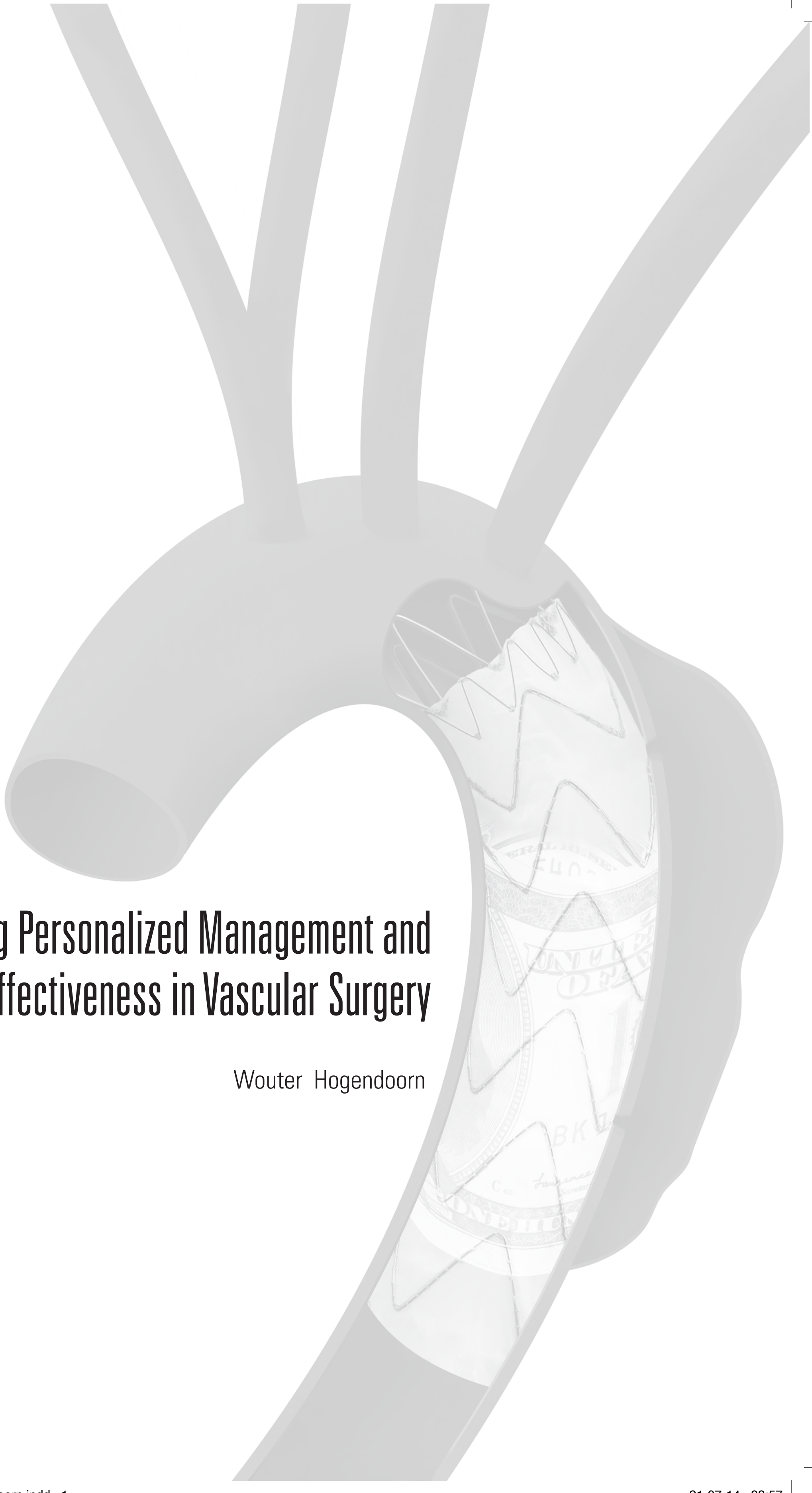

Optimizing Personalized Management and Cost-Effectiveness in Vascular Surgery

Wouter Hogendoorn

Optimizing Personalized Management and Cost-Effectiveness in Vascular Surgery

Wouter Hogendoorn, Utrecht University, Faculty of Medicine, University Medical Center, Utrecht, the Netherlands.

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en kosteneffectiviteit in de vaatchirurgie
(met een samenvatting in het Nederlands)

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PART THREE General Discussion of the thesis

CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

The last two decades there has been an enormous increase in surgical research and tremendous progress in the field of vascular surgery. The most important alteration in vascular surgery has been the shift from open surgical repair towards the endovascular solution.[1] This shift has happened in the major interventions, for example the shift from open surgical repair for abdominal aortic aneurysms (AAA) to endovascular aortic repair (EVAR)[2] and in the minor surgeries, where stenting and percutaneous transluminal angioplasty (PTA) currently play a major role in the treatment of peripheral arterial disease (PAD).[3] Meanwhile, new endovascular techniques and devices continue to evolve. This is a positive and necessary development, but the increasing number of techniques and devices is accompanied by an increase in choices, decisions and costs. Traditionally, new devices or other products were developed to improve patient outcome, but recently, most clinical trials are expected to only show non-inferiority by the United States Food and Drug Administration.[4] Do all these new devices actually add something to the health of the patient? And is this sometimes small increase in effect worth the sometimes large increase in cost? Moreover, new techniques will bring new complications with them. An example of this is the term "endoleak", first described in 1996.[5] An endoleak is characterized by persistent blood flow within the aneurysm sac following an intervention such as an EVAR. With the increasing use of the new chimney graft technique, there is also an increase in endoleaks.[6] Further, another new endovascular device has been developed to decrease the number of endoleaks.[7]

Most studies evaluate the effect of an intervention on the health of the patient. However, most studies assess the early morbidity and mortality and do not evaluate the quality of life of the patient, before, during and after treatment. This is, however, a very important determinant of whether a treatment is successful. Therefore it is important to evaluate the quality of life of the patient, and additionally, to evaluate the costs. If there is only a small gain in health, but there is a large increase in the costs, is an intervention worth it, if there is already a good alternative available?

Since the majority of vascular diseases have a low incidence and prevalence, level 1 evidence provided by randomized controlled trials (RCTs) is lacking, and since RCTs are expensive and time-consuming it can be questioned if these will be in conducted in the near future.[8] Comparison of the effect of different treatment modalities for a disease is still necessary and decision models can be utilized to evaluate the different treatment options. Decision models have the ability to combine different studies and integrate multiple variables providing an elegant method to study vascular diseases if Level 1 evidence is lacking.[9]

PURPOSE AND OUTLINE OF THIS THESIS

The general aim of the studies described in this thesis is to evaluate the cost-effectiveness and to select the preferred treatment for different clinical patient groups for several vascular surgical diseases by means of decision analysis. This thesis consists of 2 parts. In **PART ONE**, several new endovascular techniques and devices are described. In **PART TWO** of this thesis, the cost-effectiveness and the most effective treatment options for several vascular surgical diseases are evaluated using decision analysis.

In **Chapter 2**, the outcomes of all available data of the thoracic endovascular aortic repair (TEVAR) with the chimney graft technique until now are discussed. The chimney graft technique involves placement of a stent or stent-graft parallel to the main aortic stent-graft to extend the proximal or distal sealing zone while maintaining side branch patency. TEVAR with the chimney technique is a viable treatment option and may expand treatment strategies for patients with challenging thoracic aortic pathology and anatomy in the emergent and elective setting. However, the Achilles' heel of the chimney graft technique is the occurrence of endoleaks. How to treat a patient with an endoleak after EVAR with or without the chimney graft technique is reported in **Chapter 3**, with the use of another new technique, the Aptus HeliFX EndoAnchors. Both previously reported techniques and devices can be used in the acute setting to treat emergencies, including ruptured aortic aneurysms and dissections. One of the most important and major complications that must be prevented is paraplegia. How to prevent paraplegia is a hot topic, not only in the field of vascular surgery, but also in other specialties involved in the treatment of these pathologies, such as interventional radiology and anesthesiology, and the current surgical and anesthetic considerations for the endovascular treatment of ruptured descending thoracic aortic aneurysms is discussed in **Chapter 4**.

In general, major interventions, including EVAR and TEVAR, benefit more from the shift towards the endovascular solution, because the high morbidity and mortality associated with open repair will be decreased. However, open surgical repair is still prevalent and in some cases, open surgical repair is still required. In **Chapter 5**, an example of successful surgical repair of a giant superior mesenteric artery aneurysm is reported. Superior mesenteric artery aneurysms are the third most common splanchnic aneurysms, but account for only 5.5% of all splanchnic aneurysms. Splenic artery aneurysms are by far the most common splanchnic artery aneurysms, accounting for more than 60% of all splanchnic aneurysms.[10] Since there are no clear guidelines for the treatment of splenic artery aneurysms, a systematic review and meta-analysis was performed, evaluating the three most utilized treatment options for splenic artery aneurysms: open repair, endovascular repair and conservative management. This resulted in clear short and long-term outcomes, reported in **Chapter 6**, but it is still unclear which therapy would fit which patient, based on variables such as age, gender and risk-profile and whether these interventions are cost-effective or not. These questions, for splenic artery aneurysms, as well as chronic mesenteric ischemia, popliteal artery aneurysms and chronic and acute type B aortic dissections, are answered in **PART TWO** of this thesis, where the cost-effectiveness and most effective treatments for the previously mentioned vascular diseases are evaluated using decision analysis. Decision analysis is a tool that can be used to choose an option that maximizes the overall health benefit of a patient. It is an explicit, quantitative, and systematic approach to decision making under conditions of uncertainty.[9] The strength of decision models is that they not only report mortality or complications as outcomes, but can also incorporate quality of life values, expected reinterventions, disease-specific mortality rates and costs. This leads to a more complete evaluation of the 'best' treatment. Decision models are especially practical for diseases with a low prevalence, when randomized controlled trials are not available. However, many clinicians may perceive decision models as a black box. For this reason, the most important steps when performing decision analysis are described in a practical guide for surgeons in **Chapter 7**. Subsequently, cost-effectiveness analyses for the previously mentioned splenic artery aneurysms, popliteal artery aneurysms and chronic mesenteric ischemia are presented in **Chapters 8, 9** and **10**, where open repair, endovascular repair and conservative management are evaluated on both effectiveness and lifetime costs. In **Chapter 11**, the preferred treatment for patients with an uncomplicated chronic dissection of the descending aorta is discussed. Several options for treatment, including open surgical repair, thoracic endovascular aortic repair and optimal medical therapy are available. A treatment strategy decision chart for the optimal treatment strategy, based on four basic patient characteristics: age, sex, surgical risk profile, and maximum initial aortic diameter was created. This tool was developed to guide the clinician in the preferred treatment, taking into account several variables which will have impact on the health of the patient and effectiveness treatment including long-term complications, reinterventions rates and quality of life. If patients with a complicated acute dissection of the descending aorta should be treated, is discussed in **Chapter 12**. TEVAR has shown superior short term results, including a significantly lower perioperative morbidity and mortality compared with open surgical repair, while open surgical repair is associated with lower disease-related complications and reintervention rates. This trade-off is evaluated using a clinical decision model. Finally, **Chapter 13** provides a summary of this thesis, a general discussion and future perspectives and **Chapter 14** provides the summary and discussion in Dutch.

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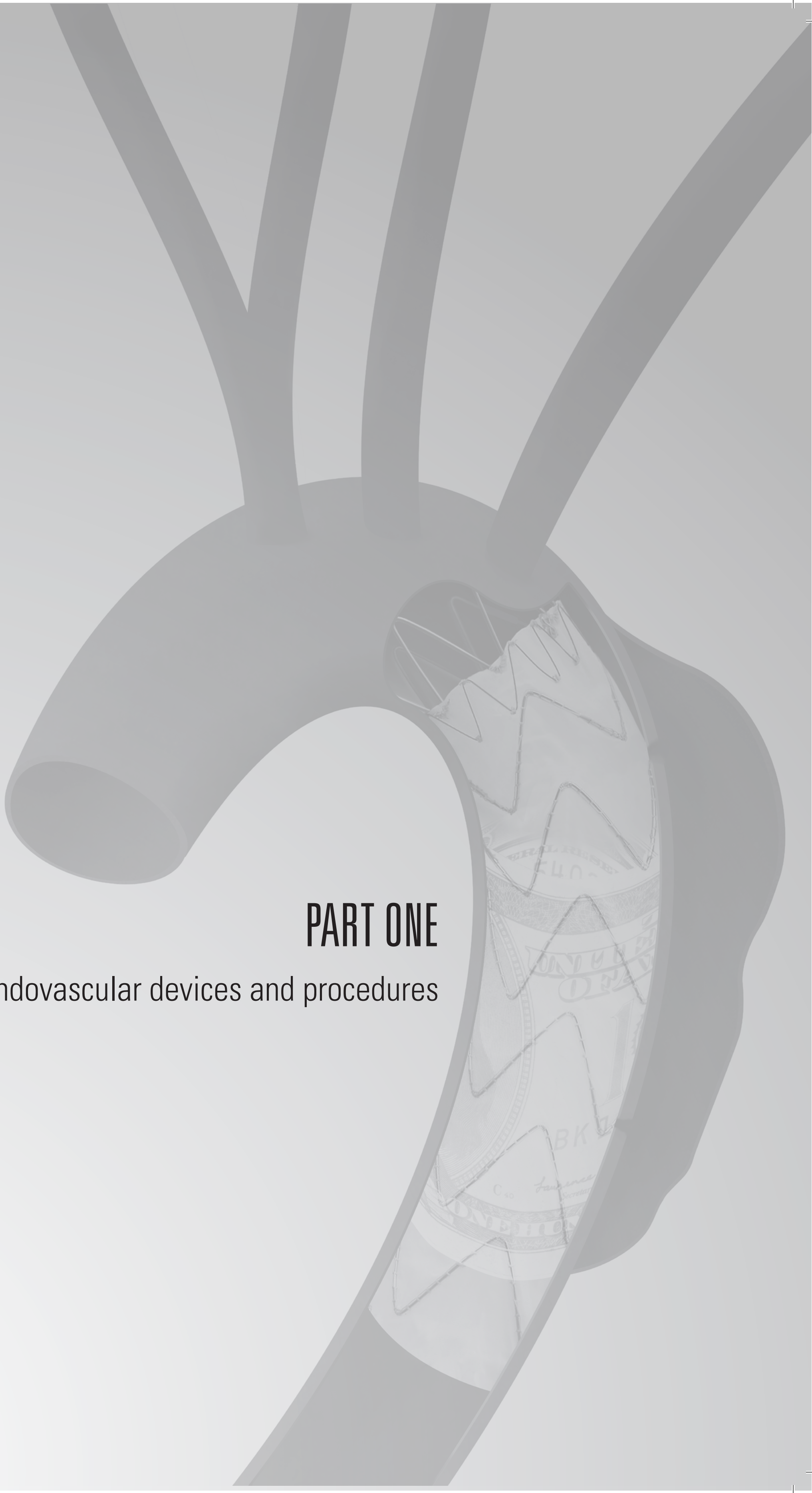

PART ONE

New endovascular devices and procedures

CHAPTER 2

Thoracic endovascular aortic repair with the chimney graft technique

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ABSTRACT

Objective

To provide insight into the safety, applicability and outcomes of thoracic endovascular aortic repair (TEVAR) with the chimney graft technique.

Methods

Original data regarding the chimney technique in TEVAR in the emergent and elective setting were collected from MEDLINE, Embase and Scopus databases. All variables were systematically extracted and included in a database. Patient and procedural characteristics, details and outcomes were analyzed using SPSS version 19.0 (SPSS Inc, Chicago, Ill).

Results

In total, 94 patients with 101 chimney stented aortic arch branches were analyzed (brachiocephalic artery, *N* = 20; left common carotid artery, *N* = 48; left subclavian artery, *N* = 33). Balloon expandable stents were used in 36%, and self-expandable stents in 64% for the aortic side branch. Most of the interventions were elective: 72% vs. 28% emergent. Technical success was achieved in 98%, in both elective and emergent settings combined. Endoleaks were described in 18%; with type 1a being most frequently reported: 6.4% overall, and 6.5% in elective setting. Stroke was reported in 5.3% of all the patients, of which 40% were fatal. Overall peri-operative mortality was 3.2%. Median follow-up time was 11 months and chimney stents remained patent in all patients.

Conclusion

TEVAR with the chimney technique is a viable treatment option and may expand treatment strategies for patients with challenging thoracic aortic pathology and anatomy, in the emergent and elective setting. Patency of the thoracic chimney stents appears to be good during short term follow-up. Other complications such as endoleak and stroke deserve attention by future research to further improve treatment strategies and the prognosis of these patients.

INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) is still increasing and considered as a safe and viable treatment option in properly selected patients with descending thoracic aortic pathology.[1,2] However, the currently available endovascular grafts can only be used in patients that meet several strict anatomical criteria, limiting use in a large subset of patients.

One of the most common problems in treating aortic arch pathologies is a short proximal landing zone.[3] While a sufficient length and quality proximal landing zone has to be established to assure maximum potential for successful proximal fixation, vital aortic arch side branches must be preserved.[4] Custom made, single or multi-branched aortic stent grafts have been used, but these devices are not applicable in time-sensitive settings.[5,6]

To further expand the applicability of endovascular repair of aortic arch and descending aortic pathology, alternatives have been proposed such as the ''chimney graft'' technique, which involves placement of stents in side branches of the aorta alongside the main endovascular stent graft.[7,8] These techniques are also described as the snorkel[9], double barrel[10] or sandwich technique[11]. The periscope technique, where the stent-graft is placed distally from the main aortic stent-graft, is another variant of the chimney technique.[12]

One advantage of the chimney technique is that readily available, on-the-shelf stents can be used. When these stents are placed in the side branches parallel to the aortic stent graft, a prolonged proximal landing zone can be created and continued perfusion of the aortic side branches can be maintained. However, the use of these chimney grafts is not defined in the IFU (Instructions for Use) of these devices and so the use is off-label. To protect safety of patients, it is important to have a critical look at the use of the chimney technique before they become a widely accepted intervention in the elective setting.

The use of chimney grafts in the elective setting is derived from the use in the emergent setting. Chimney graft use in the emergent setting is becoming widely accepted as useful technique, although long term results are not yet published. Elective TEVAR with the chimney technique is used more often and is a potential new technique to replace the hybrid repair for thoracic aortic diseases, but evidence for good results in the elective setting is still lacking. In order to improve the prognosis of patients after TEVAR with the chimney technique, more insight into the safety, applicability and outcomes are necessary. It is important to determine what complications have been reported for the specific type of complications, and if the chimney technique is a safe technique for all the aortic arch side branches. The purpose of this study is to perform a meta-analysis of all available data regarding TEVAR with the chimney technique in general and in the elective setting specifically.

METHODS

Literature search

MEDLINE, Scopus, Embase and the Cochrane Database were searched without date limit through October 2012. MEDLINE was searched through the PubMed search engine with the following search string: ("chimney"[Title/Abstract] OR "chimneys"[Title/Abstract] OR

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"periscope"[Title/Abstract] OR "periscopes"[Title/Abstract] OR "snorkel"[Title/Abstract] OR "snorkels"[Title/Abstract] OR "barrel"[Title/Abstract] OR "barrels"[Title/Abstract] OR "parallel"[Title/Abstract] OR "sandwich"[Title/Abstract] OR "sandwiches"[Title/Abstract]) AND ("aorta"[Title/Abstract] OR "aortic"[Title/Abstract]) AND ("intraluminal"[Title/Abstract] OR "intravascular"[Title/Abstract] OR "endovascular"[Title/Abstract] OR "endograft"[Title/Abstract] OR "endografts"[Title/Abstract] OR "stentgraft"[Title/Abstract] OR "stentgrafts"[Title/Abstract] OR "stent"[Title/Abstract] OR "stents"[Title/Abstract] OR "graft"[Title/Abstract] OR "grafts"[Title/Abstract]). This resulted in a selection of 189 articles. The other databases were searched with similar search strings. There were no limitations on the search.

Selection of articles

All titles and abstracts were screened on relevance by two independent authors by using specific predefined criteria: articles were included if 1) the indication for endovascular treatment involved aortic arch pathology; 2) the chimney graft technique was used in one or more of the thoracic aortic side branches and 3) one or more outcome variables were reported. Articles were excluded if they did not describe use of the chimney technique in the thoracic aorta, such as articles that were limited to patients with use of the chimney graft technique in the abdominal aortic side branches only. This resulted in a selection of 55 remaining articles out of 698 screened. Full text

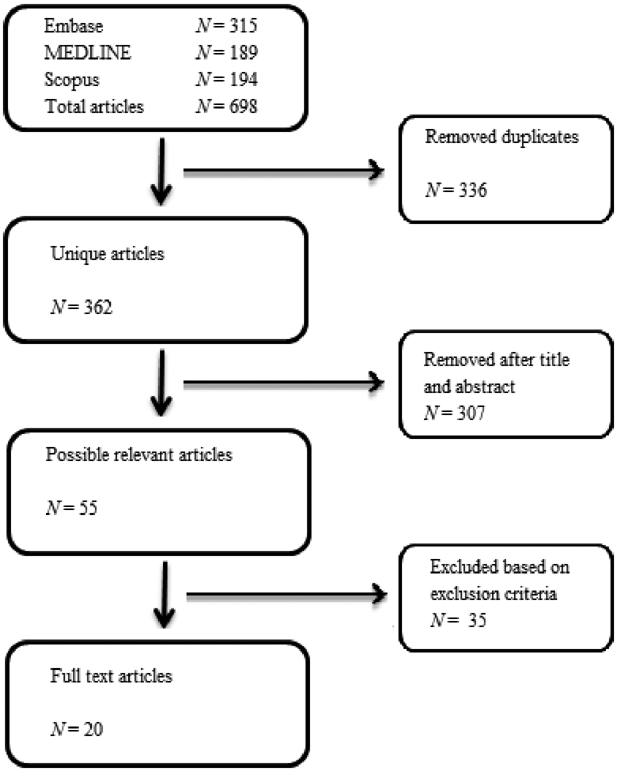

Figure 1 Article selection flowchart for *TEVAR* with chimney techinque. *N* = number of articles.

versions were obtained of all these 55 articles and were completely read and evaluated for the inclusion and exclusion criteria. Additionally, the references of these articles were screened for any missing relevant articles. No language or publication date restrictions were applied. After appraisal of the full text versions for clinical relevance based on the inclusion and exclusion criteria, a final selection of 20 articles remained (Figure 1).[10,13-31]

Data extraction

Two independent authors extracted the data from these 20 articles. The variables that were extracted included: Author, year of publication, study type, total number of patients in study, age, gender, comorbidities (coronary artery disease (CAD), hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and chronic renal insufficiency (CRI)), past surgical history, symptoms, indication for aortic repair, elective or emergent procedure, procedure type, access vessel, length, diameter and deployment zone of main body aortic stent graft, type, access vessel, length, diameter and involved aortic side branch of deployed chimney stent, additional surgical procedures (including revascularization with bypass), technical success, duration of hospitalization in days, follow-up period in months, imaging modalities and results during follow-up, postoperative antiplatelet or anticoagulant medication, chimney graft related complications, occurrence of endoleak, type of endoleak, peri-operative, or early (<30days) morbidity and mortality, and morbidity and mortality during follow-up.

Statistical Analysis

Data were analyzed with SPSS version 19.0 (SPSS Inc., Chicago, Ill). Continuous variables are given as mean ± standard deviation, follow up time in median (Interquartile range, IQR). For age, a pooled standard deviation was performed to calculate the mean age (± standard deviation) for the whole group. For creation of a publication-date graph, hazard analysis was performed.

RESULTS

The original data of 94 patients who underwent a thoracic chimney procedure were identified from the 20 papers. A total of 101 chimney stents were used in these 94 patients. Table I shows the availability of data reported by the articles per variable.

In Figure 2, the distribution of reported cases of TEVAR with the chimney technique is shown by year of publication. An increasing trend of reported cases can be seen during the most recent years.

Patient characteristics and procedure indications

The mean reported age was 63 ± 17 years (range 9-85) and 78% of the patients were male. The presence of hypertension was explicitly described for 43% (*N* = 40) of the patients, but was not necessarily the etiology of the disease being treated, while smoking was described in 16% (*N* = 15).

The indication for thoracic endovascular aortic repair was reported in 83% (*N* = 78) of the patients. Of these patients, the two most common indications were thoracic aortic aneurysms (*N* = 31;

33%) and aortic dissections (*N* = 27; 29%). Less frequent indications were traumatic aortic transections (*N* = 7; 7.4 %), penetrating atherosclerotic ulcers (*N* = 6; 6.4%) and other indications (*N* = 7; 7.4%), including aortoesophageal fistula (*N* = 1), aortotracheal fistula (*N* = 1), mobile aortic arch thrombus (*N* = 1), stent graft migration and endoleak type I after initial TEVAR (*N* = 1), accidental left common carotid artery occlusion due to misplaced scallop for chronic type B dissection (*N* = 1) and short neck, without specification of underlying aortic pathology (*N* = 2).
Of all thoracic aortic aneurysms, 23% (*N* = 7) were ruptured. The incidence of rupture in patients who presented with thoracic aortic dissections was lower: 7.4% (*N* = 2).

Types of stent graft and chimney graft

The type of stent graft used for TEVAR was described in 61 patients and length and diameter in respectively 16 (mean: 144mm ±39) and 31 (mean: 35mm ±6.4) patients. The most used stent graft was the Gore TAG endoprosthesis (W. L. Gore & Assoc, Flagstaff, AZ, USA) (*N* = 26) followed by the Zenith TX2 endograft (Cook Medical Incorporated, Bloomington, IN, USA) (*N* = 20). The Hercules (Microport Medical, Shanghai, China), Relay (Bolton Medical, Sunrise, FL, USA), Valiant (Medtronic Inc., Minneapolis, MN, USA) and Talent (Medtronic Inc., Minneapolis, MN, USA) stent grafts were used less frequently.
Detailed information about the type of chimney graft was available in only 77 patients, with the length of graft reported in 44 (mean: 47mm ±14) and diameter of graft in 49 patients (10mm ±2.7). The most used chimney graft was the Fluency stent (Bard Peripheral Vascular, Tempe, AZ, USA) (*N* = 16), followed by the Sinus stent (Optimed GmbH, Ettlingen, Germany) (*N* = 12) and the Advanta V12 stent (Atrium Medical Inc., Hudson, NH, USA) (*N* = 11). Self-expandable chimney stents were utilized in 64% of patients (*N* = 56), while the remainder of patients had balloon-expandable stents.

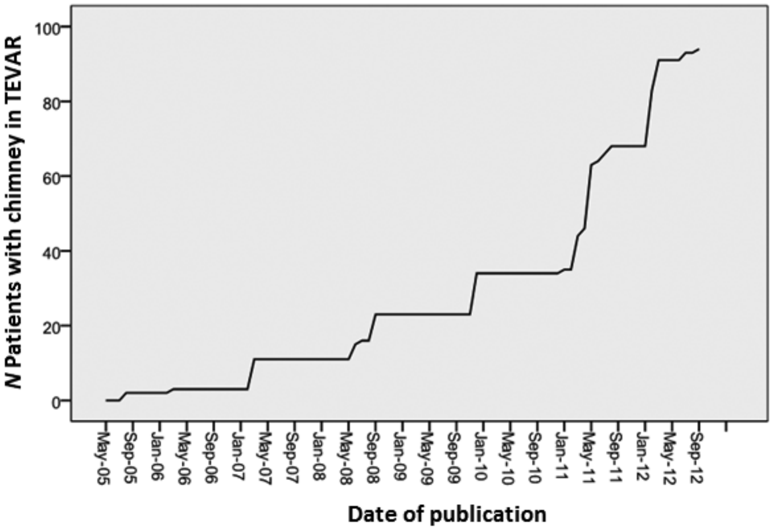

Figure 2 Patients with TEVAR and chimney procedure by publication date in years. *TEVAR*, thoracic endovascular aortic repair; *N*, number of patients.

Table I Availability of information for data extraction. Presented are the number and percentage of patients for which the article explicitly described information about the predefined variable.

Variable	*N* Patients	%
Characteristics		
Date of publication	94	100%
Age	80	85%
Indication for procedure	78	83%
Gender	72	77%
Symptoms	5	5.3%
Comorbidities, presence of		
Hypertension	40	43%
Coronary artery disease	16	17%
Hyperlipidemia	7	7.4%
Chronic obstructive pulmonary disease	7	7.4%
Diabetes mellitus	5	5.3%
Chronic renal insufficiency	4	4.3%
Other comorbidities	16	17%
Smoking	15	16%
Past surgical history	9	9.6%
Endovascular aortic stent grafts		
Proximal zone of stent graft placement	94	100%
Access vessel for aortic stent graft	71	76%
Type stent graft	61	65%
Diameter stent graft	31	33%
Length stent graft	16	17%
Chimney stent grafts		
Total number of chimneys	94	100%
Chimney branch placement	94	100%
Access vessel chimney graft	86	92%
Balloon- or self-expanding chimney stent	82	87%
Type of chimney graft	77	82%
Diameter chimney graft	49	52%
Length chimney graft	44	47%
Procedure variables		
Bypass used	86	92%
Elective or emergent procedure	86	92%
Peri- and post-operative outcomes		
Technical success	94	100%
Patency	94	100%
Endoleak	94	100%
Complications / outcome	94	100%
Mortality	94	100%
Imaging for follow-up	86	92%
Length of follow-up specified	52	55%
Postoperative medication(s)	32	34%

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Elective or emergent chimney graft placement and bypasses

Data about stent graft placement and additional surgical revascularization procedures, including bypass, were available for 86 patients. Seventy two percent of the interventions were elective (*N* = 62) while 28% were emergent (*N* = 24). Results specified for the patients who were treated with the chimney technique in the elective setting are described in detail at the end of this results section. In 24% (*N* = 15) of the elective chimney graft procedures an additional surgical revascularization with a bypass was performed. A comparable percentage (25%) was reported for the 24 emergent cases, as shown in Table II. The most commonly performed surgical procedures were left carotid-subclavian bypass/transposition, (*N* = 9; 43%) and carotid-carotid-subclavian bypass/transposition, (*N* = 10; 48%). In 2 cases, only a carotid-carotid bypass was described, with intentional coverage by the stent graft of the left subclavian artery. An additional three bypasses were reported with no further specification of the type of bypass. Overall mortality in the bypass group was lower (4.2%, N=1) compared with the patients who did not receive a bypass (11.3%, N=7). However, overall morbidity was higher in the group who received bypasses: Endoleaks 33% vs. 11.3% and stroke 8.3% vs. 3.2% for patients with and without bypass, respectively.

Placement main aortic stent graft and chimney graft

A total of 101 chimney grafts were used in 94 patients. As expected, the majority of the chimney grafts were placed in the aortic side branches which were covered by the aortic stent graft. In five patients, more than one side branch was treated with a chimney stent-graft, and a more distal branch (left common carotid artery (LCCA), (*N* = 4) or left subclavian artery (LSA), (*N* = 1)) was used for a second chimney graft to maintain the blood flow to these vessels. In one patient there was total endovascular thoracic aortic arch debranching, since all thoracic aortic side branches were chimney-stented. In two cases of chimney grafting of the brachiocephalic artery (BCA), chimney stent grafts were used that extended from the brachiocephalic artery all the way into the right subclavian and right common carotid arteries distally.

Twenty chimney grafts were deployed in the brachiocephalic artery, 48 in the left common carotid artery and 33 in the left subclavian artery. (Table III, Figure 3). Technical success was established in all but two cases (98%), one in the elective and one in the emergent setting. Persistent endoleak, requiring direct reintervention was the cause of failure in both patients. In one patient conversion open repair with arch replacement was performed, the second patient was immediately endovascular treated by crushing the left subclavian chimney stent.

Table II Total number of bypasses and transpositions in elective vs. emergent chimney procedures.

	Type bypass / transposition				Total
	No bypass	RCCA-LCCA	LCCA-LSA	RCCA-LCCA-LSA	
Elective	47	2	4	9	62
Emergent	18	0	5	1	24
Total	65	2	9	10	86

vs., versus; *RCCA-LCCA*, carotid-carotid bypass; *LCCA-LSA*, left common carotid artery to subclavian bypass/transposition; *RCCA-LCCA-LSA*, carotid-carotid-subclavian bypass/transposition.

Follow-up, imaging and patency

Length of follow-up was reported in 52 (55%) patients and the median follow-up time was 11 months (IQR = 2.5 – 15). Imaging during follow up was described for 86 patients. Computed tomography angiography (CTA) was the most common modality used (*N* = 85, 99%). In one report of a 9 year old boy who was treated with TEVAR in combination with the chimney technique for a mycotic ascending aortic aneurysm as bridge to definitive open surgery, chest radiography and carotid duplex ultrasound were used to evaluate the chimney graft configuration and carotid patency after one year.25 In all reported cases (*N* = 94), the chimney grafts remained patent.

Table III Deployment branch of chimney graft per aortic arch zone.

		Placement Endovascular Aortic Stent Graft			Total
		Zone 0	Zone 1	Zone 2	
Placement Chimney Graft	BCA	20	0	0	20
	LCCA	4	44	0	48
	LSA	1	0	32	33
Total		25	44	32	101

BCA, brachiocephalic artery; *LCCA*, left common carotid artery; *LSA*, left subclavian artery

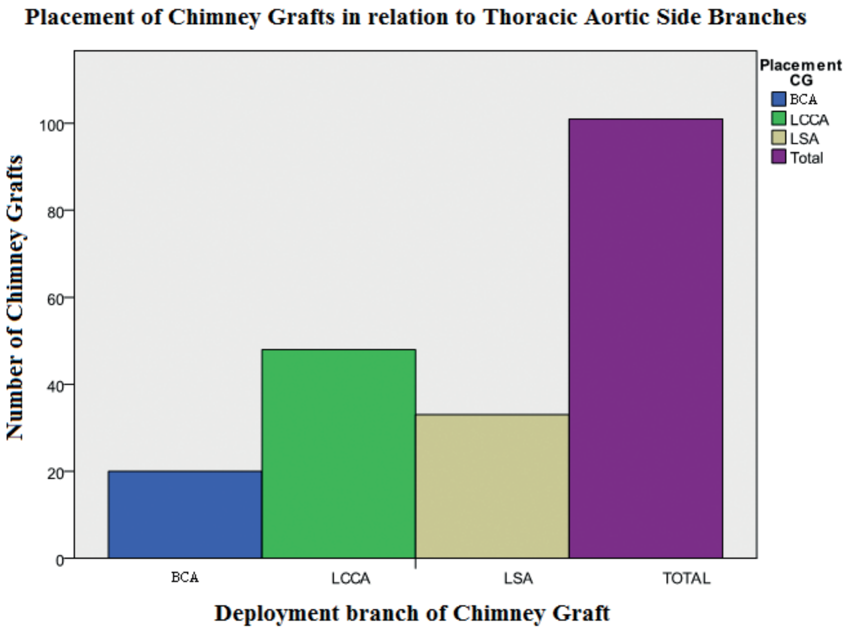

Figure 3 Placement of chimney graft in relation to stent graft deployment zone. *CG*, Chimney graft; *BCA*, brachiocephalic artery; *LCCA*, left common carotid artery; *LSA*, left subclavian artery.

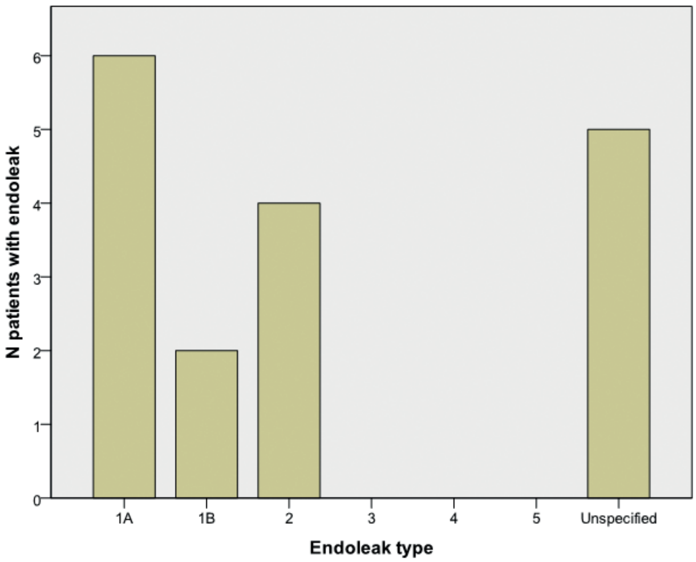

Figure 4 Endoleaks ordered by type.

Complications

28 complications were reported in 26 patients during follow-up. Reported peri-operative mortality was 3.2% (*N* = 3) of which 67% (*N* = 2) were procedure-related stroke. The third patient died seven days postoperatively of "progressive cardiac insufficiency". Unfortunately, no further details were provided in this report.

Overall mortality, including during the follow-up period, was 8.5% (*N* = 8). Four (50%) patients with a fatal course were non-device or aortic pathology related causes (Pulmonary cancer (*N* = 1), progressive cardiac insufficiency (*N* = 1) and "non-device- or aneurysm-related causes" not further specified in the report (*N* = 2)). Two patients (25%) died because of a chimney related stroke and for two patients (25%), the cause of death was not further described, and so it is unknown if these were related or not.

Of the 28 complications, the most frequently encountered were endoleaks: *N* = 17 (61%). In 5 (18%) cases stroke occurred. Other complications included contained rupture (*N* = 2), non-STEMI (*N* = 1), hemorrhage due to iliac artery rupture (*N* = 1), pseudo aneurysm of brachial artery (*N* = 1) and a heavily calcified femoral artery which required surgical repair with a patch (*N* = 1).

