic	651 (59%)	310 (51%)	

*Independent samples t-test, Wilcoxon rank sum test, or Pearson's χ^2-test where appropriate. **Sensitivity analysis was performed in patients undergoing LSA revascularization concomitant to TEVAR alone, as opposed to staged (total cohort: n = 1,712 patients; open: n = 1,109 patients; endo: n = 603 patients). Data are reported as median [interquartile range] for continuous variables and as number (percentage) for categorical variables. Abbreviations: PAU: Penetrating Atherosclerotic Ulceration; IMH: Intramural Hematoma.

Table III presents procedural details. Compared with an open approach, endovascular revascularization had shorter median procedural time (135 [IQR, 102-191] *vs.* 174 [112-249] min, p<.001) and longer fluoroscopy time (23 [15-33] *vs.* 16 [10-25] min, p<.001), lower estimated blood loss (100 [50-200] *vs.* 123 [50-300] ml, p<.001), and less preoperative spinal drain use (40% *vs.* 49%, p<.001). The number of aortic zones covered were similar between cohorts (4 [3-4] *vs.* 4 [3-4], p=.30). Compared with open revascularization, patients undergoing endovascular LSA revascularization were less likely to be elective TEVARs (69% *vs.* 78%), and correspondingly presented with urgent (<24 hours: 24% *vs.* 19%), or emergent indications (<4 hours: 7.4% *vs.* 3.4%) (p<.001). Compared

with an open approach, endovascular revascularization was less frequently performed by LV and MV hospitals (LV: 6.8% *vs.* 10%; MV: 73% *vs.* 79%) and surgeons (LV: 8.5% *vs.* 13%; MV: 65% *vs.* 73%) but more commonly performed by HV hospitals (20% *vs.* 11%) and surgeons (27% *vs.* 14%) (p<.001).

Table III. Procedural details of 2,489 patients undergoing zone 2 TEVAR stratified by open surgical or endovascular LSA revascularization.

Variable	Open LSA (n = 1,842)		Endo LSA (n = 647)		P-value*
Total procedural time, min.	174	[112-249]	135	[102-191]	**< .001**
Total procedural time, min. (sensitivity analysis**)	210	[161-281]	136	[103-190]	**< .001**
Contrast use, ml	100	[65-150]	100	[70-140]	.81
Fluoroscopy time, min.	16	[10-25]	23	[15-33]	**< .001**
Fluoroscopy time, min. (sensitivity analysis**)	14	[10-22]	24	[15-34]	**< .001**
Days between staged procedures	0	[-2, 0]	0	[0, 0]	**< .001**
Aortic zones covered	4	[3-4]	4	[3-4]	.30
Estimated blood loss, ml	123	[50-300]	100	[50-200]	**< .001**
Estimated blood loss, ml (sensitivity analysis**)	200	[100-300]	100	[50-200]	**< .001**
>2 Packed RBC transfusions	87	(4.7%)	23	(3.6%)	.26
Spinal cord drainage					**< .001**
Preoperative	906	(49%)	259	(40%)	
Postoperative, prophylactic	30	(1.6%)	13	(2.0%)	
Postoperative, therapeutic	20	(1.1%)	4	(0.6%)	
Urgency					**< .001**
Elective	1,433	(78%)	443	(69%)	
Urgent (<24 hours)	345	(19%)	155	(24%)	
Emergent (<4 hours)	63	(3.4%)	48	(7.4%)	
Urgency (sensitivity analysis**)					**.017**
Elective	795	(72%)	408	(68%)	
Urgent (<24 hours)	261	(24%)	146	(24%)	
Emergent (<4 hours)	52	(4.7%)	48	(8.0%)	
Hospital volume					**< .001**
Low (≤13 procedures/year)	189	(10%)	44	(6.8%)	
Medium (14-80 procedures/year)	1,452	(79%)	472	(73%)	
High (≥81 procedures/year)	201	(11%)	131	(20%)	
Surgeon volume					**< .001**
Low (≤1 procedures/year)	243	(13%)	55	(8.5%)	
Medium (2-31 procedures/year)	1,345	(73%)	419	(65%)	
High (≥32 procedures/year)	254	(14%)	173	(27%)	
Anesthesia	1,824	(99%)	642	(99%)	.60

*Independent samples t-test, Wilcoxon rank sum test, or Pearson's χ^2-test where appropriate. **Sensitivity analysis was performed in patients undergoing LSA revascularization concomitant to TEVAR alone, as opposed to staged (total cohort: n = 1,712 patients; open: n = 1,109 patients; endo: n = 603 patients). Data are reported as median [interquartile range] for continuous variables and as number (percentage) for categorical variables. Abbreviations: RBC: Red Blood Cells.

Table IV presents perioperative outcomes. Compared with an open approach, endovascular revascularization was associated with a lower stroke risk (2.6% vs. 4.8%, p=.026; aOR 0.50[95%C.I., 0.25-0.90]), but comparable SCI (2.9% *vs.* 3.5%, p=.60; 0.64[0.31-1.22]) and perioperative mortality risk (3.1% *vs.* 3.3%, p=.94; 0.71[0.34-1.37]). Compared with an open approach, TEVAR procedures with endovascular LSA revascularization had lower rates of overall composite in-hospital complications (20% *vs.* 27%, p<.001; 0.64[0.49-0.84]). Regarding stroke type, there were heterogeneous differences in proportions between cohorts, although not significant (e.g., left carotid ischemic stroke: n=2 [0.3%] *vs.* n=18 [1.0%]). Length of ICU stay was similar between cohorts, while length of hospital stay was shorter after endovascular revascularization (7 [4-12] *vs.* 8 [4-13] days, p<.001).

Table IV. Univariable and multivariable outcomes of in-hospital complications and perioperative mortality in 2,489 patients undergoing zone 2 TEVAR stratified by open surgical or endovascular LSA revascularization.

Variable	Open LSA (n = 1,842)	Endo LSA (n = 647)	P-value*	aOR [95% C.I.] (Ref: Open LSA)	P-value
Stroke	88 (4.8%)	17 (2.6%)	**.026**	**0.50 [0.25-0.90]**	**.030**
Stroke type (brain location)			.23	-	-
Right carotid ischemic stroke	7 (0.4%)	0 (0%)		-	-
Left carotid ischemic stroke	18 (1.0%)	2 (0.3%)		-	-
Right vertebrobasilar ischemic stroke	8 (0.4%)	1 (0.2%)		-	-
Left vertebrobasilar ischemic stroke	11 (0.6%)	2 (0.3%)		-	-
Bilateral ischemic stroke	39 (2.1%)	9 (1.4%)		-	-
Hemorrhagic stroke	5 (0.3%)	3 (0.5%)		-	-
Spinal cord ischemia	64 (3.5%)	19 (2.9%)	.60	0.64 [0.31-1.22]	.20
Perioperative mortality	60 (3.3%)	20 (3.1%)	.94	0.71 [0.34-1.37]	.33
Any complication	493 (27%)	128 (20%)	**< .001**	**0.64 [0.49-0.84]**	**.002**
Acute kidney injury	172 (9.3%)	62 (9.6%)	.91	0.96 [0.65-1.39]	.82
Reintubation	134 (7.3%)	20 (3.1%)	**< .001**	**0.41 [0.22-0.71]**	**.003**
Pneumonia	61 (3.3%)	14 (2.2%)	.18	0.78 [0.35-1.58]	.51
Bowel ischemia	13 (0.7%)	7 (1.1%)	.51	-	-
Leg ischemia	19 (1.0%)	9 (1.4%)	.60	-	-
Myocardial infarction	25 (1.4%)	7 (1.1%)	.74	-	-
Congestive heart failure	15 (0.8%)	2 (0.3%)	.29	-	-
Postoperative dialysis	27 (1.4%)	17 (2.6%)	.14	-	-
In-hospital reintervention	217 (12%)	53 (8.2%)	**.014**	**0.60 [0.40-0.86]**	**.007**
Length of stay, ICU	3 [2-5]	3 [2-5]	.28	-	-
Length of hospital stay	8 [4-13]	7 [4-12]	**< .001**	-	-

*Wilcoxon rank sum test, or Pearson's χ^2-test where appropriate. Data are reported as median [interquartile range] for continuous variables and as number (percentage) for categorical variables. Models were adjusted for age (continuous/year), sex (male/female), race (white/black/asian/hispanic/other), aortic diameter (continuous/mm), renal function (eGFR <30, eGFR 30-45, eGFR 45-60, eGFR >60), overall TEVAR center volume (low/medium/high), treatment urgency (elective/urgent/emergent), aortic coverage length (number of aortic zones covered), and surgery year. Abbreviations: ICU: Intensive Care Unit; Ref.: Reference.

Estimated 5-year survival was 80% [95% C.I.: 75-85%] and 82% [95% C.I.: 80-85%] in the endovascular and open cohorts, respectively. After adjustment, 5-year survival was similar between cohorts (aHR 0.85 [0.64-1.13]) (**Figure 2**).

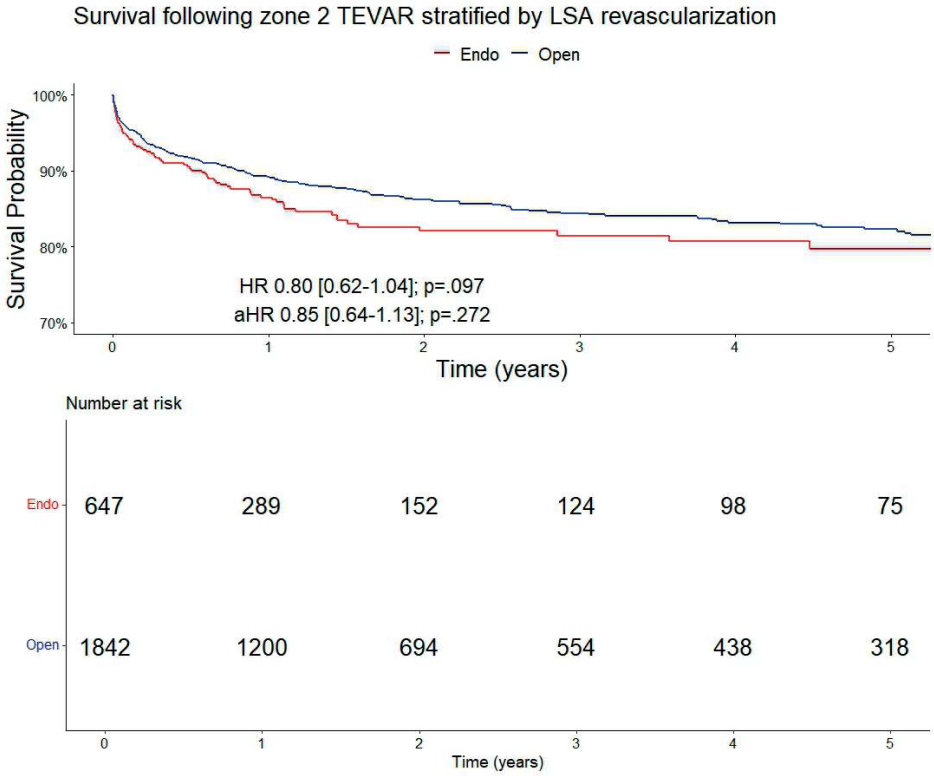

Figure 2. Estimated 5-year survival for patients undergoing zone 2 TEVAR stratified by open or endovascular LSA revascularization.

Given the lower-than-expected preoperative antiplatelet agent use in our population (<50% of patients, **Table I**), we examined primary and secondary outcomes after stratifying for aspirin, P2Y12-inhibitor use, or both, regardless of open or endovascular LSA revascularization. On univariable analysis, there were neither any differences between patients with or without aspirin nor between patients without, with single, or with dual antiplatelet therapy.

Trend analysis showed a downward trend for open revascularization over the study period (2013 to 2023: 100% to 22%, p<.001) whereas endovascular revascularization techniques showed a reciprocal upward trend (2013 to 2023: 0% to 78%, p<.001) (**Figure 3**). In our cohort, endovascular revascularization became more frequent than open revascularization in 2022 (**Figure 3**). More specifically regarding endovascular revascularization

type, there were upward trends for covered stent in fenestration (p<.001), covered stent (p=.011), BMS (p<.001), and BMS in fenestration (p=.008) groups. The side-arm branch group increased notably over the last 3 years (2021 to 2023: 0% to 28%) (**Figure 3**).

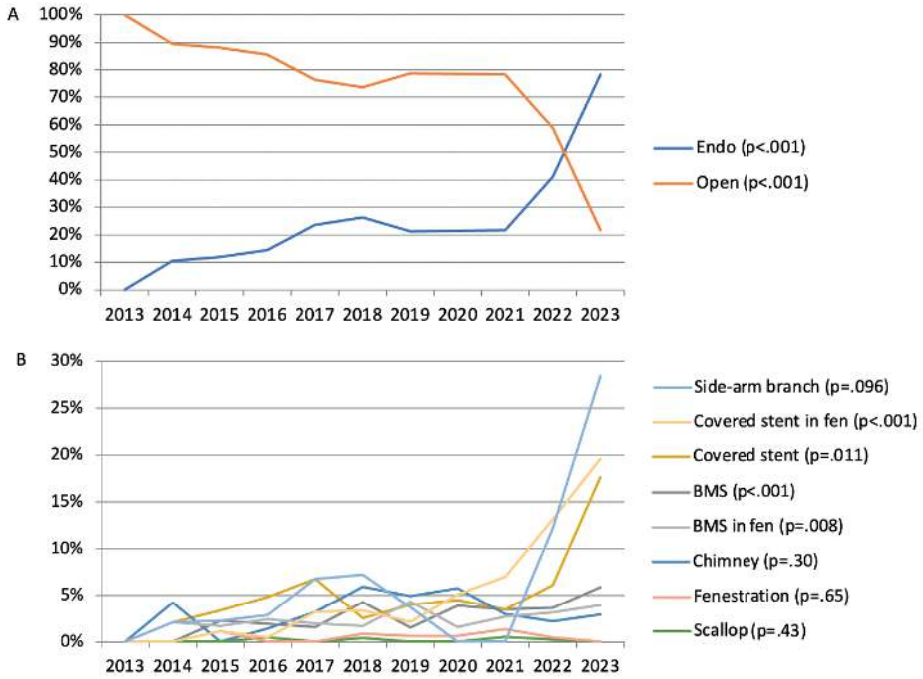

Figure 3. (A) Line-graphs visualizing trends in open and (any) endovascular LSA revascularization approach in the Vascular Quality Initiative over the study period. (B) Line-graphs visualizing trends in specific endovascular approaches separately in the Vascular Quality Initiative over the study period.

Sensitivity analysis in patients undergoing TEVAR and concomitant LSA revascularization

Of 1,712 (69%) patients undergoing concomitant LSA revascularization to TEVAR, 1,109 (65%) were open and 603 (35%) were endovascular revascularizations. Of note, compared with an open approach, patients undergoing endovascular revascularization were more likely to have an asymptomatic presentation (49% *vs.* 41%) (p=.004) (**Table II**).

Considering only LSA revascularization procedures performed at time of the index TEVAR, differences between cohorts regarding procedure time, fluoroscopy time, and estimated blood loss were enhanced, driven predominantly by a notable increase in these parameters among the open revascularization cohort (**Table III**). Specifically, compared with an open approach, endovascular revascularization had shorter procedure time (136 [103-190] min *vs.* 210 [161-281], p<.001), longer fluoroscopy time (24 [15-34] min

vs. 14 [10-22] min, p<.001), and lower estimated blood loss (100 [50-200] ml *vs.* 200 [100-300] ml, p<.001) (Table III).

Supplementary **Table SII** presents perioperative outcomes of our sensitivity analysis. Compared with an open approach, endovascular LSA revascularization had fewer stroke (2.8% *vs.* 5.0%, p=.041; aOR 0.60[95%C.I., 0.30-1.11]), similar spinal cord ischemia (2.7% *vs.* 3.5%, p=41; 0.68[0.30-1.43]), and similar perioperative mortality (3.3% *vs.* 3.5%, p=.94; 0.71[0.34-1.41]). Compared with an open approach, endovascular LSA revascularization had lower rates of overall composite in-hospital complication (20% *vs.* 29%, p<.001; 0.63[0.47-0.84]). Length of hospital stay was shorter after endovascular LSA revascularization (7 [3-12] *vs.* 8 [4-13] days, p=.001).

Table SII. Sensitivity analysis of perioperative outcomes in 1,712 patients undergoing zone 2 TEVAR and concomitant LSA revascularization stratified by open surgical or endovascular LSA revascularization.

Variable	Open LSA (n = 1,109)	Endo LSA (n = 603)	P-value*	aOR [95% C.I.] (Ref: Open LSA)	P-value
Stroke	56 (5.0%)	17 (2.8%)	**.040**	**0.60 [0.30-1.11]**	**.12**
Stroke type (brain location)			.15	-	-
Right carotid ischemic stroke	7 (0.6%)	0 (0%)		-	-
Left carotid ischemic stroke	12 (1.1%)	2 (0.3%)		-	-
Right vertebrobasilar ischemic stroke	3 (0.3%)	1 (0.2%)		-	-
Left vertebrobasilar ischemic stroke	7 (0.6%)	2 (0.3%)		-	-
Bilateral ischemic stroke	25 (2.3%)	9 (1.5%)		-	-
Hemorrhagic stroke	2 (0.2%)	3 (0.5%)		-	-
Spinal cord ischemia	39 (3.5%)	16 (2.7%)	.41	0.68 [0.30-1.43]	.33
Perioperative mortality	39 (3.5%)	20 (3.3%)	.94	0.71 [0.34-1.41]	.35
Any complication	318 (29%)	118 (20%)	**< .001**	**0.63 [0.47-0.84]**	**.002**
Acute kidney injury	107 (9.6%)	58 (9.6%)	1	1.00 [0.66-1.49]	.98
Reintubation	90 (8.1%)	16 (2.7%)	**< .001**	**0.27 [0.13-0.51]**	**< .001**
Pneumonia	39 (3.5%)	13 (2.2%)	.16	0.62 [0.26-1.31]	.23
Bowel ischemia	10 (0.9%)	7 (1.2%)	.79	-	-
Leg ischemia	12 (1.1%)	9 (1.5%)	.61	-	-
Myocardial infarction	13 (1.2%)	6 (1.0%)	.93	-	-
Congestive heart failure	4 (0.4%)	2 (0.3%)	1	-	-
Postoperative dialysis	20 (1.9%)	16 (2.6%)	.46	-	-
In-hospital reintervention	157 (14%)	47 (7.8%)	**< .001**	**0.49 [0.33-0.73]**	**< .001**
Length of stay, ICU	3 [2-5]	3 [2-5]	.13	-	-
Length of hospital stay	8 [4-13]	7 [3-12]	**.001**	-	-

*Wilcoxon rank sum test, or Pearson's χ^2-test where appropriate. Data are reported as median [interquartile range] for continuous variables and as number (percentage) for categorical variables. Models were adjusted for age (continuous/year), sex (male/female), race (white/black/asian/hispanic/other), aortic diameter (continuous/mm), renal function (eGFR <30, eGFR 30-45, eGFR 45-60, eGFR >60), overall TEVAR center volume (low/medium/high), treatment urgency (elective/urgent/emergent), aortic coverage length (number of aortic zones covered), and surgery year. Abbreviations: ICU: Intensive Care Unit; Ref.: Reference.

DISCUSSION

This study compared perioperative outcomes of open and endovascular LSA revascularization in the setting of TEVAR with proximal landing in zone 2. Patients undergoing TEVAR with endovascular LSA revascularization had almost half the postoperative stroke rates as compared with open LSA revascularization, and this difference remained in adjusted analyses. However, postoperative spinal cord ischemia, perioperative and 5-year mortality were similar between patients undergoing TEVAR with either open or endovascular LSA revascularization. Moreover, the incidence of any in-hospital complication as a composite outcome was lower with endovascular LSA revascularization. The relevance and reliability of these findings are underscored by the analogous results identified in our sensitivity analysis.

Most notably, we found postoperative stroke rates to be almost 2-fold lower after endovascular LSA revascularization (2.6% *vs.* 4.8%) during zone 2 TEVAR. This observation warrants further discussion since, the observed 4.8% stroke rate after TEVAR with open LSA revascularization in this real-world registry is higher than those reported in prior single-center observational cohort studies. For example, two studies reported perioperative stroke rates of 0%,[9,10] while van der Weijde *et al.*[11] found 2% and Protack *et al.*[12] observed 3.5% postoperative stroke rates. In contrast, after zone 2 TEVAR and endovascular LSA revascularization, there is a wide range of stroke rates reported in prior series which are all limited by their sample size. After endovascular LSA revascularization, the observed 2.6% stroke rate in our 647 patients is lower than a 3.2% stroke rate reported by Piffaretti *et al.*[26] in 31 patients, while Ramdon *et al.*[27] observed an 18% stroke rate in 17 patients. However, there are other studies reporting a 0% stroke rate after endovascular LSA revascularization as well (n=24 patients).[28,29]

We observed that staged procedures occurred more frequently if LSA revascularization was performed using either open bypass or transposition, as demonstrated by the 5.7% incidence of preoperative revascularizations in the endovascular cohort as compared with 38% in the open cohort. Therefore, this analysis of VQI practitioners determined that if procedures are staged, LSA revascularizations are most likely performed prior to TEVAR and are typically done using either open bypass or transposition.

Following this reasoning, our study would have had additional value if we were able to determine if stroke occurred due to the LSA revascularization or zone 2 TEVAR procedure itself. Since the SVS-VQI includes endovascular repairs of the thoracic and thoracoabdominal aorta and staging is a common strategy among providers, adjunctive or re-operative procedures whether prior to, concomitant to, or after the index

TEVAR procedure, are documented but secondarily. Accordingly, this limits our ability to perform an isolated study of LSA revascularization perioperative outcomes prior to TEVAR, thereby limiting our ability to ascribe the exact cause of stroke. Moreover, in the absence of data on this specific matter, we are unable to report a stroke rate after isolated LSA revascularization without arterial occlusive disease and without TEVAR. Nevertheless, a word of caution is warranted regarding the observed stroke rate in our open LSA revascularization cohort, which might be underestimated since patients undergoing LSA revascularization may have had a fatal or disabling stroke which precluded subsequent planned staged TEVAR and SVS-VQI enrollment. In any case, this would have only magnified the differences in postoperative stroke between open and endovascular LSA revascularization as observed in our study. Moreover, our sensitivity analysis found similar outcomes. This observation is further underscored by our subgroup analysis stratified by preoperative antiplatelet exposure where there were no differences in any of the outcomes, specifically stroke, and regardless of LSA revascularization strategy.

Regarding stroke type however, the reported brain lesion location may provide some additional insight into the causes of stroke in this study (**Table IV**). Although we did not find significant differences in relative proportions between the LSA open and endovascular revascularization cohorts, there seemed to be more left carotid ischemic stroke (left: 1.0% *vs.* 0.3%) and bilateral ischemic stroke (2.1% *vs.* 1.4%) in the open subgroup (**Table IV**). Potential reasons for this observed discrepancy might be the anatomy (e.g., calcified plaque precluding endovascular approaches), instrumentation, or cross-clamp application for arteriotomy and/or bypass grafting of the left carotid artery during open LSA revascularization. However, given the low number of events we cannot draw robust conclusions on this component of the analysis.

Two recent meta-analyses with different methodological designs also compared open and endovascular LSA revascularization in the setting of TEVAR. Besides applying their specific search strategy to the same databases, Zhang *et al.*[20] included 28 studies with 2,759 patients (87% open) until June 2021 and Lin *et al.*[21] included 14 studies with 1,695 patients (71% open) until May 2023. This discrepancy in the included articles is because the more recent review by Lin *et al.*[21] only included comparative studies, while Zhang *et al.*[20] considered single-arm studies as well. Both meta-analyses identified parallel grafts (e.g., chimney, periscope), fenestration, and single-branched stent-grafts in the available literature. Our study adds a considerable number of patients, particularly in the endovascular revascularization cohort. Both meta-analyses concluded that both open and endovascular LSA revascularization are safe and feasible in terms of perioperative outcomes, whereas our findings appear to favor endovascular LSA revascularization due to lower rates of some in-hospital complications.

Another study by D'Oria *et al.*[30] utilized data from the SVS-VQI to compare perioperative outcomes of open and endovascular LSA revascularization performed concurrently with zone 2 TEVAR and found that both approaches were safe based on similar perioperative outcomes. In contrast, our study favors endovascular LSA revascularization, likely related to an additional five years of data (Jan 2013 – May 2023 *vs.* Jan 2013 – Dec 2018) with a larger sample size (n=2,489 [open: n=1,894; endo: n=647] *vs.* 837 [open: n=721; endo: n=116]). Nevertheless, we observed similar perioperative and 5-year mortality between cohorts, in line with these prior studies.[20,21,30]

Regarding hospital and surgeon volume, we observed that endovascular LSA revascularization was more frequently performed by HV hospitals and surgeons (**Table III**). Such observations may reflect technical challenges related to endovascular revascularization, HV hospital access to clinical trial devices, equipment, and training, and a limited widespread utilization of these emerging techniques as shown in our longitudinal trend analysis (**Figure 3**). Given our findings, trend analysis, and prior evidence[20,21], the adoption of endovascular LSA revascularization is likely to increase further over the next decade, presumably driven by increased utilization of the thoracic single-branched endoprostheses (i.e., FDA approval in 2022; Gore® Medical, Flagstaff, Arizona), which has been demonstrated to have favorable mid-term results.[31] And while open surgical LSA revascularization has shown to be associated with favorable patency rates at 10 years in the setting of TEVAR (estimated freedom from occlusion: 97% ± 2%)[13], endovascular revascularization on the contrary needs to be evaluated regarding its mid- to long-term safety and patency. Therefore, additional studies with larger sample size or randomized evidence comparing open and endovascular revascularization techniques may provide more decisive data on the topic.

Limitations

This study is inherently limited by its retrospective observational design and utilization of data from a large collaborative registry. The usual limitations including potential miscoding or under-diagnosis of complications could be present, the absence of postoperative stroke evaluation by a neurologist, or patient selection bias (e.g., absence of suitable anatomy for endovascular revascularization like short distance between the left carotid and LSA or severely diseased LSA up to the vertebral artery, or the presence of occlusive disease in the left internal carotid artery or dissected LSA which likely disfavored open revascularization). Specifically, regarding procedural details in our sensitivity analysis, we observed larger differences in procedural time, fluoroscopy time, and estimated blood loss between both cohorts (longer and more in case of open revascularization concomitant to TEVAR, **Table III**), highlighting potential errors in data entries for staged procedures in our main cohort where procedural details might not adequately reflect

summed values after multiple, staged interventions (although open procedures might be more complex as well). Moreover, variable definitions for specific endovascular LSA revascularization techniques are unclear (i.e., how are covered stents or BMS positioned if not through branch, fenestration, nor chimney), and thus we would like to underscore the need for continuous teaching of data abstractors and clarifications of these variable definitions (e.g., addition of proportions of bypass or transposition). Additionally, there is no data on atherosclerotic disease of the arch or supra-aortic branches in the VQI. The limited sample sizes for the multiple specific endovascular revascularization techniques precluded a stratified outcome analysis by each technique. Lastly, data for endoleak variables was missing in almost 60% of cases which precluded reliable analyses of endoleak occurrence or its implication on outcomes.

CONCLUSIONS

In patients undergoing TEVAR starting in zone 2, endovascular LSA revascularization had lower rates of postoperative stroke and overall composite in-hospital complications, but similar SCI, perioperative and 5-year mortality rates compared with open LSA revascularization. Future comparative studies are needed to evaluate the mid- to long-term safety of endovascular LSA revascularization and assess differences between specific endovascular techniques.

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Twenty-five years of observations from the International Registry of Acute Aortic Dissection (IRAD) and its impact on the cardiovascular scientific community

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CENTRAL MESSAGE

Over its first 25 years of existence, the International Registry of Acute Aortic Dissection (IRAD) has advanced our understanding and management of patients with acute aortic dissection.

PERSPECTIVE

IRAD was established in 1996 to assess the presentation, diagnosis, management, and outcomes of patients with acute aortic dissection. In the absence of widespread level A evidence based on randomized clinical trials or meta-analyses on acute aortic dissection, IRAD aimed to provide credible observations based on the data from a large collaborative international registry.

ABSTRACT

Objective: The International Registry of Acute Aortic Dissection (IRAD) celebrated its 25th anniversary in January 2021. This study evaluated IRAD's role in promoting the understanding and management of acute aortic dissection (AD) over these years.

Methods: IRAD studies were identified, analyzed, and ranked according to their citations per year (c/y) to determine the most-cited IRAD studies and topics. A systematic search of the literature identified cardiovascular guidelines on the diagnosis and management of acute AD. Consequently, IRAD's presence and impact were quantified using these documents.