Overall, endoleaks were reported for 18% of the patients. Of these endoleaks, ten were a type 1 endoleak (1A, *N* = 6; 1B, *N* = 2; unspecified type 1 *N* = 2), four were type 2 endoleak and the remaining were unspecified (Figure 4).

More detailed information about complication in relation to the type of chimney graft was available in 22 cases. The results are shown in Table IV. Of these 22 complications, 6 occurred with brachiocephalic artery chimney grafting, 13 with left common carotid artery chimney grafting, and 3 complications were reported with left subclavian artery chimney grafting. When compared with the overall numbers of chimney grafts, complications were reported in 30% (6

of 20) of brachiocephalic chimney grafts, 27% (13 of 48) of LCCA chimney stents and 9.1% (3/33) of the left subclavian chimney stents.
Of the 17 endoleaks, 5 resolved spontaneously during follow-up, 6 required re-intervention, of which 50% (*N* = 3) had coil embolization and 1 was still present at the moment of report and waiting for reintervention. For 5 patients, treatment after endoleak was not described.

Elective setting

In total, 62 patients (mean reported age: 65 ± 18 years (range 9 – 85); 74% male) were treated in the elective setting and in total 69 chimney grafts were placed. Bypass procedures were performed in 24% of the elective cases (*N* = 15) and technical success was achieved in all these patients, except one. Sixteen chimney grafts (23%) were deployed in the brachiocephalic artery, 31 (45%) in the left common carotid artery and 22 (32%) in the left subclavian artery.
Length of follow-up was reported in 33 patients and the median follow-up time was 10.5 months (IQR = 1 – 12). 100% of the chimney grafts were patent at time of the last follow-up.

Complications in the elective setting

Fourteen complications (23%) were reported during follow-up of the 62 patients treated with the chimney technique in the elective setting. Reported 30-day mortality was 3.2% (*N* = 2) and were caused by procedure-related stroke in both patients.
Overall mortality, including the follow-up period, was 4.8% (*N* = 3). The third patient died after 30 months of "non-device- or aneurysm-related causes", not further specified in the report.[13]
Of the 14 complications, endoleaks were the most frequent complications: *N* = 11 (79%) and the other three cases (21%) were strokes. Overall, endoleaks were reported for 18% of the patients in the elective setting. Of these endoleaks, four were a type 1a endoleak (6.5%), one was a type 1b endoleak (1.6%), three unspecified type 1 (4.8%) and three were type 2 endoleak (4.8%). Of the 11 endoleaks, 5 resolved spontaneously during follow-up, 4 required re-intervention, of which 75% (*N* = 3) had minimally invasive coil embolization and for two patients the management or outcome were not described.
In total, in 44% (7/16) of the interventions where the chimney graft was placed in the brachiocephalic artery, a complication occurred (6 endoleaks and 1 stroke). For the LCCA this was lower, with 22% (5 endoleaks, two strokes in 31 interventions). In none of the 22 patients where the chimney graft was placed in the LSA, a complication occurred.

DISCUSSION

Based on results of this meta-analysis, TEVAR with the chimney technique appears to be a viable option for treatment of patients with thoracic aortic pathologies, for both emergent and elective setting. After a median follow-up of 11 months, chimney stents remained patent in all patients. Technical success was achieved in 98%. Endoleaks were described in 18%; with type 1a being most frequently reported, 6.4% and 6.5% for respectively total group and patients in the elective setting. Overall, nearly 50% of these endoleaks required no reintervention or minimally invasive coil embolization. In the elective setting specifically, this was more than 73%.

Table IV Complications detailed per patient.

Complication	Gender, Age	Comor-bidities	Indication	Elec-tive	Stent graft (Type and size)	Chimney (Type and size)[a]	Chimney Branch	Bypass	FU (months)	Management / Outcome
Type 1a EL[14]	M, 70	CAD, HT, HL, DM, CRI, SMK	Asymptomatic 7cm saccular aneurysm of aortic arch	Yes	Gore TAG 150x27	SE Luminex 40x12 + SE 12x60 Wallstent	BCA	RCCA-LCCA-LSA	10	Resolved after reversal of heparin anticoagulation
Type 1a EL[27]	M, 69	NA	Ruptured arch aneurysm	No	Gore TAG 37	SE Zenith x18+ SE wallstent 90x14	BCA	RCCA-LCCA-LSA	3	Wait for treatment
Type 1a EL[27]	M, 65	NA	Ruptured descending TAA	Yes	Cook Thoracic SG 40	SE Zenith x14 + SE wallstent 60x16	BCA	RCCA-LCCA-LSA	24	Coil embolization
Type 1a EL[23]	M, 83	HT, HL	Thoracic aneurysm	Yes	Gore TAG 200x40	SE Excluder iliac extender 70x14.5	BCA	RCCA-LCCA-LSA	NA	Disappeared after coiling
Type 1a EL[24]	NA	NA	Ruptured arch aneurysm with short neck	Yes	Zenith 40	SE Zenith x12	BCA	RCCA-LCCA	1.6	Coil embolization
Early type 1a EL / acute dissection after 2 months[15]	M, 35	CAD	Stanford type B dissection	No	Gore TAG	BE 37x9	LSA	None	2	Crushing of stent / open surgical repair
Type 1b EL after 2 months[15]	F, 64	NA	Thoracic pseudo aneurysm 9.5 cm	Yes	Gore TAG	BE 56x8	BCA	RCCA-LCCA	2.3	Additional stent graft
Type 1b EL at 5 months[15]	F, 39	NA	Traumatic transection	No	Talent	BE 37x9	LSA	None	5	Unknown
Early type 1 EL22	NA	NA	Short neck	Yes	Unknown	SE SMART bare stent	LCCA	None	6	Resolved during follow up

Table IV continued

Persisting type 1 EL[18]	F, 40	CAD, HT	SG migration + EL after TEVAR	No	Zenith TX2	BE Advanta	LCCA	LCCA-LSA	NA	Arch replacement
Early minor type 2 EL[20]	M, 78	HT	Thoracic aortic aneurysm, 58mm wide	Yes	Gore TAG	BE stainless, Palmaz-Genesis	LCCA	LCCA-LSA	0.7	Resolved in 3 weeks
Type 2 EL[26]	NA	HT	Acute non-A, non-B Aortic Dissection	Yes	Hercules 140x34	SE Fluency 60x8	LCCA	None	15	Resolved after 2 weeks
Type 2 EL[26]	F, 29	HT	Acute non-A, non-B Aortic Dissection	Yes	Hercules 160x34	SE Fluency 60x8	LCCA	None	11	Resolved after 11 months
Stroke due to pre-existing chronic occlusion of RCCA[24]	NA	NA	Ruptured TAA; accidental covering of left CCA	Yes	Zenith 42	BE Advanta x9	LCCA	None	0	Permanent right-sided weakness + dysarthria
Lethal stroke due to chronic RICA occlusion[27]	M, 76	NA	Ruptured descending TAA	Yes	Cook Thoracic SG 42	BE Advanta 38x10	LCCA	None	0	Died
Stroke and death[15]	M, 85	HT, CAD ,CRI, DM	Thoracic aneurysm 7.5cm	Yes	Gore TAG	BE 10x37	LCCA	LCCA-LSA	5	Died
Contained rupture[24]	NA	NA	Expanding type B dissection; misplaced scallop for LCCA	No	Zenith 46	SE Luminex x10	LCCA	LCCA-LSA	2	Successful open arch reconstruction
Contained rupture and transient paraplegia[27]	M, 48	NA	Accidental CCA occlusion due to misplaced scallop	No	Cook Thoracic SG	BE Advanta 38x9 + SE Fluency 38x10	LCCA	None	25	Conversion to open repair
Pseudo aneurysm of brachial artery[18]	M, 61	CAD, HT	Thoracic aortic aneurysm	No	Zenith TX2	BE Advanta	LSA	None	10	Surgical repair
Heavily calcified femoral artery[18]	M, 62	HL	Penetrating aortic ulcer	No	Valiant	BE Genesis	LCCA	LCCA-LSA	4	Repaired with patch

Table IV continued

Hemorrhage from iliac rupture[27]	F, 47	NA	Acute type b dissection with end organ ischemia	No	Cook Thoracic SG 30	BE Jograft 28x9	LCCA	None	54	Open repair
Non STEMI[15]	M, 77	CAD, HT	Aortotracheal fistula and chronic type B dissection	No	Gore TAG	BE 37x7	LCCA	LCCA-LSA	25	NA

BCA, Brachiocephalic artery; *BE*, balloon-expandable stent; *CAD*, coronary artery disease; *CCA*, common carotid artery; *CRI*, chronic renal insufficiency; *DM*, diabetes mellitus; *EL*, endoleak; *F*, female; *FU*, follow-up; *HL*, hyperlipidemia; *HT*, hypertension; *LCCA*, left common carotid artery; *LSA*, left subclavian artery; *M*, male; NA, not available; *RCCA*, right common carotid artery; *RICA*, right internal carotid artery; *SE*, self-expandable stent; *SG*, stent graft; *SMK*, smoking; *STEMI*, *ST* elevation myocardial infarction; *TAA*, thoracic aortic aneurysm; *TEVAR*, thoracic endovascular aortic repair. a *Stent* manufacturers: *Advanta; Atrium Medical Corp, Hudson, NH; Excluder; W. L. Gore and Associates, Flagstaff, Ariz; Fluency; Bard, Murray Hill, NJ; Gore Tag; W. L. Gore and Associates; Hercules; Microport Medical, Shanghai, China; Jograft; Abbott Vascular, Abbott Park, Ill; Luminexx; Bard Peripheral Vascular, Inc. Tempe, Ariz; Palmaz; Cordis Corp, Miami Lakes, Fla; SMART; Cordis Corp, Bridgewater, NJ; Talent; Medtronic Inc, Minneapolis, Minn; Wallstent; Boston Scientific, Natick, Mass; Zenith; Cook, Bloomington, Ind.*

TEVAR with the chimney technique is a relatively new procedure, and is performed in many different institutions, therefore, the collection of original data representing a large cohort of patients with TEVAR utilizing the chimney technique is challenging. These complex procedures are frequently not included in large registries because they do not fulfill the inclusion criteria of the thoracic pivotal trials, largely due to the fact that the use of these chimney grafts is not defined in the IFU (Instructions for Use) of these devices and so the use is off-label. The largest group of patients with TEVAR utilizing the chimney technique that has been presented previously consisted of only 15 patients.[30]

The presented approach has several limitations. Data collection was restricted to information available in the existing literature and information about many variables could not be retrieved for all of the patients. Regrettably, this is inherent to meta-analyses in general. For example: data regarding type of chimney graft, balloon or self-expandable, were only available for 87% of patients, and this parameter may play a major role in the mechanism of complications. Furthermore, length of follow-up varied between the reviewed cases and articles, as well as type, accuracy and frequency of follow-up. Description of imaging during follow-up was available in 92%, but length of follow-up was specified in only 55%. However, with a median follow-up time of 11 months, and most complications likely occurring during the first weeks after initial intervention the short-term results are acceptable. Outcomes for the long-term patency rates must show the long-term results.

Repair of the thoracic aorta remains challenging. As "off the shelf" options for branched or fenestrated thoracic grafts become available, the use of the chimney technique will obviously decrease. Depending on geography and the local regulatory environment, these "off the shelf" options may not be available for several years. In the interim, chimney grafts will remain a useful intervention option in the treatment of these anatomically difficult patients, especially in the emergent setting to treat life threatening situations. However, as shown in this meta-analysis, the chimney technique could also provide a viable option in the elective setting in the treatment of thoracic aortic diseases.

The hybrid repair or two-staged open-endovascular repair has traditionally been an option that combines the advantages of the open and endovascular approach and has shown reasonable results. First, an open debranching of the aortic arch side branches is performed and afterwards, endovascular stenting of the thoracic aorta is performed. Donas et al32 reported in their meta-analysis a technical success of 100%, 97.8% patency and an overall endoleak rate of 20.6%, after a mean follow-up time of 14.5 months which is all comparable with results of the chimney technique in the current meta-analysis. However, 50% of all the endoleaks were type I (in total 10.3% of all the patients) which is higher than for the chimney technique. Excellent results were described for procedure-related neurological deficits, which did not occur during the subsequent follow-up. However, the early and long term mortality risks were high, with 15.5%. In another, more recent review by Antoniou et al[33] similar results were shown: a type I and III endoleak rate of 9%, perioperative mortality of 9% and a stroke rate of 7%. However, the overall technical success was low with 86%. Possible explanation for this low technical success is in the definition. Should slow-flow peri-operative endoleaks that resolved, be counted as technical failure or not? There are no clear guidelines or definitions for this, and because of this fact, it is more complex to compare each variable directly. Overall, hybrid repair and TEVAR with the chimney technique show similar results and seem to be equally safe and effective in the elective setting and the chimney technique could potentially replace the hybrid technique in specific patients in the future, depending on anatomy and comorbid conditions.

The upcoming branched and fenestrated stent graft intervention has several advantages, such as the minimally invasive insertion and the potentially lower risk for stroke, but the disadvantages include the high costs, higher contrast and radiation use[34], and the fact that the stent graft must be custom made, what will lead to prolonged waiting time of four to six weeks.[35] The results in small series and case-reports are promising, but long term-results and larger studies are needed to prove either equality or superiority over hybrid repair and the chimney technique.

Endoleaks, and especially type 1a endoleak, are often described as the Achilles' heel of the chimney technique. The placement of the chimney graft along the thoracic endograft increases the risk for type 1a endoleaks, in comparison to TEVAR without the chimney technique, by creating gutters next to the chimney graft and affecting a good proximal seal which can potentially lead to non-resolving type 1a endoleaks. However, the relatively low total endoleak incidence of 18% is promising. The type 1a endoleak risk is with 6.4% in the total group and 6.5% in the elective setting also promising, and to highlight these results even more, many of these endoleaks spontaneously resolved during follow-up or could be treated with minimally invasive coil embolization. In the elective setting, only one type 1a endoleak needed an additional stent graft placement. This total endoleak risk is comparable with endoleak risks described for TEVAR without the chimney technique. Morales et al.[36] evaluated 200 thoracic aortic aneurysms treated with TEVAR and found an overall endoleak rate of 19.5% during a mean follow up period of 30 months. Parmer et al.[37] reported an overall endoleak incidence of 29% after a mean follow up of 17.3 months in 69 patients after TEVAR, although the type 1a endoleak was remarkably low, with only 3.8%. The lower endoleak rate in their study could be due to the variance of diseases in our meta-analysis, where in Parmer et al. only patients with thoracic aortic aneurysms were treated with TEVAR. Alsac et al.[38] reported an endoleak rate of 19.4% in 67 patients after a mean follow up period of 27 months. A possible explanation for this comparable outcome for the TEVAR with chimney graft technique is the expansion of the proximal landing zone, although the median follow-up time in this meta-analysis is shorter the results in the current analysis appear to indicate that most of the endoleaks occur in the first weeks after intervention.

Another important observation is that the chimney stents remained patent in all patients in our meta-analysis. Moulakakis et al.[39] reported in their meta-analysis an overall patency for the chimney technique for EVAR of 97.8% (*N* = 134) after a mean follow-up of nine months. The three thrombosed chimney grafts were in the abdominal aorta (2 renal arteries, 1 superior mesenteric artery) in three different patients. A possible explanation for the higher patency in the thoracic aortic branches is that it may be caused by the smaller diameter of the stented branches in the abdominal aorta, potentially leading to a higher risk of thrombosis. Additionally, the higher blood flow velocity in the thoracic aorta may contribute to the higher observed patency of the thoracic chimney stents.[40]

Regarding the lethal complications in this study, 2 patients died in the postoperative period because of a stroke. In one patient, a chimney stent was placed in the LCCA, during TEVAR for a symptomatic 7.8 cm thoracic aortic aneurysm. Two days after TEVAR, the patient was extubated and had a profound neurologic deficit and CT showed embolic infarcts to bilateral hemispheres, due to embolization from his aorta. In the second patient, the LCCA was chimney-stented, but this patient suffered from a lethal intra-operative stroke due to a chronic occluded right internal carotid artery, which was not known by the proceduralists at the time of the intervention. One important lesson from this case is the importance of careful evaluation of the carotid arteries during the pre-operative work-up before the chimney technique is applied.

Other important findings in this meta-analysis are the higher rate of complications and endoleaks when the BCA or LCCA are stented in comparison with the LSA only (30% and 27% vs. 9.1%). In the patients treated in the elective setting, the difference is even more noticeable: complications occurred in 44% if the BCA was chimney stented, 22% in the LCCA and no complications were reported for the elective setting if only the LSA was involved. This could be due to the fact that in most patients where the BCA or LCCA is stented, the disease extends to a more proximal portion of the thoracic aorta. This may be an indicator of patient disease and could potentially be related to the overall condition of the patient, ultimately contributing to a higher incidence of complications if more proximal aortic side branches are involved during the chimney procedure. Another possible explanation is that the BCA and LCCA perfuse more vital areas, such as the brain, that are less "forgiving" than the LSA. Additionally, patients with more proximal disease required on average more chimney stents or more additional surgical revascularization procedures, resulting in an overall increased complexity of the procedure which may also have contributed to a higher risk of complications. The results in this meta-analysis show that chimney grafts placed in the LSA are a viable option in the elective setting and could be used to treat thoracic aortic diseases, requiring coverage of the LSA. Future studies must focus on the use of the chimney graft in different side branches of the aortic arch.

In this meta-analysis, a total of 16 different stents were identified which are used for chimney stenting. The numbers for each type of stent were not sufficient to allow for reliable comparisons. The complication and endoleak risks of the balloon expandable and self-expandable rate were nearly the same: 16% and 20%. They both have advantages and disadvantages. Whereas the balloon expandable stent is more accurate for placement and has a greater radial force, the self-expandable stent is more flexible and may therefore potentially cause less vessel trauma. Future research may provide more insight in outcomes by chimney stent type.

Future research should also focus on long-term results and long term patency of these chimney stents. Furthermore, it will be interesting to evaluate the chimney technique in the different side branches and for different indications, to further explore the safety of these chimney stents. At last, we would like to encourage authors to include more specific device and procedural information in their articles, including the diameters of the aorta, endografts and chimney stent grafts, since this is lacking in most of the reports and will enable faster identification of factors that may improve the technique and outcomes.

In conclusion, TEVAR with the chimney technique is a viable and relatively safe treatment for patients with challenging thoracic aortic pathology, in both emergent and elective settings. The relatively high success rate, low complication rate and good patency of chimney stents during follow-up may contribute to further development of the chimney technique. Complications such as endoleak and stroke deserve attention by future research to further improve treatment strategies and the prognosis of these patients.

2

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CHAPTER 3

Successful treatment of a proximal type I endoleak with HeliFx EndoAnchors

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ABSTRACT

Purpose

To report the use of Aptus HeliFX EndoAnchors for endovascular treatment of a proximal type I endoleak after previous endovascular aneurysm repair (EVAR) of a ruptured abdominal aortic aneurysm (AAA).

Case Report

An 81-year-old man had been treated with EVAR after a ruptured 12 x 11cm AAA. Standard computed tomographic angiography (CTA) follow-up demonstrated a proximal type I endoleak. Due to the highly angulated neck and close position of the endograft to the renal arteries, placement of a proximal extension cuff was prohibited, therefore, the endoleak was treated with an alternative approach using the Aptus HeliFX EndoAnchors. Nine EndoAnchors were successfully placed circumferentially on the proximal site of the endograft. This successfully treated the endoleak, by excluding the aneurysm sac from the circulation. CTA follow-up after three months showed no residual type I endoleak.

Conclusion

This case shows that placement of EndoAnchors can serve as a viable treatment option for proximal type I endoleaks after failed EVAR.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has been widely accepted as an effective, safe and minimally invasive treatment for infrarenal abdominal aortic aneurysms (AAA).[1-3] This technique, however, has several limitations and complications. Endoleaks are the most common complication after EVAR and occur in approximately 25% of the patients during the entire follow-up. Furthermore, endoleaks are the most frequent indication for reintervention after EVAR and are the number one cause of rupture in patients treated with EVAR.[4,5] Especially type I endoleak (inadequate sealing at proximal or distal end of the stent graft) and type III (stent graft defect / failure) are associated with AAA rupture after EVAR and require urgent treatment. We report a case of successful treatment of a proximal type I endoleak after EVAR with the Aptus HeliFX EndoAnchors (Aptus Endosystems, Inc., Sunnyvale, CA, USA).

CASE REPORT

An 81-year-old man with a history of diabetes, hyperlipidemia and benign prostate hyperplasia presented to an outside hospital with syncopal episodes accompanied by back pain, lethargy and respiratory distress and without fever or leukocytosis. A computed tomography angiography (CTA) scan was performed at that time and showed a ruptured infrarenal AAA of 12.2 x 11.3 cm with a large retroperitoneal hematoma and a highly angulated neck of 90 degrees. The patient emergently underwent EVAR with placement of a Gore Excluder endoprosthesis (W. L. Gore and Associates, Flagstaff, Ariz) (Figure 1A) with ballooning of the proximal seal zone. During postoperative imaging, there was a good proximal seal and there were no signs of an endoleak, initially. During his hospitalization the patient stabilized but subsequently he became symptomatic again after three days when he developed recurrent significant back pain. A CTA was performed to investigate the symptoms. During CTA follow-up, an infrarenal type I endoleak was revealed (Figure 1B and 1C) and the patient was immediately transferred from the outside hospital to our hospital for subsequent care.

Due to the proximal sealing, which was very close to the renal arteries (Figure 1B), the most important challenge was to exclude the endoleak from the blood flow without covering the renal arteries and maintain flow into these arteries.

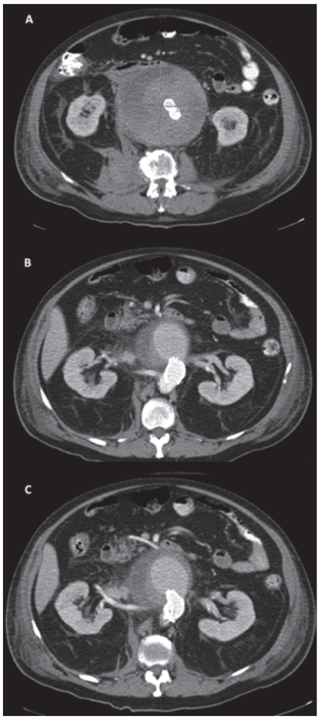

Figure 1 Computed tomography angiography of the abdomen of (A) transverse image of 12 x 11 cm abdominal aortic aneurysm after endovascular repair for ruptured abdominal aortic aneurysm; (B) Type Ia endoleak, stent graft and patent left and (C) right renal artery.

This was performed by attaching the original aortic stent-graft to the aortic wall with HeliFX EndoAnchors to fix the position of the endograft, because of the highly angulated aortic neck (Figure 2).

The left and right common femoral arteries were accessed percutaneously. A calibrated pigtail catheter was advanced across the aortic endograft to a point above the celiac axis. Abdominal aortography was performed in anteroposterior and lateral projections. The right and left renal arteries were both patent without evidence of significant stenosis, however, it showed a large proximal type I (type Ia) endoleak (Figure 3). Subsequently, the sheath of the APTUS deployment system was introduced and advanced to the level of the proximal portion of the endograft. Nine HeliFX EndoAnchors (staples) were sequentially deployed under fluoroscopy, evenly distributed throughout the proximal portion of the endograft (Figure 4A and 4B). Fluoroscopy and the Aptus HeliFX system confirmed successful deployment of all staples through the stent graft and aortic wall (Figure 4C and 4D).

Following deployment of the staples, a repeat aortic angiography was performed. This showed no evidence of endoleak while both renal arteries were still patent (Figure 5A and 5B). In the absence of a demonstrable endoleak no further action was taken at this time. The post-operative period was uncomplicated and the patient was discharged from the hospital after two days. CTA follow-up after three months and Doppler ultrasound after six months showed a patent endograft and no endoleaks (Figure 6).

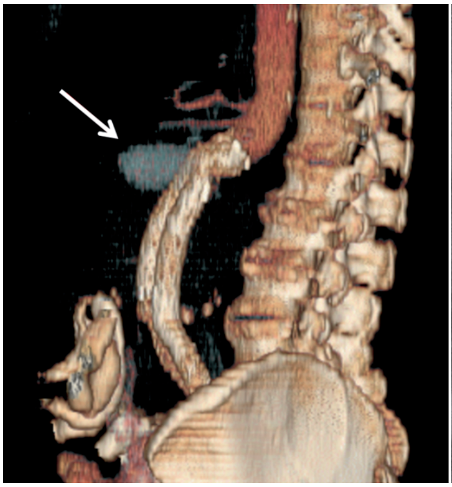

Figure 2 Three-dimensional computed tomography angiographic reconstruction shows a type Ia endoleak due to inadequate proximal sealing of stent graft and severe angulation of the aortic neck.

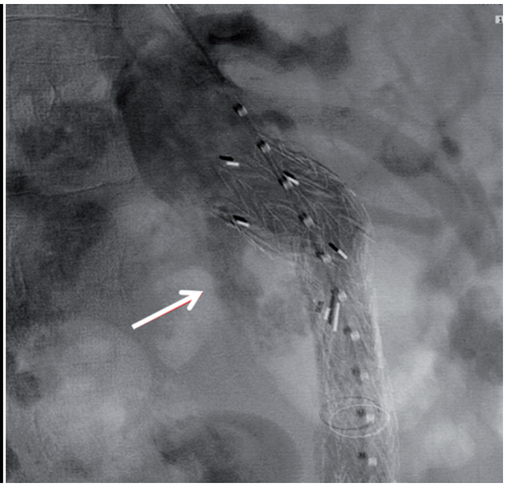

Figure 3 Intra-procedural aortography showing filling of the aneurysm sac by a type Ia endoleak.

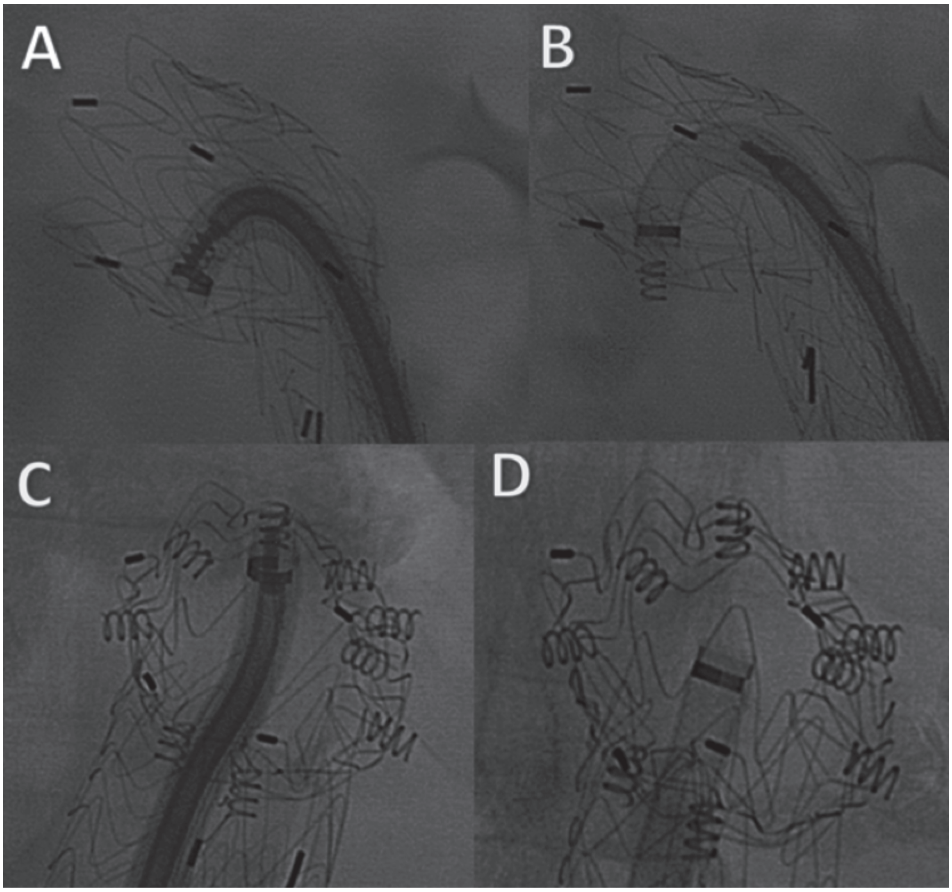

Figure 4 Intra-procedural angiography showing (A and B) images of placement of the first HeliFX EndoAnchors on the proximal site of the stent graft and (C) placement of the last EndoAnchor. (D) All the nine HeliFX EndoAnchors are sequentially deployed, and were evenly distributed throughout the proximal portion of the aortic stent graft. Fluoroscopy and the HeliFx system confirmed successful deployment through the stent graft and aortic wall.

DISCUSSION

This case shows that placement of EndoAnchors can serve as a viable treatment option for proximal type I endoleaks after failed EVAR.

Causes for type I endoleaks include a calcified aortic wall, ongoing dilatation of the abdominal aorta, inadequate deployment of the endograft or if the diameter of the stent graft is not large enough.6 In our patient, the highly angulated neck has likely contributed to the development of a proximal type I endoleak. The patient became symptomatic after three days and a CTA showed a proximal type 1 endoleak. This underscores that early endoleaks can happen, even with a negative initial completion angiography.

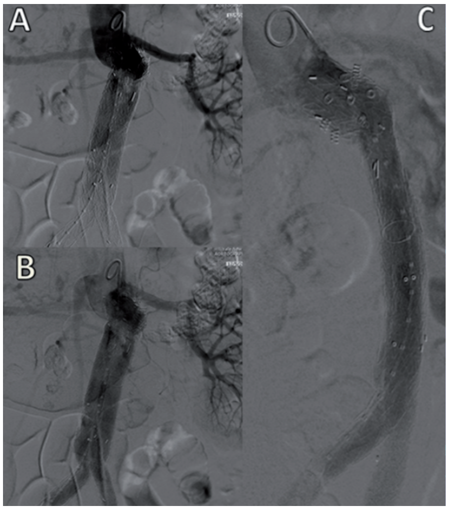

Figure 5 (A and B) Anteroposterior view of completion aortography showed no evidence of endoleak after treatment of the proximal portion of the stent graft with the HeliFX EndoAnchors. Additionally, both renal arteries, infrarenal aorta and common iliac arteries are patent. (C) Lateral view.

Figure 6 Three-dimensional computed tomography angiographic reconstruction shows a patent stent graft without signs or evidence for a type Ia endoleak.

Endoleaks are the most common complication in patients treated with EVAR, and especially type I and type III are life threatening when not operated.5 Type I endoleaks need urgent intervention because the increased pressure in the aneurysm sac can lead to aneurysm rupture, which is frequently fatal. Overall mortality for rupture after EVAR due to endoleaks occurs in 50% of the patients, and this emphasizes the need for urgent repair.7

Type I endoleaks can be treated with several techniques. The first approach is to dilate the stent graft with an endovascular balloon to obtain a better sealing at the landing zone. However, this is not sufficient in most of the cases and an extension cuff should be placed subsequently. Because the proximal part of the endograft was right below the renal arteries, this was not possible in our patient. If an extension cuff would cover vital branches, the chimney technique could be performed to allow continued perfusion into these side branches.8 The Palmaz stent is another viable option to create a better proximal seal of the aortic stent graft.9 If these endovascular techniques are not suitable, open repair should be considered. However, as shown by our report, the HeliFX EndoAnchor can serve as a viable alternative for treatment of type I endoleaks and is also a minimally invasive treatment. Although the risk is small, the Palmaz stent struts could potentially partially cover the renal artery orifices affecting the renal artery blood flow, while the HeliFX EndoAnchors do not affect the renal artery blood flow, since the HeliFX EndoAnchors were deployed distal to the renal artery orifices.

The HeliFX EndoAnchors are evaluated and approved by the U.S. Food and Drug Administration (FDA) for aortic grafts of Cook (Zenith; Cook Inc, Bloomington, Ind), Gore (Excluder; W. L. Gore and Assoc, Flagstaff, Ariz) and Medtronic (Endurant, Talent and AneuRX; Medtronic, Minneapolis, Minn), the major three endograft producers. The staples are 3 mm in width and 4.5 mm in depth and secure a good sealing of the graft to the aortic wall. Additionally, they have a helical design what also imparts a potentially less traumatic profile to the tip of the staples if it penetrates the aortic wall.10,11 The number of staples used depends on the size or diameter of the graft, tissue integrity and the angulation of the aortic neck. However, it is recommended to place at least four to six staples. In our case, we used nine EndoAnchors to secure an optimal proximal sealing of the stent graft. Potential risks of the EndoAnchors are early deployment of the staples into the bloodstream, change or migration of the staples and inadequate penetration of the aortic wall due to severe calcification. No problems related to aortic wall penetration are reported in published studies, although a heavily calcified aorta is a contraindication for placement of the EndoAnchors. Additionally, open conversion is nowadays a rare re-intervention, and only very specific situations could potentially be affected by the presence of Aptus HeliFX EndoAnchors. If open repair is necessary in the future, the EndoAnchors can be unwound.

At this moment, the Aptus HeliFX EndoAnchors are another good endovascular tool for the repair of type I endoleaks and could potentially be used to prevent endoleaks in high-risk patients. Future studies must evaluate the role of these EndoAnchors in more calcified aortic walls and can provide more insight into the long-term safety and durability of these EndoAnchor staples.

CONCLUSION

As shown in this case report, EndoAnchors can serve as a safe and feasible treatment option for patients with challenging anatomy and type I endoleaks. This may hopefully lead to a better prognosis of patients with AAAs treated with EVAR. Early results of treatment with the HeliFX EndoAnchors are promising, although follow-up studies are necessary to evaluate the long-term safety and durability.

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CHAPTER 4

Surgical and anesthetic considerations for the endovascular treatment of ruptured descending thoracic aortic aneurysms

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ABSTRACT

Purpose

Ruptured descending thoracic aortic aneurysm (rDTAA) is a life-threatening disease. In the last decade, thoracic endovascular aortic repair (TEVAR) has evolved as a viable option and is now considered the preferred treatment for rDTAAs. New opportunities as well as new challenges are facing both the surgeon and the anesthesiologist. This review describes the impact of current developments and new modalities for the surgical and anesthetic management of rDTAAs.

Recent findings

A collaborative approach between the anesthesiologist and surgeon during critical moments such as induction, moment of aortic occlusion and placement of the aortic stent-graft is mandatory. Important issues to consider on pre-operative imaging evaluation are correct sizing of the aortic stent-graft and localization of the artery of Adamkiewicz. Emergency TEVAR should preferentially be started under local anesthesia and could be switched to general anesthesia after stent placement. Patients should be kept in permissive hypotension pre-operatively and during the intervention before stent-graft deployment and relative hypertension after deployment. The use of a proactive spinal cord protection protocol could decrease the risk of spinal cord ischemia and/or paraplegia and consists of permissive hypertension after stent deployment, cerebrospinal fluid drainage to maintain adequate spinal cord perfusion, relative hypothermia and possibly use of mannitol.

Summary

In order to improve outcomes of TEVAR for rDTAA, a close communication between the anesthesiologist and the surgeon and a thorough understanding of the events during the procedure is mandatory. The use of a proactive spinal cord protection protocol may decrease the rates of devastating spinal cord ischemia.

INTRODUCTION

Rupture of the thoracic aorta is a rare but life-threatening emergency with an annual incidence of 5 per 100,000 people and with reported overall mortality rates up to 97%. Ruptured descending thoracic aortic aneurysms (rDTAA) account for approximately 30% of all thoracic aortic ruptures and only 41% of these patients arrive at the hospital alive.[1]

Considering the fact that untreated patients reach nearly 100% mortality, "no treatment" is not a viable option. A team effort of both the anesthesiologist and vascular surgeon is vital to successful management of the case. Open repair (OR) of rDTAAs with an interposition graft has been the traditional treatment for decades. However, this procedure requires a large open thoracotomy as well as placement of a high-level aortic cross-clamp with or without the use of left atrial-femoral bypass. Therefore the open repair of rDTAA registers a high morbidity and mortality. During the last decade, thoracic endovascular aortic repair (TEVAR) has evolved as a viable option for the treatment of rDTAAs. Short-term results are considered good and include a 30-day mortality of 19% (vs. 33% for OR) and low 30-day complication rates, including myocardial infarction (3.5% vs. 11.1%, OR) and stroke (4.1% vs. 10.2%, OR). TEVAR is now considered as the first-choice treatment in patients with rDTAA.[2] Furthermore, the feasibility of TEVAR is described for hemodynamically stable and unstable patients with ruptured aneurysms.[3] Unlike the risks of stroke and myocardial infarction, which are significantly decreased, the risks of spinal cord ischemia (SCI) and/or paraplegia are still high (3.9% vs. 5.5%, OR) for both patients with ruptured and non-ruptured thoracic aneurysms after TEVAR.[4,5] Prevention of SCI has become one of the most important objectives during TEVAR and strategies for protection of the spinal cord are still evolving.

Considering the low incidence of rDTAAs and the emergency setting of this highly fatal condition, large studies describing the optimal anesthetic protocol for rDTAAs are lacking. The purpose of this review is to evaluate the most recent and relevant literature on the surgical and anesthetic considerations for the interventional treatment of rDTAA with a special focus on prevention of SCI. Knowledge of new modalities of spinal cord protection is important to decrease the morbidity and mortality in patients with rDTAAs. Furthermore, the importance of pre-operative imaging, spinal cord protective protocols and different types of anesthetic techniques will be discussed.