Results: Ninety-seven IRAD studies were identified, of which 82 obtained more than 10 cumulative citations. The median c/y index was 7.33 (25th-75th percentile, 4.01-16.65). Forty-two studies had a greater than median c/y index and were considered most impactful. Of these studies, most investigated both type A and type B AD (n = 17, 40.5%) and short-term outcomes (n = 26, 61.9%). Nineteen guideline documents were identified from 26 cardiovascular societies located in Northern America, Europe, and Japan. Sixty-nine IRAD studies were cited by these guidelines, including 38 of the 42 most-impactful IRAD studies. Among them, partial thrombosis of the false lumen as a predictor of postdischarge mortality and aortic diameters as a predictor of type A occurrence were determined as most-impactful specific IRAD topics by their c/y index.

Conclusions: IRAD has had and continues to have an important role in providing observations, credible knowledge, and research questions to improve the outcomes of patients with acute AD.

INTRODUCTION

Over the last decades, our understanding of the pathogenetic mechanisms and clinical characteristics of acute aortic dissection (AD) has increased, favoring specific treatments for improving results. Nonetheless, acute AD remains a life-threatening disease with a low incidence, making it challenging to diagnose and manage.

In 1996, the International Registry of Acute Aortic Dissection (IRAD) was established to create a large, multicenter database containing clinical information on acute AD treated at international aortic centers.[1] Its primary goal was to assess the presentation, diagnosis, management, and outcomes of acute AD.

In 2021, IRAD celebrated its 25th anniversary. During this time, IRAD included more than 50 sites in 12 countries, enrolling 10,649 patients and is continuing to expand. Actually, more than 12,000 patients have been enrolled, and IRAD has published more than 100 scientific reports. In the absence of widespread level A evidence based on multiple randomized clinical trials or meta-analyses on acute AD, real-world data from large international, collaborative registries—like IRAD—seemed of primary importance.[2]

The aim of this study was to evaluate IRAD's role in promoting the understanding and management of acute AD over its first 25 years of existence. IRAD studies were ranked according to their citations per year (c/y) to identify the most impactful topics. These were then analyzed within the worldwide cardiovascular guidelines on the diagnosis and management of acute AD, identified through a systematic search of the literature. Consequently, IRAD's role was discussed through the consideration of its emphasis in other publications and cardiovascular society guidelines and consensus documents.

METHODS

Study Design and Objective

The present study used 2 methodologic pathways that were performed in parallel to evaluate and quantify the achievement of IRAD's primary objective at its establishment in 1996.

Ranking of IRAD Studies

First, all IRAD studies were analyzed to determine the most-cited IRAD studies and topics. Articles were identified using the Scopus citation database, using ("International Registry of Acute Aortic Dissection" OR "IRAD") as string, ultimately on September 30,

2022. A time-range filter from January 1996 to December 2020 was applied. Moreover, the internal list of IRAD publications from the coordinating center, University of Michigan, was used to identify additional IRAD studies not acquired by querying Scopus. In parallel, analytical data regarding the total number of citations for each IRAD publication were obtained from Scopus. Consequently, articles with at least 10 cumulative citations were ranked by the average number of c/y, according to the following formula:

$$\text{c/y index} = \text{c/y index} = \frac{\text{total citations}}{(2020 - \text{publication year})}$$

Articles with a greater than median c/y index (50th percentile), were considered the most impactful IRAD studies. These studies were screened based on their full text and the topics that were investigated were extracted. Topics were categorized based on the AD subtype (ie, Stanford type B and/or A), clinical profiles and/or patient demographics, diagnostic imaging findings and/or modalities, management strategy (ie, medical, surgical, endovascular, and/or hybrid), time of follow-up for main outcomes (ie, short-term [in-hospital, 30-day], medium-term [1-3 years], longer-term [≥5 years]), predictors, discussion of postoperative complications, or any specific topics.

Systematic Review to Identify International Guidelines on Aortic Dissection

Second, a systematic literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[3] (Online Data Supplement) and a methodologic guide to perform a systematic review of clinical practice guidelines (CPGs).[4]

PICAR framework

To focus our research question and develop the search strategy, the Population (eg, "aortic dissection(s)," "acute aortic dissection(s)," Intervention(s)) (eg, "therapy," "management," "medical," "endovascular repair"), Comparator(s), Attributes of eligible CPGs (eg, "guideline(s)," "practice guideline(s)," "clinical practice guideline(s)," "expert," "consensus"), and Recommendation characteristics (PICAR) framework[4] was primarily determined, adapted from and comparable with the Patient, Intervention, Comparison, Outcome framework.[5]

With this methodologic approach we identified the international guidelines that were connected to a cardiovascular society and address the diagnosis and/or management of AD. In this way, the presence and consistency of impactful IRAD studies and topics could be quantified.

Search strategy and study selection

Two authors (T.M. and D.B.) independently performed the research process, including the systematic search, study selection, data acquisition, management, and analysis. In case of discrepancies, a third author (S.T.) was consulted to provide consensus.

The PubMed (Medline), Scopus, and Web of Science databases were queried on April 4, 2022. The PICAR framework facilitated the development of the search strategy, first for PubMed. Medical Subject Headings terms and free key terms were identified. Boolean operators were used to connect different terms. Per PICAR category, Medical Subject Headings terms and key terms were combined with "OR." Afterward, the different categories were combined with "AND." Subsequently, the search strategy was translated to comparable searches for Scopus and Web of Science. A time frame filter from January 2010 to December 2022, was applied without language filter. Detailed search queries including filters are provided in Table E1.

Guideline selection was performed from April 4 to June 14, 2022. First, duplicates were removed, and articles were screened on title and abstract. Next, full-text screening was performed after retrieval of the full text. The Rayyan software was used to facilitate the selection process; however, no automation tools were used to perform title, abstract, nor full text screening.[6]

Inclusion and Exclusion Criteria

Every clinical practice guideline, expert consensus, position statement, scientific statement, clinical policy, or reporting standard document, that addresses the diagnosis and/or management of acute AD was included. Exclusion criteria were (1) review that was not connected to a cardiovascular society and (2) non-English written document that prevented data acquisition.

Quantification of IRAD's Role in International Guidelines on Aortic Dissection

Reference lists of included guidelines were screened for the presence of IRAD studies. The IRAD studies were listed for every guideline separately, and every IRAD publication that was represented in one of the included guidelines was listed. Moreover, for the ranked IRAD studies according to c/y, quartiles were determined and the most impactful IRAD topics were extracted from the respective articles with a greater than median (50th percentile) c/y index. Both steps were compared to evaluate the consideration of the most impactful IRAD topics by the cardiovascular societies in their guidelines.

Data Acquisition and Analysis

Data regarding the ranking of the IRAD studies and guidelines was summarized in previously established tables using Microsoft Word and Excel documents (Microsoft Corp). Data extraction included baseline characteristics of IRAD studies (eg, title, lead author, journal, publication year, analytical data as total citations), baseline guideline characteristics (eg, first author, publication year, cardiovascular society, country or continent, document type, title, journal), and reference characteristics of guidelines (eg, total number of references, total number of recommendations, number of IRAD studies present). Data were reported in textual form, as number (n) and percentage (%), or as median (interquartile range or range) where applicable.

RESULTS

Ranking of IRAD Studies

After querying the Scopus database, a total of 85 IRAD studies were identified. The internal list of IRAD publications identified an additional 12 studies, leading to a total of 97 publications over the first 25 years. Five documents of the internal list were not considered (book chapter [n = 2], cardiology patient page [n = 2], and editorial/commentary [n = 1]). Up to September 11, 2022, the internal list consisted of 109 IRAD publications, affirming the ongoing IRAD output. Median total number of citations were 50 (25th-75th percentile, 18-140). There were 82 studies with more than 10 cumulative citations. The median c/y index was 7.33 (25th-75th percentile, 4.01-16.65). There were 42 studies with a greater than median c/y index (Table 1 and Appendix E1). The study with the highest c/y index was the first study that introduced IRAD in 2000, reaching 115.5 c/y.[1]

Table 1 lists the 42 IRAD studies with a greater than median c/y index from greater c/y indices to lower c/y indices, indicates if they are considered by the included guideline documents, and summarizes the categorized IRAD topics that are investigated in the respective study. Most of the 42 most impactful IRAD studies investigated both Stanford type A and type B ADs (n = 17, 40.5%), followed by a focus on type A AD alone (n = 15, 35.7%). Twenty-six studies (61.9%) focused their main outcomes, mainly survival, in the short term. Regarding management strategies, medical, surgical, and endovascular treatments for AD were mostly evaluated together (n = 13, 38.2%), followed by medical and surgical treatments, surgical treatment alone, or no focus on outcomes according to management strategy (n = 7, 16.7%). Figure 1 graphically summarizes these data using bar charts.

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies.

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/ year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
1.	Hagan PG, 2000	2310	115.50	x	TAAD, TBAD	x	x	Medical, surgical	Short-term	-	-	-
2.	Pape LA, 2015	346	69.20	x	TAAD, TBAD	x	x	Medical, surgical, endo, hybrid	Short-term	-	-	-
3.	Evangelista A, 2018	127	63.50	x	TAAD, TBAD	x	x	Medical, surgical, endo, hybrid	Medium-term	Mortality	x	Women, Elderly, Marfan, Intramural hematoma (review)
4.	Tsai TT, 2007	427	32.85	x	TBAD	x	x	Medical, surgical, endo	Medium-term	Mortality	-	Partial false lumen thrombosis
5.	Pape LA, 2007	416	32.00	x	TAAD	x	x	Medical, surgical	Short-term	Dissection at smaller diameters	-	Aortic diameter
6.	Fattori R, 2013	205	29.29	x	TBAD	x	x	Medical, endo	Longer-term	-	x	-
7.	Tsai TT, 2006	369	26.36	x	TBAD	x	x	Medical, surgical, endo	Medium-term	Follow-up mortality	-	-
8.	Trimarchi S, 2005	390	26.00	x	TAAD	x	x	Surgical	Short-term	Operative mortality	-	-

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies. (*continued*)

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/ year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
9.	Suzuki T, 2003	430	25.29	x	TBAD	x	x	Medical, surgical, endo	Short-term	Mortality	x	-
10.	Fattori R, 2008	289	24.08	x	TBAD	x	x	Medical, surgical, endo	Short-term	Mortality	x	-
11.	Tsai TT, 2009	257	23.36	x	TAAD, TBAD	x	x	Medical, surgical, endo	Short-term	-	-	Intramural hematoma, aortic diameter, partial false lumen thrombosis (review)
12.	Evangelista A, 2005	347	23.13	x	TAAD, TBAD	x	x	Medical, surgical	Short-term	-	-	Acute intramural hematoma
13.	Mehta RH, 2002	381	21.17	x	TAAD	x	x	Medical, surgical	Short-term	Mortality	x	-
14.	Trimarchi S, 2006	293	20.93	x	TBAD	x	x	Surgical	Short-term	Surgical mortality	-	-
15.	Tsai TT, 2005	307	20.47	x	TAAD, TBAD	x	x	Medical, surgical, endo	Short-term	Mortality	-	Acute aortic syndromes (review)
16.	Januzzi JL, 2004	308	19.25	x	TAAD, TBAD	x	-	-	Short-term	-	x	Young patients (< 40 years)

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies. (*continued*)

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
17.	Rampoldi V, 2007	241	18.54	x	TAAD	x	x	Surgical	Short-term	Mortality	-	-
18.	Suzuki T, 2009	203	18.45	x	TAAD, TBAD	x	-	-	-	-	-	D-dimer diagnosis
19.	Di Eusanio M, 2013	122	17.43	x	TAAD	x	x	Medical, surgical, endo	Short-term	-	x	Mesenteric malperfusion
20.	Booher AM, 2013	118	16.86	x	TAAD, TBAD	x	x	Medical, surgical, endo	Short-term	-	-	-
21.	Trimarchi S, 2010	167	16.70	x	TAAD	x	-	Medical, surgical, endo	Short-term	Mortality	-	Age
						75th percentile: 16.65 c/y						
22.	Berretta P, 2016	66	16.50	x	TAAD	x	x	Surgical	Short-term	Mortality	-	-
23.	Nienaber CA, 2004	262	16.38	x	TAAD, TBAD	x	x	Medical, surgical, endo	Short-term	-	x	Gender
24.	Tsai TT, 2006	229	16.36	-	TAAD	x	x	Medical, surgical	Medium-term	Follow-up mortality	-	-

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies. (*continued*)

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/ year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
25.	Rogers AM, 2011	140	15.56	x	TAAD, TBAD	-	-	-	-	-	-	Clinical risk markers
26.	Suzuki T, 2012	115	14.38	x	TAAD, TBAD	x	-	-	Longer-term	Mortality	-	Type-selective benefits of medications
27.	Ramanath VS, 2009	158	14.36	-	TAAD, TBAD	x	x	Medical, surgical, endo	Medium-term	Mortality		Acute aortic syndromes (review)
28.	Harris KM, 2012	111	13.88	x	TAAD, TBAD	x	x	Medical, surgical, endo, hybrid	Medium-term	-	-	Acute intramural hematoma
29.	Harris KM, 2011	118	13.11	x	TAAD	x	x	-	-	-	-	Delayed recognition and treatment
30.	Trimarchi S, 2010	131	13.10	x	TBAD	x	x	Medical, surgical, endo	Short-term	Mortality	-	Recurrent and/or refractory pain and refractory hypertension
31.	Mehta RH, 2002	225	12.50	x	TAAD	x	x	Medical, surgical	Short-term	Mortality	x	Elderly
32.	Tolenaar JL, 2014	67	11.17	x	TBAD	x	x	Medical, surgical, endo	Short-term	Mortality	-	-

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies. (*continued*)

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/ year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
33.	Moore AG, 2002	201	11.17	x	TAAD, TBAD	x	x	Medical, surgical, endo	-	-	-	Choice of imaging
34.	Mehta RH, 2002	194	10.78	x	TAAD, TBAD	x	-	-	-	-	-	Chronobiological patterns
35.	Parikh N, 2017	31	10.33	-	TAAD	x	x	Surgical	Short-term	-	-	Changes in operative strategy
36.	Bossone E, 2013	63	9.00	x	TAAD	x	x	Medical, surgical, endo	Longer-term	-	-	Stroke
37.	Di Eusanio M, 2014	49	8.17	x	TAAD	x	x	Surgical	Medium-term	Mortality	x	-
38.	Jonker FHW, 2012	60	7.50	x	TBAD	x	x	Medical	Longer-term	Aortic expansion	-	Aortic expansion
39.	Collins JS, 2004	118	7.38	x	TAAD	x	x	Medical, surgical	Short-term	Mortality	x	Patients with and without previous cardiac surgery

Table 1. The 42 IRAD studies with a higher than median (50th percentile, 7.33) citations per year index listed from higher c/y indices to lower c/y indices, their inclusion in worldwide cardiovascular guidelines, and the topics that are addressed in these studies. (*continued*)

						Topics addressed in most impactful IRAD publication						
Nr.	**First author, year**	**Total citations*, n**	**Citations/ year*, n**	**Cited by included guideline documents**	**Dissection subtype**	**Clinical profiles, demographics, presentation**	**Diagnostic finding, imaging modalities**	**Management: medical, surgical, endo, or hybrid**	**Survival: short-term, medium-term, or longer-term****	**Predictors of:**	**Complications**	**Specific topic**
40.	Trimarchi S, 2012	59	7.38	x	TBAD	x	x	Medical, surgical, endo	Short-term	Complicated and uncomplicated dissection	-	-
41.	Jannuzzi JL, 2002	132	7.33	x	TAAD, TBAD	x	x	-	Short-term	-	x	Iatrogenic aortic dissection
42.	Larsen M, 2017	22	7.33	-	TAAD	x	x	Surgical	Short-term	Mortality	x	-
						50th percentile: 7.33 c/y						

*Up to December 31st, 2020. Publications with more than 10 cumulative citations were considered in the percentile calculation. **Definitions of topics addressed by the IRAD publications: Short-term: in-hospital mortality and/or 30-day mortality; Medium-term: 1 – 3 year mortality; Longer-term: 5 year mortality or more. Abbreviations: endo: endovascular; c/y: citations per year. Data are presented in textual form, as numbers (n), or as signs: (x): affirmative; (-): not discussed in the respective IRAD publication.

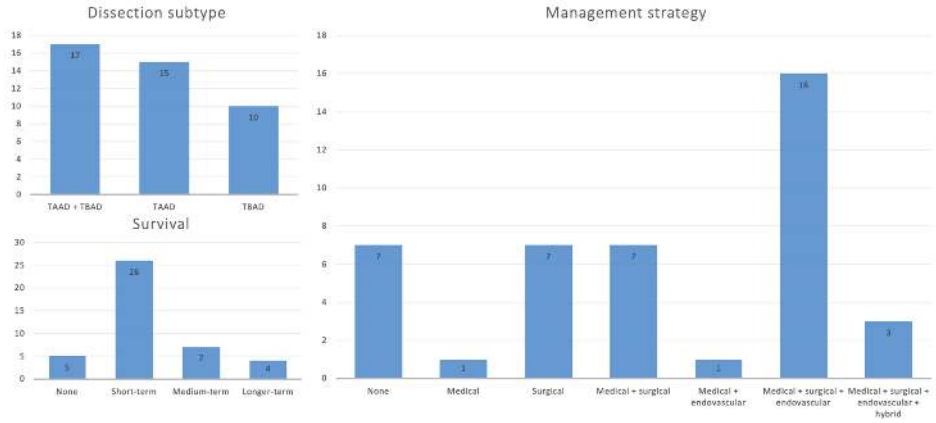

Figure 1. Bar charts of the topics discussed among the 42 most impactful IRAD studies with a higher than median (50th percentile, 7.33) citations per year index, categorized according to the aortic dissection subtype, time of follow-up for survival, and management strategies, that were investigated by the respective studies. *TAAD*, Type A aortic dissection; *TBAD*, type B aortic dissection

Guideline Selection and Characteristics

Initially, 5044 articles were identified, of which 4311 were screened after duplicate removal (Figure 2). Of these, 4209 were found not eligible solely based on title and abstract screening. Full-text assessment of the remaining studies finally led to the inclusion of 18 international cardiovascular guideline documents.[7-24] The most important reason for exclusion at this stage was a study being a review article and/or lacking connection to a cardiovascular society. On November 2, 2022, the new American College of Cardiology/American Heart Association aortic guidelines were published and subsequently included, leading to a total of 19 eligible cardiovascular guideline documents.[25]

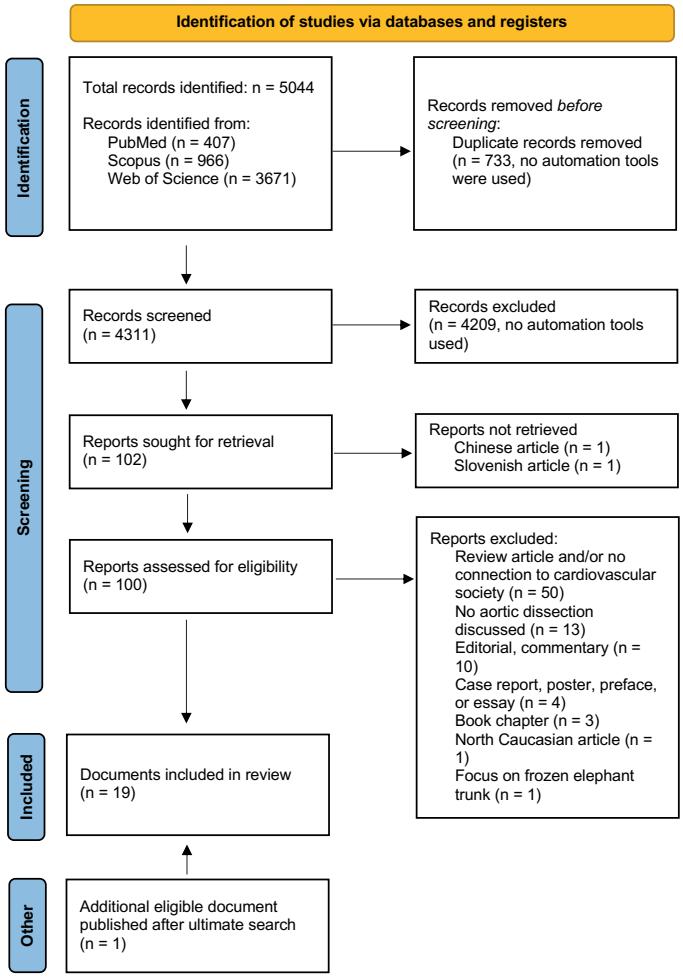

Figure 2. Flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 for new systematic reviews to identify international guidelines that address the diagnosis and/or management of aortic dissection.

Table 2 summarizes baseline characteristics of the 19 guideline documents that were included. Document types consisted mostly of guidelines (n = 8, 42.1%), expert consensus documents (n = 5, 26.3%), or position/scientific statements (n = 4, 21.1%). The geographic locations of the 26 cardiovascular societies that are connected to these documents were United States of America (n = 13, 50%), Europe (n = 4, 15.4%), Canada (n = 4, 15.4%), Germany (n = 2, 7.7%), Spain (n = 2, 7.7%), and Japan (n = 1, 3.8%).

Table 2. Baseline characteristics of the 19 included guideline, position or scientific statement, expert consensus, clinical policy, or reporting standards documents, identified through a systematic search of PubMed, Scopus, and Web of Science

Nr.	First author, year	Society	Region	Type	Title	Journal
1.	Hiratzka LF, 2010	ACCF, AHA, AATS, ACR, ASA, SCA, SCAI, SIR, STS, SVM	United States of America	Guidelines	Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease	Journal of the American College of Cardiology
2.	Grabenwöger M, 2012	EACTS, ESC, EAPCI	Europe	Position Statement	Thoracic Endovascular Aortic Repair (TEVAR) for the treatment of aortic diseases	European Journal of Cardio-Thoracic Surgery
3.	Fattori R, 2013	ACC	United States of America	Interdisciplinary Expert Consensus Document	Management of Type B Aortic Dissection	Journal of the American College of Cardiology
4.	JCS Joint Working Group (Chair: Takamoto S), 2013	JCS (working groups)	Japan	Guidelines	Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection	Circulation Journal
5.	Boodhwani M, 2014	CCS	Canada	Position Statement	Position Statement on the Management of Thoracic Aortic Disease	Canadian Journal of Cardiology
6.	Erbel R, 2014	ESC	Europe	Guidelines	Guidelines on the diagnosis and management of aortic diseases	European Heart Journal
7.	Diercks DB, 2015	ACEP	United States of America	Clinical Policy	Critical Issues in the Evaluation and Management of Adult Patients with Suspected Acute Nontraumatic Thoracic Aortic Dissection	Annals of Emergency Medicine
8.	Appoo JJ, 2016	CCS, CSCS, CSVS	Canada	Joint Position Statement	Joint Position Statement on Open and Endovascular Surgery for Thoracic Aortic Disease	Canadian Journal of Cardiology
9.	Riambau V, 2017	ESVS	Europe	Clinical Practice Guidelines	Management of Descending Thoracic Aorta Diseases	European Journal of Vascular and Endovascular Surgery
10.	Torsello G, 2019	AWMF of Germany, DGG	Germany	Guidelines	S2k guidelines for the diagnosis and treatment of type B aortic dissection	Gefässchirurgie
11.	Czerny M, 2019	EACTS, ESVS	Europe	Expert Consensus Document	Current Options and Recommendations for the Treatment of Thoracic Aortic Pathologies Involving the Aortic Arch	European Journal of Vascular and Endovascular Surgery, European Journal of Cardio-Thoracic Surgery

Table 2. Baseline characteristics of the 19 included guideline, position or scientific statement, expert consensus, clinical policy, or reporting standards documents, identified through a systematic search of PubMed, Scopus, and Web of Science (*continued*)

Nr.	First author, year	Society	Region	Type	Title	Journal
12.	Ohle R, 2020	CMA	Canada	Clinical practice guideline	Diagnosing acute aortic syndrome	Canadian Medical Association Journal
13.	Lombardi JV, 2020	SVS, STS	United States of America	Reporting Standards	Reporting standards for type B aortic dissections	Journal of Vascular Surgery
14.	Malaisrie SC, 2021	AATS	United States of America	Expert consensus document	Surgical treatment of acute type A aortic dissection	The Journal of Thoracic and Cardiovascular Surgery
15.	Czerny M, 2021	ESC (working groups), EAPCI of ESC, EACTS	Europe	Expert Consensus Document	Current options and recommendations for the use of thoracic endovascular aortic repair in acute and chronic thoracic aortic disease	European Journal of Cardio-Thoracic Surgery
16.	López Gómez A, 2022	SSCES, SARPT	Spain	Consensus document	Anaesthetic-surgical guide in the treatment of ascending aorta and surgery of the ascending aorta and aortic arch	Revista Española de Anestesiología y Reanimación
17.	MacGillivray TE, 2022	STS, AATS	United States of America	Clinical practice guidelines	Clinical practice guidelines on the management of type B aortic dissection	The Journal of Thoracic and Cardiovascular Surgery
18.	Fleischmann D, 2022	AHA (councils)	United States of America	Scientific Statement	Imaging and Surveillance of Chronic Aortic Dissection	Circulation: Cardiovascular Imaging
19.	Isselbacher EM, 2022	ACC, AHA	United States of America	Clinical practice guideline	Guideline for the Diagnosis and Management of Aortic Disease	Circulation

Abbreviations: ACCF: American College of Cardiology Foundation; AHA: American Heart Association; AATS: American Association for Thoracic Surgery; ACR: American College of Radiology; ASA: American Stroke Association; SCA: Society for Cardiovascular Anesthesiologists; SCAI: Society for Cardiovascular Angiography and Interventions; SIR: Society of Interventional Radiology; STS: Society of Thoracic Surgeons; SVM: Society for Vascular Medicine; EACTS: European Association for Cardio-Thoracic Surgery; ESC: European Society for Cardiology; EAPCI: European Association of Percutaneous Cardiovascular Interventions; ACC: American College of Cardiology; JCS: Japanese Circulation Society; CCS: Canadian Cardiovascular Society; ACEP: American College of Emergency Physicians; CSCS: Canadian Society of Cardiac Surgeons; CSVS: Canadian Society for Vascular Surgery; ESVS: European Society for Vascular Surgery; AWMF: Association of the Scientific Medical Societies; DGG: German Society for Vascular Surgery and Vascular Medicine; CMA: Canadian Medical Association; SVS: Society for Vascular Surgery; SSCES: Spanish Society of Cardiovascular and Endovascular Surgery; SARPT: Society of Anaesthesiology, Resuscitation and Pain Therapy.

IRAD's Role in International Guidelines on Aortic Dissection

In total, 69 IRAD studies were identified that were cited by the selected cardiovascular guidelines. Tables E2 and E3 provide full bibliographic data of the IRAD studies that are present among the guidelines, listed separately for every guideline in Table E2 and listed by publication year in Table E3. Moreover, Table E2 provides the total number of references and recommendations in these documents, together with the n (%) of IRAD studies among the references. Eighteen of the 19 guidelines cited IRAD studies and the median percentage of IRAD studies present among the guidelines was 5.2 (range 0%-15%). The guidelines by Isselbacher and colleagues[25] (2022), Hiratzka and colleagues[7] (2010), and Riambau and colleagues[15] (2017) most often cited IRAD studies (n = 25, n = 20, and n = 18, respectively). Table E3 includes how often the IRAD studies are cited by the 19 guideline documents. The study that was cited most often by the guidelines was the study by Hagan and colleagues[1] in 2000 and was present in 9 guidelines (47.4%), followed by the study of Pape and colleagues[26] in 2015, present in 8 guidelines (42.1%) (Table E3). Regarding the 42 most impactful IRAD studies according to their c/y index, 38 (90.5%) were cited by the guidelines (Table 1).[27,28]

Most Impactful Specific Topics Investigated by IRAD

Several specific topics have been investigated by IRAD (Table 1). Originating from studies listed from higher c/y indices to lower c/y indices, the most impactful specific IRAD topics that were investigated by studies that belonged to the highest quartile of c/y (>75th percentile), were (1) partial thrombosis of the false lumen (FL) as a predictor of postdischarge mortality; (2) aortic diameters as predictor of type A AD occurrence; (3) the prevalence, presentation, management, and outcomes of acute intramural hematoma (IMH); (4) the characterization of young patients (<40 years) with AD; (5) the diagnostic performance of D-dimer testing to rule out AD; (6) mesenteric malperfusion in type A AD; and (7) role of age on outcomes of type A AD. Specific IRAD topics that were investigated by studies that belonged to the second highest c/y quartile (50th percentile-75th percentile) are reported in Table 1.

Least impactful specific topics investigated by IRAD

There were 40 studies with a lower than median c/y index (Appendix E2) and 15 studies with fewer than 10 cumulative citations (Appendix E3). Of these least-cited studies, 12 (80%) were published between 2015 and 2020 and were thus published during more "recent" years. The 3 specific topics addressed by the remaining 3 least-cited studies, published in 2014, 2013, and 2004, respectively, were (1) the association between pulse pressure and presentation, complications, and outcomes of patients with type A AD; (2) characterization of painless type B AD; and (3) the effect of renal insufficiency on the presentation, complications, and outcomes of patients with acute AD.

DISCUSSION

This study confirms that IRAD has been an impactful multicenter, observational registry in determining the understanding, management, and outcomes of acute AD over the last 25 years. The data originating from the analysis of 10,649 patients have been consistently considered by 26 cardiovascular societies all over the world and have been highlighted in 18 of 19 identified guideline or consensus documents (Figure 3).