Pre-operative considerations

The descending thoracic aorta is considered to start distal to the left subclavian artery (LSA) and to end at the diaphragm and is anatomically more amendable to endovascular repair than the abdominal aorta given the absence of major side branches. However, a good postoperative outcome relies on a thorough understanding of some important pre-operative considerations for TEVAR.

Pre-operative imaging

First and most important, in rDTAA, every second counts and there is no time for extensive pre-operative imaging to explore the anatomy of the thoracic aorta. Pre-operative imaging for TEVAR is particularly important to investigate the curvature and the diameter of the thoracic aorta and the involvement of any of the vital aortic arch side branches. If the patient is stable and imaging is performed, ECG-gated Computed Tomography Angiography (CTA) is recommended. The CTA allows for a dynamic imaging of the thoracic aorta and cardiac structures and function, including the coronary arteries. Additionally, this could help improve stent-graft sizing, reduce risk of false detection of a dissection flap due to motion artifact of the aortic wall, and simultaneously allows preoperative cardiac risk stratification, which could positively impact anesthetic care.[6] More importantly, identification of the exact location of the artery of Adamkiewicz is useful in evaluating the operative risk of SCI.

Pre-operative imaging should be focused, to prevent delay in therapeutic care of the ruptured thoracic aorta. First, computed tomography (CT) imaging should always extend from the supra aortic vessels to the common femoral arteries. Time for complex imaging reformatting, including multiplanar reformatting, 3D rendering and center-line measurements, is often not available in the emergency setting. However, one must ensure to have imaging available at least 10 mm proximal and 10 mm distal to the affected aortic territory (in some instances more) in order to evaluate for adequate graft landing zones. To ensure a good sealing in highly angulated anatomy, more length is frequently required.[7]

Stent graft sizing

Due to the hypotension induced by bleeding from the ruptured aneurysm with a subsequent decreased pressure on the thoracic aortic wall, the aortic dimensions measured on CTA could be smaller than under normotensive conditions. As a result, an oversizing of the stent graft should be performed to compensate for the enlargement of the aorta to its normal dimensions. Generally, 15% - 20% oversizing is recommended to guarantee an optimal seal, prevent endoleaks and graft migration under normotensive conditions.[8] However, too much oversizing should also be avoided. In a study evaluating the incidence of collapsed GORE TAG thoracic endoprostheses (W. L. Gore and Associates, Flagstaff, Ariz), which included 33,289 deployed devices, excessive over sizing was one of the main risk factor for graft collapse.[9]

Preoperative anesthetic considerations

In emergency situations, the main therapeutic goal is to minimize the time between arrival at the hospital and surgical repair. Time is often not available for extensive preoperative evaluation and optimizing the patient for the intervention. Patients with ruptured aneurysms should be kept in a permissive hypotension pre-operatively, with systolic blood pressures between 50 and 100 mm Hg while maintaining consciousness.[10] Immediate availability of blood products as well as obtaining patient's consent for transfusion should be a priority.

Furthermore, the intervention should preferentially be performed in a dedicated hybrid / endovascular suite with excellent fluoroscopic imaging and with capabilities for potential conversion to traditional open surgery with thoracotomy.[11]

Intraoperative considerations

The overall intraoperative anesthetic goals are represented by establishing a stable hemodynamic environment, optimal for a secure stent deployment while maintaining good cardiac function as well as adequate blood flow to the spinal cord and abdominal vital organs.

Type of anesthesia

With the previously described goals set forward, local, regional or general anesthesia have all been successfully used in patients undergoing emergency TEVAR.[12-14] There are, however, no large comparative studies showing superiority of one technique over the other. In a recent study by Carmona et al., successful deployment of the Talent or Valiant stent graft (Medtronic Inc., Fridley, MN, USA) was achieved in all 25 patients with rDTAAs. In this study population, 32% of patients received only epidural anesthesia with no significant difference in outcome being reported.[15]

It is the authors' experience that in certain patient population with multiple preoperative co-existing diseases and mild hemodynamic instability, the TEVAR for rDTAA should be performed under local anesthesia. The advantage of such an anesthetic choice is the fact that there are minimal perturbances in blood pressure, which are commonly encountered during general anesthesia induction, and that the need for mechanical ventilation is obviated. In a large study of more than 6,000 patients who underwent endovascular abdominal aortic repair (EVAR) for pathologies of the abdominal aorta, general anesthesia was associated with an increased postoperative hospitalization period and increased pulmonary morbidity, when compared with local anesthesia. In contrast, employment of local anesthetic techniques was associated with decreased length of hospitalization, reduced postoperative morbidity and lower overall costs.[16] Although this study was for abdominal aortic aneurysms (AAA), the results are likely applicable for patients with thoracic aortic aneurysms as well. However, patient co-operation is a mandatory pre-requisite in cases performed under local anesthesia given the necessity of a motionless field during deployment of the stent graft. It must be mentioned that this may not be an attainable goal especially in emergency situations when patients are in pain and stress.

There are no clear guidelines pertaining to the type of anesthesia employed in interventions for rDTAAs. TEVAR could be started under local anesthesia and once control of the ruptured thoracic aorta has been obtained via stent deployment, the need for general anesthesia could be re-evaluated.[17] If additional interventions are required (carotid stent or carotid subclavian bypass) then induction of general anesthesia should be considered. However, in situations of cardiovascular collapse due to major hemorrhage, general anesthesia should be induced and the airway controlled. Since level one evidence studies are lacking, the type of anesthesia should be discussed between the anesthesiologist and the vascular surgeon and the plan should be tailored to the patient's disease, indication and setting of the intervention.

Intraoperative monitoring

The surgical team should ideally prepare and drape prior to induction of anesthesia. Standard ASA monitors should be immediately employed. Adequate large intravenous access should be obtained as soon as possible. Arterial access should be obtained in the right arm, since left brachial access could be necessary for additional stent grafting or the thoracic aortic stent graft may cover the left subclavian (LSA) take-off. However, placement of the arterial line should not delay the commencement of the TEVAR.

In situations in which general anesthesia is used, placement of a transesophageal echocardiography (TEE) probe is extremely useful. The utility of TEE is multifold. First and foremost, TEE confirms the aortic pathology as well as the extent of the disease process. This fact becomes of paramount importance in emergency situations where the hemodynamic instability of the patient precluded the possibility of obtaining a CTA. In addition, the use of intraoperative TEE allows for a continuous assessment of the cardiac function, especially at the time of aortic occlusion, and represents a reliable monitor of intravascular volume status. Post stent deployment, in addition to angiography, TEE can be used to identify various endoleaks.[18]

A cerebral oximeter using near-infrared spectroscopy (NIRS) could be useful in such cases as it has the capacity of monitoring cerebral regional oxygen saturation. Several reports have identified that decreased cerebral oxygen saturation during cardiovascular surgery is associated with insufficient cerebral perfusion.[19] Although not presently reported in the literature, this monitoring device could be useful in alerting the clinician about inadequate cerebral flow in situations where the proximal landing zone of the stent impinges on the left carotid take-off.

Due to the devastating outcomes of SCI, monitoring the spinal cord should be of prime importance in these cases. To date, the best available devices for spinal cord function monitoring are represented by registering the somato-sensory evoked potentials (SSEPs) and the motor-evoked potentials (MEPs). However, these monitoring techniques require special equipment and trained personnel which may not be readily available at the time the emergency rDTAA arrives to the OR. Interestingly, a recently published case series identified the use of spinal cord NIRS as a very good monitoring alternative to the traditional MEPs. The authors have placed the NIRS probes midline over the spinous processes of vertebrae T1-T3 (control zone) and T8-T10 (at risk zone). They have identified that in each case the NIRS correlated well with changes in the MEPs. The authors concluded that spinal cord NIRS might provide real time information regarding spinal cord ischemia.[20] The utility of NIRS as a spinal cord monitoring device remains to be tested in large trials. However, it represents a promising non-invasive technology that could be utilized in high-risk individuals undergoing emergency TEVAR.

Management of the spinal cord

As previously mentioned, despite the absence of aortic cross clamping during TEVAR, paraplegia due to SCI remains a devastating complication of this procedure.

The cause of SCI is not clearly elucidated but it most likely is multifactorial. The main issue is related to inadequate blood flow to the arteries providing direct or collateral vascularization of the spinal cord. The blood supply of the spinal cord consists of an extensive network of collaterals. Probably the most important cause is represented by the complete coverage of a varying number of intercostal arteries by the stent graft. The largest anterior segmental medullary artery providing the main blood supply to the spinal cord is the artery of Adamkiewicz. In 75% of people, the artery of Adamkiewicz originates between the T8 and L1 vertebral segments. Recently, the importance of identifying the artery of Adamkiewicz was investigated in patients with type B aortic dissection. Patients in whom the artery of Adamkiewicz was localized were treated with longer stent devices capable to provide a better structural stability to the affected aorta yet without covering the artery of Adamkiewicz. Furthermore, 0% of these patients developed paraparesis compared with 2.1% of patients in which the artery was not located.[21] More importantly, while during the open procedure the intercostal arteries can be reimplanted, during TEVAR this procedure is not possible. A second important cause contributing to the etiology of SCI is graft coverage of the LSA, which gives rise to the left vertebral artery, which in turn gives rise to posterior spinal arteries. The hypogastric and pelvic arteries also provide collateral circulation to the anterior spinal artery. As such, patients who have undergone an abdominal aortic aneurysm repair have this vascular network damaged and are therefore at higher risk of SCI. In addition to stent coverage of the origin of the main or collateral blood supply of the spinal cord, the flow is also compromised by embolization of debris material dislodged from the aortic wall during catheter manipulation.

In summary, factors that contribute to a higher risk of spinal cord ischemia either reduce direct or collateral blood supply or lower the spinal cord perfusion pressure (Table I).[22] The goal of spinal cord protection during TEVAR for rDTAAs is to optimize the oxygen delivery to the spinal cord and to minimize the oxygen demand of the spinal cord. The spinal cord perfusion pressure (SCPP) is equal to mean aortic pressure (MAP) minus the higher of the two pressures: cerebrospinal fluid pressure (CSFP) or central venous pressure (CVP) (SCPP = MAP –CSFP).[23] Based on this physiology, current recommendations are to maintain MAP between 90 and 110 mmHg after stent deployment, and the CSFP and CVP below 10mm Hg.

Several techniques have been described and successfully used to reverse recurrent SCI following TEVAR for a descending thoracic aortic aneurysm.[24] Although this reactive approach to treat SCI could be successful, prevention of SCI is better than treatment afterwards. Bobadilla et al. have successfully used a proactive spinal cord ischemia protection protocol in 94 consectutive TEVARs, most of which were acute. They observed a paraplegia rate of 1.1%, much lower than other reported series.[25] This spinal cord protection protocol included routine spinal drainage in all patients to maintain a spinal fluid pressure of 8 mmHg intraoperatively and 10 mmHg postoperatively. Secondly, all patients received methylprednisolone and mannitol, resulting in further reduction of cerebrospinal fluid pressures. Lastly, a moderate intraoperative hypothermia between 32°C and 35°C was allowed to help reduce the metabolic activity of the spinal cord and thus decrease oxygen requirements. During the entire procedure, the MAP was kept above 85mm Hg. This study suggests that proactive approaches, instead of reactive, could result in a better long-term outcome to prevent SCI after TEVAR in the elective and emergency setting. Their results are amplified by another recent study, focusing on accurate hemodynamic control, represented by high-normal perioperative blood pressure and this seems to protect against severe postoperative complications.[26] However, a balance should be maintained between hypothermia and normothermia, since it has been described that hypothermia is a risk factor for mortality after ruptured AAA repair. It should be noted that the temperature for patients treated with open repair was lower than for patients undergoing EVAR, and that efforts to correct hypothermia are more frequently successful in patients undergoing EVAR. Therefore, a body temperature around 35.5°C (96°F) is recommended to decrease both mortality and the risk of paraplegia.[27] If time does not allow placement of a spinal drain, such as in unstable patients actively bleeding, the spinal drain should be placed as soon as the situation permits.[28]

Another recent study focused on the neuroprotective impact of intrathecal papaverine in patients who underwent descending thoracic aneurysm and thoracoabdominal aortic aneurysm repair. There was no difference between post-operative mortality and stroke, but permanent paraplegia (3.6% vs. 7.5%) and paraparesis (1.6% vs. 6.3%) were significantly lower in the intrathecal papaverine group, and the authors concluded that intrathecal papaverine may enhance spinal cord perfusion and provide additional spinal cord protection.[29] Larger studies should assess the long-term risks and benefits before the clinical implementation of intrathecal papaverine.
A flow chart presenting a perioperative management strategy designed to prevent and treat SCI is represented in Figure 1.[30]

Table I Risk Factors Associated With Development of Spinal Cord Ischemia After TEVAR.

Demographics	Age Male gender Lower body mass index Preoperative renal failure Prior abdominal aortic aneurysm repair
Anatomical	Prior distal aortic vascular graft Thoracic aortic pathology Extent of thoracic or thoracoabdominal aneurysm Number of patent lumbar arteries
Perioperative	
Preoperative	Emergency operation
Intraoperative	General anesthesia Procedure duration Endovascular stent coverage - Total length of aortic coverage - Extent of uncovered distal aorta - Coverage of left subclavian artery Number of thoracic stents used Concomitant open abdominal aortic surgery Hypotension Hypogastric artery occlusion Arterial access site injury Bleeding
Postoperative	Hypotension Postoperative renal failure

TEVAR, thoracic endovascular aortic repair. Adapted with permission from Ullery BW, Wang GJ, Low D, et al. Neurological complications of thoracic endovascular aortic repair. *Semin Cardiothorac Vasc Anesth* 2011; 15:123-40.

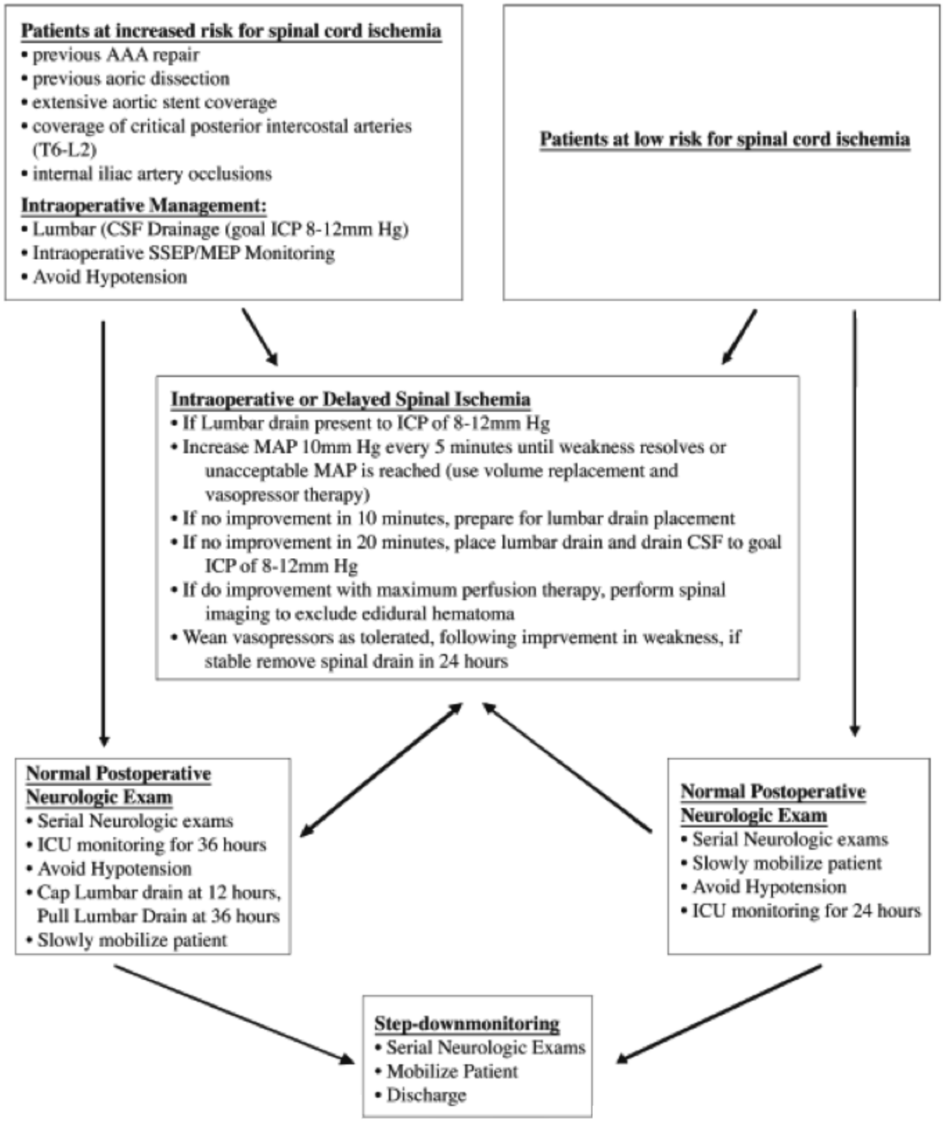

Figure 1 Perioperative management strategies to prevent and treat spinal cord ischemia in patients undergoing TEVAR (adapted from McGarvey et al30).
TEVAR, thoracic endovascular aortic repair; *CSF*, cerebrospinal fluid; *SSEP*, somatosensory-evoked potential; *MEP*, motor-evoked potential; *MAP*, mean arterial pressure; *ICP*, intra cranial pressure measured through the lumbar cerebrospinal fluid drain; *AAA*, abdominal aortic aneurysm.
(Adapted with permission from McGarvey ML, Mullen MT, Woo EY, et al. The treatment of spinal cord ischemia following thoracic endovascular aortic repair. *Neurocrit Care* 2007; 6:35–39.)

Intraoperative surgical considerations

Custom-made, branched stent-grafts have been used for the treatment of rDTAAs, but applicability of these devices is less feasible in emergency situations as they are not available "off the shelf". However, the goal of endovascular treatment is to perform a minimally invasive procedure to repair rDTAA. The use of heparin is recommended for endovascular repair in patients with rDTAA, but at a lower dose than in elective TEVAR.[17]

To provide a good proximal seal, a proximal landing zone of sufficient length has to be established, but involvement of the LSA and left common carotid artery (LCCA) can thwart this good proximal landing zone. Thus, coverage of the LSA or LCCA may be required to obtain adequate proximal seal. However, the LSA supplies blood flow to the left arm, left vertebral artery (important for spinal cord perfusion) and left internal mammary artery (important in case of previous coronary artery bypass graft with grafting of the left anterior descending coronary artery), and may require an additional revascularization procedure in approximately 10% of patients. Indications for LSA revascularization include absent right subclavian artery, functional left arm arteriovenous shunt, patent left internal mammary artery coronary bypass graft, left axillary-femoral bypass graft and extensive thoracic aortic coverage with history of prior abdominal aortic replacement. Options to preserve flow in the LSA, in situations where it needs to be covered, include carotid-LSA bypass. Similarly, carotid-carotid-LSA bypass can be performed if both the LCCA and the LSA are covered.[31] This is particularly important to prevent a steal phenomenon, which is caused by collateral flow from the left vertebral artery in retrograde direction to the LSA, causing "stealing" of blood from the brain to the left arm.[32]

Innovations to improve the proximal seal with a complete minimally invasive approach are currently underway. The Valiant Mona LiSA (Medtronic, Inc., Minneapolis, MN) is a new device based on the Valiant Captivia thoracic stent graft (Medtronic, Inc., Minneapolis, MN) and is currently being evaluated by the Food and Drug Administration's (FDA) Early Feasibility Pilot Program. This new device features an integrated branch-graft for the LSA and should make a complete minimally invasive approach with preserving the LSA available for patients worldwide.

Another option to maintain the blood flow into the vital aortic arch side branches is the use of a chimney graft, which involves placement of stents in side branches of the aorta alongside the main endovascular stent graft (Figure 2). A recent meta-analysis showed good short-term results with technical success in 98% of patients and 100% patency of chimney grafts after a mean follow-up of 11 months.[33] The chimney technique is a viable option for patients with rDTAA. However, a considerable percent of these patients develop postoperative stroke (5%) and/or endoleaks, a fact that deserves attention. In case the proximal landing zone needs to be extended and is covering or impinging on the take-off of the LCCA, the chimney technique could also be a viable option. Patency described in this meta-analysis[33] is 100% after a mean follow-up of 11 months. However, the risk for complications is higher if the LCCA is covered compared with coverage of just the LSA. Total complications after chimney stenting are 27% for LCCA vs. 9.1% for LSA.[33] A possible explanation is that the LCCA perfuses more vital areas, such as the brain, that are less "forgiving" than the areas perfused by the LSA. Another option is to perform a carotid-carotid bypass to preserve flow into the LCCA. However, a recent study comparing several techniques for revascularization for vascular diseases in zone 0 and 1

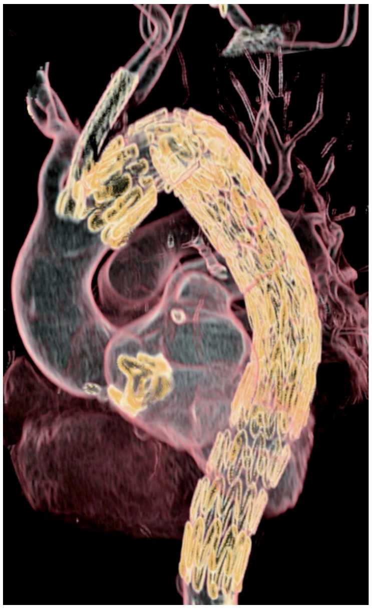

Figure 2 Computed tomography angiography shows a patent stent graft after successful thoracic endovascular aortic repair of a ruptured descending thoracic aortic aneurysm with placement of a chimney stent in the left common carotid artery.

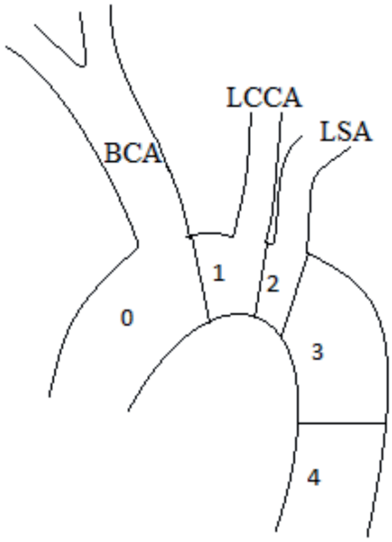

Figure 3 Zones in aortic arch.
BCA, brachiocephalic artery; *LCCA*, left common carotid artery; *LSA*, left subclavian artery.

(Figure 3) of the aortic arch showed that carotid-carotid bypass has more complications compared with the chimney-technique.[34] Independent of the technique employed, post-operative angiography is of critical importance to evaluate the patency of the stents and prevent major complications.

Post-operative considerations

The use of EVAR and TEVAR has led to a decrease of patients with post-operative delirium. In a study with 256 patients with abdominal and thoraco-abdominal aortic aneurysms, 29% of patients in the open repair group vs. 13% of patients in the endovascular group developed postoperative delirium. To highlight this difference even more, the patients in the endovascular group were significantly older and it is well known that age is an independent risk factor for delirium.[35]

In order to employ a timely treatment of SCI, at the end of the procedure every attempt should be made to obtain a neurologic exam in the operating room. Even if the decision is made to maintain the patient intubated and sedated, the anesthetic agents should be decreased in order

to allow for a thorough neurologic evaluation. In the intensive care unit, if the patient is hemodynamically unstable or has other co-morbidities that require mechanical ventilation, the patient should continue to be routinely evaluated neurologically every hour.
Furthermore, attention should be paid to the analysis of laboratory results, since these are a good predictor for the survival of patients treated for ruptured aneurysms. Higher international normalized ratio (INR) and activated partial thromboplastin time (APTT) and lower values of pH and bicarbonate concentration are associated with a higher rate of mortality. In patients with these impaired markers, extra attention should be paid to prevent post-operative mortality. Furthermore, patients with a higher intraoperative diuresis and first post-operative day diuresis were more likely to survive their intensive care unit hospitalization after ruptured aneurysm repair.[36]
Besides all the advantages of TEVAR, it should be noted that there are disadvantages for the patient, anesthetist and surgeon. One of these problems is the cumulative radiation exposure, which has been recently investigated by researchers from Milan, Italy. Overall radiation exposure was predicted by estimating the life-expectancy of the patients treated with TEVAR and the total number of required CT-scans. Three post-operative CT-scans in the first year with a yearly evaluation thereafter and a life expectancy of 15 years is estimated to increase the lifetime risk in radiation-induced leukemia and solid-tumor cancer by more than 2.7%. Obese patients had significantly higher radiation exposure, and therefore, the risks of cumulative radiation exposure must be balanced with the expected reduction in morbidity and mortality for patients treated with TEVAR, especially for younger or obese patients.[37]

CONCLUSION

Endovascular treatment of rDTAAs is a challenging team effort for both the anesthesiologist and the surgeon. Limited time is available to prepare the patient for this intervention and the preoperative evaluation should be focused. Close communication during the intervention between the anesthesiologist and the surgeon is required, especially during the critical moments including induction and during placement of the aortic stent graft. During TEVAR, patients should be kept in permissive hypotension prior to stent deployment, while maintaining sufficient spinal cord perfusion. After stent deployment in order to decrease the risk for SCI the MAP should be increased and the CSFP should be decreased by actively draining fluid. The use of proactive spinal cord protection protocols could lead to a decrease of paraplegia rates. Future studies should focus on outcomes after different anesthetic techniques and spinal cord protective measures are employed.

KEY POINTS

- In order to improve outcomes of TEVAR for rDTAA, a close communication between the anesthesiologist and the surgeon and a thorough understanding of the events during the procedure as well as their inherent risk factors is mandatory.
- The use of a proactive spinal cord protection protocol may decrease the rates of devastating spinal cord ischemia and/or paraplegia.

- Spinal cord near-infrared spectroscopy (NIRS) represents a promising non-invasive technology that could be utilized in high-risk individuals undergoing emergency TEVAR and provides real time information regarding spinal cord ischemia.
- Important issues to consider on pre-operative imaging evaluation are correct sizing of the aortic stent graft and localization of the artery of Adamkiewicz.
- New endovascular techniques, such as the chimney technique, have shown good early results for the treatment of emergency situations, with low neurological complication rates.

4

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CHAPTER 5

A giant superior mesenteric artery aneurysm mimicking an abdominal aortic aneurysm

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ABSTRACT

Superior mesenteric artery aneurysms (SMAAs) are a rare clinical finding but can present with a wide range of symptoms. SMAAs are associated with a high rupture risk and high morbidity and mortality. We present a case of a 38-year old female who presented with acute abdominal pain and a pulsatile palpable mass in the right epigastric region without other signs or symptoms.

INTRODUCTION

Visceral artery aneurysms (VAAs) are a rare entity in clinical practice with a reported incidence ranging from 0.1% to 2%. Splenic artery and hepatic artery aneurysms account for the majority of these aneurysms, 60% and 20% respectively. Although only 5.5% of VAAs is attributable to superior mesenteric artery aneurysms (SMAAs),[1,2] they are clinically important due to the high rupture risk with mortality risk, up to 40%.[2,3] Two decades ago, most patients with SMAAs presented with fever, abdominal pain and a pulsatile abdominal mass and had an infection as underlying cause.[4,5] Due to the increased use of computed tomography (CT) scans and other cross sectional imaging, the incidence of detected SMAAs is rising, and more SMAAs are asymptomatic. We report on a patient who presented with a large pulsatile mass mimicking an abdominal aortic aneurysm (AAA). A giant SMAA was found and subsequently successfully treated.

CASE REPORT

A 38-year-old white female presented to the emergency department with abdominal pain that started 48 hours prior to admission and was not associated with nausea or vomiting. On exam she was afebrile and a pulsatile mass in the right epigastric region was appreciated (Figure 1). The vascular surgery service was emergently consulted to manage a symptomatic abdominal aortic aneurysm (AAA). A CT scan of the abdomen was obtained and this revealed a 6 x 7 cm SMAA (Figure 2) which was confirmed by angiography (Figure 3). Emergent transperitoneal laparotomy was performed and a giant aneurysm, approximately 8 cm distally from the origin of the superior mesenteric artery (SMA) was successfully excised and continuity restored with a reversed saphenous vein graft (Figure 4). The patient had an uneventful recovery and was doing well up to a 5-year follow-up. Pathological examination of the surgical specimen revealed degenerative changes in the arterial wall and large amounts of thrombus. No bacteria were identified microscopically. Culture of the aneurysm wall did not grow any bacteria.

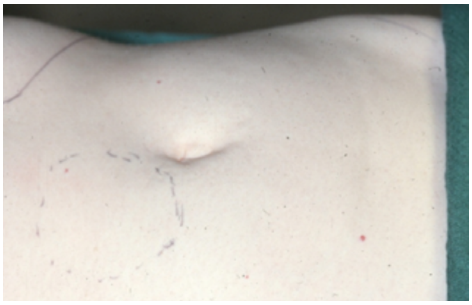

Figure 1 Marking indicates the location of the pulsatile mass in the right epigastric region.

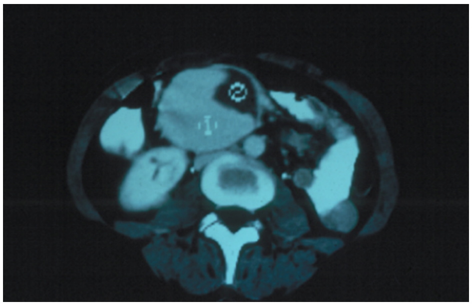

Figure 2 Computed tomography of the abdomen showing a large saccular aneurysm of the superior mesenteric artery, 6 x 7 cm in width and diameter.

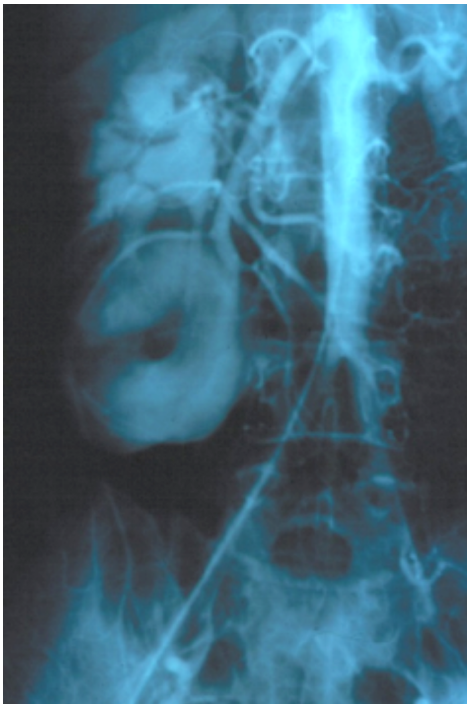

Figure 3 Abdominal angiography showing a superior mesenteric artery (SMA) aneurysm, 8 cm from the origin of the SMA and with a length of 7 cm.

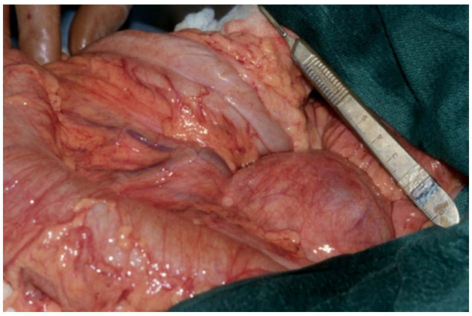

Figure 4 Intraoperative picture of the giant superior mesenteric artery aneurysm.

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DISCUSSION

Aneurysms of the SMA are rare and account for 5.5% of all VAAs. Due to this very low incidence, large studies documenting their outcomes are lacking in literature. DeBakey and Cooley described the first successful resection without revascularization of an mycotic SMAA due to bacterial endocarditis in a young female in 1953.[6] Studies with more than five patients with SMAAs are shown in Table I.[2,7-9] SMAAs are usually located within the first five centimeters from the origin of the SMA and can be fusiform or saccular.[10] In contrast to most other aneurysms, both men and women are equally affected, although men are reported to have a higher rupture risk.[2] There is no typical age of onset of SMAAs and it depends mostly of the etiology of the disease. Most patients with mycotic aneurysms are younger than 50 years, and patients with atherosclerotic aneurysms are usually in their seventh or eighth decade.[11] The fact that it is a disease which can affect patients of all ages is illustrated by a case of a 9-year-old boy with Ehlers-Danlos syndrome and a SMAA.[12]

Historically, mycotic aneurysms represented the majority of all SMAAs with a reported percentage up to 63%[13], and most of them were caused by non-hemolytic *Streptococci*, although a wide range of other pathogens is reported. Currently, the most frequent cause for aneurysms of the SMA is atherosclerosis. This is underscored by the series from the Mayo Clinic that only 5% of patients were thought to have infection as primary cause for the aneurysm while 62% of the patients had calcified SMAAs.[2] Other more recent papers validate this finding.[8] Despite the relative small number of reports, a wide range of other etiologies has been described including collagen vascular diseases, arteritis, trauma and arterial dysplasia.[10]

Two decades ago, over 90% of all patients were symptomatic.[3] However, more recently diagnosed SMAAs are asymptomatic and discovered as incidentally findings on abdominal imaging.[2] Stone et al reported in their study that 48% of all patients were asymptomatic[2] and in the study by Jiang et al, this was even higher with 70% asymptomatic patients.[8] These findings are consistent with the fact that more abdominal CT scans and other cross-sectional imaging are being performed. Another possible explanation is the widespread use of antibiotics which could potentially prevent the infectious cause of SMAAs. Although a decrease of 50% for infectious causes is described in recent literature[2,10], the SMA remains the most affected visceral artery for infections.[14]

Patients can present themselves with a wide range of symptoms including abdominal pain, nausea, vomiting, a pulsatile mass or gastro-intestinal bleeding. Mycotic aneurysms are usually accompanied by a triad of fever, abdominal pain and a pulsatile mass. A pulsatile mass is present in 50% of symptomatic patients. Acute presentation, including small bowel ischemia due to thrombosis and excessive hemorrhage due to rupture is described in up to 38% of patients.[10] This is concerning, because the mortality rate after rupture is close to 35%.[2] In these patients, emergent laparotomy is recommended. The indications for repair include SMAAs with a diameter exceeding two centimeter, symptomatic SMAAs and rapidly growing SMAAs. Because the natural history of SMAAs is not well defined, there is still some controversy about the absolute indications.[9,15]

Open repair is still considered the gold standard for all SMAAs in patients who require treatment. Open surgical repair can be performed by surgical resection with arterial reconstruction, as illustrated by our case-report, or by ligation of the vessel without reconstruction. The primary goal of therapy is to exclude the aneurysmal sac from the blood circulation. Ligation without reconstruction should only be performed in cases where sufficient collaterals are present to provide collateral flow.[16]

The evolution of endovascular techniques has also impacted the management of visceral artery aneurysms. These minimally invasive procedures generally carry less operative morbidity and mortality, shorter hospitalization, fewer complications and a better perioperative quality of life.[17] The recent literature shows that endovascular treatment could play an important role in the emergent treatment of ruptured SMAAs and technical success rates up to 90% have been reported.[18] However, endovascular treatment such as stenting and coil embolization is not a feasible option in every VAA, and SMAA in particular. In the current literature there are only a few case-reports and small case series that report the use of endovascular treatment of SMAAs.[8,19,20] For planning of the endovascular procedure, the whole affected artery must be carefully assessed with angiography or CT angiography, to evaluate the proximal and distal landing zone and presence of side branches. Covering of these side branches could potentially lead to mesenteric ischemia with devastating consequences. However, even if careful angiographic evaluation is performed, it is not likely to show all side branches.

Table I Largest studies with SMAAs.

Article	# of pts.	Age, M/F	Info aneurysms	Symptoms	EM / EL	OR / EV / NM	Tech. success	30-day mortality	Complications (FU)
Carmeci 2000 [7]	5*	59y 2/3	NA	100% AbP 80% R	NA	4/1/0	100%	0%	0% (36)
Stone 2002 [2]	21	59y 14/7	62% calcified 5% infectious	48% AS 24% AbP 38% R	8 / 13	12/3/6	NA	38% in EM 0% in EL	0% in EM 25% in EL (56)
Marone 2011 [9]	6*	58y 6/0	Mean size: 3.4cm	NA	NA	3/3/0	100%	17%	17% (NA)
Jiang 2011 [8]	10	57y 4/6	Mean size: 3.5cm	70% AS 10% AbP 10% R	1 / 9	2/5/2	100%	10%	11% (30.9)

SMAAs, superior mesenteric artery aneurysms; # *of pts.*, number of patients; *M*, male; *F*, female; *OR*, open repair; *EV*, endovascular repair; *NM*, non-operative management; *FU*, follow-up (in months); *AbP*, abdominal pain; *AS*, asymptomatic; *R*, rupture; *EM*, emergent; *EL*, elective; *NA*, not available.
**part of study for all visceral artery aneurysms*

Jiang et al. reported that they found many more branches originating from the aneurysm during surgical treatment than was apparent on preoperative SMA angiography. Future studies are still needed to show the long-term results of stenting and coil embolization of SMAAs, before it can be considered safe and effective.