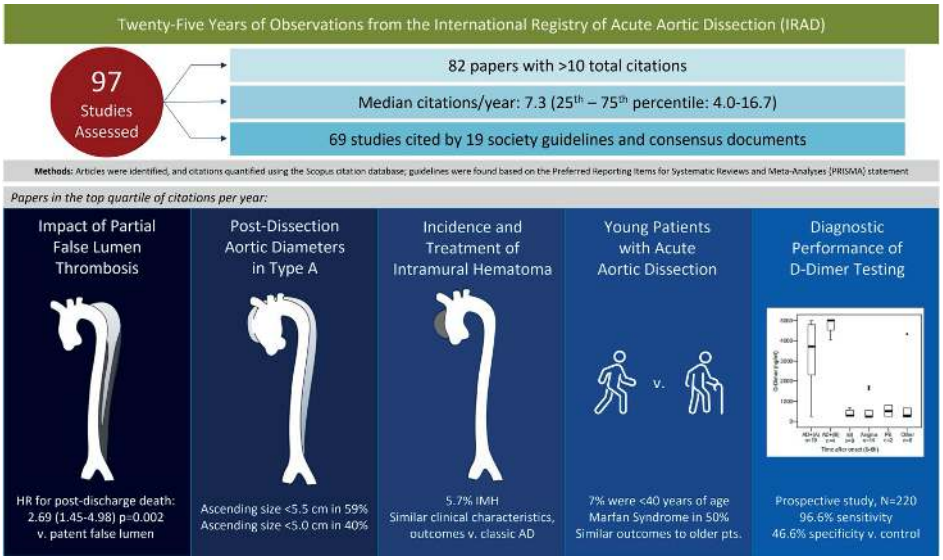

Figure 3. Twenty-five years of observations from the International Registry of Acute Aortic Dissection (*IRAD*). *Middle lines* of the boxplots represent median D-dimer values. *Lower* and *upper border* of the box represent the 25th and 75th percentile (interquartile range), respectively. *Lower* and *upper whiskers* represent the minimum and maximum values of nonoutliers, respectively. *Points* represent positive outliers. *HR*, Hazard ratio; *IMH*, intramural hematoma; *AD*, aortic dissection.

Retrospective observational cohort studies and meta-analyses of cohort studies provide modest grade evidence regarding the pyramid of scientific evidence; however, they point clearly in the direction of open surgical repair for type A (Grade I, level B),[12] whereas thoracic endovascular aortic repair for complicated acute type B AD has now become the first treatment of choice (Grade I, level B[23]-C[12,15]). This challenges the design of a randomized clinical trial that would compare different treatment modalities for different AD subtypes. In the absence of widespread level A evidence, the importance of IRAD has proven considerable by providing real-world data that have been considered to be reliable and informative by the guideline writing groups on AD. Consequently, these guidelines suggested indications to the cardiovascular medical community based on IRAD observations.

The most impactful specific IRAD topic identified in this study was partial thrombosis of the FL as a predictor of postdischarge mortality in type B AD. As acute type B AD was found to be associated with considerable postdischarge mortality[29] in the past, IRAD[30] attempted to seek predictors of follow-up mortality. Consequently, partial thrombosis of the FL was identified as an independent predictor of mortality (hazard ratio, 2.69; 95% confidence interval, 1.45-4.98; P = .002) as compared with a patent FL in AD. Such adverse hemodynamic situation, encompassing high systolic antegrade FL flow with significant diastolic retrograde flow, may identify patients at greater risk for aortic dilatation.[31]

Second, IRAD has investigated the dissection risk associated with increases in aortic size (ie, diameter).[32] In a cohort of 591 patients presenting with type A AD, 59% had aortic diameters <5.5 cm, whereas 40% had aortic diameters <5.0 cm, which would not provide an indication of elective repair based on current recommended surgical "cut" points. Similar observations were found in type B AD.[33] It was concluded that methods other than aortic size alone should be considered to identify patients at high risk for dissection. Hopefully, genetics, biomarkers, and/or more predictive imaging methods will help us in this regard.

Moreover, IRAD has aimed to better identify similarities and differences between AD and IMH and found that IMH had a prevalence of 5.7% in 1010 patients presenting with an acute aortic syndrome and had comparable clinical characteristics and outcomes if left untreated.[34]

Rather than using a subjective ranking as in a previous editorial by Elefteriades and Ziganshin,[35] this study objectively ranked the IRAD studies of the first 25 years using citation metrics. Over these decades, major advances in both open surgical repair and endovascular repair techniques have occurred, leading to differences in operative strategies for several AD subtypes.[28] In parallel, the patient's clinical presentations remained similar, and the use of computed tomography angiography increased for type A. Moreover, an overall increase in interventional procedures for AD was observed, with an increase in endovascular procedures and a decrease in medical and surgical management over time for type B. Short-term outcomes did not improve over time in type B, whereas overall mortality has decreased for type A.[26]

Future Perspectives

IRAD continues to collect and analyze data on AD from an ever-expanding number of aortic centers around the world. In the current era, newer and advanced therapeutic options are upcoming like endovascular aortic repair of the more proximal aortic zones that could eventually include the aortic root and valve. The feasibility of such therapy as

well as the analysis of type A, arch dissections, and uncomplicated type B AD will most likely represent important fields of study, if evidence favors thoracic endovascular aortic repair in certain patient subgroups.

Limitations

Potentially impactful IRAD studies that were published in recent years could not be included among the most impactful IRAD studies as ranked by the present study, since they had less time to be cited and thus reach a minimum of 10 citations and consequent c/y index. Nevertheless, a few studies from recent years (eg, 2018) were included in the current ranking, and we believe that the present analysis uses appropriate methodological pathways to evaluate the role and impact of IRAD on the cardiovascular community.

Conclusions

This study quantified the role of IRAD in promoting the understanding and management of acute AD over its first 25 years of existence. It shows that a considerable number of IRAD findings have been incorporated in 18 of 19 identified cardiovascular guideline documents, underlining the importance and the credibility of this registry. IRAD has had and continues to have an important role in providing and analyzing real-world data to improve the outcomes of patients with acute AD.

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Part V

Discussion and summary

15

Discussion

DISCUSSION

In light of contemporary advancements regarding available technologies, medical devices, and expanding indications for aortic surgery (more frequent use of endovascular repair), this thesis has provided multidisciplinary perspectives on aortic biomechanics, anatomy, open surgical or endovascular treatment of the aorta, and the interaction between these aspects. Thereby, specific gaps in evidence were answered which might ultimately contribute to the improvement of the clinical outcomes of patients with aortic disease.

In **Part I** of this thesis, we introduced key aortic terminology and concepts serving as the fundament of this thesis in **Chapter 1**. Then, the systematic review presented in **Chapter 2** has assessed the cardiovascular haemodynamical changes that seem to occur after thoracic endovascular aortic repair (TEVAR), specifically in patients with blunt thoracic aortic injury (BTAI). Since BTAI commonly occurs in young and healthy patients with a long life expectancy, it can be considered an appropriate disease entity to evaluate such long term changes. However, since BTAI is a rare occurrence and most patients die before arriving to the hospital,[1,2] the conclusions are limited by the number of available studies (n=12) and patients (n=265), with a moderate (75%) to low (25%) risk of bias. Nevertheless, the review does highlight a considerable body of evidence underscoring that aortic stiffness, blood pressure, cardiac mass, and aortic size of untreated adjacent segments may increase during TEVAR follow-up, which can have adverse consequences for a patient's cardiovascular system and target organs.[3] When performing follow-up after TEVAR in younger patients, it is important to consider that there may be negative long term cardiovascular consequences of stent-graft implantation. In this regard, additional studies could aim to clarify which patient characteristics are associated with a high(er) cardiovascular risk at follow-up, such as specific aortic wall compositions, or patients with genetic aortopathies.

In **Part II** of this thesis, we investigated specific elements related to aortic biomechanics that may have contributed to the observations in **Chapter 2**, by utilizing a mock cardiovascular circulatory flow loop.

Experimental perspectives

With TEVAR now being firmly established as the first-line treatment option for aortic disease involving zones 2 – 5, outcomes remain largely dependent on anatomical characteristics of the landing zone of interest, such as increased arch angulation, distal descending tortuosity, or prior aortic surgery.[2,4–6] In addition to anatomical factors, physiological factors might affect the outcomes after TEVAR. Numerous prior clinical

and experimental studies have highlighted that TEVAR increases aortic pulse wave velocity (PWV), the accepted surrogate for aortic stiffness, which independently predicts the occurrence of future cardiovascular events, all-cause mortality, and cardiovascular mortality.[3,7–13] As introduced in **Chapter 2**, aortic stiffness may play a role in determining long term outcomes after TEVAR, which remain a matter of concern for current open, endovascular, and/or hybrid aortic treatment modalities together with their durability.[14]

One of the gaps in evidence is if and how specific aortic geometry influences blood flow dynamics. There is scarce prior evidence suggesting changes in aortic flow dynamics with altering geometrical configurations, like an increased arch angulation.[15–18] In **Chapter 3**, we showed that an increased arch angulation – as demonstrated in a type III arch[19] – is associated with higher PWV, systolic, diastolic, and mean arterial blood pressures. Although these observations do not represent additional indications for aortic surgery, they are another piece of the puzzle, and might provide useful for optimizing blood pressure management in patients with an increased arch angulation. Moreover, this might indicate patients with faster aortic growth before treatment that may benefit from closer imaging follow-up before intervention.

Another gap in evidence is if open aortic surgery impacts aortic stiffness. In contrast to TEVAR, there is a paucity of available data after open surgery of the aorta, but the biomechanical properties of surgical grafts (e.g., Dacron®) and the native aorta differ as well.[20,21] If and how this relates to TEVAR-induced stiffening remains unknown. In **Chapter 4**, we showed that open surgical interposition grafting of the proximal descending aorta increases aortic PWV, decreases diastolic and mean arterial blood pressures, while systolic blood pressures remain stable. Compared to prior data on TEVAR-induced aortic stiffening, obtained with the same set-up and similar thoracic aortic samples (**Chapter 3**), open surgery stiffened the aorta similarly in this study. In other words, aortic PWV increased both after open surgery and after TEVAR, and there was no statistically significant difference between the aortic PWV after both treatment modalities. Despite the experimental nature and low sample size of these findings, they may pave the way for future investigations focusing on changes in aortic stiffness after open surgical repair of different aortic segments, and how this may related to stiffening induced by TEVAR in these segments.

A third gap in evidence addressed in **Chapter 5**, is related to differences in TEVAR-induced stiffening between older and newer thoracic stent graft generations of the same device manufacturer. Device manufacturers are constantly developing newer generation stent grafts with improvements in delivery systems, proximal device configurations, or conformability.[22–25] **Chapter 5** confirms that TEVAR increases aortic PWV, with

both a second and third generation thoracic aortic stent graft and without statistically significant differences in the absolute post-TEVAR values. Thus, the study shows that improvements in device design do not necessarily result in a lower aortic PWV after TEVAR, calling for further improvements in device compliance (without losing adequate seal and strength), to improve long term TEVAR outcomes.

Although these studies are limited by their experimental study design, the use of *ex vivo* porcine thoracic aortas, and a mock cardiovascular circulatory flow loop, advantages are that direct comparisons between different arch angulations (i.e., type I *vs.* III arch) or treatment modalities can be performed, within the same aorta, which is not feasible with *in vivo* analyses. The findings of these studies suggest an interplay between aspects related to biomechanics, anatomy, and the outcomes of open surgical or endovascular treatment of the aorta, of which all may play their role in determining a patient's cardiovascular health.

Computational and imaging perspectives

As mentioned, TEVAR is largely dependent on the anatomical suitability of the aortic region of interest.[2,4–6] Therefore, imaging plays a vital role during diagnosis, screening, planning, and follow-up, for example when performing a meticulous preoperative, intraoperative, and postoperative assessment. Conventional imaging techniques consist of ultrasound, computed tomography angiography (CTA), or magnetic resonance imaging (MRI) with or without three dimensional reconstructions.[2,26] Moreover, four-dimensional flow MRI may provide specific additional insight into blood flow patterns associated with the progression of acute aortic syndromes or aneurysm formation and growth.[27,28]

Over recent years, there has been a rise in the development and application of *in silico* computational tools to evaluate certain haemodynamical parameters and to assist preprocedural planning as well.[29–32] Therefore, **Part III** starts with **Chapter 6**, which showed that there are currently 14 severely heterogeneous TEVAR simulation models available in the literature, mostly of intermediate quality based on a 16-item rating rubric (64%), not specifically developed for numerical simulation studies. The study highlights that this is a rapidly expanding field, depending on close collaborations between cardiovascular surgeons and engineers. It attempts to stimulate improvements in the reliability and homogeneity of computational tools to support their implementation in clinical practice. In this regard, **Chapter 7** shows the potential, workflow, and reliability of a TEVAR simulation methodology to predict perioperative adverse events and short-term postoperative technical results. The novel high-fidelity numerical (i.e., finite element analysis) methodology used in this study was developed by our group during the course of this thesis. First, by characterizing the specific thoracic stent graft material parameters with

experimental crimp/release tests and deploying the stent graft in a rigid aortic phantom with physiological anatomy for verification analysis.[33] Then, the overall applicability of the TEVAR modeling was assessed to demonstrate reliability of the model following a step-by-step method based on the American Society of Mechanical Engineers (ASME) V&V40 protocol.[34,35] By applying this TEVAR simulation methodology to a patient-specific case in **Chapter 7**, we showed that this numerical virtual simulation method was able to reproduce a distal kinking of a thoracic stent graft during zone 2 TEVAR. Thereby, it highlights the potential of clinical implementation of such computational tools during the preoperative phase.

During preoperative assessment, CTA plays an important role to assess aortic anatomy and plan TEVAR. Especially in light of expanding indications for endovascular repair of the ascending aorta and arch,[4,6,36,37] morphometric or geometric analyses may provide specific insights for planning TEVAR with a proximal landing in these zones. Focusing on sex-related differences, **Chapter 8** is an electrocardiogram-gated CTA-based retrospective morphometric analysis of the ascending aorta and arch in 116 patients that were evaluated for transcatheter aortic valve replacement (TAVR). Therefore, the extrapolation of the findings of this study to patients with aortic disease warrant caution but may provide useful for planning TEVAR as stent graft attachment is usually in healthy aortic segments. The study primarily evaluated factors associated with aortic diameters in both sexes and evaluated sex-specific differences in aortic size. In both sexes, different associations were found between clinical characteristics and size in specific aortic segments (i.e., sinotubular junction [STJ], mid-ascending, distal ascending, zone 1, zone 2). For example, body surface area was independently associated with larger mid-ascending to zone 2 diameters in men, whereas in women it was only with larger zone 2 diameters. Diabetes mellitus was independently associated with smaller STJ to zone 1 diameters in men, whereas in women it was only with distal ascending and zone 1 diameters. On average, the study showed men to have 7.4% larger ascending aorta and arch diameters compared with women on both systolic and diastolic measurements. Insight into such sex-related differences may help tailoring aortic disease management by sex and different morphometric limits of the ascending aorta and arch regarding surgical thresholds for repair or imaging follow-up may be established.

Ultrasound is another valuable tool that may be adopted during diagnosis and screening of abdominal aortic aneurysms, with the advantage of limiting contrast and radiation exposure to patients.[26] A gap in evidence regarding the reproducibility of measuring anteroposterior abdominal aortic diameters with ultrasound however, remains which caliper placement method (i.e., outer to outer [OTO], inner to inner [ITI], leading edge to leading edge [LELE]) can be considered the most reproducible between observers.

Therefore, **Chapter 9** conducted a meta-analysis of 21 available diagnostic test accuracy studies and concluded that the OTO and ITI methods' interobserver reproducibility was 2.5 times smaller (indicating better reproducibility) than LELE, but without statistically significant differences between the three methods. Considering studies published >2010, the pooled estimate for LELE was the smallest, also without statistically significant differences between the three methods. Although there are inherent differences between the three methods, with OTO resulting in consistently larger diameters as compared with ITI (4 – 7 mm), the meta-analysis cannot conclude on the superiority of one or the other method regarding reproducibility, also reflected by a low evidence certainty derived from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Clinical perspectives on thoracic aortic disease

Part IV of this thesis utilized real-world data from different large international collaborative registries and single-center experiences and was able to answer specific gaps in evidence related to the surgical treatment of thoracic aortic disease.

One of these gaps in evidence is if the outcomes of TEVAR are different for males and females, specifically in the long term. Prior studies have shown conflicting results, with four studies reporting similar short-, mid- and long term mortality rates for both males and females, whereas two more recent studies have reported higher short- and long term mortality rates in females after TEVAR.[38–43] **Chapter 10** investigated TEVAR outcomes of 805 patients enrolled in the Global Registry for Endovascular Aortic Treatment (GREAT) and found no differences between males and females in terms of 30-day to 5-year mortality (freedom from 5-year all-cause mortality males: 67% [95% CI, 62.1-72.2] *vs.* females: 65.9% [95% CI, 58.5-74.2], p=.847) and complication rates after TEVAR for any indication, nor after stratification by aortic pathology in dedicated subgroup analyses (besides a higher proportion of type II endoleak after TEVAR in females with complicated type B aortic dissections).

Another gap in evidence is if surgeon volume impacts the outcomes of patients undergoing TEVAR for BTAI. Regarding open surgical or endovascular treatment of the aorta, prior studies investigating hospital and vascular surgeon volume-related outcomes have largely focused on the abdominal aorta.[44] Two prior studies investigated the impact of surgeon volume on TEVAR outcomes specifically, for aortic dissections and thoracic aortic aneurysms, and did not find surgeon volume to be associated with perioperative and 5-year mortality.[45,46] For BTAI specifically, a previous study found lower perioperative mortality at higher volume hospitals,[47] but the potentially mediating effect of surgeon volume was not evaluated in this context.[48] Therefore, **Chapter 11** utilized the data from

1,321 patients undergoing TEVAR for BTAI enrolled in the Vascular Quality Initiative (VQI). The study found that compared with low volume surgeons (0-1 TEVAR procedures for any indication during the preceding year), medium (2-8 TEVAR) to high (≥9 TEVAR) surgeon volume was independently associated with lower perioperative mortality and postoperative stroke, regardless of hospital volume. Most notably, on univariable analysis and with higher surgeon volume, periprocedural ischemic/hemorrhagic stroke rates were lower (LV: 6.5%, MV: 3.6%, HV: 1.5%, p=.006).

Another key aspect of expanding TEVAR indications to the aortic arch is that it necessitates supra-aortic branch management. With zone 2 coverage, LSA revascularization is recommended based on a reduced risk of perioperative neurological events like stroke and spinal cord ischemia.[49–51] Open surgical LSA revascularization is traditionally performed with bypass or transposition, and **Chapter 12** shows that it is associated with favorable patency rates at 10-years follow-up (estimated freedom from occlusion: 97% ± 2%, freedom from severe stenosis: 90% ± 4%) based on single-center data from 90 patients undergoing zone 2 TEVAR and open surgical LSA revascularization. With ongoing technological advancements, endovascular alternatives to preserve antegrade LSA flow during zone 2 TEVAR have become available and have been compared to the historical benchmark of open bypass or transposition. **Chapter 13** utilized data from 2,489 patients enrolled in the VQI that underwent zone 2 TEVAR and LSA revascularization. After stratifying by revascularization type (open *vs.* any endovascular) and compared with open LSA revascularization, endovascular LSA revascularization had lower rates of postoperative stroke (2.6% *vs.* 4.8%, p=.026; aOR 0.50 [95%C.I., 0.25-0.90]) and overall composite in-hospital complications (20% *vs.* 27%, p<.001; 0.64 [0.49-0.84]), but comparable rates of spinal cord ischemia (2.9% *vs.* 3.5%, p=.60; 0.64 [0.31-1.22]), perioperative mortality (3.1% *vs.* 3.3%, p=.94; 0.71 [0.34-1.37]) and 5-year mortality (aHR 0.85 [0.64-1.13]). This appears to favor a further application of endovascular alternatives to preserve antegrade LSA flow in specific patients; however, mid- to long term outcomes, patency, and stratified outcomes for specific endovascular LSA revascularization techniques remain largely unknown.

In **Chapter 14**, this thesis concludes with a study that evaluated the role of the International Registry of Acute Aortic Dissection (IRAD) in promoting the understanding and management of patients with acute aortic dissection over the first 25 years of IRAD's existence. The impact of 97 IRAD studies was quantified with cumulative citation metrics, and a systematic search of the literature identified 19 cardiovascular guideline documents addressing the management of acute aortic dissection. Consequently, based on an analysis of the consideration of IRAD studies in cardiovascular society guidelines and consensus documents, and in the absence of widespread level A evidence, the study

concluded that IRAD has had, and continues to have, an important role in improving the outcomes of patients with (acute) aortic dissections.

Future perspectives

As reflected in the dedicated *Future perspectives* sections of the different chapters in this thesis as well, additional research is needed to better clarify the interplay between aortic biomechanics, anatomy, open surgical or endovascular treatment of the aorta, and clinical outcomes of patients with aortic disease. We should aim to better clarify causal pathways between aortic stiffness, specific changes in blood pressures, cardiac hypertrophy, and aortic dilatation or growth. As an example, how relevant is left ventricular hypertrophy after TEVAR for patients of different age groups, and does this lead to a decline in systolic or diastolic cardiac function, immediately or during follow-up? Does this impact mortality of patients that undergo surgical repair of the aorta? Or, how relevant is an increased growth or wall stress in the ascending aorta or distal abdominal aorta following TEVAR of the descending aorta or arch?

In general, more homogeneity in methodological approaches and outcome assessments between future studies could help the comparability of studies and pooling of data to obtain a higher level of evidence. Moreover, additional standardized imaging at certain points during the pre- and postoperative phase (e.g., echocardiography, aortic PWV using the carotid-femoral method, 4D-flow cardiovascular magnetic resonance imaging [MRI]) may aid in generating potentially useful data for future studies investigating specific aspects of aortic biomechanics. As mentioned, close collaborations between medical doctors and engineers seem necessary to obtain a better understanding of aortic biomechanics including blood flow dynamics.

Overall, long term data remains scarce and needed, studies may focus on the isolated study of specific aortic zones or consider other geometrical characteristics and/or treatment length. Device manufacturers could also aim to reduce the mismatch in biomechanical properties (device compliance) and/or bio-compatibility between the aorta and surgical materials and devices.

The added value of computational tools and imaging analyses may become more apparent if we manage to identify and correlate certain numerical parameters like optimal proximal landing zone configurations and/or stent-graft apposition with clinical outcomes, so that computational findings may be better quantified and consequently guide clinical practice. Incorporation or combination of *in silico* computational tools and findings with *in vivo*, or *ex vivo* analyses may help to better clarify specific aspects related to aortic biomechanics, anatomy, and surgical treatment of the aorta, as each study may

contribute in a different way due to advantages (and disadvantages) of specific study designs. We may also better examine the role of artificial intelligence techniques like machine-learning, as it may help reducing the time needed for solving mathematical equations involved in numerical methodologies, or in speeding up the segmentation process.

To further improve the outcomes of patients with aortic disease, specific aspects like how sex or aneurysm shape influences outcomes of patients undergoing TEVAR could be further studied, especially if larger sample sizes are obtained and/or with expanding indications of TEVAR to the more proximal aortic zones (i.e., aortic arch, ascending aorta). This may better determine if we should tailor certain diagnostic, screening, treatment, or follow-up practices by sex, or in other words to female needs. As highlighted, additional work is required to better understand if sex-specific (morphological) variations may impact TEVAR outcomes. Specific variables associated with aortic size could be considered by medical doctors and device manufacturers when developing new intraluminal arch or ascending aortic devices or planning interventions. Moreover, additional data is required to determine the most reproducible method of anteroposterior abdominal aorta diameter measurements with ultrasound, in light of technological advancements regarding ultrasound probes and machines.

For sex-specific TEVAR outcomes, a meta-analysis could be performed given the growing body of evidence on the matter. Regarding the outcomes of TEVAR for BTAI specifically, future studies may aim to better clarify if treatment delay, patient stabilization, and heparinization may be a reason for the observed lower perioperative mortality and stroke rates with higher surgeon volume in these patients, as the data presented in this thesis suggests there may be a benefit. Moreover, for left subclavian artery (LSA) management during zone 2 TEVAR, this thesis highlighted the need for additional study of the mid- to long term safety, outcomes, and patency of emerging endovascular LSA revascularization techniques and assess differences between different solutions. In the absence of widespread level A evidence in the form of randomized controlled trials or meta-analyses for many aspects related to the surgical management of aortic disease, additional real-world data from collaborative registries with large sample sizes may provide useful insights for answering specific remaining hypotheses in the field of cardiovascular surgical care.

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Samenvatting en discussie in het Nederlands

DISCUSSIE

In het licht van hedendaagse ontwikkelingen op het gebied van beschikbare technologieën, medische apparatuur en uitbreidende indicaties voor aortachirurgie (met daarbij vaker endovasculaire reparatie), heeft dit proefschrift multidisciplinaire perspectieven behandeld over de biomechanica van de aorta, anatomie, open chirurgische en endovasculaire behandeling van de aorta, en de interactie tussen deze aspecten. Daarbij zijn specifieke onbeantwoorde onderzoeksvragen beantwoord die mogelijk zullen bijdragen aan de verbetering van de klinische uitkomsten van patiënten met een aortaziekte.

In **Deel I** van dit proefschrift hebben we in **Hoofdstuk 1** fundamentele terminologie en concepten met betrekking tot de aorta geïntroduceerd. Vervolgens heeft de systematische review gepresenteerd in **Hoofdstuk 2** de cardiovasculaire hemodynamische veranderingen geëvalueerd die op lijken te treden na endovasculaire behandeling van de aorta door het ontplooien van een stent in de thoracale aorta (TEVAR), specifiek in patiënten met stomp traumatisch thoracaal aortaletsel (BTAI). Aangezien BTAI vaak voorkomt bij jonge en gezonde patiënten met een relatief lange levensverwachting, kan BTAI worden beschouwd als een geschikte ziekte om dergelijke lange termijn veranderingen te evalueren. Echter, aangezien BTAI zelden voorkomt en de meeste patiënten sterven voordat ze in het ziekenhuis aankomen,[1,2] zijn de conclusies van deze review beperkt door het aantal beschikbare studies (n=12) en het totale aantal patiënten (n=265), met daarnaast een matig (75%) tot laag (25%) risico op bias. Desalniettemin benadrukt de review dat er een aanzienlijke hoeveelheid bewijs bestaat die aangeeft dat aortastijfheid, bloeddruk, linker ventriculaire hartmassa en aortagrootte van onbehandelde aangrenzende segmenten kunnen toenemen tijdens de opvolging van patiënten na een TEVAR behandeling, wat nadelige gevolgen kan hebben voor de cardiovasculaire gezondheid en bepaalde doelorganen van de aorta (zoals de nieren en hersenen).[3] Tijdens de opvolging van jongere patiënten is het dus belangrijk om in overweging te nemen dat er negatieve gevolgen zouden kunnen optreden op de lange termijn na TEVAR. Toekomstige studies kunnen zich richten op het verduidelijken van patiëntkarakteristieken die geassocieerd kunnen zijn met een verhoogd cardiovasculair risicoprofiel, zoals patiënten met specifieke aortawand composities of patiënten met genetische aandoeningen van de aorta.

In **Deel II** van dit proefschrift hebben we specifieke elementen onderzocht die verband houden met de biomechanica van de aorta die mogelijk hebben bijgedragen aan de observaties in **Hoofdstuk 2**, door gebruik te maken van een gesimuleerd cardiovasculair circulatiesysteem in een experimenteel lab.

Experimentele perspectieven

Hoewel endovasculaire behandeling van de aorta nu stevig gevestigd is als de eerstelijnsbehandeling voor ziekte van de aorta descendens (landingszone 2 – 5), blijven de resultaten grotendeels afhankelijk van de anatomische kenmerken van de landingszones, zoals een bochtigere aortaboog, een kronkelig verloop van de aorta descendens, of eerdere aortachirurgie.[2,4–6] Naast anatomische factoren kunnen ook fysiologische factoren de uitkomsten van een TEVAR-behandeling beïnvloeden. Talrijke eerdere klinische en experimentele studies hebben aangetoond dat TEVAR de golfsnelheid van het bloed (PWV) verhoogt. PWV is het internationaal geaccepteerde surrogaat voor stijfheid van de aortawand, dat op zijn beurt onafhankelijk de kans op toekomstige cardiovasculaire complicaties, algehele mortaliteit en cardiovasculaire mortaliteit voorspelt.[3,7–13] Zoals geïntroduceerd in **Hoofdstuk 2**, kan aortastijfheid een rol spelen in het bepalen van de lange termijn resultaten na TEVAR, een blijvend aandachtspunt voor onze huidig beschikbare open, endovasculaire en/of hybride behandelingsopties van aortaziektes, samen met hun duurzaamheid.[14]

Een onbeantwoorde onderzoeksvraag is of en hoe specifieke aortageometrie de stroming van bloed beïnvloedt. Er is beperkt eerder bewijs dat veranderingen in de bloedstroom optreden met veranderende geometrische configuraties van de aorta, zoals een scherpere kromming van de aortaboog, oftewel een verhoogde boogangulatie.[15–18] In **Hoofdstuk 3** hebben we aangetoond dat een verhoogde boogangulatie – zoals aangetooond in een type III aortaboog[19] – geassocieerd is met een hogere PWV, systolische, diastolische, en gemiddelde arteriële bloeddrukken. Hoewel deze observaties geen aanvullende indicaties voor aortachirurgie vertegenwoordigen, vormen ze een stukje van de puzzel en kunnen ze nuttig zijn voor het optimaliseren van bloeddrukregulatie in patiënten met een scherpere bochting van de aortaboog. Bovendien zou dit een rol kunnen spelen bij het identificeren van subgroepen patiënten die mogelijk een snellere groei van aortadiameter vóór behandeling vertonen en die dus mogelijk baat hebben bij nauwere opvolging voorafgaand aan een eventueel chirurgisch herstel van de aorta.