SMAAs remain a rare entity with a wide range of clinical presentations. In the light of more abdominal cross-sectional imaging, more asymptomatic SMAAs are being detected and the relative portion of mycotic aneurysms during diagnosis is decreasing. High rupture and other complication rates are associated with SMAAs, so early treatment is recommended for symptomatic, rapidly growing and relatively large SMAAs. Open repair, primarily ligation and excision of the aneurysm, remains the gold standard. Endovascular treatment has developed into a viable option, but more research is needed to evaluate and optimize this treatment. Because of the low incidence and the lack of large studies, there are no guidelines for postoperative management. However, it is recommended to perform follow-up when symptoms occur, especially in the first years after intervention, when the risk of bypass occlusion is the highest, although the complication and reintervention rate are very low due to the good long-term results.[15]

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CHAPTER 6

Open repair, endovascular repair and conservative management of true splenic artery aneurysms

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ABSTRACT

Objective

True splenic artery aneurysms (SAAs) are a rare, but potentially fatal pathology. For many years, open repair (OPEN) and conservative management (CONS) were the treatments of choice, but throughout the last decade endovascular repair (EV) has become increasingly utilized. The purpose of the present study was to perform a systematic review and meta-analysis evaluating the outcomes of the three major treatment modalities (OPEN, EV and CONS) for the management of SAAs.

Methods

A systematic review of all studies describing the outcomes of SAAs treated with OPEN, EV or CONS was performed using seven large, medical databases. The PRISMA guidelines for Systematic Reviews and Meta-Analyses were followed to ensure a high quality review. All articles were subject to critical appraisal for relevance, validity, and availability of data regarding characteristics and outcomes. All data were systematically pooled, and meta-analyses were performed on several outcomes, including early and late mortality, complications and number of reinterventions.

Results

Original data of 1,321 patients with true SAAs were identified in 47 articles. OPEN contained the largest number of patients (n = 511; 38.7%, 31 articles), followed by CONS (n = 425; 32.2%, 16 articles) and EV (n = 385; 29.1%, 33 articles). Fewer symptomatic patients (9.5% (CONS) vs. 28.7% (OPEN) and 28.8% (EV); p<.001) and fewer ruptured aneurysms (0.2% (CONS) vs. 18.4% (OPEN) and 8.8% (EV); p<.001) were included in the CONS group, while no significant differences in existing comorbidities were found. The only identified difference in baseline-characteristics between OPEN and EV was the number of ruptured aneurysms (18.4% vs. 8.8%; p<.001). The 30-day mortality of OPEN was higher compared with EV (5.1% vs. 0.6%; p<.001), while a larger number of patients treated with EV suffered minor complications. EV required more reinterventions compared with OPEN and CONS (3.2%/year (EV) vs. 0.5% (OPEN) and 1.2% (CONS), p<.001). The relative risk of 30-day mortality for ruptured vs. unruptured aneurysms was 17.27 (p<.001).

Conclusions

EV of SAA has better short-term results compared to OPEN, including a significantly lower perioperative mortality. OPEN is associated with fewer late complications and fewer reinterventions during follow-up. Patients treated with CONS showed a higher late aneurysm-related mortality rate. These patients were usually older, had smaller aneurysm sizes and fewer symptoms and ruptures compared to patients in the OPEN and EV groups. Ruptured splenic aneurysms are predictors of a significantly higher perioperative mortality compared to non-ruptured aneurysms, in both the OPEN and EV group.

INTRODUCTION

True splenic artery aneurysms (SAAs) are a rare, but potentially fatal pathology. The splenic artery is considered aneurysmal when the size of the artery is more than 1 cm in diameter. True splenic aneurysms are defined as expansions of all wall layers, whereas pseudoaneurysms are defined as expansions of the artery with focal disruption of the arterial wall.[1] Although rare, SAAs are the third most common abdominal aneurysms after aortic and iliac artery aneurysms, and account for the vast majority of all visceral artery aneurysms.[2] Previous studies have shown a high risk for SAA rupture when the aneurysm measures more than 2 cm. Although usually asymptomatic, most splenic artery aneurysms can potentially rupture, resulting in life-threatening complications.[2-5] This emphasizes the importance of timely management, whether it is interventional or conservative treatment.

SAA was first described in 1770 by Beaussier,[6] but surgical repair was not reported until 1940.[7] Open repair (OPEN) or conservative management (CONS) was the treatment of choice for many years. During the last decade, however, endovascular repair (EV) of SAAs has been increasingly utilized with good short-term results.[8-11] As this disease is rare, most studies are retrospective reporting only a small number of patients and therefore, no Level 1 evidence is available. With the more frequent use of diagnostic tests, there has been an increase in the detection of SAAs and thus an increasing need for clear directives. The current general consensus has been to intervene in all symptomatic patients and aneurysms exceeding 2 cm in diameter, but no clear guidelines for indications of treatment have been reported. All three management options have pros and cons. OPEN has shown excellent long-term results but high perioperative mortality[12-15]. EV has shown low short-term morbidity and mortality but a higher reintervention rate as result of long-term complications[8-11]. CONS has no immediate procedural risk but an increasing risk of aneurysm rupture potentially resulting in life-threatening hemorrhage.[2-5]

The purpose of the present study was to perform a systematic review and meta-analysis evaluating the outcomes of the three treatment modalities (OPEN, EV and CONS) for the management of SAAs.

METHODS

Literature search

The PRISMA guidelines for Systematic Reviews and Meta-Analyses were employed when performing this systematic review and meta-analysis.[16] To identify all articles describing treatment of SAAs, MEDLINE, EMBASE, Web-of-science, Scopus, PubMed as supplied by publisher, Cochrane Library CENTRAL and Google Scholar were systematically searched until Dec 12, 2013. No publication date restriction was applied. The following search string was used for EMBASE: *('spleen artery aneurysm'/de OR (('spleen artery'/de OR spleen/de) AND ('aneurysm surgery'/exp OR aneurysm/exp)) OR ((spleen OR splenic) NEAR/3 aneurysm*):ab,ti) AND (therapy/exp OR therapy:lnk OR surgery/exp OR surgery:lnk OR procedures/de OR (therap* OR treat* OR curing OR cure OR repair OR technique* OR procedure* OR equipment* OR surg* OR operat*):ab,ti).* This resulted in 1,121 articles. A similar search string was used for other search engines. Details of search strings and number of articles can be found in Appendix Figure 1. A total of 2,702 articles were identified and after removal of duplicate articles, 1,490 unique articles remained.

Selection of articles

Review of titles and abstracts was performed independently by 2 investigators (W.H. and A.L.). For a paper to be excluded, both reviewers had to agree that the article was ineligible for inclusion. Disagreements between reviewers were discussed and were resolved by consensus. Articles were included if: (1) original data of characteristics and outcomes of true SAAs were reported, (2) they described OPEN, EV or CONS management and (3) reported at least 10 patients. Exclusion criteria included: (1) papers without original data, (2) articles specifically reporting pregnant patients with SAAs, because of the different pathophysiology, (3) papers with less than ten patients, (4) not describing OPEN, EV, CONS management, (5) describing false / pseudoaneurysms, (6) if there was no clear distinction between splenic aneurysms and visceral aneurysm and (7) if no useful information regarding the outcomes was presented. To prevent inclusions of duplicate cases, articles published by identical authors or institutions were studied in detail; the most recent paper was included. Due to the fact that administrative data, for example Medicare files, are considered to be less reliable and less consistent and could have been published previously in other included articles, these articles were not included. To identify additional relevant articles, references of included papers were searched manually and retrieved 3 additional articles. A total of 47 relevant articles were identified and included in the final selection (Figure 1).

Data extraction

Two independent investigators (W.H. and A.L.) analyzed the included articles and extracted the data. All extracted characteristics and outcomes were systematically included in a database. If a variable was described only for the whole group in a paper that described multiple types of treatment, but not specific for OPEN, EV or CONS, this variable was not included in the analysis. The variables extracted included year of publication, institution, number of patients, number of aneurysms, age, gender, size of the SAA, percentage of symptomatic patients, type of symptoms, percentage of ruptures, number of patients with hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease (CAD), number of patients smoking, type of treatment, type of intervention, type of surgery, number of splenectomies, elective or emergency cases, technical success, conversion from EV to OPEN, 30-day minor complications, type of morbidity, major complications, 30-day mortality, cause of death < 30 days, late complications, late (>30 days) mortality, number of reinterventions, length of hospitalization in days, follow-up in months, number lost to follow-up and overall survival. Original data of 1,321 patients with true SAAs treated with OPEN, EV or CONS were analyzed.

Statistical analyses

Statistical analyses were performed using IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA), Review Manager (RevMan) version 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Microsoft Excel® 2010. Continuous variables were described using

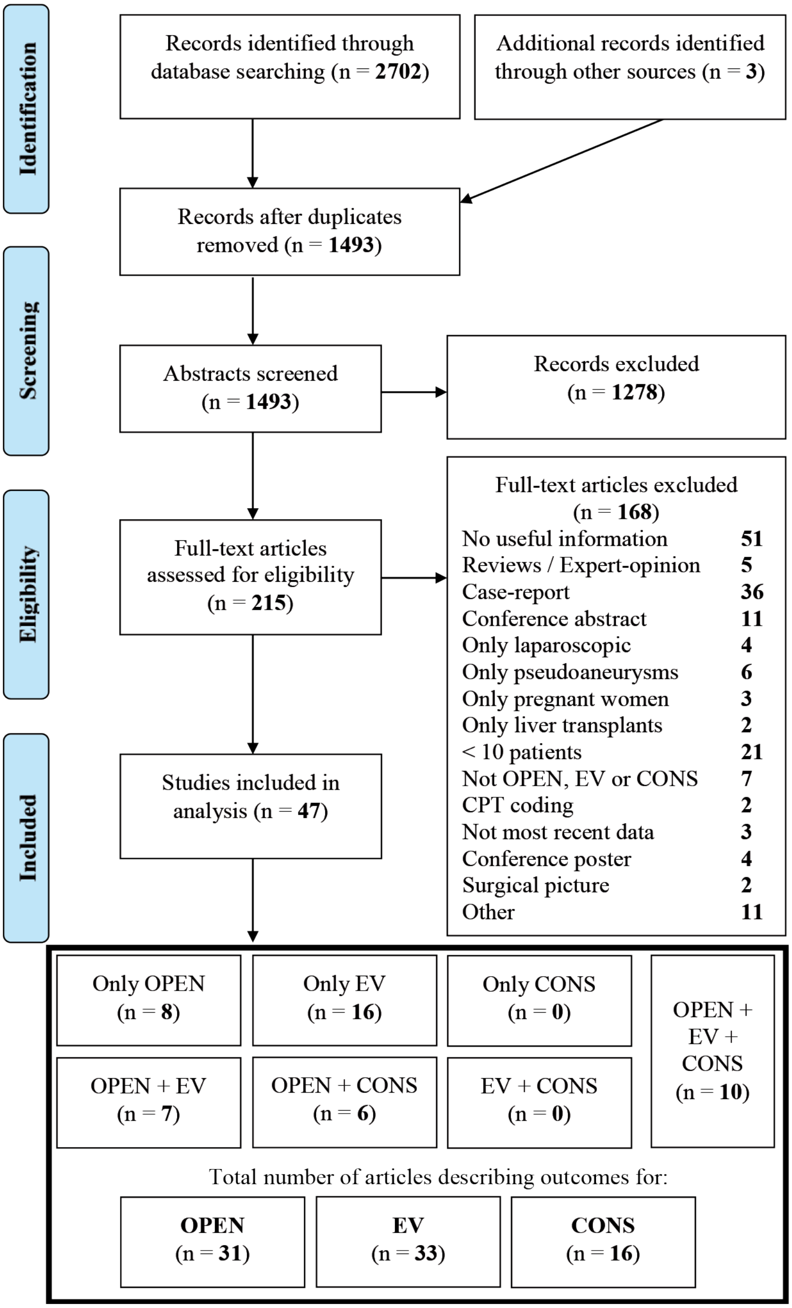

Figure 1 Flow diagram for literature search and selection, following the PRISMA Guidelines, for splenic artery aneurysms. *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *n*, number.

means and standard deviations, if possible, while categorical factors were reported in frequencies and percentages. Some of the percentages were calculated into rates per year, for example for the reinterventions, following the equation: *rate = –ln(1 – prob)/time*. Continuous variables were compared using the t-test for two groups or ANOVA for more than 2 groups. Categorical characteristics and outcomes were used to compare variables and outcomes between OPEN, EV and CONS using the χ^2-test or Fisher's exact test when the expected number was less than five.

Adjustment for learning curve and ruptures

Given the importance of the time of publication, an additional analysis was performed for OPEN vs. EV only using data from articles published after 2000. The year 2000 was chosen as cut-off point, because before 2000 there was still a learning curve for the EV group, and only small case-studies or case-reports were published. Another comparison was performed between ruptured and unruptured aneurysms.

RESULTS

Literature search

Original data of 1,321 patients with true SAAs were identified in 47 articles. OPEN contained the largest number of patients (*n* =511; 38.7%), followed by CONS (*n* = 425; 32.2%) and EV (*n* = 385; 29.1%). In total, 31 articles described characteristics and outcomes for patients treated with OPEN,[2-5,12-15,17-39] 33 articles for EV[1,3-5,8-11,13-15,17-23,29-32,40-50] and 16 for CONS.[2-5,17-28] Details of the number of articles and patients are shown in Figure 1. Figure 2 shows the distribution of the different types of treatment by publication date. An increase of patients treated with EV can be seen after 2000. Availability of the studied variables in the analyzed articles is shown in Table I.

Study characteristics

Baseline characteristics, frequencies and significance levels are given in Table II. Patients in the CONS group were older compared with the OPEN and EV groups: mean age was 61.4 years (CONS) vs. respectively 56.3 years (OPEN) and 56.7 years (EV) and contained a higher number of female patients (75.1% (CONS) vs. 63.9% (OPEN) and 60.0% (EV); *p*=.001). Patients in the CONS group had smaller aneurysms (mean aneurysm size: 2.1cm) compared with OPEN (3.1cm) and EV (3.0cm), a smaller number of patients were symptomatic (9.5% (CONS) vs. 28.7% (OPEN) and 28.8% (EV); *p*<.001) and less ruptured aneurysms were included in the CONS group (0.2% (CONS) vs. 18.4% (OPEN) and 8.8% (EV); *p*<.001). Due to the lack of reported standard deviations, ranges and inter-quartile ranges in the evaluated reports, no standard deviation and, therefore, no statistical significance could be calculated for age and size of aneurysm. There were no significant differences in the presence of different comorbidities (hypertension, hyperlipidemia, diabetes mellitus, CAD and smoking) between the groups. There were no significant differences in any of the baseline-characteristics between the OPEN and EV group, except for the number of ruptured aneurysms, which was higher in the OPEN group compared with the EV group (18.4% vs. 8.8%; *p*<.001).

Table I Availability of data in the evaluated reports.

Variable available	All patients (n=1,321) no. (%)	OPEN (n=511) no. (%)	EV (n=385) no. (%)	CONS (n=425) no. (%)
Age	1,277 (97)	506 (99)	384 (99)	387 (91)
Gender	847 (64)	341 (67)	265 (69)	241 (57)
Number of aneurysms	1,321 (100)	511 (100)	385 (100)	425 (100)
Size of aneurysm	999 (76)	347 (68)	297 (77)	355 (84)
Location of aneurysm	448 (34)	183 (36)	219 (57)	46 (11)
Presence of Symptoms	1,070 (81)	415 (81)	278 (72)	377 (89)
Presence of Rupture	1,212 (92)	456 (89)	354 (92)	402 (95)
Presence of Hypertension	656 (50)	209 (41)	113 (29)	334 (79)
Presence of Hyperlipidemia	397 (30)	77 (15)	86 (22)	234 (55)
Presence of Diabetes	472 (36)	113 (22)	103 (27)	256 (60)
Presence of CAD	434 (33)	92 (18)	102 (26)	240 (56)
Presence of Smoking	459 (35)	98 (19)	102 (26)	259 (61)
Type of intervention	896 / 896 (100)	511 (100)	385 (100)	NA
Elective / Emergency	779 / 896 (87)	439 (86)	340 (88)	NA
Technical success	882 / 896 (98)	498 (97)	384 (99)	NA
Splenectomy	870 / 896 (97)	511 (100)	359 (93)	NA
Conversion	375 / 385 (97)	NA	375 (97)	NA
30-day morbidity	1,231 (93)	438 (86)	378 (98)	415 (98)
30-day mortality	1,307 (99)	498 (97)	384 (99)	425 (100)
Length of hospital stay	233 / 896 (26)	64 (13)	169 (44)	NA
Length of follow-up	1,104 (84)	377 (74)	342 (89)	385 (91)
Lost to follow-up	560 (42)	119 (23)	227 (59)	214 (50)
Late complications	909 (69)	335 (66)	354 (92)	220 (52)
Late mortality	918 (69)	334 (65)	349 (91)	235 (55)
Reinterventions	1,211 (92)	450 (88)	384 (99)	377 (89)
Survival	895 (68)	317 (62)	241 (63)	337 (79)

No., number; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *CAD*, coronary artery disease; *NA*, not applicable.

Management

The type of surgical intervention was resection of the aneurysm combined with splenectomy in the majority of the cases in the OPEN group followed by reconstruction of the splenic artery, while the preferred method of endovascular therapy was embolization followed by stenting of the SAA (Table II).

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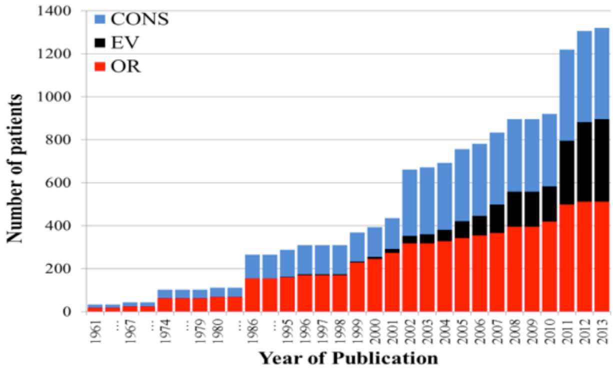

Figure 2 Number of patients treated with OPEN, EV or CONS for SAAs by year of publication. *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *SAA*, splenic artery aneurysm.

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Early outcomes

Technical success was achieved in 97.8% of the OPEN cases and in 95.2% of the EV cases (Table III). In 1.8% of the EV cases, conversion to open surgery was necessary to successfully exclude the aneurysm. The 30-day mortality in the OPEN group was much higher compared with patients treated with EV (5.1% vs. 0.6%; $p<.001$), while a larger number of patients treated with EV suffered minor complications (wound infection, post-embolization syndrome). The incidence of major long-term complications was low and was not different with 1.1% and 0.8% for respectively OPEN and EV. The length of hospitalization was longer in the OPEN group: mean length of stay was 9.8 days vs. 2.0 days for EV.

Late outcomes

The mean length of follow-up was much shorter for EV compared with OPEN and CONS: 30.8 months vs. respectively 61.2 and 61.8 months, due to the relatively new procedures and techniques of EV. During these follow-up periods, patients in the EV group developed more late complications and required more reinterventions compared with OPEN and CONS. Patients in the CONS group, however, had a higher late mortality rate compared with OPEN and EV (Table III). Patients in the EV group developed on average 3.7% complications per year and 3.2% required reinterventions per year. Patients initially treated with CONS required 1.2% interventions/year while the OPEN group only required 0.5% reinterventions/year ($p<.001$).

Adjusting for the learning curve

After 2000, more minor complications, and less late mortality following OPEN were reported compared to the period before 2000 (Table IV). All the other outcomes were not significantly different statistically. This comparison was not performed for patients treated with EV, since there were insufficient cases prior to 2000 to perform a meaningful analysis (n = 5).

Outcomes between OPEN and EV after 2000 are reported in Table V and show the same outcomes as reported for the outcomes of all time periods combined, which were given in Table III. Technical success (p=.018) and 30-day mortality ($p<.001$) are higher in the OPEN group, while the number of acute minor complications (p=.012), number of late complications ($p<.001$) and number of reinterventions (p=.007) are higher in the EV group.

Table II Baseline characteristics of patients with splenic artery aneurysms.

Characteristic	OPEN (n = 511) no. (%) or mean	EV (n = 385) no. (%) or mean	CONS (n = 425) no. (%) or mean	All groups p-value	OPEN vs. EV p-value
Age, y	56.3	56.7	61.4	*	*
Gender, % female	218 (63.9)	159 (60.0)	181 (75.1)	.001	.322
No. of aneurysms/patient	1.16	1.06	1.13	*	*
Size of aneurysm, cm	3.1	3.0	2.1	*	*
Location: proximal	27 (14.8)	41 (18.7)	4 (10.3)	.316	.291
Location: mid	50 (27.3)	71 (32.4)	11 (28.3)	.523	.267
Location: distal / hilar	106 (57.9)	107 (48.9)	24 (61.5)	.114	.070
Symptomatic	119 (28.7)	80 (28.8)	35 (9.5)	<.001	.977
Ruptured SAA	84 (18.4)	31 (8.8)	1 (0.2)	<.001	<.001
Hypertension	84 (40.1)	54 (47.7)	154 (46.2)	.299	.189
Hyperlipidemia	18 (23.7)	28 (33.1)	68 (29.1)	.426	.194
Diabetes	13 (11.3)	13 (12.5)	26 (10.0)	.782	.801
CAD	15 (16.0)	15 (14.7)	50 (21.0)	.343	.758
Smoking	29 (29.7)	19 (18.8)	55 (21.1)	.139	.070
Type of intervention					
Ligation	63 (12.3)	NA	NA		
Reconstruction	100 (19.6)	NA	NA		
Resection	51 (10.0)	NA	NA		
Splenectomy	291 (56.9)	6 (1.6)	NA		
Stent	NA	13 (3.4)	NA		
Embolization	NA	365 (94.8)	NA		
Other	6 (1.2)	1 (0.3)	NA		

No., number; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *CAD*, coronary artery disease; *SAA*, splenic artery aneurysm; *NA*, not applicable.
* Due to the lack of reported standard deviations, ranges and inter-quartile ranges in the evaluated reports, no standard deviation and, therefore, no statistical significance could be calculated for age and sizes and number of aneurysms.

Ruptured vs. unruptured SAAs

Since the only difference in the baseline characteristics between OPEN and EV was the number of patients with ruptured SAAs, an analysis of the 30-day mortality for patients with ruptured and unruptured aneurysms specifically was performed. Data was available for 810 patients describing both ruptured/unruptured SAAs and the 30-day mortality. These results are shown as a sub-analysis in Table V and demonstrate that in both ruptured and unruptured groups a higher mortality was reported in the OPEN group compared with the EV group.

Table III Outcomes of patients with splenic artery aneurysms after treatment.

Outcome	OPEN (n = 511) no. (%) or mean	EV (n = 385) no. (%) or mean	CONS (n = 425) no. (%) or mean	All groups p-value	OPEN vs. EV p-value
Technical success	487 (97.8)	366 (95.2)	NA	NA	.041
Conversion	0 (0.0)	7 (1.8)	NA	NA	NA
Minor Complications	49 (11.3)	95 (25.1)	NA	NA	<.001
Major Complications	3 (1.1)	3 (0.8)	NA	NA	.690
30-day mortality	25 (5.1)	2 (0.6)	2 (0.5)	<.001	<.001
Length of hospital stay, d	9.8	2.03	NA	*	*
Length of follow-up, m	61.2	30.8	61.8	*	*
Late complications	9 (2.5)	34 (9.1)	2 (0.8)	<.001	<.001
Late mortality	7 (2.1)	5 (1.4)	11 (4.9)	.040	.510
Reinterventions	9 (2.4)	30 (7.9)	22 (5.8)	.004	<.001

No., number; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *d*, days; *m*, months; *NA*, not applicable.
* Due to the lack of reported standard deviations, ranges and inter-quartile ranges in the evaluated reports, no standard deviation and, therefore, no statistical significance could be calculated for length of hospital stay and follow-up.

Table IV Outcomes of patients with splenic artery aneurysms following OPEN before and after the year 2000.

OPEN + Outcome	Before 2000 no. (%) or mean (n = 228)	After 2000 no. (%) or mean (n = 283)	p-value
Technical success	208 (96.7)	279 (98.6)	.221
Conversion	0 (0)	0 (0)	NA
Minor Complications	10 (4.9)	39 (16.9)	<.001
Major Complications	0 (0)	3 (1.4)	.566
30-day mortality	11 (5.2)	14 (5.0)	.932
Length of hospital stay, d	NA	9.8	*
Length of follow-up, m	72.8	54.2	*
Late complications	0 (0)	9 (3.3)	.122
Late mortality	6 (7.1)	1 (0.4)	.001
Reinterventions	1 (1.0)	8 (2.9)	.457

No., number; *OPEN*, open repair; *d*, days; *m*, months; *NA*, not applicable.
* Due to the lack of reported standard deviations, ranges and inter-quartile ranges in the evaluated reports, no standard deviation and, therefore, no statistical significance could be calculated for length of hospital stay and follow-up. +Analysis by year of publication only performed for patients treated with OPEN, because of the lack of patients treated with EV before 2000 (n = 5)

Table V Outcomes of patients with splenic artery aneurysms following treatment after the year 2000.

After 2000 Outcome	OPEN no. (%) or mean (n = 283)	EV no. (%) or mean (n = 380)	p-value
Technical success	279 (98.6)	362 (95.2)	.018
Conversion	0 (0)	7 (1.8)	NA
Minor Complications	39 (16.9)	95 (25.3)	.012
Major Complications	3 (1.4)	3 (0.9)	.407
30-day mortality	14 (5.0)	2 (0.6)	<.001
Unruptured	5 (2.6)	0 (0.0)	.008
Ruptured	9 (20.4)	2 (6.7)	.196
Length of hospital stay, d	9.8	2.03	*
Length of follow-up, m	54.2	30.7	*
Late complications	9 (3.3)	34 (9.2)	.006
Late mortality	1 (0.4)	3 (1.2)	.405
Reinterventions	8 (2.9)	30 (8.0)	.007

No., number; *OPEN*, open repair; *EV*, endovascular repair; *d*, days; *m*, months; *NA*, not applicable.
* Due to the lack of reported standard deviations, ranges and inter-quartile ranges in the evaluated reports, no standard deviation and, therefore, no statistical significance could be calculated for length of hospital stay and follow-up.

DISCUSSION

The results of this meta-analysis show that EV of the SAA has better short-term results compared with OPEN. However, OPEN is associated with fewer late complications and reinterventions during follow-up. Patients who were treated with CONS were not at immediate risk of perioperative mortality, but showed a higher late aneurysm-related mortality rate. These patients were usually older, had smaller aneurysms when compared with patients in the OPEN and EV groups and had fewer symptoms and ruptures. Except for the difference in number of ruptured SAAs, there were no other differences between the OPEN and EV group, thus making them eligible for comparison.

SAAs account for up to 75% of all visceral artery aneurysms and are more commonly reported in female patients compared to male patients at a ratio of 4:1.[3,14,51] We observed a higher number of female patients in the articles used in this meta-analysis, with females accounting for 66.0% of the patients. With a mean age of 58.0 for the whole group, SAAs are predominantly found in elderly women. It is not exactly clear why SAAs predominate in women, but a hormonal contribution has been postulated.[52]

This meta-analysis, with more than 1,300 included patients, is by far the most extensive analysis of patients with true SAAs to date. Given the rarity of the disease, most published articles are, not surprisingly, small retrospective studies. The strength of a meta-analysis is that, by pooling many studies, the effective sample size is greatly increased, and therefore more characteristics and outcomes can be evaluated.[53] There are, however, some limitations. First, data collection was restricted to information available in the existing literature, and information about many variables could not be retrieved for all of the patients. For example, data regarding the size of the aneurysm was only available for 76% of patients. Regrettably, this is inherent to meta-analyses in general. The second limitation is that no statistical comparison could be performed for several characteristics, including age and size of aneurysm, due to the lack of comprehensive statistical information in the articles. To perform an accurate statistical test, one needs at least the standard deviations, ranges or inter-quartile ranges when combining the means and unfortunately, these were poorly described in the literature. When crudely comparing the patient ages and aneurysm sizes between groups, OPEN and EV were performed in very similar patient populations (56.3y vs. 56.7y and 3.1cm vs. 3.0cm), consisting of younger patients with larger aneurysms compared with CONS (61.4y and 2.1cm).

Another limitation of this systematic review is that only publications with more than 10 patients were included. As a result, no case-reports or case-series were included. This reduced the number of patients included in this review, but increased the data quality. Furthermore, since case-reports and case-series usually report successful interventions, whereas retrospective reviews with more than ten patients will include the failures, this approach reduced selection bias and publication bias.

In order to strengthen the results presented in this paper, additional analyses were performed by year of publication (before and after 2000) and specifically for patients with and without ruptured aneurysms. Initially, we planned to perform an additional analysis of outcomes for patients with splenectomy versus patients without splenectomy. This was unfortunately not possible since this was not well described in the included studies. Most studies described how many patients had a splenectomy, as well as the number of patients who had complications or died, but they failed to report the morbidity and mortality and long-term survival. Because of this, a Kaplan-Meier survival curve could not be created. Combining the perioperative mortality and long-term mortality showed that OPEN has a higher combined mortality compared with EV and CONS. This is also likely to be the result of higher number of patients with ruptured aneurysms. Additionally, EV has a lower combined mortality compared with CONS. This is likely to be the result of inclusion of older patients with more comorbidities in the CONS group compared with the EV group. The last important limitation is our inability to stratify patients based on the location of the SAA since location was reported in only 34% of the patients. Additionally, detailed outcomes related to the location of the SAA were available in only two papers, preventing us from performing an extensive analysis.[42,45] The incidence of splenectomies in the series was high: 56.9%. As the location of the aneurysm on the splenic artery was not known in most cases, it is not possible to comment whether some of these splenectomies could be avoided. It has been reported in series of splenorenal bypass procedures that, provided that the splenic artery is transected proximal to the left gastroepiploic artery, this is well tolerated and no splenectomy is indicated.[54] Finally, although there were some studies reporting that the post-embolization syndrome (PES) occurred more frequently in treated aneurysms located in the splenic hilum, no studies reported differences in mortality between aneurysms located in different segments of the splenic artery.[5,22,46,49]

One final caveat is with regards to the type of articles included in this meta-analysis. Since most articles in our meta-analysis were retrospective, treatment of SAA was not randomized and the indication for treatment may be primarily based on the risk of future events. The resulting imbalance in the underlying risk profile between the EV and OPEN groups can generate bias by indication. However, the only difference in baseline characteristics between the groups was the number of ruptured aneurysms, and an analysis stratified for rupture vs. non-rupture was performed to prevent this type of bias.

There is no Level 1 evidence comparing the treatment options for the management of true SAAs and this current study provides the most extensive overview of the current literature. The only prospective randomized comparison for the management of SAAs was a comparison of open and laparoscopic intervention for true SAAs.[39] However, we did not include laparoscopic intervention in our analysis, since there are only two studies reporting more than ten patients which we feel will increase the uncertainty for the pooled outcomes and will decrease the quality of this meta-analysis. Laparoscopic aneurysm repair of the splenic aneurysm is the most performed laparoscopic intervention of all aneurysms because of the easy-to-access location.[55] The largest study of laparoscopic interventions, consisting of 16 patients, reported no conversions, need for re-operation or related mortality.[56]

The interesting fact that more people developed minor complications in the EV group compared to the OPEN group has not been extensively discussed in previous papers. No significant difference was found between the number of major complications between OPEN and EV. Still, most reviews report a "higher morbidity and mortality" for patients treated with OPEN.[51,57] In this meta-analysis, we included PES as a minor complication, which can be responsible for this higher number of minor complications. PES, which can present as fever, abdominal pain, pleural effusion, and possibly pancreatitis after splenic infarction, is the most common complication after EV and can potentially require prolonged hospitalization. It is reported in up to 30% of patients, which is similar to the 25.1% reported in this meta-analysis.[41] It must be noted that most OPEN repairs included splenectomy as part of the procedure which prevents post-embolization syndrome.

This meta-analysis, which pooled the characteristics and outcomes of all the available data in the literature is descriptive rather than prescriptive. Therefore, it is not possible to guide treatment based on this meta-analysis. Currently, it is the general consensus to treat all patients with symptomatic and ruptured aneurysms and asymptomatic patients with a splenic artery aneurysm exceeding 2.0cm. Additionally, it is recommended that female patients of childbearing age who present with aneurysms smaller than 2cm in diameter should be treated in anticipation of future pregnancy.[46] However, it is not clear whether these treatment recommendations are similar for elderly or high-risk patients. Future research, with a more individual-based approach should give these answers. Additionally, there is currently no evidence to support the superiority of stenting or embolization. Surgical excision of the SAA is recommended when the pancreas is not close to the aneurysm, both proximally and distally. Proximal and distal ligation of the artery is recommended when the aneurysm is close to the pancreas. Splenectomy will be required if aneurysm is located in the hilus of the spleen.[58]

A lot of questions remain regarding the optimal treatment of true SAAs, and one cannot make recommendations tailored to the patient based on these results. The decision about which intervention would be preferred in a 50-year-old low risk woman would be different from a 90-year-old high-risk man. Furthermore, it is not only the morbidity, mortality and number of reinterventions which are important considerations, but also the quality-of-life, associated interventional and life-time costs and expected reinterventions over the remaining lifetime. All three major treatment modalities have pros and cons and a well conducted risk-benefit analysis could be performed with a clinical decision model to create patient-tailored recommendations for treatment of true SAAs. Finally, the long-term importance of splenectomy on, for example, post-splenectomy infection and prevention of sepsis in asplenic patients, should be assessed in future research.

CONCLUSIONS

EV of the SAA has better short-term results compared with OPEN, including a significantly lower perioperative mortality. However, OPEN is associated with less late complications and less reinterventions during follow-up. Patients treated with conservative management showed a higher late aneurysm-related mortality rate. These patients were usually older, have smaller aneurysm sizes compared with patients in the OPEN and EV groups and had fewer symptoms and ruptures. Other than the difference in number of ruptured SAAs, there were no significant differences between the OPEN and EV groups. Ruptured splenic aneurysms are predictors for a significant higher perioperative mortality compared with non-ruptured aneurysms, in both the OPEN and EV group.

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APPENDIX

Figure 1

Database	Number retrieved	After duplicates removed
Embase.com	1,121	1,116
Medline (OvidSP)	535	83
Web-of-science	312	77
Scopus	615	183
PubMed as supplied by publisher	17	8
Cochrane	2	1
Google Scholar	100	22
Total	2,702	1,490

Embase.com 1,121

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Medline (OvidSP) 535

((("splenic artery"/ OR spleen/) AND (aneurysm/)) OR ((spleen OR splenic) ADJ3 aneurysm*).ab,ti.) AND (exp therapeutics/ OR therapy.xs. OR exp "Surgical Procedures, Operative"/ OR surgery.xs. OR methods/ OR methods.xs. OR (therap* OR treat* OR curing OR cure OR repair OR technique* OR procedure* OR equipment* OR surg* OR operat*).ab,ti.)

Cochrane 2

(((spleen OR splenic) NEAR/3 aneurysm*):ab,ti) AND ((therap* OR treat* OR curing OR cure OR repair OR technique* OR procedure* OR equipment* OR surg* OR operat*):ab,ti)

Web-of-science 312

TS=((((spleen OR splenic) NEAR/3 aneurysm*)) AND ((therap* OR treat* OR curing OR cure OR repair OR technique* OR procedure* OR equipment* OR surg* OR operat*)))

Scopus 615

TITLE-ABS-KEY((((spleen OR splenic) W/3 aneurysm*)) AND ((therap* OR treat* OR curing OR cure OR repair OR technique* OR procedure* OR equipment* OR surg* OR operat*)) AND (clinical* OR patient* OR trial* OR retrospect* OR prospect*))

PubMed as supplied by publisher 17
(((spleen OR splenic) AND aneurysm*[tiab])) AND ((therap*[tiab] OR treat*[tiab] OR curing[tiab] OR cure[tiab] OR repair[tiab] OR technique*[tiab] OR procedure*[tiab] OR equipment*[tiab] OR surg*[tiab] OR operat*[tiab])) AND english[la] AND publisher[sb]

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surgery|surgical|operative) (clinical|patient|patients|trial|retrospective|prospective)

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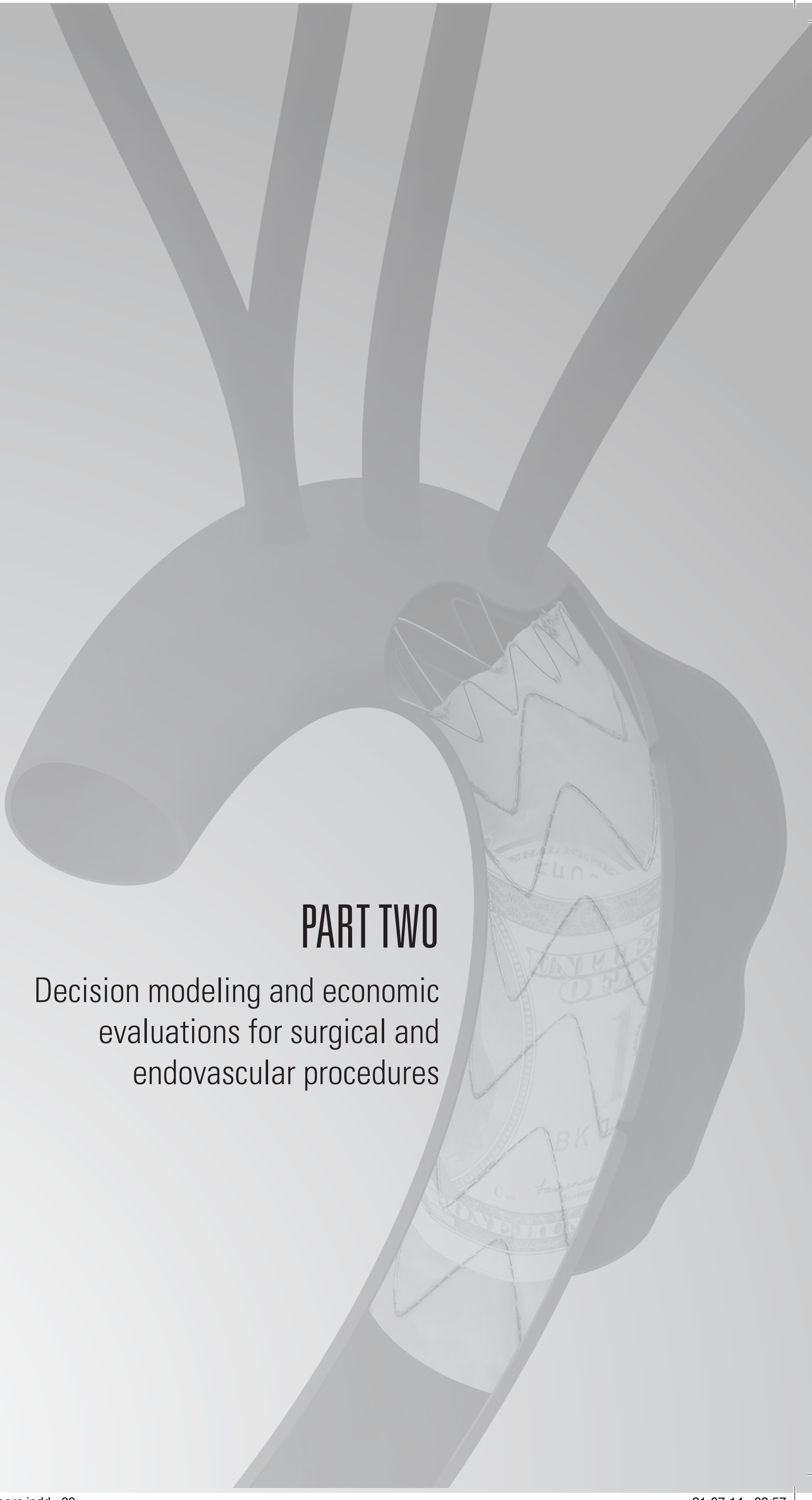

PART TWO

Decision modeling and economic evaluations for surgical and endovascular procedures

CHAPTER 7

Clinical decision analysis for surgeons: An introductory overview

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ABSTRACT

This paper addresses the use of decision analysis and Markov models to make contemplated decisions in surgical problems. Decision analysis and decision modelling in surgical research is increasing, but many surgeons are unfamiliar with the techniques and skeptical of the results. The goal of this review is to familiarize surgeons with terms and definitions used in decision analytic papers, to provide the reader a practical guide to read these papers, so that he/she can understand the conclusions in such reports and assess the quality of the clinical decision models published in the surgical literature. First, a brief explanation of decision analysis and Markov models is presented in simple steps, followed by an overview of the components of a decision and Markov model. Subsequently, more detailed, but commonly used terms and definitions are described and explained including quality-adjusted life years, disability-adjusted life years, discounting, half-cycle correction, time period, probabilistic sensitivity analysis, incremental cost-effectiveness ratio and willingness-to-pay. Finally, the advantages and limitations of research with Markov models are described and future perspectives and new modelling techniques will be discussed. It is important that surgeons and other clinicians are able to understand conclusions from decision analytic studies and mandatory that they are familiar with the specific definitions mentioned in this introductory overview in order to keep up with surgical research. Decision analysis can guide treatment strategies when complex clinical questions need to be answered and is a necessary and welcome addition to the surgical research armamentarium.

INTRODUCTION

Making decisions in surgical practice involves careful analyses of benefits and harms following several different treatment options. In surgery, these decisions are frequently, but necessarily, made in the face of uncertainty because of limited information, an incomplete clinical picture and the time-sensitive setting. However, making the right decision is important because of both short- and long-term consequences. The perspectives of the patient, the healthcare system, and society in general are all relevant to the decision. An objective analysis of expected outcomes from different perspectives based on the best-available evidence and patient values and preferences is essential to decide on the optimal treatment option.

Making decisions is part of daily practice of the surgeon. Almost all surgical decisions are made in the face of uncertainty, and based on a combination of clinical experience and research results (evidence based medicine (EBM)). Traditionally, randomized controlled trials (RCTs) provide the highest level of evidence,[1] although this is not always available, especially in surgical practice because of the time-limited setting. Since EBM plays an increasingly important role for surgeons, clinicians in general, patients, healthcare insurance companies and policy-makers, alternatives for evidence when RCTs are lacking are required, although decision models also use the evidence from RCTs where available.

With the increase of treatment options there will also be an increase in choices, decisions and costs. When there is no Level 1 evidence available, clinicians have the disposition to make uninformed, complex decisions based on clinical experience, which will have a huge impact on outcomes, costs and quality of life of the patient. Intuition is not a good advisor when it comes to complex decisions.[2] Therefore, decision analysis for EBM is currently increasingly utilized. The aim of this review is to give the clinician an introductory overview of clinical decision analysis and Markov modelling and to emphasize the importance of understanding decision models by providing a practical step-by-step guide of clinical decision models.

What is decision analysis?

Decision analysis is defined as a systematic, quantitative approach to decision making under situations of uncertainty.[3] This technique is ideal for answering all kinds of clinical problems, because of the certain uncertainty around surgical practice. The goal is to analyze the different treatment options and choose the optimal strategy based on maximizing benefit and minimizing costs by taking into account morbidity, mortality, quality of life, costs and expected reinterventions. The last decades, the use of decision analysis is increasingly utilized and is becoming more-and-more an accepted technique. In Figure 1, the increase of decision analytic papers is shown by performing a search on PubMed including the keywords "*decision model*", "*decision analysis*", "*Markov model*", "*decision analyses*" and "*cost-effectiveness analysis*". An increase from a few hundred papers in the late '80s to more than 10,000 decision analytic papers now can be seen. Nevertheless, many surgeons are unfamiliar with the methods used. With the following step-by-step guide we want to increase the familiarity of decision models applied to surgical problems.

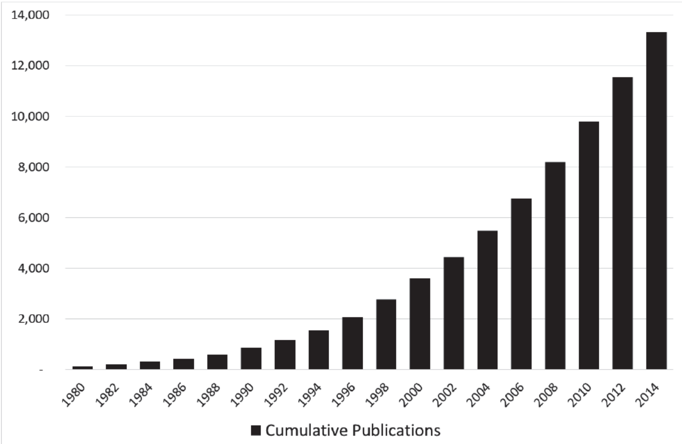

Figure 1a Cumulative number of publications of decision analysis papers by year of publication.

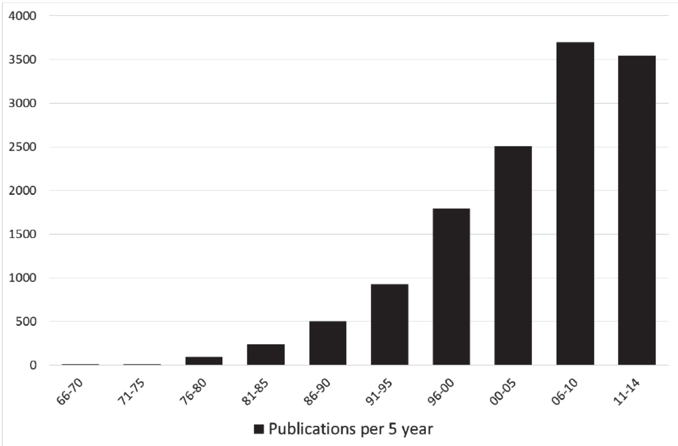

Figure 1b Number of publications of decision analysis papers by five year time interval.

How to create a decision analysis model

Traditionally, decision analysis can be summarized in four basic steps which will be discussed below and is briefly reported in Table I.

1) Define the problem and list the options. First, one needs to identify and define the problem and goal. This needs to be done from several viewpoints and a specific patient group needs to be determined. Is the goal to increase the health, to decrease the costs or to prevent a certain complication? This needs to be exactly determined. Afterwards, what are the (treatment) options? In vascular surgery for example, the three most evaluated treatment options with decision models are open repair, endovascular repair and conservative management.[4-6] However, other options, such as laparoscopic repair or two different open surgical procedures can be evaluated.[7,8] For each of the treatment options it is necessary to list the pros and cons and all

Table I Brief overview of steps for creating a Markov model for a clinical problem.

Step	Explanation	Tools
Define the problem and list the options	What is the problem? What happens if no action is taken? Who is involved and which perspective? What is the goal? Increase effect? Decrease costs? Less reinterventions? What are the treatment options? What are the pros and cons of these treatment options?	Discuss the options with experts. Brainstorm. Make a clear overview of the problem and treatment options.
Model the consequences	What are the possible consequences following each of the treatment options? What are the possible outcomes? What are the long-term possibilities? What type of model do I need? What cycle length? Do I need to make assumptions?	Create a model. Long-term outcome: Markov model. Short-term: Decision tree. List assumptions made in the model.
Find the evidence and enter it in the model	What are the probabilities for moving from state to state? What is the quality of life value for the health states? What is the life expectancy? Which costs are involved and which should we use? Discounting?	Meta-analyses. Own clinical data. Expert opinion. Quality of life value. Cost-analysis. Guesstimate.
Determine the preferred treatment	What is the outcome? Does it make sense? What if we increase a certain probability, does the outcome increase/decrease as expected? What if the patient is different: older, female instead of male or a high risk patient? Does it change the optimal treatment option? Can the outcome be optimized? Is further research necessary? Is the cost of future studies justified?	Integrate all the outcomes (QALYs, NHB). Analyze reference-case. Choose optimal treatment. Perform one- and multi-way sensitivity analysis. Validation of the model. Probabilistic sensitivity analysis. Value of information analysis.

the possible events and outcomes for each treatment strategy. It is essential to realize that each decision has a consequence. Additionally, decision analysis should not be used when clinical studies clearly indicate the optimal treatment option, but should be used to evaluate trade-offs. Determination of the perspective of the decision analysis should be clearly stated. Is the decision maker a clinician who wants to optimize the health of the patient or a policy maker, trying to reduce the national health care costs?

2) Model the consequences. The structure of the decision model is the key in any decision analysis. Historically, the simple decision tree was used to evaluate different treatment options. However, there are some inherent limitations to decision trees for complex clinical questions, including usually the limited time horizon. Decision trees, however, are helpful for clinical problems with a short time horizon. When the clinician wants to model the prognosis or long-term outcomes, one can choose for a Markov model. Since the introduction of Markov models in medical decision-making, thirty years ago,[9] Markov models have been applied with increasing frequency. Therefore, this paper will mainly discuss decision analysis using a Markov model. Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once, which both are the case in chronic diseases.[10] Markov models assume that a patient is always in one of a finite number of discrete health states, from perfect health to death, and all possible events are modeled as transition from one health state to another health state. All the health states are related to the studied disease and present the natural history. As shown in Figure 2, every year (one-year cycles are usually used, but any time frame can be used) the patient has a chance to move from the *Sick* health state to the *Well* health state (X%), to the *Dead* health state (Y%) or remain in the *Well* health state (Z%).[10]

The advantage of Markov models over simple decision trees is that decision trees cannot model risks over time and unrealistic simplifying assumptions may be required, such as a short time horizon. Markov models can involve risks that are changing over time, which is important to calculate, and are able to let the patient reenter the health state every 'year', which is impossible in decision trees with one end point. The moment that an event occurs may be very important for the total effect of the intervention. For example, a patient with an abdominal aortic aneurysm (AAA) is at risk for a rupture, but the time at which the possible rupture will occur is uncertain. This has important consequences, because this will have impact on the quality of life. One can imagine that an immediate ruptured AAA will have a completely different impact on the patient compared with a rupture fifteen years from now, on both the health of the patient and the health care costs. Additionally, aortic-related complications can occur more than once, which cannot be modeled with decision trees, but can be with Markov models. Depending on the goal of the study, a time limit can be set, for example the total expected costs in the next ten years or during the remaining lifetime. More detailed information of Markov models will be discussed later on in this paper.

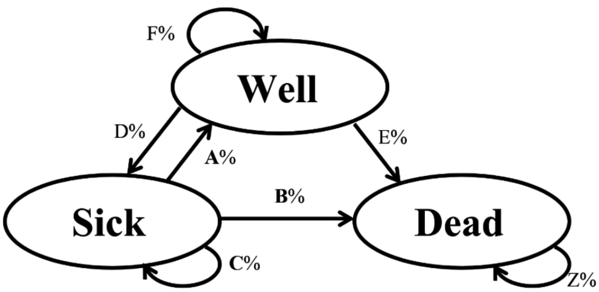

Figure 2 Overview of a simple Markov model shown in a bubble diagram. Every cycle (one-year cycles most commonly used, but any time period can be used), if the patient is in the Sick health state, the patient has a chance to move from the *Sick* health state to the *Well* health state (A%), to the *Dead* state (B%) or remain in the *Sick* health state (C%). The same applies to a patient in the *Well* health state: this patient has a chance to move from the *Well* health state to the *Sick* health state (D%), to the *Dead* state (E%) or remain in the *Well* health state (F%). The *Dead* state is an absorbing health state: patients in this health state always stay in this health state (Z%).

Although Markov models can vary from very simple models11 to complicated detailed models[12], the model has to include at least the following five components. First, the clinical starting point (the problem and goal), (2) the different treatment options the clinician wants to evaluate, which are depicted by the first branches, (3) all the possible events that follow the assessed treatment options, (5) the health states a patient can end up and (5) all the possible outcomes such as the quality of life of the patient, the total costs or the number of reinterventions.

3) Find the evidence and enter it in the model. When the structure of the model has been created, one can start with updating the model with the input variables: probabilities, costs, quality of life values. For example, one needs to know the probability that a patient can die from an intervention, the chance on long-term complications and the percentage of patients that require a reintervention within the first five years. For costs, one needs to include, for example, costs of the intervention, costs of hospital stay per day and length of hospitalization. Also quality of life is important, since an uncomplicated recovery will yield higher effectiveness compared with patients suffering from paraplegia for the rest of their lives. The outcomes in decision models are usually given in quality-adjusted life years (QALYs), and if it is a cost-effectiveness analysis in QALYs and costs, but also other outcomes such as number of reinterventions, and life-expectancy are used. Total QALYs for treatment options are calculated by the length of stay in a health state multiplied by the QoL value for that specific health state. The QoL value, or utility, of a health state is per definition a value between 1 and 0, with 1 being in perfect health and 0 dead. It has been proposed, however, that health states with a QoL value lower than zero do exist, for example in case of extreme torture, vegetative states, or major depression.
Data to enter in the decision model can be derived from published studies, for example meta-analyses[13] following the EBM-hierarchy, from own clinical data[14] and in case no published data and no own clinical data is available, a guesstimate should be considered. For all the input data applies that the larger the sample size of the group from which the probability has been derived, the less the uncertainty around the variable value. For all the necessary input variables the first analysis is performed with the most likely probability for each of the variables, in the reference-case analysis. It is common to include all the used (point estimate) input variables (probabilities, costs, quality of life values) and their ranges in a table in the paper of the study, accompanied by the references. This is done so the clinician or expert on the topic can assess the quality of the input variables, which is important, since the quality of the input data largely determines the quality of the decision analysis.

4) Determine the preferred treatment. We now have formulated the research question, determined the goal, created the structure of the decision model and populated the model with all the necessary input variables and time has come to analyze this decision model. Commercial statistical software packages are available to perform the analysis. After having created a complete model and debugging the theoretical model one can start with analyzing the reference-case with the most likely values for each of the input variables. Depending on your goal, the decision model selects the preferred treatment based on highest effect (highest QALYs), lowest costs, least number of reinterventions or other predetermined outcomes. **Quality-adjusted life**

years (QALY) are calculated by the length of stay in a health state multiplied by the utility (quality of life value) for that specific health state. However, some other related definitions are less well-known. One of these terms is the DALY (**disability-adjusted life year**).[15] The DALY is conceptually the opposite of QALY: whereas the QALY represents years of life gained (adjusted for quality), the DALY is the number of years of life and ability lost, however, DALYs are usually use on the population level and QALYs on the individual level.
Since one is not sure that the used point-estimate probability is exactly that probability (e.g. perioperative mortality: 5%), and the value is more likely to contain a range of values (e.g. perioperative mortality: 2% – 8%), **sensitivity analysis** for each of the input variables has to be performed. With sensitivity analysis one can analyze the impact of change of a certain variable on the preferred treatment strategy and can tell something about the robustness of the conclusions of an analysis over a range of structural assumptions, probability estimates or outcome values. With one-way sensitivity analysis the impact of one of the variables at a time can be analyzed, with two-way sensitivity analysis the impact of two variables at the same time (for example, the chance on operation and the chance on major complications during operation can be analyzed) and with multi-way analyses, the effect of chance of multiple variables at the same time can be assessed.
And finally, the strength of Markov models is **probabilistic sensitivity analysis**. Probabilistic sensitivity analysis provides a useful technique to quantify the level of confidence that the decision-maker has in the conclusions of an decision analytic evaluation.[16] In general, each input variable is assigned a point estimate value in the reference-case analysis, as described previously. For example, the perioperative mortality of an intervention is 5% reported in a meta-analysis. The meta-analysis may, however, also have published the level of confidence around that estimate. For example, it might be reported that the 95% confidence interval is 4.1% to 7.2%. With probabilistic sensitivity analysis, a distribution is assigned to all input variables rather than assigning a single value to each input variable. Some considerations should be noted, for example, probabilities must always remain between 0 and 1, while costs should always be positive. Each time the model is run, the software will be able to randomly 'select' one value for each parameter and record the model's results. The decision model runs a large number of times (the number most commonly used is 10,000 samples), and the decision analytic software program will report the result of each of the outcomes, and present the variation in results. In most decision models, the 95% CI is not an abbreviation of confidence interval, but of **95% credibility interval**, which reflects the uncertainty around the input variables. The results of these 10,000 samples are typically presented using a cost-effectiveness scatter plot (Figure 3).[6] To compare two treatment strategies, each sample of both interventions is plotted on a graph showing the incremental costs and incremental effectiveness of the evaluated treatment options. For each of the 10,000 samples, the difference of the costs between the two treatment strategies is divided by the difference in QALYs between the two treatment strategies to calculate the **incremental cost-effectiveness ratio (ICER)** (Figure 4). The ICER is used to analyze the cost-effectiveness of the new treatment intervention. The evaluated treatment intervention is considered as cost-effective when the costs for the new treatment are lower and the effectiveness higher and in case the ICER is lower compared with the **willingness to pay threshold** (WTP). The WTP is defined as the maximum amount that

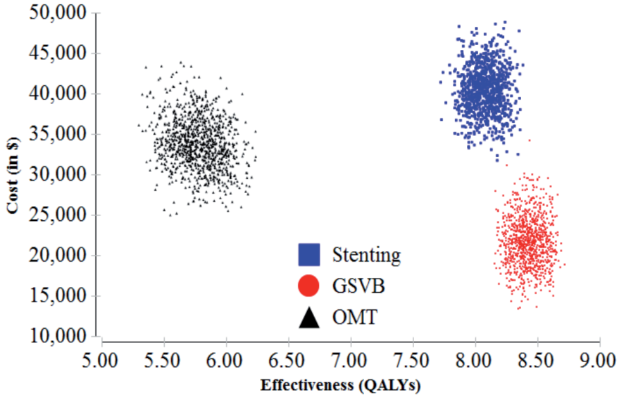

Figure 3 Cost-effectiveness scatterplot of great saphenous vein bypass (GSVB), endovascular repair (Stenting), and optimal medical treatment (OMT) of popliteal artery aneurysms (aPAAs) for 65-year-old patients, based on the model used in reference [6]. Each point represents a single patient value based on the analysis of 10,000 samples with probabilistic sensitivity analysis. Depicted is that GSVB is dominant over the other two treatment options, because the effectiveness is higher and costs are lower. In case no autologous vein is available, stenting is more effective, but also more costly. If stenting is cost-effective depends on the incremental cost-effectiveness ratio (ICER) and willingness-to-pay (WTP).
QALYs, Quality-adjusted life-years.

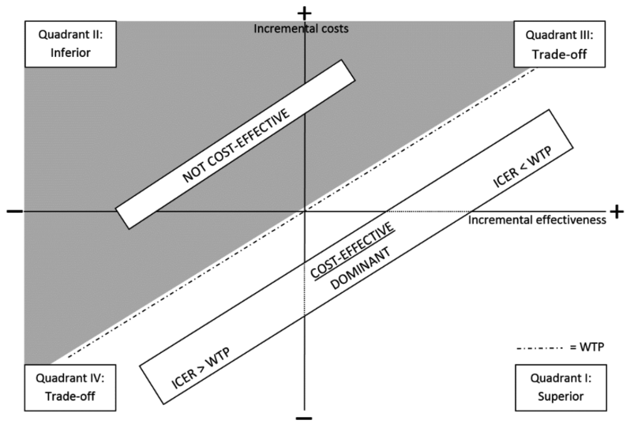

Figure 4 Graph shows trade-off between costs and effectiveness. If both effectiveness is gained and costs are saved with a new treatment strategy, that strategy is superior in terms of cost-effectiveness by dominance. Similarly, if effectiveness of the new treatment is less and costs are increased, the new treatment is inferior. If effectiveness is gained at an additional expense, then we must decide if the additional cost is justified. If the ICER is less than the WTP, we consider the strategy cost-effective.[3]
WTP, willingness to pay; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life year.

society is willing to pay for one additional year in perfect health (1 QALY). The amount of the WTP threshold differs between countries, and no official threshold exists, due to lack of explicit scientific evidence.

Frequently reported WTPs are £20,000 – £30,000 UK pounds in the United Kingdom and $50,000 – $100,000 in the United States.[17] For evaluating interventions in developing countries, the World Health Organization (WHO) reports the following general guidance: an ICER of less than the gross domestic product (GDP) per capita is considered very cost effective, between 1 and 3 times GDP is cost effective, and more than three times GDP is not cost effective.[18] The WTP threshold is included in Figure 4 with the diagonal line, and is, in this example, set to $60,000/QALY. In general, the higher the WTP, the more samples are considered cost-effective, since that means one wants to pay more for an additional year in perfect health (1 QALY). The advantage of calculating the ICER is that the ICER of the presented study can be compared with ICERs of other published studies, on the same topic, or on other medical topics. This can be useful for clinicians or policymakers if there is not enough money to fund all research projects or developments of new medical devices or medication, and a decision can be made based on which project can yield the most additional QALYs with the available monetary funding. A list of the most commonly used terms is given in Table II.

Advantages and limitations of decision models

There are numerous advantages and limitations of decision analysis. The greatest advantage is that clinical decision problems can be structured stepwise in a logical fashion. Clinicians are faced with decisions every day and the increase in options also increase the number of choices. Simple choices can be made based on one's own expertise, but for more complicated questions, decision analysis can guide the clinician towards the preferred treatment option. Introduction to the terminology of decision analysis can increase the awareness of the importance of decision models.

In a decision model, one can identify the trade-off of the decision problem, and which details should play a major role in deciding on the preferred treatment. Additionally, one knows that endovascular interventions, in general, do have better short-term outcomes (less perioperative morbidity and mortality), but less favorable long-term outcomes (more reinterventions and device-related complications) compared with open interventions. But for which patient is endovascular treatment preferred? With decision analysis one can objectively determine a threshold and not just subjectively decide on this important decision with major consequences. Furthermore, if the uncertainty about the outcome is large, and this is because there is not enough information for one of the variables (for example, chance of stroke during an intervention), decision analysis can also guide clinicians in the direction of novel research topics, which can prevent unnecessary future research.

Despite the previously mentioned advantages, there are also limitations to decision modeling. The first and most important limitation is that decision models are complex. With a decision model, one attempts to create a real-life model, but recreating reality is impossible. Therefore, assumptions have to be made to keep the decision model workable and tractable, for example, when the necessary input variables are not available and one needs to make an assumption. For example, the patency rates of endovascular repair of popliteal artery aneurysms are not available and the investigators decided to use a constant hazard rate of the patency rate in the fifth year, for patency rates after five years.6 These assumptions must be discussed with a multidisciplinary team to include all perspectives and clearly stated in each decision analytic paper to inform the reader.

Another limitation is that surgeons and other clinicians consider these models as a 'black box' and don't understand what is happening. It is important that the outcomes show face validity, in other words, that the outcomes make sense. Furthermore, clinicians should not use outcomes of decision models instead of their clinical experience, but it can be a helpful tool to understand which determinants play a major role in making the decision.

Table II Definitions commonly found in papers using Markov models or decision analysis.

Term	Meaning
Discounting	A process for computing how much a quantitative measure of resource cost or health outcome at some point in the future is worth today.[3] It is usually applied to both costs and effectiveness to adjust future effectiveness and costs because life-years and cost in the near future are considered to have more value than life-years and cost in the distant future.[22] Discount rates between 1% and 10% have been reported, but the most commonly used percentage is 3% on both costs and effect.[23] However, differences between countries exist and differences between cost discount and effect discount are also frequently reported.
Time period / Cycle length	The most commonly used time period is a 1-year interval, but it can be as short or long as the decision-maker wants. In case another time period is used, it is important to adjust all the input variables (costs, probabilities, utilities) to the time period used.
Half-cycle correction	Is applied to prevent overestimation or underestimation, because most events generally do occur throughout a cycle and not only at the beginning or end.
Quality adjusted life years (QALYs)	Are calculated by the length of stay in a health state multiplied by the utility (quality of life value) for that specific health state. The cycle sum is added to a running total that is referred to as the cumulative QALYs.
Sensitivity analysis	Any test of the robustness of the conclusions of an analysis over a range of structural assumptions, probability estimates, or outcome values.
Probabilistic sensitivity analysis (PSA)	Uncertainty of all input variables is modeled with probability distributions of their values. For each run of the model, a value of each input variables is randomly picked from the distribution of the value.
Incremental cost-effectiveness ratio (ICER)	The difference of the costs between two treatment strategies divided by the difference in effectiveness between two treatment strategies: $ICER = \frac{\bar{C}_2 - \bar{C}_1}{\bar{E}_2 - \bar{E}_1} = \frac{\Delta C}{\Delta E}$
Willingness to pay threshold (WTP)	The maximum amount that society is willing to pay for one additional year in perfect health (1 QALY).

FUTURE PERSPECTIVES

Not every surgeon should be able to conduct their own decision analysis, but must be able to understand, and if necessary, review decision models. Currently, more and more guidelines for decision models and cost-effectiveness analysis are being published, and helpful checklists are available to assess the quality of these analyses.[19]

The progress of Markov models and decision analysis is still evolving and more and more modelling techniques are reported and important. One of the most important techniques nowadays is validation of the model. There are several type of validation. The first type of validation, face validation, refers to the structure of the model and the input variables. Based on the data, assumptions and the structure, the results should make clinical sense. If the model provides unexpected results, is there a 'probably a mistake in the model or the model can suggest additional research that may clarify the etiology of the discrepancy? The second type of validation, internal validation, means that mathematical calculations used in the model are correct and consistent. Any equations or parameters used in the model should be compared to the original source data. Hunink et al.[3] reported standard methods for testing for internal validity and should include a structured walk-through, where the model is explained to another person so that both may detect errors during that walk-through and manual verification of the model, where the model is evaluated and the outcomes are compared with hand-calculated estimates or with estimates from another available Markov model. Sensitivity analysis, which is described earlier, should be performed and assessed if the outcomes make sense, in other words, if the perioperative mortality increases, the effectiveness should decrease and extreme analysis should be performed, wherein model behavior with input values well beyond their normal range should be examined. Finally, external and predictive validation should be performed. With external validation, the model should be compared to actual observed events such as the number of expected reinterventions in the model and actual reinterventions from a clinical trial. These comparative data should not have been used in the model, because otherwise it can influence the model. Lastly, predictive validation is the strongest form of validation and assesses the ability to predict future events. Examples are when models are developed to mimic planned clinical trials prior to their results becoming available or when a model extrapolates outcomes from a randomized trial with limited follow-up duration, but extended follow-up subsequently occurs in that randomized trial and these outcomes are compared later.

Since more and more research is performed, tons of information is accumulated, and more information usually means more evidence and less uncertainty in Markov models. However, performing more research to decrease uncertainty is justified only if the expected benefit to future patients exceeds the cost of performing the research, especially with the ever increasing healthcare costs in mind. Therefore, it is essential to know how much future research can contribute in optimal decision making. **Value of information analysis** estimates the expected benefit of obtaining more information through future research, but is not the actual value of future research, since prediction of future research is impossible. Instead, the value of information is the expected value of future research. Value of information analysis is performed to determine whether future research is justified and to guide the design of a new study. The new study is performed, and the information obtained is incorporated into the model. This process is repeated over and over until the cost of the future studies are higher than the benefit from obtaining more information. Besides this, creating Markov models can also detect gaps in surgical research. When creating a model, and no or almost none information is available this creates a new research topic.

Outcomes of decision models can also be used for communication with the patient. A study of thoughts of surgeons on shared decision-making (SDM) showed that ninety-one per cent of the clinicians agreed with the concept of SDM.[20] Shared decision-making is increasingly important and several tools can be used for patient-centered care, for example with an easy to use treatment strategy decision chart.[5] If a decision is shared, there is a greater chance that it will increase patient satisfaction, and can potentially lead to a quicker recovery.[21] Additionally, outcomes of Markov models can be made available to the public and integrated in web-based tools and mobile applications. Patients searching for information on the internet can easily fill in their variables and see their preferred treatment options. However, these options are still in its infancy and can and should not replace the contact between the patient and the clinician.

CONCLUSION

Decision analysis studies are increasingly found in surgical literature. It is important that surgeons and other clinicians are able to understand conclusions from decision analytic studies and mandatory that they are familiar with the specific definitions mentioned in this introductory overview in order to keep up with surgical research. Decision analysis can guide treatment strategies in case complex clinical questions need to be answered and is a necessary and welcome addition to the surgical research armamentarium.

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CHAPTER 8

A comparison of open and endovascular revascularization for chronic mesenteric ischemia in a clinical decision model

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ABSTRACT

Objective

Open revascularization (OR) has been the treatment of choice for chronic mesenteric ischemia (CMI) for many years, but endovascular revascularization (EV) has been increasingly utilized with good short-term results. In this study we evaluated the comparative effectiveness and cost-effectiveness of EV and OR in patients with CMI refractory to conservative management.

Methods

A Markov-state transition model was developed using TreeAge Pro 2012 (TreeAge Inc., Williamstown, MA) to simulate a hypothetical cohort of 10,000 65-year-old female patients with CMI requiring treatment with either OR or EV. Data for the model, including perioperative and long-term overall mortality risks, disease-specific mortality risks, complications and reintervention and patency rates, were retrieved from original studies and systematic reviews about CMI. Costs were analyzed using the 2013 Medicare database. Outcomes evaluated were quality-adjusted life years (QALYs), costs from the healthcare perspective and the incremental cost-effectiveness ratio (ICER). Extensive sensitivity analyses were performed and different clinical scenarios evaluated. Probabilistic sensitivity analysis was performed to assess robustness of the model.

Results

For a reference-case 65-year-old female patient with CMI and an average risk for operation, EV is preferred with 10.03 QALYs (95%CI: 9.76 – 10.29) vs. 9.59 after OR (95%CI: 9.29 – 9.87). The difference is comparable to 5 months in perfect health: 0.44 QALYs (95%CI: 0.13 – 0.76). For 65-year-old men, this was 8.71 QALYs (95%CI: 8.48 – 8.94, EV) vs. 8.42 (95%CI: 8.14 – 8.63, OR). Sensitivity analysis showed that for younger patients, EV results in a higher increase in QALYs compared with older patients. Total expected reinterventions per patient are 1.70 for EV vs. 0.30 for OR. Total expected healthcare costs for the reference-case patient were $39,942 (95%CI: $28,509 – $53,380) for OR and $38.217 (95%CI: $29,329 – $48,309) for EV. For men, this was $39,375 (95%CI: $28,092 – $52,853) for OR and $35,903 (95%CI: $27,685 – $45,597) for EV. For patients younger than 60 years, EV is a more expensive treatment strategy compared with OR but with an ICER for EV of less than $60,000/QALY. For patients 60 and older, EV dominated OR as preferential treatment, because effectiveness was higher than for OR and costs were lower.

Conclusion

The results of this decision analysis model suggest that EV is favored over OR for patients with CMI in all age groups. Although EV is associated with more expected reinterventions, EV appears to be cost-effective for all age groups.

INTRODUCTION

Chronic mesenteric ischemia (CMI) is an uncommon disease caused by stenosis or occlusion of one or more visceral arteries, including the celiac, superior mesenteric (SMA) and inferior mesenteric arteries. Flow is usually limited in at least two of the three mesenteric vessels before symptoms occur, due to the presence of extensive collateralization.[1] CMI, or intestinal angina, causes postprandial pain, usually within the first hour, which could lead to food aversion, malnutrition and weight loss in more than 80% of patients.[1,2] Ultimately, this may lead to acute bowel infarction, potentially resulting in perforation, sepsis and subsequent death.[3] To treat symptoms and prevent complications, revascularization is usually required.[4]

Open revascularization (OR) of the visceral vessels, including endarterectomy, direct reimplantation and bypass grafting, has been the treatment of choice for many years.[5] Endovascular revascularization (EV) was described in 1980 and is now increasingly utilized.[6] Since 2002, angioplasty and/or stenting of the visceral arteries, has been performed more frequently than OR[7] and several large studies reported good short-term results.[8,9]

Unfortunately, there is currently no Level 1 evidence available comparing these two CMI treatment modalities. Furthermore, most studies have focused on survival, patency rates or reinterventions as outcomes, but studies assessing quality of life (QoL) and costs are lacking. The primary goal of this study was to compare effectiveness of EV and OR with respect to quality-adjusted life years (QALYs) for patients with CMI refractory to conservative management by means of a decision analysis. The secondary objective was to determine the cost-effectiveness of the different treatment strategies.

METHODS

A Markov cohort model was developed using TreeAge Pro 2012 software (TreeAge Inc., Williamstown, MA, USA) to simulate a hypothetical cohort of 10,000 65-year-old female patients with CMI refractory to conservative management and requiring an intervention. A Markov cohort model is a convenient way to analyze the prognosis for clinical problems with risks that change over time. The Markov model assumes that a patient is always in one of a finite number of discrete health states. All possibilities are modeled as transitions from one health state to another. Each health state is assigned a QoL value (utility), and the contribution of this QoL-value to the overall outcome of the different strategies depends on the time spent in the health state.[10]

Two different treatment strategies were assessed: OR and EV. The primary outcome was QALYs. Secondary outcomes were total expected lifetime costs, cost-effectiveness of the different treatment options and expected reinterventions. Data and probabilities to populate the decision model, including perioperative mortality risks, technical failures, complication and reintervention rates, disease-specific mortality and patency rates, were retrieved from a recent and extensive meta-analysis for CMI, which provided a summary of best available current evidence.[11] The most contemporary data from this article were used in the model. Variables that were not explicitly reported in the meta-analysis were obtained by performing additional analyses of the original articles that were used in the meta-analysis. The ranges of values of the variables derived from these articles were used to perform one-way, two-way and multi-way sensitivity analyses of the model. These data are summarized in Table I.

Decision model

In the model, all patients started with an intervention (OR or EV, as determined by the assigned treatment group) and transitioned to other health states after this intervention. The possible transitions between the health states are shown in Figure 1. After an intervention, patients could recover completely without complications (*well postoperative*), they could have major, long-term systemic complications (e.g. stroke, renal failure needing dialysis; *major complications*), additional partial bowel resection (*bowel resection*) or they could die (perioperative mortality; *death*). Bowel resection was a specific health state, which was not included in the *major complications* state because of its relevance to CMI. Once patients entered into the *major, long-term complications*, they could no longer regain good health status. Another possible health state for the EV group after intervention was *conversion to OR*.

Patients in the *well postoperative* health state could remain in this health state if the treated vessel remained patent or if they were asymptomatic. If the patient became symptomatic and an additional intervention on the treated vessel was required, this could be either OR or EV. After these interventions, the same health state options were possible as after the initial intervention. Possible options for patients in the *bowel resection* health state were the same as for the *well postoperative* health state and recurrent mesenteric insufficiency subject to reintervention was also possible. The last possible health state was the *bowel resection + major complications* health state for patients who undergo bowel resection and suffered a major complication.

The model cycled at 1-year intervals with a half-cycle correction, until all patients in the model were categorized as dead. Half-cycle correction was applied to prevent over- or underestimation, because most events generally do occur throughout a cycle and not only at the beginning or end.[12] To keep the model manageable, assumptions were made: 1) No distinction was made between different types of OR. In a report of 16,000 patients who underwent OR for CMI, the majority were treated with bypass (93%) compared with endarterectomy (4%) or embolectomy (3%).[7] No distinction was made between different types of EV treatment. 2) Postoperative mortality was described as 30-day mortality. 3) Loss of patency of the treated vessel during follow-up was considered to be symptomatic and requiring a reintervention. 4) Patency rates are not consistently described in the literature with some reports utilizing either primary assisted or secondary patency rates. We use the term secondary patency rate to refer to either primary assisted or secondary patency since the consequences are similar. 5) Primary and secondary patency rates were assumed to have a constant hazard rate after the fifth year. Only data from patients with classic presentation of CMI were included; acute on chronic patients were omitted from analysis.