Een volgende onbeantwoorde onderzoeksvraag is of open aortachirurgie de stijfheid van de aortawand beïnvloedt. In tegenstelling tot veranderingen in aortastijfheid na TEVAR, is er een gebrek aan beschikbare data na open chirurgie van de aorta, terwijl de biomechanische karakteristieken van chirurgische protheses (bijv., Dacron®) ook verschillen van de karakteristieken van de natieve aorta.[20,21] Of en op wat voor manier dit zich verhoudt tot een toegenomen aortastijfheid na TEVAR is tot op heden ongeweten. In **Hoofdstuk 4** hebben we aangetoond dat open chirurgische interpositie-grafting van de proximale aorta descendens de PWV door de aorta verhoogt, diastolische en gemiddelde arteriële bloeddrukken verlaagt, terwijl systolische bloeddrukken daarentegen

stabiel blijven. Bij een vergelijking met eerder verkregen data over aortastijfheid na TEVAR in hetzelfde experimenteel lab, met hetzelfde gesimuleerde cardiovasculair circulatiesysteem, en met vergelijkbare thoracale varkensaorta's (**Hoofdstuk 3**), vonden we dat de stijfheid van de aorta vergelijkbaar was na open chirurgische vervanging of endovasculair herstel van de aorta. In andere woorden, de PWV door de aorta nam toe na beide behandelingsmodaliteiten en er was geen statistisch significant verschil in de absolute PWV-waardes na zowel open chirurgie als TEVAR. Ondanks de experimentele aard en het lage aantal experimenten, maken deze bevindingen de weg vrij voor toekomstige studies die zich kunnen richten op het onderzoeken van potentiële veranderingen in aortastijfheid na open chirurgische behandeling van verschillende segmenten van de aorta en hun relatie tot veranderingen na TEVAR.

Een derde onbeantwoorde onderzoeksvraag werd behandeld in **Hoofdstuk 5** en heeft betrekking op het onderzoeken van verschillen in verstijving van de aortawand na TEVAR met een oudere en nieuwere generatie stent-graft van dezelfde fabrikant. Stentontwikkelaars ontwikkelen voortdurend nieuwere generatie stents met zogenaamde verbeteringen in de systemen en mechanismen om de stent te kunnen ontplooien, configuraties van het proximale deel van de stent, of de conformiteit.[22–25] **Hoofdstuk 5** bevestigt dat de PWV doorheen de aorta toeneemt na TEVAR, maar dat dit met zowel een tweede als derde generatie stent-graft gebeurt, zonder statistisch significante verschillen in de absolute PWV-waardes na TEVAR met beide stents. De studie toont dus aan dat zogezegde verbeteringen van nieuwere generaties stents niet noodzakelijkerwijs leiden tot een verminderde impact op de aortawandstijfheid, en dit roept dus de noodzaak op tot het verder blijven ontwikkelen van de compliantie van toekomstige stents (zonder verlies van adequate appositie en sterkte), om zo hopelijk de lange termijn uitkomsten na TEVAR te verbeteren.

Alhoewel deze studies beperkt zijn door hun experimentele onderzoeksopzet, het gebruik van *ex vivo* thoracale aorta's van varkens en een gesimuleerd cardiovasculair circulatiesysteem, zijn de voordelen dat directe vergelijkingen kunnen worden verricht tussen verschillende aortaboogangulaties (bijv. type I *vs.* type III-boog) of behandelingsmodaliteiten, en dit met het gebruik van dezelfde aorta, wat niet haalbaar is met *in vivo* analyses. De bevindingen van deze studies suggereren een samenspel tussen aspecten van biomechanica, anatomie en de uitkomsten van open chirurgische of endovasculaire behandeling van de aorta, die allemaal een rol kunnen spelen in het bepalen van de cardiovasculaire gezondheid van een patiënt.

Computergestuurde en beeldvormingsperspectieven

Zoals eerder vermeld, is TEVAR grotendeels afhankelijk van een geschikte aorta-anatomie in het gebied waar een thoracale stent wordt ontplooid.[2,4–6] Daarom speelt beeldvorming een cruciale rol tijdens de diagnosestelling, het screenen, de planning, en de opvolging, bijvoorbeeld wanneer een grondige pre-, intra-, en postoperatieve beoordeling van de aorta uitgevoerd wordt. Conventionele beeldvormingstechnieken zijn echografie, computertomografie-angiografie (CTA), of magnetische resonantie beeldvorming (MRI) met eventuele driedimensionale (3D) reconstructies. Bovendien kan vierdimensionale (4D) MRI van de bloedstroom specifieke aanvullende inzichten bieden in bloedstroompatronen die geassocieerd kunnen zijn met de progressie van acute aortaziektes of de vorming en groei van aneurysmata.

In de afgelopen jaren is er een toename geweest in de ontwikkeling en toepassing van *in silico* computergestuurde tools om bepaalde hemodynamische parameters te evalueren en ook om de pre-procedurele TEVAR planning te ondersteunen.[29–32] Daarom begint **Deel III** van dit proefschrift met **Hoofdstuk 6**, waarin we aantonen dat er momenteel 14 heterogene TEVAR-simulatiemodellen beschikbaar zijn in de literatuur, voornamelijk van intermediaire kwaliteit (64%) op basis van een beoordelingsrubriek van 16 punten die niet specifiek is ontwikkeld voor het beoordelen van numerieke simulatiestudies. De studie benadrukt dat dit een snel uitbreidend onderzoeksgebied is, sterk afhankelijk van een nauwe samenwerking tussen cardiovasculaire chirurgen en ingenieurs. Het poogt verbeteringen na te streven in de betrouwbaarheid en homogeniteit van computergestuurde tools om hun implementatie in de klinische praktijk te ondersteunen en bevorderen. In dit opzicht toont **Hoofdstuk 7** het potentieel, de workflow en de betrouwbaarheid van een TEVAR-simulatiemethodologie om perioperatieve complicaties en korte termijn postoperatieve technische resultaten te voorspellen. De nieuwe hoogwaardige numerieke (d.w.z. finite element analysis) methodologie die werd gebruikt in deze studie, werd ontwikkeld door onze onderzoeksgroep tijdens het beloop van dit proefschrift. Allereerst werden specifieke parameters van alle materialen van de thoracale stentgraft gekarakteriseerd met experimentele krimp-/loslaat-tests en werd de stent vervolgens ontplooid in een rigide, transparant en 3D geprint aortamodel met fysiologische anatomie voor een verificatieanalyse.[33] Vervolgens werd de algehele toepasbaarheid van de TEVAR simulatie of modellering beoordeeld om zo de betrouwbaarheid van het model te evalueren volgens een stapsgewijze methode gebaseerd op het American Society of Mechanical Engineers (ASME) V&V40-protocol.[34,35] Door deze TEVAR simulatiemethodologie toe te passen op een patiënt specifieke casus in **Hoofdstuk 7**, konden we aantonen dat deze numerieke virtuele simulatie methode in staat was om een distale kink van een thoracale stent te reproduceren zoals waargenomen tijdens een TEVAR procedure met proximale landing in zone 2 van de distale aortaboog. Hiermee

wordt het potentieel van een implementatie van dergelijke computergestuurde tools in de klinische praktijk, met name tijdens de preoperatieve fase, benadrukt.

Tijdens de preoperatieve beoordelingsfase speelt CTA een belangrijke rol in het beoordelen van de anatomie van de aorta en het plannen van een TEVAR-procedure. Met name in het licht van hedendaagse uitbreidende indicaties voor endovasculaire behandeling van de aorta ascendens en aortaboog,[4,6,36,37] kunnen morfometrische en geometrische analyses specifieke inzichten bieden voor het plannen van TEVAR met een proximale landing in deze zones. Specifiek gericht op het onderzoeken van sekse-gerelateerde verschillen, is **Hoofdstuk 8** een retrospectieve morfometrische analyse van de aorta ascendens en aortaboog gebaseerd op elektrocardiogram-gestuurde CTA data van 116 patiënten die werden geëvalueerd voor een transcatheter aortaklepvervanging (TAVR). De extrapolatie van de bevindingen van deze studie naar patiënten met aortaziekte moeten daarom voorzichtig plaatsvinden maar lijkt nuttig voor het plannen van TEVAR, aangezien stentgraft landing meestal plaatsvindt in gezond aortaweefsel. Deze studie evalueerde factoren die geassocieerd zijn met aortadiameters in beide geslachten en evalueerde sekse-specifieke verschillen in aortagrootte. In beide geslachten werden verschillende associaties gevonden tussen klinische patiëntkarakteristieken en grootte in specifieke aortasegmenten (d.w.z. de sinotubulaire overgang [STJ], mid-ascendens, het distale deel van de aorta ascendens, zone 1, zone 2). Zo was lichaamsoppervlakte onafhankelijk geassocieerd met grotere diameters ter hoogte van de mid-ascendens in mannen, terwijl dit in vrouwen alleen het geval was met grotere diameters van zone 2. Diabetes mellitus was onafhankelijk geassocieerd met kleinere STJ tot zone 1 diameters in mannen, terwijl dit in vrouwen alleen het geval was ter hoogte van het distale deel van de aorta ascendens en zone 1 diameters. Gemiddeld genomen toonde de studie aan dat mannen 7,4% grotere diameters van de aorta ascendens en aortaboog hadden vergeleken met vrouwen, zowel bij metingen in systole als in diastole. Dergelijke inzichten in sekse-gerelateerde verschillen kunnen mogelijk helpen bij het personaliseren van behandelingen van de aorta volgens geslacht en zouden bijvoorbeeld verschillende morfometrische limieten van de aorta ascendens en aortaboog kunnen bepalen met betrekking tot indicaties voor chirurgisch herstel of opvolging door middel van beeldvorming.

Echografie is een ander waardevol hulpmiddel die kan worden gebruikt bij de diagnose en screening van abdominale aneurysmatas, met als voordeel dat het contrast- en stralingsblootstelling aan patiënten beperkt.[26] Een volgende onbeantwoorde onderzoeksvraag is welke plaatsing van meetindicatoren of schuifmaten op een echografie apparaat tijdens anteroposterieure metingen van de diameter van de abdominale aorta kan worden beschouwd als het meest reproduceerbaar tussen gebruikers (d.w.z. van

adventitia tot adventitia [OTO], intima tot intima [ITI], of van adventitia anterieur tot intima posterieur [LELE]). Daarom voerden we in **Hoofdstuk 9** een meta-analyse uit van de data uit 21 beschikbare diagnostische nauwkeurigheidsstudies en concludeerden we dat de reproduceerbaarheid tussen gebruikers van de OTO- en ITI-methoden 2,5 keer kleiner was (duidend op een betere reproduceerbaarheid tussen gebruikers) dan LELE, maar zonder statistisch significant verschil tussen de drie methoden. Wanneer alleen de data van studies gepubliceerd na 2010 in beschouwing werden genomen voor onze analyses, dan was de reproduceerbaarheid tussen gebruikers met de LELE-methode het kleinst, echter ook zonder statistisch significante verschillen tussen de drie methoden. Hoewel er belangrijke inherente verschillen zijn tussen de drie methoden waarbij OTO consequent grotere diameter metingen oplevert in vergelijking met ITI (4 – 7 mm), kan de meta-analyse geen conclusie trekken over de superioriteit van de een of de andere methode met betrekking tot de reproduceerbaarheid tussen gebruikers, wat ook blijkt uit een lage mate van zekerheid over het gecombineerde bewijs uit de verschillende studies, zoals geëvalueerd met de GRADE-aanpak.

Klinische perspectieven op thoracale aortaziekte

Deel IV van dit proefschrift maakte gebruik van verschillende grote databases die zijn ontstaan door internationale samenwerkingsverbanden tussen ziekenhuizen en de data van patiënten behandeld in een enkel ziekenhuis (single-center). Hierdoor konden specifieke onderzoeksvragen over de chirurgische behandeling van thoracale aortaziekten worden beantwoord.

Een onbeantwoorde onderzoeksvraag is of de uitkomsten van TEVAR verschillend zijn voor mannen en vrouwen, specifiek op de lange termijn. Eerdere studies hebben tegenstrijdig bewijs geleverd, waarbij vier studies vergelijkbare sterftecijfers op de korte, middellange en lange termijn meldden voor zowel mannen als vrouwen, terwijl twee recentere studies hogere sterftecijfers op de korte en lange termijn voor vrouwen die werden behandeld met TEVAR rapporteerden.[38–43] **Hoofdstuk 10** onderzocht de uitkomsten van TEVAR procedures van 805 patiënten opgenomen in het Global Registry for Endovascular Aortic Treatment (GREAT) register en vond geen verschillen tussen mannen en vrouwen wat betreft de mortaliteit na 30 dagen tot aan 5 jaar na de procedure (geschatte 5-jaarsoverleving voor mannen: 67% [95% CI, 62,1-72,2] *vs.* voor vrouwen: 65.9% [95% CI, 58,5-74,2], p=.847) en complicaties na TEVAR voor eender welke indicatie of aortaziekte, noch na stratificatie naar aortaziekte in subgroep analyses (behalve een hoger percentage type II endoleak na TEVAR bij vrouwen met gecompliceerde type B aortadissecties).