Total QALYs for the different treatment groups were calculated by the length of stay in a health state multiplied by the QoL value for that specific health state. A discount rate of 3% was applied to both costs and effectiveness, to adjust future effectiveness and costs because life-years and cost in the near future are considered to have more value than life-years and cost in the distant future.[13]

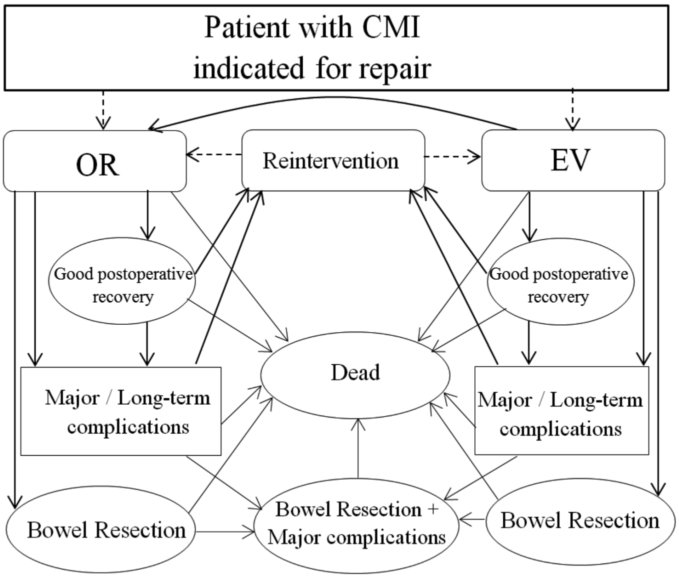

Figure 1 Simplified bubble diagram of the Markov state transition model for treatment of CMI. Each health state has a possible transition to itself which is not shown in this figure for clarity of the figure. The dotted lines indicate the start of the intervention or reintervention. *CMI*, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

Open and endovascular interventions

Table I shows that OR had higher perioperative morbidity and mortality compared with EV, while more reinterventions have been reported for the EV group.[11,14-23] To differentiate the impact of interventions in low- and high-risk patients, perioperative mortality rates were multiplied by relative risks (RR, range 0.5 - 5).

Patency

Patency rates were retrieved from a single report[20] which provided the best available evidence describing patency rates for OR and EV in patients with CMI (Table II). This study distinguished primary and secondary patency rates, which is what is required for the model, whereas the pooled patency rates reported in the meta-analysis[11] combined primary assisted and secondary patency rates as if they were the same outcome. Patency rates beyond five years were not reported and were assumed to have a constant hazard rate. The patency rates reported in the meta-analysis were used in a sensitivity analysis on the patency rates.

Mortality

Age, sex and race specific mortality tables for women and men were retrieved from the Center for Disease Control (CDC).[24] Since long-term mortality rates for patients with CMI is higher compared with the general population, but are not reported, we made an assumption and utilized the disease specific mortality rate for patients with peripheral arterial disease (PAD)[15] and adjusted the CDC mortality tables. In a similar manner, we calculated the mortality rate for patients with major morbidities, by utilizing the disease specific mortality rate for patients with chronic kidney disease. This condition was chosen because it has the most clinical impact long-term among the major complications.[25]

Table I Input variables for open revascularization and endovascular revascularization of chronic mesenteric ischemia.

Variables	Reference-case	Range for sensitivity analysis (in %) [e]	References
Open revascularization			
Technical success	95.1%	90% – 100%	11
Perioperative mortality	7.08%	0% – 13%	11
Minor / Short-term complications[a]	30.3%	10% – 50%	11
Major / Long-term complications[b]	3.9%	1.0% – 5.0%	11
Immediate conversion	NA	NA	NA
Conversion rate/year	NA	NA	NA
Reinterventions/year	1.9%	0.5% – 3.0%	20
Endovascular[c]	50%	0% – 100%	20
Open[d]	50%	0% – 100%	20
Bowel resection	8.0%	2% – 10%	14,18,19
Primary and secondary patency	Table II	NA	20
Mean hospitalization (in days)	18	7 - 30	11
Endovascular revascularization			
Technical success	93.2%	90% – 98%	11
Perioperative mortality	3.62%	0% – 6.0%	11
Minor / Short-term complications[a]	11.2%	5% – 20%	11
Major / Long-term complications[b]	1.8%	1.0% – 5.0%	11
Immediate conversion	2.9%	1.0% – 5.0%	16,21
Conversion rate/year	3.6%	1.0% – 6.0%	16,22
Reinterventions/year	13.9%	5.0% – 15%	20
Endovascular[c]	88.5%	0% – 100%	20
Open[d]	11.5%	0% – 100%	20
Bowel resection	2.6%	1.0% – 5.0%	21,23
Primary and secondary patency	Table II	NA	20
Mean hospitalization	4.5	2 - 10	11
General variables			
Mortality bowel resection	27.9%	10% – 40%	17
Major complications after bowel resection[b]	7.2%	5.0% – 15%	17
Standardized mortality rate for CMI	x1.76	-	15
+ major morbidity	x3.1	-	25
Discount rate	3%	0% – 5%	13

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Table I continued

Variables	Reference-case	Range for sensitivity analysis (in %) [e]	References
Quality of life values			
Chronic mesenteric ischemia	0.87	0.85 – 0.89	26
Well postoperative	0.90	0.88 – 0.92	26
Well after reintervention	0.90	0.88 – 0.92	26
After bowel resection	0.85	0.83 – 0.87	28
Major complications[b]	0.45	0.43 – 0.47	27
Major complications + Bowel Resection	0.40	0.20 – 0.60	-
Dead	0	0	-
Impact of Interventions (Tolls)[f]			
Open revascularization	-0.08	-0.16 – -0.04	29
Endovascular revascularization	-0.03	-0.06 – -0.01	29
Bowel resection	-0.12	-0.14 – -0.11	-
Acute complication	-0.02	-0.04 – -0.01	-

a Minor complications include infection, hemorrhage, acute renal failure or other transient complications.
b Major complications include chronic renal failure, chronic cardiopulmonary or cerebrovascular complications.
c Endovascular reinterventions include thrombolysis and percutaneous transluminal angioplasty with or without stenting.
d Open reinterventions include bypass, embolectomy, endarterectomy and bowel resection.
e Range tested in sensitivity analysis is wide range to evaluate the impact of this variable on the outcomes of the model.
f No references are used for disutilities for bowel resection.
CMI, chronic mesenteric ischemia; *NA*, not applicable.

QoL

QoL values were retrieved from published articles (Table I).[26-28] Since there are no studies describing QoL of patients with CMI, QoL values for patients with choledocholithiasis with severe pain were used.[26] These patients have similar symptoms (e.g. postprandial pain) and were assumed to have the same QoL. The QoL value for CMI patients after bowel resection was considered to be similar to patients with colitis in remission, after partial bowel resection and no symptoms.[28] QoL values for major complications caused by the interventions were assumed to be similar to QoL in patients with chronic kidney disease (one of the major complications).[27]

For the interventions, disutilities or tolls were included. These disutilities were applied every time an intervention was required and were based on the average recovery time for these interventions. These tolls were supported by the QoL-adjustments of open and endovascular repair of abdominal aortic aneurysms (AAA), reported in literature.[29] For acute complications, a disutility of -0.02 QoL (comparable with 1 week in perfect health) was subtracted. A wide range for all the QoL values (column 3, Table I) was used to explore the effect of the assumptions and to include the uncertainty around the input variables.

Table II Patency rates for open revascularization and endovascular revascularization of chronic mesenteric ischemia.

Type of revascularization	Patency	1st year	2nd year	3rd year	4th year	5th year
OR	Primary	94.0% (94.2%)	92.0% …	92.0% …	90.0% …	88.0% (80.9%)
	Secondary	99.0% …	98.0% …	98.0% …	97.5% …	97.0% (97.9%)
EV	Primary	67.0% (71%)	58.0% …	53.0% …	47.0% …	41.0% (49.1%)
	Secondary	91.0% …	88.0% …	88.0% …	88.0% …	87.5% (88.0%)

Patency rates derived from Oderich et al.[20] (and Pecoraro et al.[11], shown in parentheses). *OR*, open revascularization; *EV*, endovascular revascularization.

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Costs

To evaluate the lifetime costs and cost-effectiveness for both treatment strategies (OR and EV), procedure and hospital costs, follow-up costs and costs of major complications were analyzed from a healthcare perspective and were given in reimbursement amounts to the physician and hospital rather than charges. First, Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes were defined for the procedures (35531 (OR), 37205 (EV), 44120 (bowel resection) and 99213 (follow-up)) and reimbursement amounts were retrieved using these codes (http://www.cms.gov/apps/physician-fee-schedule/) and are shown in Table III.[30] We assumed that patients would not have imaging during follow-up unless they were symptomatic.

Length of hospital stay was multiplied by the costs of hospital stay per day to calculate the direct hospitalization costs. Costs of hospitalization per day were derived from published data on actual hospital costs and inflated to 2013 $ through the medical component of the Consumer Price Index.[31] Costs for major, long-term morbidity were retrieved from published literature regarding the costs for chronic kidney disease, Stage 3 (moderate, ICD-9 code: 583.3). All the costs were tested over a wide range with sensitivity analyses, to include the uncertainty around the variables.

Data analysis and reference-case

In the reference-case analysis, 10,000 65-year-old female patients with CMI refractory to conservative management and average risk for operation were entered into the model. Female patients were chosen because 70% – 80% of all patients with CMI are women and 65 years is the average age of intervention.[32] Validation of the model was performed by comparing the number of expected reinterventions for both procedures in this model with the reported

Table III Codes and costs for interventions and comorbidities for the treatment of chronic mesenteric ischemia.

Variable	HCPCS / CPT code	Costs (2013 US$)[c]	Range		References
OR	35531	$2,108	$ 1,581	– $2,635	30 d
EV	37205	$4,563	$ 3,422	– $5,703	30 d
Bowel resection	44120	$1,228	$ 921	– $1,535	30 d
Follow-up[a]	99213	$73	$ 44	– $143	30 d
Major complications[b]	583.3	$11,970/year	$ 5,000	– $25,000	30 d
Hospital stay / day	NA	$1,351	$ 1,013	– $1,688	31

[a] Two outpatient follow-up visits to a vascular surgeon in the first year and one annual visit for later years.
[b] Based on costs for complication of chronic kidney disease, which is the most common major complication after revascularization for CMI.
[c] Costs are given in whole dollars.
[d] CPT and HCPCS codes were defined for the procedures and reimbursement amounts were retrieved using these codes using the CMS physician fee schedule (http://www.cms.gov/apps/physician-fee-schedule/), accessed 06/01/2013.
CPT, current procedural terminology; *HCPCS*, Healthcare Common Procedure Coding System; *OR*, open revascularization, EV, endovascular revascularization; NA, not applicable.

reinterventions from a recent systematic review.[32] An additional analysis was performed for patients in whom bowel viability needed to be assessed with open revascularization and in patients who did not undergo bowel resection at all.

Analyses were performed from the perspective of the healthcare system. Calculation of the incremental cost-effectiveness-ratio (ICER) was performed by dividing the difference in costs (in 2013 US$) by the difference in effectiveness (in QALYs). The willingness-to-pay threshold, which is the maximum amount that society is willing to pay for one additional year in perfect health, was set to $60,000 per QALY, and tested in sensitivity analysis ($0 – $100,000).[33]

Sensitivity analyses were performed to assess the impact of the variable values on the outcomes of the model and included different age groups, gender, risk profiles and all the variables. A probabilistic sensitivity analysis using Monte Carlo Simulation was performed using 10,000 random samples[12] to assess the uncertainty around the variable values using distributions of the values rather than deterministic values. The type of distribution depended on the type of variable: Beta distributions were used to model the probabilities of events, parameterized by the total number of patients and the number of patients with the event of interest. Triangular distributions were used for utilities, parameterized by the best available most likely, minimum and maximum value for these utilities.[12] A difference of less than 0.1 QALYs was considered as indifferent. Outcomes are given with a 95% credibility interval (95%CI). Credibility intervals in Bayesian approaches are analogous to confidence intervals in frequentist statistics.

RESULTS

Analysis of the reference-case (10,000 65-year-old female patients with CMI refractory to conservative management and with an average risk for operation) revealed that EV was the dominant strategy for patients with CMI based on higher QALYs and lower costs. Figure 2 shows the results of probabilistic sensitivity analysis with 10,000 samples of the cost-effectiveness in a scatterplot. After 35 years of follow-up, when every patient had either died or reached the age of 100 years, EV had 10.03 expected QALYs (95%CI: 9.76 – 10.29) vs. 9.59 (95%CI: 9.29 – 9.87) for the OR group. There was a significant difference between the two strategies: 0.44 QALYs (95%CI: 0.13 – 0.76), which is comparable with an average difference of 5 months in perfect health. The total expected costs from the healthcare perspective for the reference-case patient were $39,942 (95%CI: $28,509 – $53,380) for OR and $38.217 (95%CI: $29,329 – $48,309) for EV, with a difference of $1,725 (95%CI: -$7,663 – $11,882) in favor of EV.

Results for men

Cumulative expected QALYs for 65-year-old men in the EV-group were 8.71 (95%CI: 8.48 – 8.94, EV) vs. 8.42 (95%CI: 8.14 – 8.63) in the OR group. The total expected costs for 65-year-old men were $39,375 (95%CI: $28,092 – $52,853) for OR and $35,903 (95%CI: $27,685 – $45,597) for EV. Differences between EV and OR for QALYs and costs were 0.31 QALYs (95%CI: 0.06 – 0.59) and $3,472 (95%CI: -$5,874 – $13,799), both in favor of EV.

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Sensitivity analyses

Age

Figure 3 shows the sensitivity analysis results for age at initial treatment and demonstrates that EV yielded higher effectiveness in QALYs for all ages compared with OR, with a difference ranging from 0.59 QALYs (95%CI: 0.09 – 1.04; at 50 years) to 0.13 QALYs ((95%CI: 0.07 – 0.17; at 95 years). As shown in the figure, the older the patient was at the time of initial treatment, the smaller the benefit of EV in QALYs. However, the effectiveness of treatment measured in QALYs was in favor of EV for all age groups.

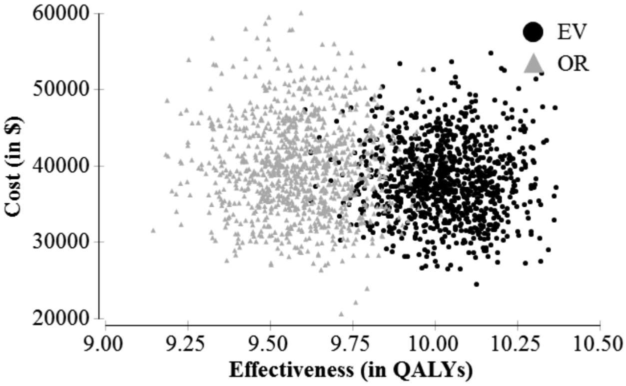

Figure 2 Cost-effectiveness scatterplot of OR and EV for treatment of CMI for the reference-case patients (65-year-old women). Each point represents one sample value based on the analysis of 10,000 reference-case samples in the Monte Carlo simulation. ▲ depicts OR while ● is for EV. The results indicate that EV is dominant over OR, since effectiveness is higher and costs are lower. See Results section for further details. *CMI*, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALYs*, quality-adjusted life years.

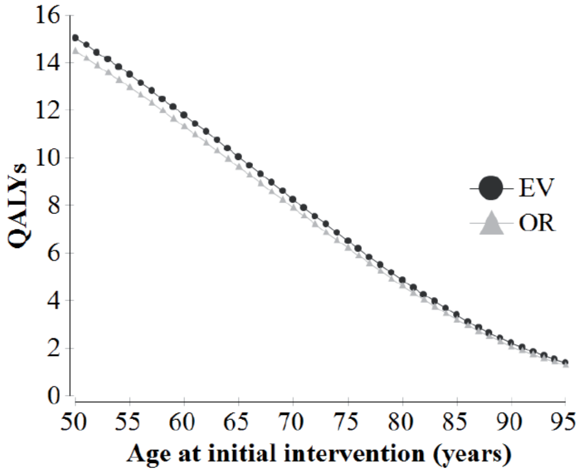

Figure 3 Total expected QALYs for OR and EV depending on age of initial intervention of CMI for the reference-case patient (65-year-old women). See Results section for further details. *CMI*, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALYs*, quality-adjusted life years.

Risk profile

Sensitivity analysis of different risk categories of patients revealed no change in preferred treatment option based on QALYs. Using RR for perioperative mortality, ranging from 0.5 (low risk) to 5 (very high risk), EV remained the preferred treatment option for all the different risk profiles, even in patients at low risk for open revascularization (Appendix Figure 1). A two-way sensitivity analysis on RR and age and on RR and number of years after intervention showed that the risk profile of the patient did not result in a significant change in QALYs gained with EV, and therefore did not result in change of preferred treatment for patients with CMI.

8

Perioperative mortality

Appendix Figure 2 demonstrates that if open surgical techniques improve and the 30-day perioperative mortality for OR decreased to 3.1% (baseline 7.1%), with all other variables unchanged, OR yielded greater effectiveness in QALYs compared with EV. This assumes the perioperative mortality for EV is 3.6%. A two-way sensitivity analysis for perioperative mortality of EV and OR is shown in Appendix Figure 3.

Reinterventions

Figure 4a depicts that an initial treatment with EV resulted in more reinterventions compared with OR. For the 65-year-old reference-case patients, 1.70 reinterventions per patient were expected in the EV group, compared with 0.32 per patient in the OR group. Figure 4b shows the number of reinterventions for both treatment groups for patients ranging from 50 to 95 years of age. A 50-year-old patient treated with EV could expect 2.68 reinterventions during the remaining part of her life, while a patient treated with OR could expect an average of 0.56 reinterventions. For a 95-year-old patient, the number of expected reinterventions throughout the remaining lifetime would be 0.26 for EV and 0.05 for OR. For every age group, the number of expected reinterventions was approximately 5 times higher after EV compared with OR. These numbers were the average for the whole group. Despite the significantly greater number

of reinterventions that are accompanied by more hospitalization periods, the QALYs were always higher for patients treated with EV compared with OR.
Validation of the model, by comparing predicted reinterventions with reported reinterventions for EV and OR, showed that EV has up to 5 times more expected reinterventions compared with OR, similar to the 4.2-fold increase reported.[32]

Costs
Figure 5 shows the total expected costs depending on the age at the time of initial intervention. For patients between 50 and 60 years of age, EV was more expensive compared with OR, mostly due to the number of reinterventions and subsequent hospitalization periods. After the age of 60, OR was more expensive than EV. However, the ICER indicates that for patients between 50 and 60 years of age, costs and effectiveness are higher for EV, but the ICER is still under the willingness-to-pay threshold of $60,000/QALY (max. $4,780/QALY, at age 50), and therefore EV is the preferred treatment option despite the higher cost in this age group (Appendix Figure 4). After the age of 60, costs for OR are higher and effectiveness is lower, and therefore OR is dominated by EV as the preferred treatment strategy.

Probabilistic sensitivity analysis
Utilizing a Monte Carlo strategy selection with a willingness-to-pay threshold of $60,000/QALY showed that EV was cost-effective in 99.8% of the reference-case samples (Figure 6). The cost-effectiveness acceptability curve (Figure 7) demonstrates the robustness of the model. Even if the willingness-to-pay -threshold decreases, EV is in a higher percentage of the cases more cost-effective compared with OR.

Length of hospital stay
Performing a sensitivity analysis on the postoperative hospitalization period for OR (18 days for the reference-case) showed that if the hospitalization period was less than 16 days, OR had lower expected costs for the reference-case patients. However, the ICER still remains under the willingness-to-pay threshold of $60,000/QALY, even if the post-operative hospitalization period for OR is shortened to 0 days (ICER: $40,333/QALY). This is based on the assumption that the post-operative hospitalization period for EV remained unchanged at 4.5 days (Appendix Figure 5).

Bowel resection and sensitivity analyses
Additional analysis on the chance of bowel resection showed that patients who underwent immediate bowel resection with OR had decreased QALYs compared with patients who did not undergo bowel resection at all (Appendix Figure 6). EV was in both patient groups preferred over OR. Performing a sensitivity analysis on disutility values over a wide range did not show a significant effect on the initial treatment choice (Appendix Figure 7). Utilization of patency rates from the systematic review instead of the large single-center study resulted in a small change in difference between the two strategies of 0.02 QALYs in favor of EV. We also assumed that 50% of reinterventions after open CMI treatment would be done by endovascular means. This assumption was tested using a wide range (0% – 100%) but it did not change the preferred treatment (Appendix Figure 8).

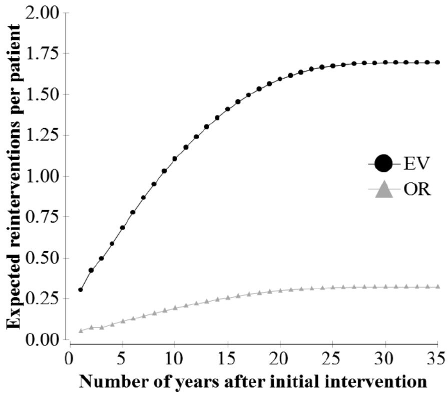

Figure 4a Cumulative expected reinterventions per patient after initial treatment of CMI for the reference-case (65-year-old women). See Results section for further details. *CMI*, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

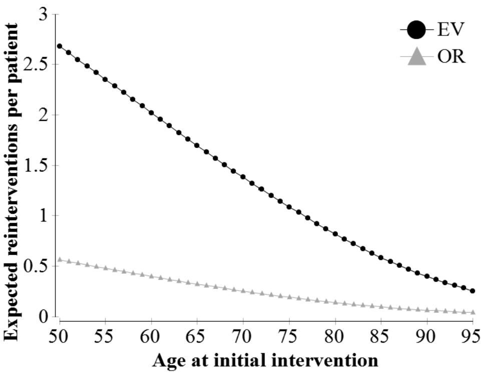

Figure 4b Number of expected reinterventions depending on the age at initial intervention for CMI for reference-case (65-year-old women). See Results section for further details. *CMI*, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

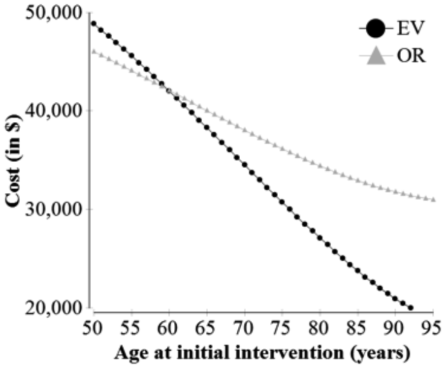

Figure 5 Total expected costs for OR and EV by age of initial intervention for the reference-case patient (65-year-old women with CMI). Shown is that EV is more expensive until the age of 60. After the age of 60, OR is more expensive. See Results section for further details.

CMI, Chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

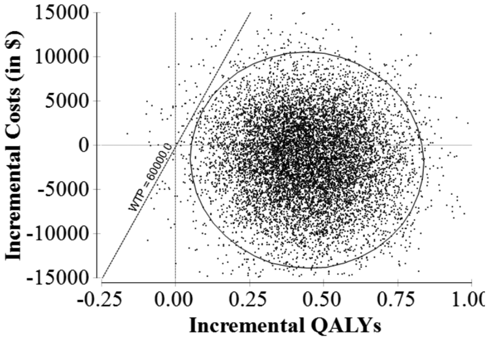

Figure 6 95% Confidence ellipse for the cost-effectiveness of EV vs. OR for 10,000 samples of the reference-case (65-year-old women with CMI). On the x-axis, the incremental QALYs for EV compared with OR. On the y-axis the incremental costs for EV compared with OR. For each of the 10,000 samples, the difference between the QALYs (incremental QALYs) and the difference between the costs (incremental Costs) for EV and OR are calculated and depicted as a dot in the figure. The circle depicts 95% of the distribution. The willingness-to-pay (WTP) of $60,000/QALY is indicated. All dots south-east of the WTP-line are considered cost-effective.

WTP, Willingness-to-pay; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year.

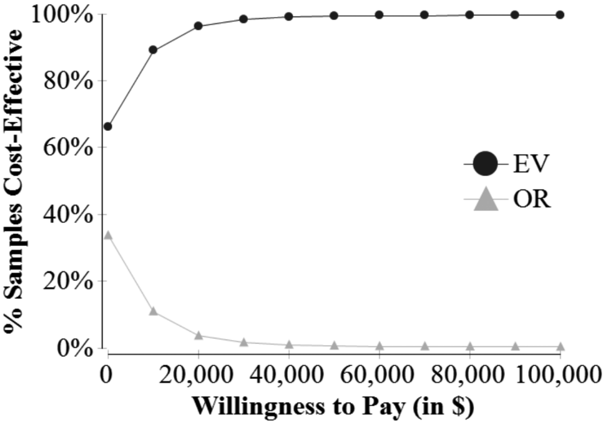

Figure 7 Acceptability curve for different WTP threshold points for the treatment of CMI. On the x-axis the WTP and on the y-axis the % of samples that is cost-effective. Shown is that even if the WTP decreases to $0, EV is cost-effective in the majority of the cases compared with OR.
WTP, Willingness-to-pay; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

DISCUSSION

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Based on the results of this decision analysis, EV is the preferred treatment for patients with CMI refractory to conservative management; the effectiveness of EV is higher compared with OR for every age group and risk profile. Although EV has a fivefold increase in expected reinterventions compared to OR, total costs are lower for patients 60 years or older. For patients younger than 60 years, the costs of EV are higher, but EV may still be preferable over OR, because the maximal ICER is $4,780/QALY, which is far under the willingness-to-pay threshold of $60,000/QALY.

The difference for the outcomes for the reference-case 65-year-old patient for EV over OR are significant (0.44 QALYs (95%CI: 0.13 – 0.76))) and equivalent to 5 months in perfect health difference. For younger patients, this difference is larger 0.59 QALYs (95%CI: 0.09 – 1.04; at 50 years) and even for 95-year-old patients EV dominates (0.13 QALYs; 95%CI: 0.07 – 0.17)). It is important to note that this difference is the average for the group and so some patients may only have a small benefit and others will have a larger benefit. Total average expected costs for the complete group are less for men compared with women and this could be explained by the fact that women have overall a higher life expectancy at time of diagnosis. In other words, women have more life years ahead of them, resulting in more follow-up visits and greater number of years at risk for complications and subsequent reinterventions, which increases the total costs. Additional analysis for patients with immediate bowel resection after assessment of bowel viability showed that these patients have lower QALYs compared with patients in whom bowel resection was not necessary. EV is the preferred treatment in both types of patients.

Decision analysis is a useful method to assess prognosis, especially in diseases that involve transitions between health states. Moreover, decision analysis can compare treatments in the same patient through computer simulation, something that is impossible in a clinical trial. The strength of decision models is sensitivity analysis: the effect of uncertainty in the parameter values can be explored and with probabilistic sensitivity analysis the effect of uncertainty around a range of variables can be analyzed. Decision analysis combined with the increasing amount of available literature can play a major role in the development for individualized medical decision making, since there is no “one size fits all” treatment for most vascular diseases.

Although decision models are useful to synthesize the best-available evidence, there are inherent limitations. First, data is usually retrieved from published data and in the current study extracted from a meta-analysis. Analysis of the literature demonstrates heterogeneity of reported outcomes and quality of reporting. For example, the duration of follow-up or the exact intervention may be different. In this regard, probabilistic sensitivity analysis is one of the strengths of our methodology since it is specifically designed when there is uncertainty around the variables. Second, assumptions had to be incorporate into the model but they likely affect both EV and OR groups to a similar degree. For example, we assigned empiric values for disutilities for interventions, supported by reported disutilities in literature.[29] However, when we tested disutility values over a wide range with a sensitivity analysis we found no significant effect on the initial treatment choice. For example, OR for CMI is usually an aorto- SMA bypass with vein or prosthetic graft. If the graft occludes later during follow-up, a repeat aorta-SMA bypass is commonly performed.[34] Therefore, assuming that 50% of reinterventions after open CMI treatment will be done by endovascular means may be higher than what happens in practice. This assumption was also tested using a wide range of reintervention rates (0% – 100%) and did not change the preferred treatment, which may be plausible because of the low reintervention rate after OR compared with EV. Because of the use of duplex or other modalities to detect restenosis, and the relative ease of performing reinterventions with EV, the threshold for repeat EV is likely significantly lower compared with OR. Furthermore, the data utilized for the hospitalization period after OR or EV was retrieved from a meta-analysis,[11] but this may have included papers from centers that had different interval dates of analysis, degree of expertise or were smaller centers. As a result, the assumed hospitalization periods may have been longer than currently practiced. This variable is recognized as an important parameter in evaluating for costs, and so extensive sensitivity analysis was performed on these variables without any change in the recommendation of EV as preferred treatment for CMI (Appendix Figure 5). Another limitation is the lack of data for some input variables specifically for patients with CMI, including QoL-values and mortality rates for patients with complications. Therefore, these variables were derived from articles that were non-specific for patients with CMI. However, these variables were chosen because they are likely to be close to the QoL values for patients with CMI and have similar symptoms, such as postprandial pain. Additionally, these variables were tested with probabilistic sensitivity analyses over a wide range, to include the uncertainty around these variables.

As stated previously, any change in input variables will affect the outcome, and so the input variables were critically evaluated. Some assumptions may have resulted in a slight advantage for the OR group. For example, the codes and costs used for calculating the total costs and cost-effectiveness of the EV group were for stenting, not just PTA. Therefore, the real average costs for EV may have been overestimated. Additionally, since no distinction was made between different types of EV, the effectiveness for EV could have been even higher if we had only used data of covered stents. Covered stents are associated with less restenosis, recurrences and reinterventions and have a better primary patency after three years compared with bare metal stents and PTA in patients undergoing primary interventions or reinterventions for CMI.[35] Furthermore, patients in the original articles which had provided data for the EV group, included relatively older patients with more comorbidities.[20] This probably represents selection bias, EV being chosen in non-surgical candidates. As a result, many variables that were used for the EV group may have been relatively biased against the EV group. Despite this, EV was still the preferred treatment for all age groups in our decision model, demonstrating the robustness of our results. The model was sensitive for changes in the perioperative mortality for OR, but this only affected results if the mortality after OR would be lower than after endovascular repair, which would be very unlikely in reality (Appendix Figure 3).

Although there are many articles describing outcomes for patients treated for CMI, the limitation is that most articles usually only report on one or two main outcomes. Overall survival, patency and complications are the most described outcomes, and although these are very important outcomes, other outcomes such as quality of life for long-term morbidities, reinterventions, risk-profile of the patient and costs are also clinically relevant. To our knowledge, there have been no prior articles reporting costs for patients treated for CMI and therefore, this is the first article describing costs for the treatment of CMI from the healthcare perspective. Furthermore, this is the first model-based study analyzing outcomes for different modalities of treatment of CMI. External validation showed results consistent with those previously reported.[32]

This clinical decision model can be used as a guide for the treatment of CMI and demonstrates that patients suitable for both OR and EV should be best managed with EV. However, not all patients are suitable for both treatment strategies, for example due to anatomical limitations, surgical access issues or extensive plaque calcification. Therefore, an individualized approach will still be needed and treatment should be tailored to the patient.

There is currently no level 1 evidence available for the management of CMI. A well conducted multicenter randomized controlled trial could provide this evidence; however, this would be impractical, expensive and time consuming. Our current study indicates the utility of decision models in analyzing published studies to provide comparative information on treatment options for diseases that have risks that change over time.

CONCLUSION

We have demonstrated that EV is preferred over OR for the treatment of patients with CMI refractory to conservative treatment. Although more reinterventions are expected for patients treated with EV, EV has higher expected QALYs and appears to be cost-effective for all age groups.

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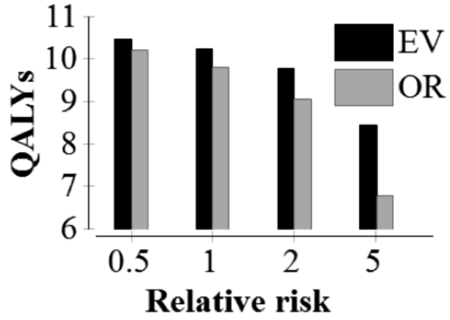
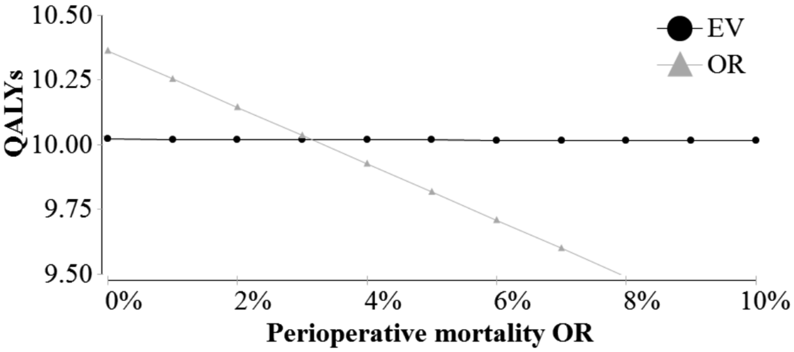
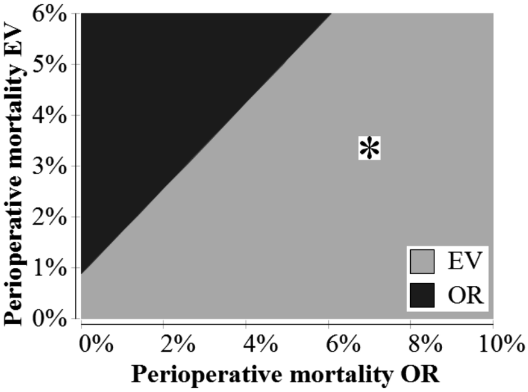
APPENDIX



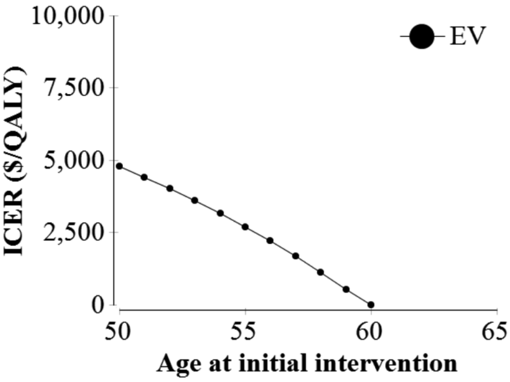
Appendix Figure 1 Total QALYs for treatment of CMI in the reference-case patient with OR and EV for different relative risks. Expected QALYs for EV are always higher, independent of the relative risk. *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year.



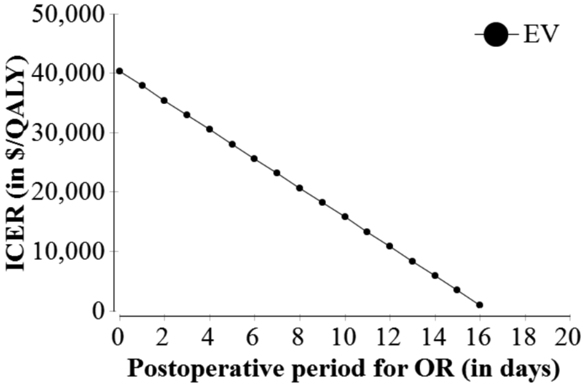
Appendix Figure 2 Total QALYs for treatment of CMI in the reference-case patient with OR and EV per perioperative mortality for OR. Expected QALYs for OR are higher if perioperative mortality of OR decreases to 3.1% (in reference-case: 7.1%), if we assume that perioperative mortality for EV is still 3.6%. *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year.



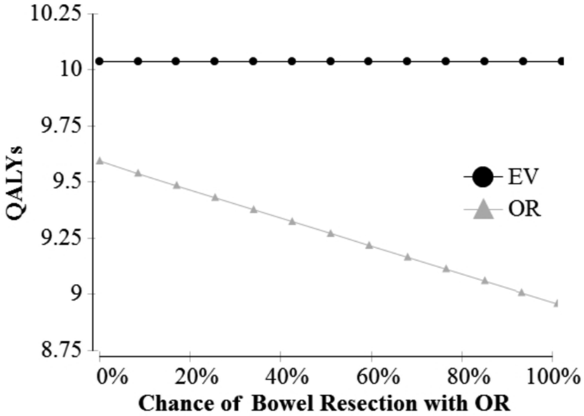
Appendix Figure 3 Two-way sensitivity analysis for perioperative mortality for EV and OR. The colored areas indicate which treatment is preferred based on QALYs. The reference-case is indicated with * : perioperative of 7.1% for OR and 3.6% for EV. *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year.



Appendix Figure 4 ICER for treatment of CMI in the reference-case patient per age at initial intervention. The ICER of EV vs. OR had a maximum at age 50: $4,032/QALY. After the age of 60, costs for EV are lower and QALYs higher implying that EV dominates OR. *ICER*, incremental cost-effectiveness ratio; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year.



Appendix Figure 5 ICER for treatment of CMI in the reference-case patient per length of postoperative period for OR. The ICER of EV vs. OR is always below the WTP-threshold of $60,000/QALY. A longer hospitalization period than 16 days for OR results in lower costs for EV and higher QALYs implying that EV dominates OR. *ICER*, incremental cost-effectiveness ratio; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization; *QALY*, quality-adjusted life year; *WTP*, willingness-to-pay.



Appendix Figure 6 Total QALYs for patients with and without bowel resection. For patients with immediate bowel resection (100% chance) for CMI the QALYs are lower compared for patients without (0%) bowel resection. *QALY*, quality-adjusted life year; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

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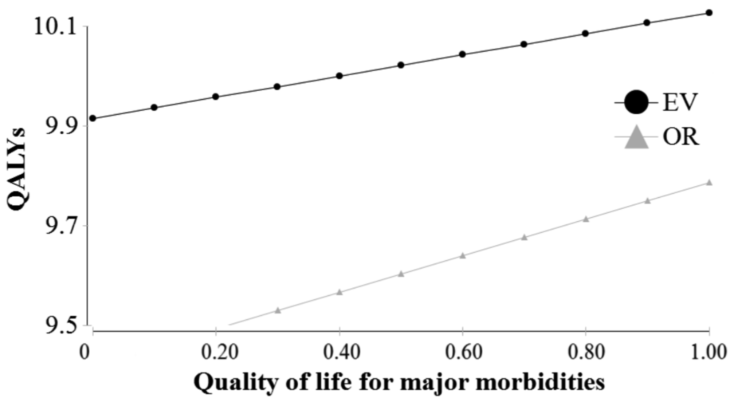
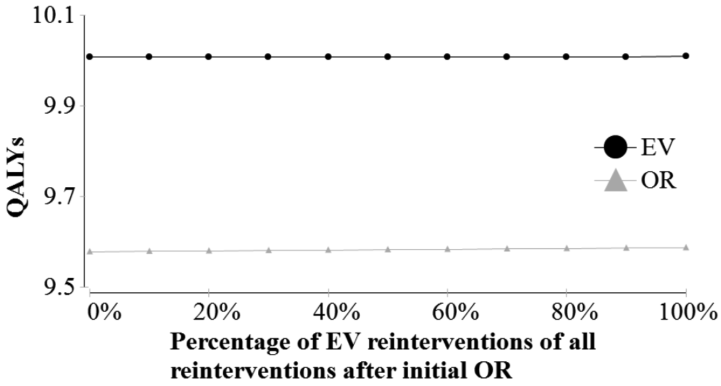


Appendix Figure 7 Total QALYs per quality of life for major morbidities for treatment of CMI in the reference-case patient with OR and EV. Expected QALYs for EV are always higher than for stenting and OR, regardless of the value of the quality of life for major morbidities. *QALY*, quality-adjusted life year; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.



Appendix Figure 8 Total QALYs for the treatment of CMI in the reference-case patient if type of reintervention after initial OR is EV, tested over a wide range (0% – 100%). *QALY*, quality-adjusted life year; *CMI*, chronic mesenteric ischemia; *OR*, open revascularization; *EV*, endovascular revascularization.

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CHAPTER 9

Cost-effectiveness of endovascular repair, open repair and conservative management of splenic artery aneurysms

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ABSTRACT

Objective

Open repair (OPEN) and conservative management (CONS) have been the treatments of choice for splenic artery aneurysms (SAAs) for many years. Endovascular repair (EV) has been increasingly used with good short-term results. In this study, we evaluated the cost-effectiveness of OPEN, EV and CONS for the treatment of SAAs.

Methods

A decision analysis model was developed utilizing TreeAge Pro 2014 (TreeAge Inc, Williamstown, MA) to evaluate the cost-effectiveness of the different treatments for SAAs. A hypothetical cohort of 10,000 55-year-old female patients with SAAs was assessed in the reference-case analysis. Perioperative mortality, disease-specific mortality rates, complications, rupture risks, and reinterventions, were retrieved from a recent and extensive meta-analysis. Costs were analyzed with the 2014 Medicare database. The willingness-to-pay was set to $60,000/QALY. Outcomes evaluated were quality-adjusted life-years (QALYs), costs from the healthcare perspective, and the incremental cost-effectiveness ratio (ICER). Extensive sensitivity analyses were performed and different clinical scenarios evaluated. Probabilistic sensitivity analysis was performed to include the uncertainty around the variables. A flowchart for clinical decision-making was developed.

Results

For a 55-year-old female patient with a SAA, EV has the highest QALYs (11.32; 95%CI: 9.52 – 13.17), followed by OPEN (10.48; 95%CI: 8.75 – 12.25) and CONS (10.39; 95%CI: 8.96 – 11.87). The difference in effect for 55-year-old female patients between EV and OPEN is 0.84 QALY (95%CI: 0.42 – 1.34), comparable with 10 months in perfect health. EV is more effective and less costly than OPEN, and more effective and more expensive compared to CONS with an ICER of $17,154/QALY. Moreover, OPEN, with an ICER of $223,166/QALY, is not cost-effective compared to CONS. In the elderly (>78 years), the ICER of EV vs. CONS is $60,503/QALY, and increases further with age, making EV no longer cost-effective. Very elderly patients (>93years) have higher QALYs and lower costs when treated with CONS. The EV group has the highest number of expected reinterventions, followed by CONS and OPEN, and the number of expected reinterventions decreases with age.

Conclusions

EV is the most cost-effective treatment for most patient groups with SAAs, independent of the gender and risk-profile of the patient. EV is superior to OPEN, being both cost-saving and more effective in all age groups. Elderly patients should be considered for CONS, based on the high costs in relation to the very small gain in health when treated with EV. The very elderly should be treated with CONS.

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INTRODUCTION

Splenic artery aneurysms (SAA) are a rare clinical entity that carries the risk of rupture and fatal hemorrhage. SAAs are the third most common intra-abdominal aneurysms[1] and are increasingly diagnosed due to the wider use of cross-sectional imaging.[2] Although the majority of SAAs are asymptomatic, previous studies have shown that SAAs, and particularly those exceeding 2cm in size, can rupture resulting in potentially life-threatening complications.[3-5] To treat symptoms and prevent complications, aneurysm repair is often required.

Conservative management (CONS) and open surgical repair (OPEN) were the preferred treatment options for many years. Endovascular repair (EV) of SAAs has been increasingly utilized since 2000 and a recent extensive meta-analysis has reported superior short-term outcomes for EV compared with OPEN.[6] However, considering the better long-term results of OPEN compared with EV and CONS shown in the meta-analysis, the preferred treatment option for patients with a SAA is still matter of debate and no clear treatment guidelines exist. Additionally, EV is usually accompanied by higher intervention costs and more reinterventions.6 Thus, the treatment of a patient with a SAA is not a straight forward decision. Importantly, a contemplated decision should be made based on not only the expected mortality and complications, but should also account for quality of life, associated interventional and life-time costs and expected reinterventions.

The purpose of this study is to assess the cost-effectiveness of the three major treatment modalities for treatment of SAAs utilizing a clinical decision model. The secondary objective is to provide guidance for the treatment of a patient with a SAA with regards to patients' age, gender and risk profile as well as associated costs, quality of life and expected reinterventions.

METHODS

A Markov cohort model was constructed using the software program TreeAge Pro 2013 (TreeAge Inc., Williamstown, MA, USA) to assess the cost-effectiveness from the healthcare perspective of OPEN, EV and CONS for 10,000 hypothetical patients treated for their SAA. In a Markov model, a patient is always in one of a finite number of discrete health states and the prognosis of clinical problems with risks that change over time can be analyzed. All possibilities are modeled as transitions from one health state to another. Each health state is assigned a quality of life (QoL) value, and the contribution of this QoL-value to the overall outcome of the different strategies depends on the time spent in this health state.[7] Overall outcomes were given in quality-adjusted life years.

Decision model

All patients entered the model with a SAA of 2.0 cm. Patients in the OPEN and EV groups started immediately with an intervention and could transition to the following health states: *well after intervention*, if only the aneurysm was excluded; *well after splenectomy*, if an additional splenectomy was performed; *major complications* if they had major complications and the patient had to stay significantly longer in the hospital, or the patient died as result of the intervention and she ended up in the *dead* health state. For patients in the EV group, it was also possible to

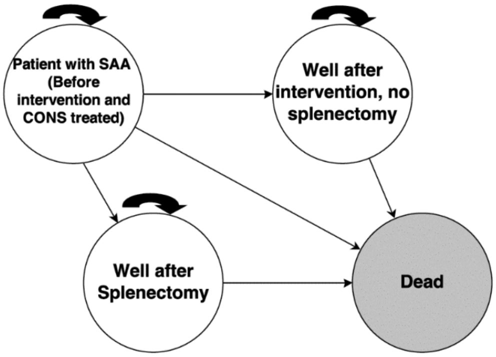

Figure 1 Simplified bubble diagram of the Markov state transition model for treatment of splenic artery aneurysms (SAA). CONS, conservative management.

transition to the OR group, if a conversion was required. Patients originally treated with CONS management remained in this health state, but were still at risk for complications or rupture of the SAA. If complications or a rupture occurred in these patients, an intervention with either OPEN or EV was required. After this intervention, the same health states as described previously were possible. For subsequent years, patients could remain in their health state, could develop complications requiring a reintervention or they could die due to the normal background mortality. A simplified overview of the decision model and health states is depicted in Figure 1. The cycle length was one year, and the model cycled until all patients had died. To prevent overestimation or underestimation, a half-cycle correction was applied, as generally most events do not specifically occur at the beginning or end of a year, but occur throughout a cycle.[8]

Input variables

Most of the input variables were retrieved from a recent and extensive meta-analysis of the three major treatment options for patients with SAAs.[6] Input probabilities required for the model, but not reported in the meta-analysis were retrieved from articles reporting the necessary probabilities. For example, the risk of infection, overwhelming post-splenectomy infection (OPSI), percentage that required hospitalization and mortality rate were extracted from studies reporting these outcomes.[9-14] Since mortality rates in patients with SAAs are higher compared with the general population, disease-specific mortality rates were modeled. As no specific mortality rates for patients with SAAs are reported, mortality rates for patients with abdominal aortic aneurysms (AAA) were used.[15] These mortality rates were assumed to be similar for patients with SAAs justified by the similar prevalence of diabetes, coronary artery disease (CAD), and hypertension: this prevalence of diabetes in patients with AAA is 15% vs. 12% in patients with SAAs. For coronary artery disease (CAD) and hypertension, the prevalence is 13% vs. 16% (CAD) and 65% vs. 48% (hypertension).[6,15] The mortality rates were tested over a wide range, including the mortality rate for AAA patients, to take the uncertainty around these mortality rates into account. Relative risk was used to differ between risk-profile of different patient groups. All the input variables used in the model are reported in Table I.

Table I Input variables for different treatment options for SAAs.

Variables	Reference-case (in %)	Range for sensitivity analysis (in %) [c]	References
OPEN			
Technical success	98.6	95.0 – 100	6
30-day mortality	5.0	1.0 – 10.0	6
Minor / Acute complications[a]	16.9	10.0 – 25.0	6
Major complications[b]	1.4	0.5 – 5.0	6
Reinterventions/year	0.5	0.0 – 3.0	6
Mean hospitalization (in days)	9.8	5.0 – 15.0	6
EV			
Technical success	95.2	92.0 – 99.0	6
30-day mortality	0.6	0.0 – 5.0	6
Minor / Acute complications[a]	25.3	10.0 – 40.0	6
Major complications[b]	0.9	0.0 – 5.0	6
Conversion	1.8	0.0 – 5.0	6
Reinterventions/year	3.2	0.0 – 5.0	6
Mean hospitalization (in days)	2.03	0.5 – 5.0	6
CONS			
Rupture/year	0.4	0.0 – 2.0	
Dead after rupture	25	0.0 – 100	32
Complications	5.8	5.0 – 10.0	6
30-day mortality	0.5	0.0 – 3.0	6
Interventions/year	1.2	0.0 – 3.0	6
General variables			6
Infection after splenectomy	3.3	2.0 – 5.0	9
OPSI + Hospitalization/year	0.5	0.2 – 2.0	9
Deceased after infection	48	0.0 – 100	11
SMR for patients			
With splenic aneurysms (RR)	x2.82		15
After splenectomy (RR)	x2.82		10,15
Relative risk for mortality (RR)	1	0.2 – 5.0	NA
Discount rate	3%	0.0 – 10.0	8

[a] Minor complications include infection, hemorrhage, post embolization syndrome or other transient complications.
[b] Major complications include chronic renal failure, cardiopulmonary, cerebrovascular or major splenic complications.
[c] Range tested in sensitivity analysis is wide range to evaluate the impact of this variable on the outcomes of the model.
SAA, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *OPSI*, overwhelming post-splenectomy infection; *SMR*, standardized mortality rate; *NA*, not applicable. *RR* relative risk

Quality of life values

QoL-values were assigned to all health states. QoL-values for patients with SAAs have not been reported therefore QoL-values for patients with AAAs were used instead. These quality of life values were assumed to be similar to patients with SAAs since both groups are usually asymptomatic and both carry the risk of rupture and life threatening hemorrhage. For patients after splenectomy, the same QoL-values were used since it has not been proven that patients after splenectomy have a different quality of life.[16-18] Additionally, since QoL-values for patients with AAA do not reflect exactly reality, and patients with SAAs could have less symptoms compared with AAA-patients, we tested all the QoL-values over a wide range with a sensitivity analysis and performed an additional analysis with the same QoL-value for patients before and after treatment of their SAA.[19] All the QoL-values used in the model are reported in Table II.

Costs

Only healthcare costs were considered. First, we retrieved the Current Procedure Terminology (CPT) codes and costs for the different interventions. Different codes were used for patients treated with OPEN with unruptured and ruptured SAAs (35111 and 35112), and a specific code for patients who required splenectomy (38100). For patients treated with EV, a combination of CPT codes was used: 36246, 75726, 75774 and 37242.[20] Codes for follow-up of patients with and without splenectomy were retrieved (99213 and 99214). Subsequently, the reimbursement amounts for these procedures were retrieved through the Medicare database (http://www.cms.gov/apps/physician-fee-schedule/). These costs included professional and technical components. For hospital costs, we included the cost of hospital stay per day and multiplied this by the mean hospitalization length per procedure.[21] Costs for initial immunization and treatment in case the patient suffered an OPSI were retrieved from an article describing the costs for the prevention of sepsis in asplenic patients.[22] Costs which were not given in 2014 US$ were inflated to 2014 US$ through the medical component of the Consumer Price Index and all costs were reported in 2014 US$. All the costs were tested over a wide range with sensitivity analysis and reported in Table III.

Analysis of the reference case

In the reference-case analysis, 10,000 55-year old female patients entered the model. 55-year old female patients were chosen, since this is the average age of diagnosis and the majority of patients with SAAs are female.[6] The primary outcomes of the analysis of the model were mean QALYs and costs. Subsequently, cost-effectiveness was determined by first considering dominance (higher effectiveness and lower costs) and for non-dominant strategies calculating the incremental cost-effectiveness ratio (ICER = *difference in costs divided by difference in effectiveness*). Secondary outcome was the number of expected reinterventions for OPEN, EV and CONS. A discount rate of 3% was applied to both effectiveness and costs, because costs and quality of life-years in the near future are considered to have more value than costs and quality of life-years in the distant future.[23] The willingness-to-pay (WTP), which is the maximum amount that society is willing to pay for one year in perfect health (1 QALY), was set to $60,000/QALY, and tested with sensitivity analysis over a wide range.[24]

Table II Quality of life values.

Variables	Reference-case	Range for sensitivity analysis	References
Quality of life values			
With SAA	0.74	(0.58 – 0.97)	17
Well postoperative	0.81	(0.65 – 0.98)	17
Well after splenectomy	0.81	(0.65 – 0.98)	17,18
Dead	0		
Quality of life adjustments			
OPEN	-0.10	(-0.15 – -0.05)	17
EV	-0.05	(-0.09 – -0.02)	17
Splenectomy	-0.15	(-0.20 – -0.08)	16
Acute complication	-0.02	(-0.04 – -0.01)	Assumption
Taking antibiotics daily	-0.005	(-0.01 – 0.00)	Assumption
Infection, no hospitalization	-0.02	(-0.04 – -0.01)	Assumption
Hospitalization for splenectomy-related infection	-0.03	(-0.05 – -0.01)	Assumption

OPEN, open repair; *EV*, endovascular repair; *SAA*, splenic artery aneurysm; *NA*, not applicable.

Table III Procedure related costs for the treatment of SAAs.

Variable	CPT code	Costs (2014 US$)	Range (2014 US$)	Reference
OPEN	35111	1,581	1,250 – 2,000	d
OPEN ruptured	35112	1,939	1,500 – 3,000	d
EV	Combination[c]	8,976	6,000 – 12,000	d 20
Splenectomy	38100	1,177	1,000 – 1,500	d
Initial immunization	NA	148	100 – 200	22
OPSI + treatment	NA	49,936	25,000 – 75,000	22
Hospital stay / day	NA	1,523	1,250 – 1,750	21
Follow-up[a]	99213	73	50 – 100	d
Follow-up splenectomy[b]	99214	329	250 – 500	d 22

[a] Two outpatient follow-up visits to a vascular surgeon in the first year and one annual visit for later years.
[b] Includes antibiotics and immunization
[c] Combination of the following CPT codes: 36246, 75726, 75774 and 37242.
[d] Costs were retrieved using the CPT codes using the CMS physician fee schedule (http://www.cms.gov/apps/physician-fee-schedule/), accessed 03/10/2014. Includes technical and professional components.
CPT, current procedural terminology; *OPEN*, open repair; *EV*, endovascular repair; *SAA*, splenic artery aneurysm; *OPSI*, overwhelming post-splenectomy infection; *NA*, not applicable.

Probabilistic sensitivity analysis using 10,000 random samples was performed to include the uncertainty around the input variables. Using probabilistic sensitivity analysis, distributions of values instead of deterministic values were utilized.[8] For the probabilities of events, beta distributions were used, parameterized by the number of patients and the number events. Triangular distributions were used for utilities, parameterized by the most likely, minimum and maximum value for these utilities. Additionally, sensitivity analyses on all the input variables, including probabilities, QoL-values and costs were performed to assess the impact of these variables on the results. Outcomes were given with a 95% credibility interval (95%CI). Credibility intervals in Bayesian approaches are analogous to confidence intervals in frequentist statistics. Validation of this model was performed by comparing the ratio of reinventions of this study with a previously published study.[5]

RESULTS

The results of the reference-case for each of the treatment options over a 45-year follow-up are shown in Table IV. The outcomes of the model show that EV is the most cost-effective treatment option to manage a true SAA. EV is more effective and less costly than OPEN and therefore dominates OPEN. The difference in effect for 55-year-old female patients between EV and OPEN is 0.84 QALY (95%CI: 0.42 – 1.34), which is comparable with more than 10 months in perfect health. EV is more effective and more costly than CONS and with an ICER of $17,154/QALY and a WTP of $60,000/QALY, is considered to be cost-effective compared to CONS. OPEN is also more effective and more costly than CONS, but with an ICER of $223,166/QALY is not cost-effective compared with CONS (Figure 2).

Table IV Outcomes for treatment of SAAs with OPEN, EV and CONS.

Treatment	**Cost (2014 US$)**	**Effect (QALYs)**	
OPEN	31,687 (24,201 – 41,159)	10.48 (8.75 – 12.25)	
EV	28,303 (19,959 – 37,581)	11.32 (9.52 – 13.17)	
CONS	12,422 (8,315 – 17,427)	10.39 (8.96 – 11.87)	
	Mean difference in costs	**Mean difference in effect**	**ICER ($/QALY)**
EV vs. OPEN	-3,384 (-15,872 – 8,249)	0.84 (0.42 – 1.34)	Dominated
EV vs. CONS	15,880 (10,553 – 22,295)	0.93 (-0.75 – 2.55)	17,154
OPEN vs. CONS	19,265 (10,447 – 29,497)	0.09 (-1.58 – 1.71)	223,166

Number of expected reinterventions depends on the age at initial intervention for SAAs for the reference-case patients (55-year-old women). See Results section for further details. EV, Endovascular revascularization; OR, open revascularization. *SAA*, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; QALYs, quality-adjusted life years; *ICER*, incremental cost-effectiveness ratio.

Varying the WTP-threshold from \$0 to \$120,000, EV was not cost-effective in the majority of the cases when the WTP is lower than \$18,000/QALY. This is shown in the acceptability curve in Figure 3.

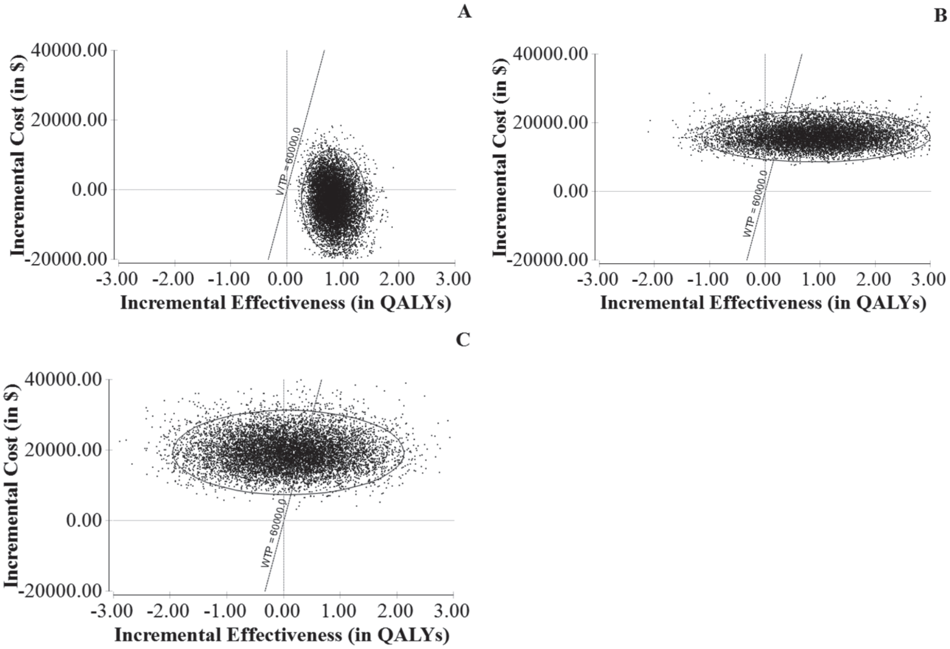

Figure 2 The 95% confidence ellipses for the cost-effectiveness of (A) EV vs. OPEN, (B) EV vs. CONS and (C) OPEN vs. CONS for 10,000 samples of the reference-case patients (55-year-old women with SAAs. For each of the 10,000 samples, the difference between the QALYs (incremental QALYs) and the difference between the costs (incremental costs) for EV and OR are calculated and depicted as a dot in the figure. The circle depicts 95% of the distribution. The willingness-to-pay (WTP) of \$60,000/QALY is indicated. All dots southeast of the WTP line are considered cost-effective.
SAA, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *QALY*, quality-adjusted life year; *WTP*, willingness to pay.

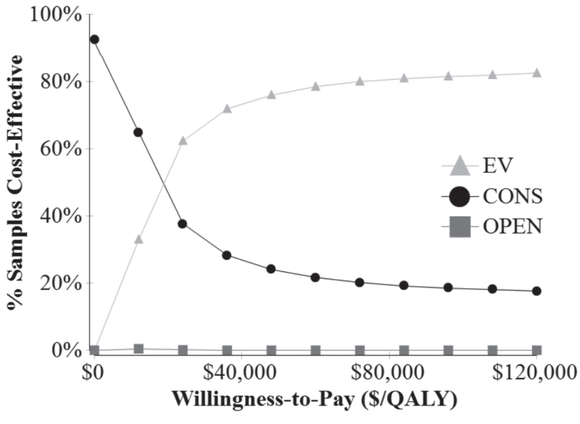

Figure 3 Figure 3. Acceptability curve of different treatment strategies for SAAs. Depicted is that the higher the WTP, the higher the proportion of samples that EV is cost-effective. Decreasing the WTP will lead to a higher chance that CONS is the most cost-effective treatment.*SAA*, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management; *WTP*, willingness to pay.

Since age is an important determinant for future costs and effectiveness, a sensitivity analysis was performed on the age at initial intervention. Since costs for EV are always lower and effect is always higher compared with OPEN, EV is preferred over OPEN. Between the age of 50 and 93, the effect for EV is higher compared with CONS, but only until the age of 77 is it considered cost-effective (ICER at age 77: \$55,250/QALY; at age 78: \$60,503/QALY). At age 93, the ICER is \$3,277,373/QALY and thus far above the WTP threshold of \$60,000/QALY. Patients older than 93 years have higher expected QALYs and lower costs when treated with CONS making this the treatment of choice for very elderly patients.

Analyses were also performed for other clinical scenarios, including the risk-profile and gender of the patient. An overview of the most cost-effective treatment for different patient groups is shown in Figure 4. As depicted in the figure, for younger patients, independent of their gender or risk-profile, EV is the most cost-effective treatment option for patients with SAAs. For male patients, and especially high-risk, male patients, EV is not cost-effective from the age of 70 years. For most female patients, this is the case when they reach the age of 80, at which point CONS becomes the preferred treatment.

Reinterventions

The number of expected reinterventions for the three treatment groups per age at initial intervention is shown in Figure 5. For every age group, the number of expected reinterventions is highest in the EV group, ranging from 1.80 reinterventions/patient (at age 50) to 0.04 reinterventions/patient (at age 95). Patients in the OPEN and CONS treatment group can expect 0.63 and 1.57 reinterventions/patient respectively at age 50, and 0.02 and 0.04 reinterventions/patient at age 95. It must be noted that these “reinterventions” are the first interventions for the CONS group.

	Females			Males		
Risk / Age	Low	Med	High	Low	Med	High
50	EV	EV	EV	EV	EV	EV
55	EV	EV	EV	EV	EV	EV
60	EV	EV	EV	EV	EV	EV
65	EV	EV	EV	EV	EV	EV
70	EV	EV	EV	EV	EV	CONS
75	EV	EV	CONS	EV	CONS	CONS
80	CONS	CONS	CONS	CONS	CONS	CONS
85	CONS	CONS	CONS	CONS	CONS	CONS
90	CONS	CONS	CONS	CONS	CONS	CONS
95	CONS	CONS	CONS	CONS	CONS	CONS

Based on a Willingness-to-pay threshold of \$60,000

Figure 4 Most cost-effective treatment of SAAs based on current data in the literature and on age, sex and risk-profile of the patient. *SAA*, splenic artery aneurysm; *EV*, endovascular repair; *CONS*, conservative management.

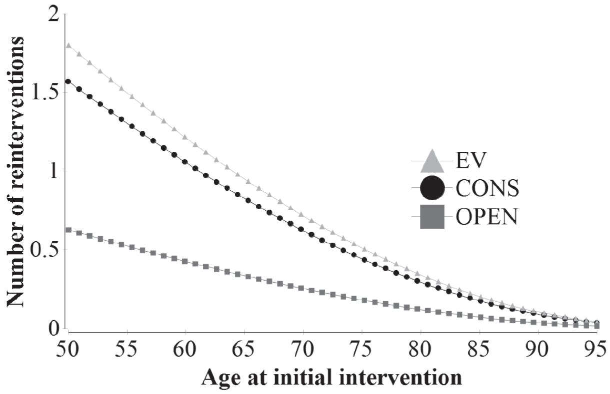

Figure 5 Number of expected reinterventions depending on the age at initial intervention for SAAs for the reference-case patients (55-year-old women).
SAA, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management.

Additional analysis with equal QoL-values before and after treatment

An additional analysis of the reference-case was performed with equal QoL-values for patients with SAAs before and after treatment, since 70% of patients are asymptomatic at time of diagnosis.[6] The QoL-values in this analysis were 0.81 before and after treatment. This change only affected the effectiveness of patients in the CONS group, and all the outcomes for the OPEN and EV group and the costs for the CONS group stayed exactly equal. The change resulted in an increase in the effectiveness of CONS, and a higher effect for CONS compared with OPEN for all age groups. It also showed that EV still is the preferred treatment based on effectiveness (QALYs), although the difference between EV and CONS decreased (0.55 QALYs (95%CI: -1.01 – 2.09), compared with 0.93 QALYs (95%CI: -0.75 – 2.55) in the initial analysis). Furthermore, the ICER of EV vs. CONS increased to $28,493/QALY. CONS is preferred over EV when patients reach the age of 82, based on higher effect and lower costs for CONS. The ICER for EV vs. CONS is higher than the WTP-threshold when patients are older than 68 years, making CONS the preferred treatment after that age.

Validation

The model was validated by comparing the ratio of reinterventions from this study with the ratio of reinventions of a previously published study (not used for input parameter values).[5] A slightly higher number of reinventions was observed in our model compared to previous published studies, but this is likely attributable to the longer follow-up period (45 years follow-up) employed.

DISCUSSION

Based on the results from this decision analysis model, EV is the most cost-effective treatment for female patients with SAAs younger than 75 years and male patients younger than 70 years old, despite the higher number of reinterventions across all age groups treated with EV. EV has higher expected effectiveness (QALYs) and lower costs compared with OPEN and is therefore the preferred treatment if a patient needs an intervention in all age groups. Patients treated with

EV have a higher gain in their QALYs compared to patients in the CONS group, except for those older than 93 years. In female patients between 75 and 93, the gain in effect is relatively small in relation to the costs, making the incremental cost-effectiveness ratio higher than the willingness-to-pay. In other words: the slight gain of additional lifetime in perfect health is not worth the high cost of intervention in this age group.

Decision analysis is a tool that surgeons and other clinicians can use to choose an option that maximizes the overall health benefit of a patient. It is an explicit, quantitative, and systematic approach to decision making under conditions of uncertainty synthesizing the best-available evidence.[25] The strength of decision models is that they not only report mortality or complications as outcomes, but can also incorporate quality of life values, expected reinterventions, disease-specific mortality rates and costs. This leads to a more complete evaluation of the 'best' treatment. Decision models are especially practical for diseases with a low prevalence, such as SAAs. Until now, there is no Level 1 evidence comparing the three major treatment modalities (OPEN, EV and CONS) of SAAs due to the lack of randomized controlled trials (RCTs). Although ideally a well-conducted large RCT would provide us with Level 1 evidence, it is unlikely that such an RCT will be conducted for this clinical problem. A well-conducted RCT is expensive, and with the low prevalence of SAAs it will take years before enough patients are included to perform a high-quality analysis. Decision analysis can fill in this gap by combining outcomes reported in published studies and by integrating different input variables, such as perioperative morbidity and mortality, early and late complications, splenic artery ruptures, quality of life before and after intervention, and intervention-, follow-up-, and hospital-related costs. Until Level-1-evidence is available, decision analysis provides the best available evidence, and it should be used to the maximum.

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The strength of decision models is that one can perform a probabilistic sensitivity analysis by using a wide range of the variables instead of one fixed number, which is particularly useful in problems with uncertainty around the variables. Therefore, even if there is some uncertainty around the input variables, the outcome can still be certain. Furthermore, decision analysis is particularly useful when the difference in outcomes between strategies is small.[8] Other decision-analysis and cost-effectiveness studies on vascular surgical topics show similar results, with smaller differences between treatment strategies. Examples include evaluation of the benefit and cost-effectiveness of open, endovascular and conservative management of asymptomatic patients with popliteal artery aneurysms (0.36 QALYs benefit)[26] and open versus endovascular interventions in patients with chronic mesenteric ischemia (0.44 QALYs difference).[27] In the decision analysis models, a mean difference of 0.84 QALYs (more than ten months in perfect health) is actually a very large difference, given the fact that this is the mean difference for the whole group.

Despite the previously mentioned strengths of decision analysis, there are inherent limitations both in these types of study and specifically to the analysis presented in this paper. First, all the input data were retrieved from an extensive systematic review and meta-analysis.[6] Although this meta-analysis was performed to a high standard and followed the PRISMA guidelines[28], the input variables for the model depend on the variables reported in the original studies included in the meta-analysis. The majority of these included studies were retrospective studies, with their inherent limitations including confounding by indication. This means that a weak, high-risk patient is less likely to undergo surgery than a fit, low-risk patient, and the outcomes are likely

to be worse for the less fit patients. However, patients of the three different treatment groups did not differ in co-morbidities, and therefore were eligible for comparison. Additionally, as previously mentioned, we used probabilistic sensitivity analysis to account for the uncertainty around the input variables, and this showed a quite robust model. Another limitation is that no QoL-values for patients with SAAs have been reported. Therefore, QoL-values of patients with AAAs were used. Although an estimate, these were the closest values to reality which were reported in the literature. To account for this, we performed an extensive sensitivity analysis over a wide range of QoL-values, and we performed an additional analysis with equal QoL-values for patients before and after treatment which did not result in a change of conclusion. Increasing or decreasing the other QoL-values will result in a similar increase or decrease of QALYs for all the three groups, because all the groups are similarly affected by the alteration of the QoL-value.
SAAs are the third most common abdominal aneurysms, after AAAs and iliac artery aneurysms and account for more than 60% of all splanchnic aneurysms.[1] The importance of treatment was discussed previously and several larger studies have shown short-term superiority of EV over OPEN.[29-31] This study shows that in the long-term, EV is also preferred over OPEN based on effectiveness, despite the higher number of reinterventions in the EV group.
This is the first study describing the costs for treatment of a SAA, evaluated from the healthcare perspective. In decision analysis models, the most important determinant for making the "correct" decision should be the effect of the intervention on the health of the patient. However, the economic pressures on healthcare systems around the world have made cost-effectiveness an important determinant of treatment choice. In this case, the intervention of choice based on patient outcome (EV) is also cost-saving compared to the alternative intervention (OPEN), making the decision between EV and OPEN relatively straight forward. However, costs play a major role in deciding to treat the patient with endovascular repair or with conservative management, which is depending on the willingness-to-pay threshold and age.
This study can guide clinicians in choosing the best treatment for several different patient groups. Based on the results of this study, the meta-analysis[6] previously performed and a systematic review of pregnant patients with SAAs,[32] we developed a flowchart for decision-making for patients with SAAs (Figure 6). Given the low incidence of SAA, most surgeons will only see a few patients with this pathology per year. This treatment decision chart can help to guide the surgeon when a patient with a SAA presents at the practice of the surgeon. A clear flowchart, also provides a useful and convenient tool for explaining the treatment choice to one's patient, which may increase the use of shared decision-making. Unfortunately, there is currently not enough evidence published to guide the surgeon on whether to perform a splenectomy or not, so this is not included in the flowchart. In general, interventions on aneurysms located in or close to the hilum of the spleen are best treated with splenectomy and aneurysms in the proximal or middle segment of the splenic artery without splenectomy.[33]
This clinical decision model shows the superiority of EV over OPEN, but as there is uncertainty around the input variables, especially for the CONS group (depicted by the wider range of difference in QALY in Figure 2B and 2C), further research is necessary. Given the low incidence of SAAs, hospitals should collaborate to set up new, well-conducted studies to improve the quality of the data. Small retrospective studies of 10 – 20 patients will not add significant new information, unless they report unexpected outcomes or focus on specific, and less reported

outcomes. Future studies should focus on the location of the intervention, and the difference between patients with and without splenectomies. Finally, this decision model could be evaluated in a prospective study, comparing the outcomes of patients who followed and did not follow the recommendations made in this paper.

CONCLUSION

EV is the most cost-effective treatment for most patient groups with SAAs, independent of the gender and risk-profile of the patient. EV is superior over OPEN in both costs and effect for all age groups. Only patients older than 80 years should be considered for CONS, based on the high costs in relation to the very small gain in health, when treated with EV. Patients older than 90 years old should not undergo an intervention but should be managed conservatively.

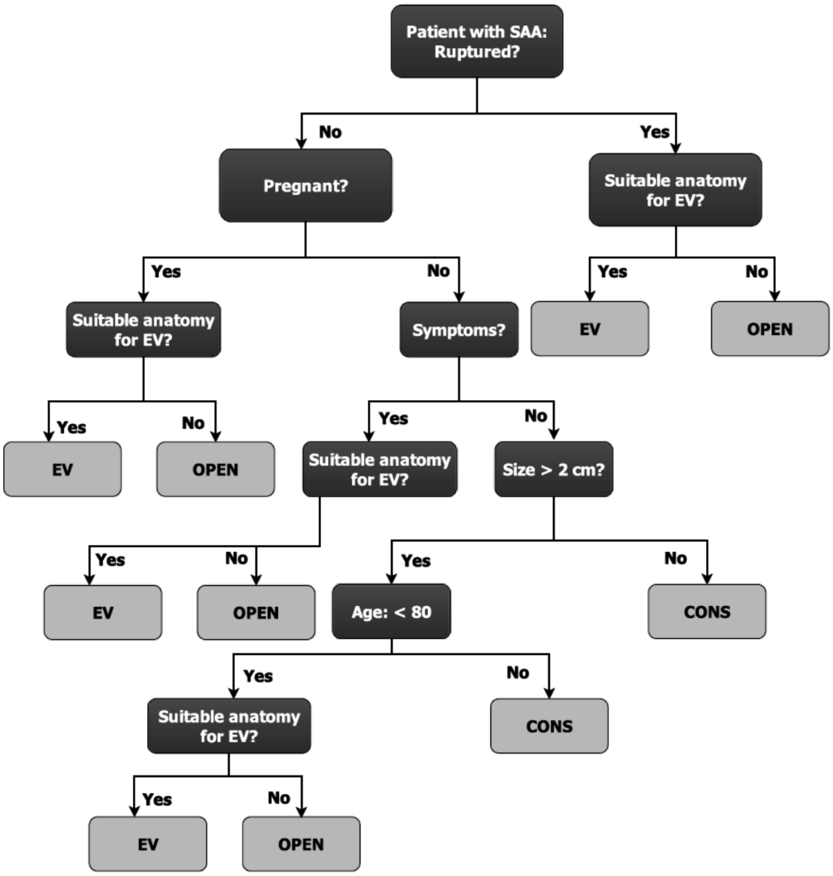

Figure 6 Flowchart for decision-making for the treatment of SAAs. *SAA*, splenic artery aneurysm; *OPEN*, open repair; *EV*, endovascular repair; *CONS*, conservative management.