Een andere onbeantwoorde onderzoeksvraag is of het aantal operaties dat een chirurg uitvoert van invloed is op de uitkomsten van patiënten die TEVAR ondergaan voor BTAI. Met betrekking tot de open chirurgische of endovasculaire behandeling van de aorta heeft eerder onderzoek onderzocht of het operatievolume van een ziekenhuis of een vaatchirurg van invloed is op klinische uitkomsten, zich voornamelijk gericht op de abdominale aorta.[44] Twee eerdere studies onderzochten specifiek de impact van het operatievolume van een chirurg op de uitkomsten na TEVAR procedures, voor aortadissecties en thoracale aneurysmata, en vonden geen verband tussen het operatievolume van de chirurg en de perioperatieve en 5-jaarsmortaliteit.[45,46] Specifiek voor de uitkomsten na TEVAR voor BTAI, vond een eerdere studie een lagere perioperatieve mortaliteit in ziekenhuizen hogere operatievolumes,[47] maar de potentiële impact van het operatievolume van de chirurg op deze bevindingen werd niet onderzocht in deze context.[48] Daarom gebruikte **Hoofdstuk 11** de data van 1,321 patiënten die TEVAR procedures ondergingen voor BTAI en werden opgenomen in het Vascular Quality Initiative (VQI) register. De studie toonde aan dat in vergelijking met chirurgen met een laag operatievolume gedurende het jaar voorgaand aan hun TEVAR-procedure voor BTAI (LV: 0-1 TEVAR procedures), een gemiddeld (MV: 2-8 TEVAR procedures) tot hoog operatievolume (HV: ≥9 TEVAR procedures) onafhankelijk geassocieerd was met een lagere perioperatieve mortaliteit en postoperatieve ischemische/bloedige beroerte, ongeacht het operatievolume van het ziekenhuis waar de procedure werd verricht. Met een toenemend operatievolume van de chirurg werd op univariabele analyse gevonden dat de proporties van postoperatieve beroerte lager waren (LV: 6,5%, MV: 3,6%, HV: 1,5%, p=.006).

Een ander belangrijk aspect gerelateerd aan het uitbreiden van de indicaties van TEVAR naar de aortaboog is dat het hierbij noodzakelijk wordt om de supra-aortale vaten te behandelen. Bij een proximale landing van een stent in zone 2 wordt aanbevolen om de linker arteria subclavia (LSA) te revasculariseren aangezien studies hebben aangetoond dat dit leidt tot een verminderd risico op perioperatieve neurologische complicaties zoals een beroerte of myelumischemie.[49–51] Traditioneel wordt hiervoor een open chirurgische LSA revascularisatie uitgevoerd door middel van het aanleggen van een bypass tussen de linker arteria carotis (LCCA) en LSA of transpositie van de LSA naar de LCCA, en **Hoofdstuk 12** toont aan dat dit geassocieerd is met blijvend gunstige doorgankelijkheid van deze bypass of transpositie na 10 jaar opvolging (geschatte vrijheid van occlusie: 97% ± 2%, geschatte vrijheid van een ernstige stenose: 90% ± 4%) op basis van de data van 90 patiënten die zone 2 TEVAR en open chirurgische LSA revascularisatie ondergingen in een enkel ziekenhuis. Daarnaast zijn er met de hedendaagse ontwikkelingen op het gebied van beschikbare technologieën tegenwoordig endovasculaire alternatieven beschikbaar om de LSA te revasculariseren en daarmee de antegrade bloedstroom door dit vat te bewerkstelligen bij een zone 2 TEVAR procedure, welke vergeleken zijn met de

historische gouden standaard of maatstaf van een open bypass of transpositie. **Hoofdstuk 13** maakte gebruik van de data van 2,489 patiënten opgenomen in het VQI-register en die een zone 2 TEVAR met LSA revascularisatie ondergingen. Na stratificatie naar het type revascularisatie (open *vs.* eender welke endovasculaire optie) en vergeleken met patiënten die een open LSA revascularisatie ondergingen, hadden patiënten die een endovasculaire revascularisatie van de LSA ondergingen lagere postoperatieve beroerte cijfers (2,6% vs. 4,8%, p=.026; aOR 0,50 [95%C.I., 0,25-0,90]) en lagere algeheel gecombineerde postoperatieve complicaties in het ziekenhuis (20% vs. 27%, p<.001; 0,64 [0,49-0,84]), maar vergelijkbare proporties van postoperatieve myelumischemie (2,9% vs. 3,5%, p=.60; 0,64 [0,31-1,22]), perioperatieve mortaliteit (3,1% vs. 3,3%, p=.94; 0,71 [0,34-1,37]) en 5-jaars mortaliteit (aHR 0,85 [0,64-1,13). Deze bevindingen lijken een verdere inpassing van endovasculaire alternatieven om de LSA te revasculariseren te begunstigen hoewel de middel- tot lange termijn resultaten, de doorgankelijkheid en de gestratificeerde uitkomsten van specifieke endovasculaire LSA revascularisatietechnieken nog grotendeels onbekend zijn.

In **Hoofdstuk 14** concludeert dit proefschrift met een studie die de rol van het International Registry of Acute Aortic Dissection (IRAD) register op het bevorderen van ons begrip en de behandeling van patiënten met een aortadissectie heeft geëvalueerd tijdens de eerste 25 jaar van het bestaan van IRAD. De impact van 97 IRAD studies werd gekwantificeerd met behulp van cumulatieve citatie-cijfers, en daarnaast identificeerde een systematische review van de literatuur 19 cardiovasculaire richtlijnen met betrekking tot de behandeling van acute aortadissectie. Vervolgens werd gebaseerd op een evaluatie van de mate waarin IRAD-studies zijn overwogen bij het opstellen van deze internationale richtlijnen, en in de afwezigheid van level A data, geconcludeerd dat IRAD een belangrijke rol heeft gespeeld, en een voortdurende rol speelt, in het verbeteren van de uitkomsten van patiënten met een (acute) aortadissectie.

Toekomstperspectieven

Zoals reeds weerspiegeld in de hieraan gewijde *Future perspectives* secties van de verschillende hoofdstukken in dit proefschrift, blijft er aanvullend onderzoek nodig naar de interactie tussen biomechanica van de aorta, anatomie, open chirurgische of endovasculaire behandeling van de aorta, en de klinische uitkomsten van patiënten met aortaziekten. We zouden moeten streven naar een verduidelijking van potentiële causale paden tussen aortastijfheid, specifieke veranderingen in bloeddruk, cardiale hypertrofie, en aortadilatatie of groei. Bijvoorbeeld, hoe relevant is het als linker ventrikelhypertrofie optreedt na TEVAR voor patiënten van verschillende leeftijdsgroepen, en leidt dit tot een verlies van de systolische of diastolische hartfunctie, direct of tijdens de opvolging? Heeft dit invloed op de mortaliteit van patiënten die een chirurgisch herstel van de aorta

ondergaan? Of, hoe relevant is een toegenomen groei of wandspanning in de aorta ascendens of distale abdominale aorta na een TEVAR-procedure van de aortaboog?

Over het algemeen zou meer homogeniteit in methodologische benaderingen en evaluaties van resultaten in toekomstige studies kunnen helpen om de vergelijkbaarheid van studies te bevorderen en het combineren van de uitkomsten van verschillende studies te bevorderen om zo een sterker bewijs voor of tegen bepaalde bevindingen aan te leveren. Bovendien zou aanvullende gestandaardiseerde beeldvorming op specifieke momenten tijdens de pre- en postoperatieve fase (bijv. echocardiografie, PWV doorheen de aorta gemeten van de LCCA tot aan de arteria femoralis, 4D-flow cardiovasculaire MRI) kunnen helpen bij het vervaardigen van potentieel bruikbare data voor toekomstige studies gericht op het onderzoeken van specifieke aspecten van de biomechanica van de aorta. Zoals eerder vermeld lijkt een nauwe samenwerking tussen artsen en ingenieurs hiervoor cruciaal om tot een vollediger begrip te komen van biomechanische kenmerken, inclusief de stroming van het bloed.

Daarnaast blijven lange termijn data schaars en dus nodig, en zouden studies zich kunnen richten op een geïsoleerde evaluatie van specifieke segmenten van de aorta, andere geometrische kenmerken van de aorta en/of het in overweging nemen van de lengte van een chirurgische behandeling. Ontwikkelaars en fabrikanten van medische apparatuur zouden ook kunnen streven naar het verminderen van het verschil in biomechanische eigenschappen (compliantie) en/of bio compatibiliteit tussen de aorta en chirurgische materialen zoals bijvoorbeeld stents of open chirurgische protheses.

De toegevoegde waarde van computergestuurde analyses kan duidelijker worden wanneer we in staat zouden zijn om bepaalde numerieke gegevens zoals optimale proximale landingszone configuraties en/of stentgraft appositie te identificeren en vervolgens te correleren met klinische uitkomsten, zodat computergestuurde bevindingen beter kunnen worden gekwantificeerd en vervolgens sturing kunnen geven aan de klinische praktijk. Het incorporeren van *in silico* computergestuurde tools en bevindingen in, of het combineren van zulke bevindingen met, *in vivo* of *ex vivo* analyses, zou kunnen helpen om specifieke aspecten van de biomechanica van de aorta, anatomie en chirurgische behandeling van de aorta te verduidelijken, aangezien elke studie op een andere manier kan bijdragen vanwege specifieke voor- en nadelen van verschillende onderzoeksopzetten. We zouden ook beter kunnen onderzoeken welke rol kunstmatige intelligentie zoals machine learning hierin zou kunnen spelen, aangezien dit mogelijk zou kunnen helpen bij het verminderen van de tijd die nodig is voor het oplossen van wiskundige vergelijkingen waaruit numerieke methodes bestaan, of in het versnellen van het beeldvormingssegmentatieproces.

Om de uitkomsten van patiënten met een aortaziekte verder te verbeteren, kunnen specifieke aspecten zoals hoe geslacht of aneurysmavorm van invloed is op deze uitkomsten verder worden onderzocht, vooral als de data van grote aantallen patiënten verkregen zou kunnen worden of indien de indicaties voor endovasculaire behandeling van de aorta verder worden uitgebreid (d.w.z. aortaboog, aorta ascendens). Hiermee zouden we beter kunnen bepalen hoe we onze huidige diagnostische, screenings-, behandelings-, en opvolgingsmodaliteiten zouden kunnen toespitsen op beide geslachten, of met andere woorden kunnen aanpassen naar vrouwelijke behoeften. Zoals benadrukt is daarnaast aanvullend onderzoek vereist om beter te begrijpen of geslacht specifieke (morfologische) variaties de uitkomsten van TEVAR beïnvloeden. Specifieke variabelen geassocieerd met de grootte van de aorta zouden in overweging kunnen worden genomen door artsen, ontwikkelaars en fabrikanten bij het ontwikkelen van nieuwe stents of protheses voor de behandeling van de aortaboog en aorta ascendens of tijdens het plannen van interventies. Bovendien is aanvullende data nodig om de meest reproduceerbare methode van plaatsing van meetindicatoren of schuifmaten tijdens anteroposteriore metingen van de diameter van de abdominale aorta met echografie te bepalen, gezien de technologische vooruitgang met betrekking tot echografie toestellen inclusief probes en software.

Specifiek voor geslacht specifieke TEVAR-uitkomsten zou men een meta-analyse kunnen verrichten gezien het groeiende aantal studies over dit onderwerp met heterogene bevindingen. Met betrekking tot de uitkomsten van TEVAR voor BTAI specifiek zouden toekomstige studies zich kunnen richten op het onderzoeken of een vertraging van de behandeling met TEVAR, en dus patiëntstabilisatie met het toedienen van heparine, een verklaring zou kunnen zijn voor de betere uitkomsten van patiënten met BTAI die we hebben geobserveerd voor chirurgen met een hoger jaarlijks TEVAR operatievolume, aangezien de data gepresenteerd in dit proefschrift aangeeft dat er mogelijk een voordeel zou kunnen zijn. Bovendien, voor het omleiden van de LSA tijdens zone 2 TEVAR procedures, heeft dit proefschrift benadrukt dat er aanvullend onderzoek naar de middel- tot lange termijn veiligheid, uitkomsten en doorgankelijk van nieuwere opkomende endovasculaire alternatieven om de LSA te revasculariseren nodig is, tezamen met het uitvoeren van gestratificeerde analyses om de uitkomsten voor specifieke endovasculaire technieken te onderzoeken. In de afwezigheid van level A data in de vorm van gerandomiseerde studies of meta-analyses voor vele aspecten gerelateerd aan de chirurgische behandeling van aortaziekte, kunnen aanvullende data voortkomend uit internationale registers door samenwerkingsverbanden, met name met grote patiënten aantallen, nuttige inzichten bieden voor het beantwoorden van specifieke resterende onderzoeksvragen in de cardiovasculaire chirurgische zorg.

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Appendix

A. REVIEW COMMITTEE

Prof. dr. R.L.A.W. Bleys
Department of Anatomy
University Medical Center Utrecht

Prof. dr. D.E. Grobbee
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht

Prof. dr. P. van der Harst
Department of Cardiology
University Medical Center Utrecht

Prof. dr. L. Hooft (voorzitter)
Department of Epidemiology and Health Economics
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

Prof. dr. J. Kluin
Department of Cardiothoracic Surgery
Erasmus University Medical Center, Rotterdam

B. ACKNOWLEDGEMENTS

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C. LIST OF PUBLICATIONS

In international peer-reviewed journals

Jabbour G, **Mandigers TJ**, Mantovani F, Yadavalli SD, Allievi S, Caron E, Rastogi V, van Herwaarden JA, Trimarchi S, Zettervall S, Abramowitz SD, Schermerhorn ML. Factors associated with and outcomes of respiratory adverse events following thoracic endovascular aortic repair. *J Vasc Surg.* 2024; in press.

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D. CURRICULUM VITAE

Tim Johannes Mandigers was born on June 2, 1994, in Veldhoven, the Netherlands. After graduating from the VWO Atheneum at the S.G. Augustinianum in Eindhoven in 2012, he obtained his Master of Medicine – Magna cum laude – at the Catholic University of Leuven, Belgium, in 2019. After his studies, he moved to Utrecht and started working as a resident not in training at the Cardiothoracic surgery department of the St. Antonius Hospital in Nieuwegein, where he was involved in research focusing on thoracic aortic disease. In August 2021, he started his PhD program at the department of Vascular surgery of the University Medical Center in Utrecht under supervision of his promotor prof. dr. van Herwaarden. From the start, he worked at the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano under supervision of his promotor prof. dr. Trimarchi in Milan, Italy. Their research mainly focused on biomechanical concepts involving thoracic aortic disease and surgical treatments, and involved close collaborations with engineers from the University of Pavia and Politecnico di Milano, as presented in this thesis. In August 2023, he moved to Boston, United States of America, to spend six months at the research lab of prof. dr. Schermerhorn at the Beth Israel Deaconess Medical Center affiliated with Harvard Medical School. At the end of February 2024, he returned to work as a medical doctor at the Cardiothoracic surgery department of the St. Antonius Hospital in Nieuwegein, the Netherlands, where he was accepted for the residency program and will formally start his surgical training in December 2024.

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