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CHAPTER 10

Decision analysis model of open repair versus endovascular treatment in patients with asymptomatic popliteal artery aneurysms

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ABSTRACT

Objective

Repair is indicated of asymptomatic popliteal artery aneurysms (aPAAs) that exceed 2 cm. Endovascular popliteal artery repair with covered stents (Stenting) is increasingly utilized. It is, however, unclear when an endovascular approach is preferred to traditional open repair with greater saphenous vein bypass (GSVB). The goal of this study was to assess the treatment options for aPAAs using decision analysis.

Methods

A Markov model was developed and a hypothetical cohort of patients with aPAAs was analyzed. GSVB, stenting and non-operative management with optimal medical therapy (OMT) were compared. Operative mortality, patency rates, quality of life values and costs were determined by comprehensive review of the best-available evidence. The main outcome was quality-adjusted life years (QALYs). Secondary outcomes were cost-effectiveness and number of reinterventions.

Results

For a 65-year-old male patient with a 2.0 cm aPAA and without significant co-morbidities, probabilistic sensitivity analysis shows that intervention is preferred over OMT (5.77 QALYs; 95%CI: 5.43 – 6.11, OMT). GSVB treatment for this patient results in slightly higher QALYs than stent placement with a predicted 8.43 QALYs (95%CI: 8.21 – 8.64, GSVB) vs. 8.07 QALYs (95%CI: 7.84 – 8.29, stenting), a difference of 0.36 QALYs (95%CI: 0.14 – 0.58). Furthermore, costs are higher for stenting ($40,464; 95%CI: $34,814 – $46,242) vs. GSVB ($21,618; 95%CI: $15,932 - $28,070) and more reinterventions are required following stenting (1.03/patient) vs. GSVB (0.52/patient), making GSVB the preferred strategy for all outcomes considered. Stenting is preferred in patients who are high risk for open repair (>6% 30-day mortality) or if the 5-year primary patency rates of stenting increases to 80%. For very old patients (>95y) and patients with a very short life expectancy (<1.5y), OMT yields higher QALYs.

Conclusions

GSVB is the preferred treatment in 65-year-old patients with aPAAs for all outcomes considered. However, patients at high risk for open repair or without suitable vein should be considered as candidates for endovascular repair. Very elderly patients and patients with a low life-expectancy are best treated with OMT. Further improvement of endovascular techniques that increase patency rates of endovascular stents could make this the preferred therapy for more patients in the future.

INTRODUCTION

Popliteal artery aneurysm (PAA) is the second most common arterial aneurysm after abdominal artery aneurysm (AAA) and accounts for 75 to 80% of all peripheral aneurysms, although the incidence is still less than 0.1%.[1,2] In 50% of patients, PAA is bilateral. PAAs are typically found in older men, with up to a 30:1 ratio, and with a mean age at time of diagnosis of 65 years.[3] A popliteal artery is aneurysmal when the diameter exceeds 2.0 centimeters or when it is more than 1.5 times the size of the normal proximal located superficial femoral artery.[4] PAAs typically occur secondary to atherosclerosis, although other etiologies such as inflammatory disorders, infections and traumas are also described.[1] Unlike an AAA, rupture is not a common complication of a PAA, and appears in less than 5% of all patients with PAA.[5] Although ruptures can be fatal, most hemorrhages are limited to the popliteal space.[6] The most common complication is thrombosis of the PAA, which can lead to complete occlusion or distal embolization that ultimately results in acute or chronic leg ischemia. Up to one-third of the patients that are followed conservatively develop limb threatening ischemia.[1]

Treatment of PAA is recommended if the patient is symptomatic, regardless of the size of the aneurysm. There is a general consensus to treat asymptomatic patients if the PAA measures more than 2.0 cm in diameter.[1] Endovascular popliteal artery repair with covered stents (Stenting) was first described in 1994 and has increased over the last two decades.[7] However, there are no clear guidelines regarding open repair with exclusion of the popliteal artery and greater saphenous vein bypass (GSVB) versus stenting.[8] Endovascular repair has good short-term results and because it is minimally invasive, has a shorter hospitalization period and less early morbidity and mortality, it has been increasingly utilized.[9-11] It is, however, unclear for which patients an endovascular approach is preferred to traditional open repair with greater saphenous vein bypass (GSVB). Although endovascular treatment is increasing, problems remain. Lower patency rates of endovascular covered stents compared with open repair have been reported after two to three years, resulting in more reinterventions and more complications.[10]

Purpose of this study was to synthesize the best-available and most up-to-date evidence from relevant articles regarding the treatment of asymptomatic PAAs (aPAAs) using a Markov decision model in order to determine the best treatment option depending on several patient characteristics.

METHODS

A decision model was developed using the software program TreeAge Pro 2012 (TreeAge Inc., Williamstown, MA, USA) to compare open repair with GSVB and stenting in patients with aPAAs. As a control, to assess the internal and external validity of the model, a non-operative optimal medical treatment (OMT) group was added to the model and these outcomes were compared with published data regarding conservative management of aPAAs. Variables were retrieved from the most relevant and up-to-date published evidence. An extensive search was performed using the MEDLINE database including the keywords “popliteal artery aneurysm”, “popliteal artery aneurysms”, “popliteal aneurysm”, “popliteal aneurysms”, “aneurysm of popliteal”, “aneurysm of the popliteal”, with a language filter for English articles. This resulted in a selection of 1481 unique articles. Subsequently, after titles and abstracts were reviewed, a total number of 1327 articles were excluded. From the remaining 154 articles, only articles which described patency rates, perioperative morbidity and mortality, successful intervention, amputation rate and percentage of reinterventions performed with either open or endovascular repair, were considered eligible. Furthermore, studies were considered eligible studies if they (1) contained original data and (2) were comparative studies, large single treatment studies (>10 patients) or described conservative management of PAAs. The references of these articles were screened for any missing relevant articles. All articles were subjected to critical appraisal as recommended by the Oxford Centre for Evidence Based Medicine.[12] Outcomes retrieved from these 35 remaining articles were calculated into a weighted mean.[1,9-11,13-43] These input variable values are shown in Tables I, II and III.

Health States

A hypothetical cohort of patients with aPAAs entered the model in five possible initial health states and subsequently transitioned in cycles of one year between nine possible health states (Figure 1). For the GSVB group, the initial health states, achieved by the initial treatment, were: "Patent Bypass", "Symptomatic after Bypass" and "Death". "Amputation" or "Patent after Bypass and Percutaneous Transluminal Angioplasty (PTA)") were included as possible health states after the first cycle.

For the stenting group, the initial health states that were possible after initial treatment included: "Patent after Stenting", "Symptomatic after Stenting" and "Death". Five other health states that were included in this arm of the Markov model were "Patent after Stent and PTA", "Patent after Bypass", "Patent after Bypass and PTA", "Symptomatic after Bypass" and "Amputation". "Patent and Symptomatic after Bypass" were included in this group, because they were potential health states after initial stenting.

Patients in the OMT group stayed in this health state until they became symptomatic and needed an intervention.

The model cycled in one year intervals with a half-cycle correction. Half-cycle correction was applied to prevent over- or underestimation, because in general, most events do not only occur at the beginning or end of a cycle.[44,45] The model cycled until all the patients died. The rewards earned in a health state were multiplied by the time spent in this specific health state and the outcomes are presented as accumulated quality-adjusted life years (QALYs) over the remaining average life time for each group.

Assumptions

The following assumptions were made: 1) No distinction was made between the medial and posterior approach of open repair. 2) Patency rates of vein grafts were used. Since these patency rates are higher than the Polytetrafluoroethylene (PTFE) patency rates, the PTFE patency rates are initially not used for comparison in this model, because they will always be dominated by the vein graft (Table III).[24,39] We performed a secondary analysis for elective PTFE bypass. 3) Patency after five years was modeled utilizing a constant hazard rate. 4) Patent is defined as asymptomatic and without any need for reintervention. Not patent is defined as thrombosed/occluded and/or symptomatic and needing reintervention.[38] 5) Secondary patency rates are described as patency rate after PTA or thrombolysis, to restore the blood flow. 6) The procedural (perioperative) mortality is defined as 30-day mortality rate. 7) Major amputations are defined as ankle amputations or higher and are a specific health state.

Table I Quality of life values for different health states and costs.

Health State	**Utilities (QoL)**	**Range**	**Distribution**	**References**
Stay the Same	0.93	0.90 – 0.96	Triangular	47-51
Patent After Bypass	0.93	0.90 – 0.96	Triangular	47-51
Patent After Stenting	0.93	0.90 – 0.96	Triangular	47-51
Patent After Bypass + PTA	0.93	0.90 – 0.96	Triangular	47-51
Patent After Stenting + PTA	0.93	0.90 – 0.96	Triangular	47-51
Patent After Bypass After Stenting	0.93	0.90 – 0.96	Triangular	47-51
Not Patent / Symptomatic	0.57	0.53 – 0.61	Triangular	47-51
Major Amputation	0.19	0.16 – 0.22	Triangular	47-51
Death	0			
Interventions				
Bypass	-0.10	-0.12 – -0.08	Triangular	49,50
Stenting	-0.06	-0.08 – -0.04	Triangular	49,50
Amputation	-0.25	-0.28 – -0.22	Triangular	49,50
PTA/Lysis	-0.04	-0.06 – -0.02	Triangular	49,50
Complication	-0.02	-0.04 – -0.01	Triangular	Assumption
Costs	(2012 US$)			
Bypass	$1,510	$1,135 – $1,885	Normal	+
Stenting	$9,733	$7,298 – $12,168	Normal	+
PTA	$4,125	$3,095 – $5,155	Normal	+
Amputation	$939	$704 – $1174	Normal	+
Hospital stay / day	$1,942	$1,500 – $2,500	Normal	+
Follow-up after bypass	$44	$22 – $66	Normal	+
Follow-up with angiography	$1,372	$1,029 – $1,715	Normal	56
Rehabilitation amputation	$2837	$2,128 – $3,546	Normal	58,59
Long-term care amputees	$5609/year	$4,207 – $$7,011	Normal	58,59
Mean hospital stay	(In days)			
Bypass	7.7	3.0 – 10.0	Normal	13
Stenting	4.3	1.0 – 6.0	Normal	13
PTA	1.2	0.8 – 1.6	Normal	13
Amputation	13.1	9.9 – 16.3	Normal	57

QoL, Quality of life; *PTA*, Percutaneous Transluminal Angioplasty; Lysis, thrombolysis. + Costs are derived from the Medicare Physician Fee Schedule (http://www.cms.gov/apps/physician-fee-schedule/).

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Table II General and intervention related input variables.

Variables	Mean	Range	Distribution	References
General				
Start Age	65 years	65 – 100 years		
Mortality rate +				52,53,54
Mortality rate after Amputation ++				16,32,33,52
GSVB				
Successful Bypass	98%	97.5% – 99.5%	Beta	28
Perioperative Mortality*	1.4%	0% – 4%	Beta	26,18,24
Primary Patency	See Table III			9-11,13,15,18,20, 28,34,38,43
Secondary Patency	See Table III			9-11,13,15,20,28, 34,38,43
Amputation rate	4% / year	3% – 6%	Beta	42
PTFE Bypass Patency	See Table III			24,37,39
Emergent Patency	See Table III			14,29
Stent				
Successful Stenting	97.5%	94% – 100%	Beta	11,23,27,36,40,
Perioperative Mortality*	0.4%	0% – 1%	Beta	11,13,22,25,28,30, 31,41,42
Primary Patency	See Table III			9-11,13,17,21,25,28, 31,34,36
Secondary Patency	See Table III			9-11,13,17,21,25,28, 31,34,36
Stenting After Stent	20%	0% – 50%	Beta	11
Amputation rate	3%	2% – 12%	Beta	25,30,42
OMT				
Stay Asymptomatic	See Table III			19
Amputation rate	30%	13% – 36%	Beta	1,35
Bypass after Symptoms	70%	30% – 95 %	Beta	1,42
Major Amputation				
Perioperative Mortality*	7%	2% – 12%	Beta	16,32,65
Per age group				
50-59y	3.6%	1% – 5%	Beta	33
60-69y	6.1%	2% – 9%	Beta	33
70-79y	9.4%	4% – 14%	Beta	33
80y or older	10.4%	5% – 15%	Beta	33

+ Mortality rate is retrieved from CDC life tables and multiplied by the relative risk of mortality for patients with aPAAs. ++ Mortality rate is retrieved from CDC life tables and multiplied by the relative risk of mortality for patients with major amputations. *Perioperative mortality is defined as 30-day mortality. *GSVB*, greater saphenous vein bypass; *PTFE*, Polytetrafluoroethylene; *OMT*, optimal medical treatment; *y*, years; *CDC*, Centers for Disease Control and Prevention; *aPAAs*, asymptomatic popliteal artery aneurysms.

Table III Primary and secondary patency rates for open and endovascular repair, specified by elective vs. emergent and GSVB vs. PTFE.

Group	Type	Patency	1y	2y	3y	4y	5y
Open	**Elective**	primary	89%	86%	85%	82%	80%
	GSVB	secondary	98%	95%	94%	92%	90%
	PTFE	Primary	77%	67%	58%	54%	50%
		Secondary	84%	78%	71%	66%	63%
	Emergent	Primary	74%	67%	60%	54%	49%
	GSVB	Secondary	92%	88%	81%	76%	70%
	PTFE	primary	N/A	N/A	N/A	N/A	N/A
		secondary	N/A	N/A	N/A	N/A	N/A
Stent	**Elective**	primary	87%	82%	77%	74%	70%
		secondary	90%	88%	85%	81%	77%
OMT	**Stay asymptomatic**		76%	50%	41%	35%	32%

GSVB, greater saphenous vein bypass; *OMT*, optimal medical treatment; *PTFE*, Polytetrafluoroethylene; *vs.*, versus; *y*, year; *N/A*, not available.

Once in this health state, the only two possible health states are to either remain in the amputation state or die. QoL for an amputation stays constant and no re-amputations are included. 8) After a failed bypass or stenting, an additional intervention (PTA / thrombolysis) was possible, but only up to two times. After repeated failure, only re-bypass, re-stenting or amputation was possible. 9) A discount rate of 3% per year was used to adjust future effectiveness and costs because life years and money in the near future are considered to have more value than life years and money in the distant future.[46]

Quality of life

QoL-values were assigned to all the health states and retrieved from published articles (Table I). No measured QoL-values have been published for patients with PAAs, and therefore data were retrieved from relevant studies describing QoL in patients with asymptomatic peripheral arterial disease (PAD) in the femoropopliteal area, and used in the reference-case.[47-50] However, since the QoL-values for PAD are not exactly the QoL-values for PAAs, an additional analysis was performed using the QoL for patients with AAA.[51] Patients in the symptomatic health states have symptoms due to acute or chronic limb ischemia (thromboembolism), radiating pain from pressure on the popliteal fossa nerves (growth of the popliteal aneurysm) or bleeding in the popliteal space (rupture). For patients with amputations, studies which describe QoL after amputation were used.[48]

Operative management

Operative mortality was defined as 30-day mortality. Variable values and their range were retrieved from published data. To define high vs. low risk, we searched for the prevalence of the most reported risk factors, such as gender (95% male), presence of hypertension (65%), diabetes (15%), smoking (35%) and cardiovascular status and history.[1,11,24,37] If a patient with a PAA has one of these risk factors, the operative bypass risk will increase compared with the peri-operative mortality of 1.4% for bypass in the reference-case. To determine the increase in risk for operation, we performed a secondary relative risk (RR) analysis. Relative risk sensitivity analysis was applied to all perioperative mortality risks and performed over a wide range between RR = 0.5 and RR = 5.

Risk associated with amputation is age dependent; therefore an age-dependent perioperative mortality risk for major amputation was integrated into the model.[33] For extra interventions, disutilities (QoL decrements) were included (Table I) to account for additional hospitalization, rehabilitation, and morbidity. Furthermore, for patients who develop short-term complications, extra disutilities are included, because these patients have a few days longer stay in the hospital which is associated with a lower short-term QoL. Values for these disutilities were retrieved from published data.[50]

Patency rates

Primary and secondary patency results for open and endovascular repair were retrieved from several different studies, since not all studies report patency for the same time period, and a weighted mean was calculated (Table III).[9-11,13,15,17,18,20,25,28,31,36,43] Patency percentages were converted to annual patency hazard rates, with a high hazard rate in the first year following intervention which tapers off during subsequent years. Beyond five years patency data is sparse and the hazard rate in the fifth year was extrapolated assuming a constant rate for the remaining lifetime of the patient. These patency rates were included in tables in TreeAge and determined when patients needed a reintervention, and were the true trade-off in this decision model: lower

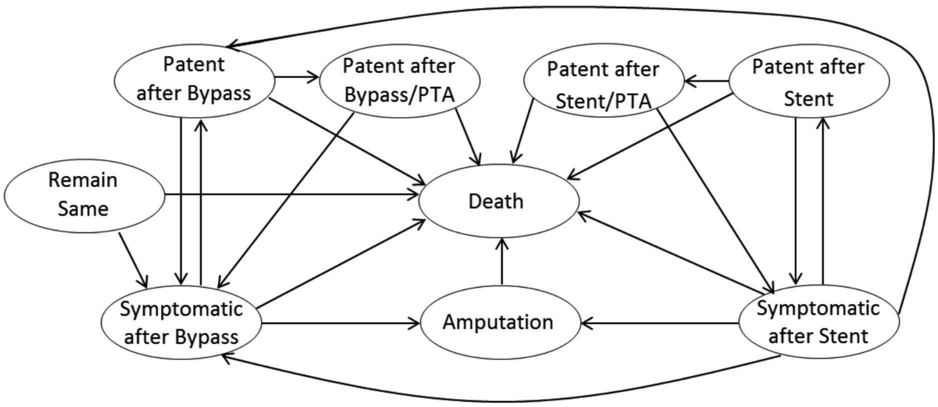


Figure 1 Simplified bubble diagram of a Markov state transition model for treatment of asymptomatic popliteal artery aneurysms. Each health state has a possible transition to itself which is not shown in this figure for clarity of the figure. * "Remain Same" health state only included in the OMT group. ** "Stent" health states only included in the Stenting group. *PTA*, Percutaneous Transluminal Angioplasty; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.

30-day mortality rates and a higher reintervention rate after stenting (assumption: not patent is equal to symptomatic and the need for reintervention) vs. a higher 30-day mortality, but higher patency rates and therefore less reinterventions after GSVB. Patency hazard rates were calculated for the initially used treatments in the reference-case (elective GSVB and elective stenting), and for emergent GSVB and elective PTFE graft use for the secondary analysis.
For the OMT group, the percentage of patients who continued to be asymptomatic was calculated in the same way as for patency using data derived from series describing the conservative management of aPAAs.[19] Annual failure rates were derived with an annual constant hazard rate, extrapolating the hazard rate for the fifth year.

Mortality rates
Mortality rate is age dependent, so a life table was integrated into the model.[52] A disease specific mortality rate was determined using hazard ratios (HR) and the life-table for an age, sex and race (ASR) adjusted control group. Because of the lack of data specifically for patients with PAAs, HRs for 65-year-old patients with asymptomatic PAD were used in the reference-case.[53] However, similar as for the QoL-values, the mortality rate for PAD is not exactly equal to the mortality rate for PAA patients. Therefore, an additional analysis was performed with mortality rates for AAA-patients.[54] It is estimated that PAAs occur in 14% of patients with an AAA[3] and AAA is present in 55% of patients with a PAA.[24] Furthermore, the prevalence of hypertension and diabetes in those with PAAs is in the range of 54.7% - 66% and 6.6% - 16%, respectively,[24,35] and for patients with AAAs the prevalence of hypertension is 66% and for diabetes 15%.[54] This mortality rate was tested in a wide range, including the mortality rate for both PAD and AAA patients. For the amputation group, the mortality rate was higher, and calculated by multiplying the mortality rate by the RR for amputees and integrated in the model.[55]

Costs
A cost-effectiveness analysis was performed to evaluate the total costs and incremental cost-effectiveness-ratios (ICERs). Costs were evaluated from a health-care perspective and costs were based on reimbursements (2012 US$). First, we defined the Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes for the procedures (27880, 35583, 37224, 37226 and 99212) and retrieved the reimbursement amounts for these procedures (http://www.cms.gov/apps/physician-fee-schedule/) through the Medicare database. These costs included both professional and technical components and are shown in Table I. Costs for follow-up arteriograms were retrieved from published data.[56] Hospital costs were calculated by multiplying the cost of hospital stay per day by the mean hospitalization length per procedure, and added to the total costs for the interventions.[13,57] For patients with complications, the costs for additional days in the hospital were also added to this total. Additionally, for patients who needed an amputation, costs for rehabilitation, follow-up and long-term care for their remaining lifetime were included.[58,59] ICERs were calculated by the difference in costs between two treatment options divided by the difference in effectiveness (QALYs) of the treatment options. The willingness-to-pay-threshold, the maximum amount that society is willing to pay for one additional year in perfect health (1.0 QALY), was assumed to be $60,000.[60]

Data analyses

In the reference-case analysis, a cohort of 65-year-old men with an aPAA of an undefined race, an operative mortality risk of 1.4% and a QoL of 93% entered the Markov model comparing GSVB, stenting and OMT. The other variables used in this reference-case are described in Table II. In order to assess the uncertainty in the variables, a probabilistic sensitivity analysis (PSA) was performed with 10,000 samples using Monte Carlo simulation. PSA is utilized because the parameters in the model are not fixed but uncertain and more realistically represented with distributions of values. Beta distributions were used for the probabilities (parameterized by the total number of patients and the number of patients with the event of interest), triangular distributions for QoL-values (parameterized by the best available minimum, maximum, and most likely value for these utilities) and normal distributions for costs and hospitalization (parameterized by mean and standard deviation).[61] Monte Carlo simulation is a computerized mathematical technique that allows one to see all possible outcomes and probabilities for any choice of action. We utilized this to calculate the model 10,000 times, each time using different randomly selected values from the distributions of these variables. Outcomes are given with a 95% credibility interval (95%CI), which reflect the uncertainty around the input variables instead of the often used 95% confidence interval, which reflects the uncertainty around outcomes.

Secondary analyses were performed for the "AAA-analysis" (AAA input variables instead of PAD variables for mortality rate and QoL-values), total expected reinterventions, cost-effectiveness, PTFE bypass grafts and sensitivity analyses for several input variables.

RESULTS

Reference-case

Figure 2a depicts the expected QALYs for each year after the three possible treatment options for 65-year-old men with an aPAA. The total expected QALYs were 8.43 (95%CI: 8.21 – 8.64) in the GSVB group versus 8.07 (95%CI: 7.84 – 8.29) in the stenting group. OMT yielded a far lower effectiveness of 5.77 QALYs (95%CI: 5.43 – 6.11). PSA showed that GSVB was the preferred initial treatment in 100% of the 10,000 simulations, with an average of 0.36 (95%CI: 0.14 – 0.58) QALYs (≥4 months in perfect health) difference compared with stenting.

For the "AAA-analysis", which used input data obtained from AAA related articles instead of PAD related articles which were used in the normal analysis, GSVB also yielded higher QALYs: 7.18 (95%CI: 6.99 – 7.37) vs. 6.92 (95%CI: 6.73 – 7.11) in the stenting group and 5.12 QALYs (95%CI: 4.84 – 5.40) for OMT. PSA showed that the difference between GSVB and stenting was 0.26 QALYs (95%CI: 0.07 – 0.45).

Life expectancy and age

If changes in the model were made regarding life expectancy and age, there also was a change in the preferred treatment option. A sensitivity analysis and threshold analysis performed on life expectancy and age is shown in Figure 2a and 2b respectively. In Figure 2a, the thresholds are shown for life expectancy after intervention. Comparing the stenting group with GSVB, the preferred treatment for a patient with a life expectancy of 2.3 years or less is stenting.

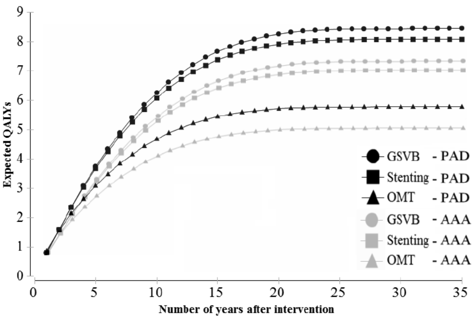
However, if the OMT group is also taken into account, the preferred treatment is OMT for 1.5 years of life expectancy or less. For 65-year-old patients with a life expectancy of more than 2.3 years GSVB would be preferred. If the analysis was performed with the AAA input variables, these numbers were also 1.5 and 2.3 years.

Figure 2b demonstrates that for elderly patients that reach the age of 88 years, stenting is the treatment with the highest expected QALYs. Every patient younger than 88 years should be treated with GSVB, unless they have a recognized terminal condition that is likely to result in death within 2.5 years, while no interventions should be performed after a patient reaches the age of 95 years. However, the differences are small and so costs and patient preferences should be taken into account.

If the analysis was performed with the AAA input variables, stenting is the treatment with the highest expected QALYs after the age of 86. No interventions should be performed after the age of 92.

Perioperative mortality

The relation between perioperative GSVB mortality risk and age of initial intervention indicated that stenting would be the preferred treatment option over GSVB in the reference-case patient, if the perioperative mortality risk of GSVB would rise to 6% (very high-risk patient) (Appendix Figure 1).



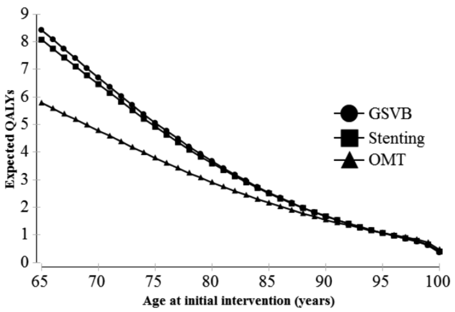


Figure 2a Total expected QALYs at *n* years after initial intervention of aPAA for GSVB, stenting and OMT. In black, the results for the reference-case (65-year-old men with an aPAA with PAD-analysis). In grey, the results for AAA-analysis. See Results section for further details. Threshold points (defined as where different lines cross, and preferred treatment changes): 1.5y (Stent/OMT) and 2.3y (GSVB/Stenting). *QALYs*, Quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment; *PAD*, peripheral arterial disease; AAA, abdominal aortic aneurysm.

Figure 2b Total expected QALYs for GSVB, stenting and OMT at the age of initial intervention for the reference-case patient (men with an aPAA with PAD-analysis). See Results section for further details. For clarity, the AAA-analysis is not depicted, due to overlap with the reference-case analysis.
QALYs, Quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.

Perioperative mortality analysis performed with the RR approach showed the same results. If the RR approach was only applied for open repair and amputation, the threshold point was at an RR = 4.21, which is comparable with a perioperative mortality for bypass of 5.9%. When the RR approach was also applied to stenting, GSVB would always be the preferred treatment for a RR between 0.5 and 5, since the threshold point occurs at 5.41 (Figure 3).

Patency

A sensitivity analysis on the patency rates was performed in order to model the effectiveness of the stenting group if there were improvements in the endovascular techniques. Figure 4 shows the total expected QALYs if different 5-year primary patency rates were utilized. By improving the 5-year primary patency rate of stenting to 80%, stenting becomes the preferable option for treating aPAAs. Other threshold points occur when there is improvement of 3-year primary stent patency to 85% and 5-year secondary patency to 86%.

PTFE

Changing the type of bypass from GSVB to PTFE, and thereby changing the patency rates (Table III), will also change the preferred treatment option. With 7.66 QALYs (95%CI: 7.46 – 7.86), PTFE bypass yields lower outcomes than stenting (7.96 QALYs; 95%CI: 7.73 – 8.18). The QALYs

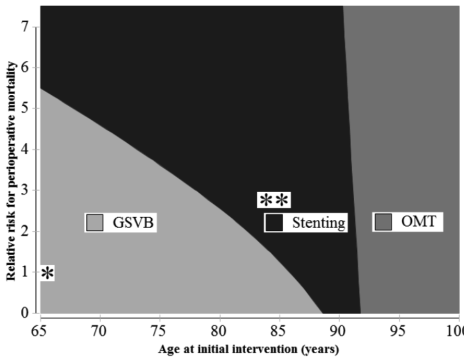


Figure 3 Two-way sensitivity analysis depicts the relation between age of initial treatment and relative risk for perioperative mortality. On the x-axis, the age of initial intervention is represented, and on the y-axis the relative risk. For example: A 65-year-old patient with a RR of 1 (reference-case, *): GSVB is preferred. For an 85-year-old patient with a RR of 3 (**), stenting is preferred.
GSVB, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.

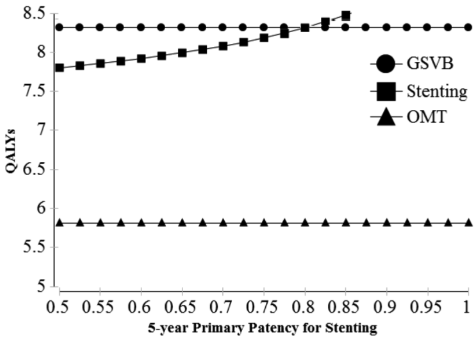


Figure 4 Total expected QALYs for different 5-year primary patency rates of stenting for the reference-case (65-year-old men with an aPAA). Threshold patency (defined as where stenting is preferred above GSVB) is 80%. Both interventions are preferred over OMT for the reference-case, regardless of the 5-year primary stent patency. *aPAA*, asymptomatic popliteal artery aneurysm; *QALYs*, Quality-adjusted life years; *GSVB*, greater saphenous vein bypass; stenting, endovascular repair with covered stent; *OMT*, optimal medical treatment.

for the stenting group also decrease, because bypass with PTFE is performed after stent occlusion. PSA revealed that when no suitable vein is available, stenting is preferred over open repair with PTFE graft in 100% of the 10,000 samples in the reference-case. For the AAA-analysis these numbers were: 6.57 QALYs (95%CI: 6.40 – 6.75) for PTFE bypass and 6.84 QALYs (95%CI: 6.64 – 7.03) for stenting.

Reinterventions

Figure 5 shows that the total expected reinterventions were 0.52 per patient in the GSVB group and 1.03 per patient in the stenting group. Patients in the OMT group would be expected to undergo a total of 1.13 interventions per patient during their lifetime. Most reinterventions occur in the first five years after initial intervention. Furthermore, 45% of interventions in the OMT group were amputations, versus 3.9% and 8.7% in the GSVB and stenting groups, where most reinterventions were PTA or thrombolysis (Table IV). The percentages for type of reintervention in the AAA-analysis were the same.

Table IV Total expected reinterventions for three different treatment groups of aPAAs

Type of reintervention	GSVB group (reint/ patient (%))	Stenting group (reint/patient (%))	OMT group (reint/ patient (%))
Bypass	0.14 (26.9%)	0.28 (27.2%)	0.34 (30.1%)
Stent	N/A	0.06 (5.8%)	N/A
PTA/thrombolysis	0.36 (69.2%)	0.60 (58.3%)	0.28 (24.8%)
Amputation	0.02 (3.9%)	0.09 (8.7%)	0.51 (45.1%)
Total	0.52 / patient	1.03 / patient	1.13 / patient

aPAAs, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *reint*, reinterventions; *OMT*, optimal medical treatment; *PTA*, percutaneous transluminal angioplasty; *N/A*, not applicable.

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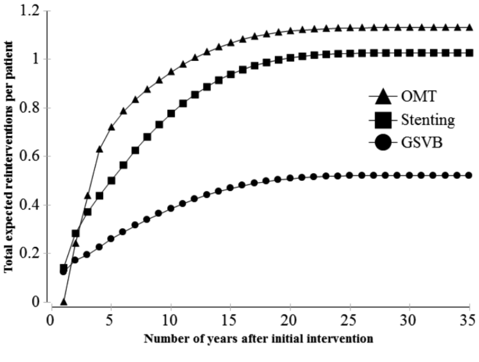

Figure 5 Total expected reinterventions per patient after initial treatment of aPAAs for reference-case (65-year-old men with an aPAA). X-axis is the number of years after initial intervention and on the y-axis the total expected reinterventions per patient. See Results section for further details. Note that these are the first interventions for OMT, since no initial intervention was performed in the OMT group.
aPAA, asymptomatic popliteal artery aneurysm; *GSVB*, greater saphenous vein bypass; stenting, endovascular repair with covered stent; *OMT*, optimal medical treatment.

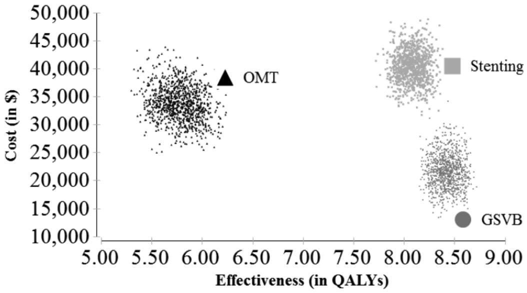

Figure 6 Cost-effectiveness scatterplot of GSVB, stenting and OMT for treatment of asymptomatic aPAAs for the reference-case patients (65-year-old men with an aPAA). Each point represents a single patient value based on the analysis of 10,000 reference-case patients in the Monte Carlo simulation. Depicted is that GSVB is dominant over the other two treatment options, because the effectiveness is higher and costs are lower. *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment; *aPAA*, asymptomatic popliteal artery aneurysm; *QALYs*, quality-adjusted life years.

Costs

Figure 6 depicts PSA for the cost-effectiveness in a scatterplot with 10,000 random samples. Total expected costs from the health-care perspective for the reference-case patient are $21,618 (95%CI: $15,932 - $28,070) for GSVB, $40,464 (95%CI: $34,814 – $46,242) for stenting and $33,672 (95%CI: $27,478 – $40,336) for OMT. Since costs are higher and expected QALYs are lower for stenting and OMT compared with GSVB, stenting and OMT were 'dominated' and not the preferred option. However, in case no autologous vein is available, stenting was preferred, with an ICER of $2,953/QALY compared with OMT (Table V). Sensitivity analysis with a willingness-to-pay threshold of $60,000 showed that after the age of 88 years (difference between GSVB and OMT is 0.22 QALYs), intervention is not cost-effective (ICER: 88y = $50,739/QALY; 89y = $68,043/QALY).

If the analysis on the costs was performed with the AAA-analysis, the expected costs were $20,985 (95%CI: $15,505 – $27,374) for GSVB, $38,024 (95%CI: $32,589 – $43,591) for stenting and $31,284 (95%CI: $25,451 – $37,421) for OMT. GSVB is dominating stenting and OMT, and ICER for stenting compared with OMT is $3,743/QALY (Table V).

Sensitivity analyses on assumptions

Sensitivity analyses performed on the assumptions made in the model did not significantly change the outcomes of the model. Some assumptions (PTFE, patency, perioperative mortality) were already described previously in this section. Furthermore, the variables for the medial and posterior approach (e.g. perioperative mortality) were within the range tested in PSA. The QoL for patients with amputation was tested in the widest range possible (0 – 1) and this did not change the preferred treatment (Appendix Figure 2). If an unlimited number of additional PTAs were possible, instead of only two after each intervention, there were no changes in the outcomes (Appendix Figure 3). Additionally, testing the discount rate over a wide range (0% – 100%) showed that QALYs for GSVB remained the highest (Appendix Figure 4) and costs the least over the complete range that was tested (Appendix Figure 5).

Table V Total expected costs and ICERs for three different treatment groups of aPAAs.

	GSVB	Stenting	OMT	GSVB-AAA	Stenting-AAA	OMT-AAA
Costs	$21,618	$40,464	$33,672	$20,985	$38,024	$31,284
Benefit	8.43	8.07	5.77	7.18	6.92	5.12
Incr. Costs	-	$6,792*	-	-	$6,749*	-
Incr. benefit	-	2.30*	-	-	1.80*	-
ICER, in $/QALY	Dominant	2,953/QALY*	-	Dominant	3,743/QALY*	-

* Incremental costs and effectiveness of stenting compared with OMT. Note that GSVB is dominant compared with stenting and OMT since both the benefit is higher and the cost is lower making an ICER irrelevant for this comparison. The first three columns are the reference-case; the last three columns are performed with the "AAA-analysis". Costs are in US $, benefit in QALYs.
ICER, Incremental cost-effectiveness ratio; *aPAAs*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *OMT*, optimal medical treatment; *AAA*, *abdominal aortic aneurysms*; *QALYs*, quality adjusted life years.

DISCUSSION

Over the last decade, there is an increase in reports in the literature on endovascular popliteal aneurysm repair using covered stents.[21,27,30,34,62] These minimally invasive procedures generally carry less operative morbidity and mortality, shorter hospitalization, fewer complications and a better perioperative QoL. The short term results are promising, but the few articles with long-term outcomes report a much worse patency for five years and beyond, compared with open repair.[9,11] These articles often describe the primary and secondary patency rates as the primary outcome, but pay less attention to other important and relevant variables such as operative mortality, technical success, QoL and costs. Not all the advantages described for endovascular aortic repair (EVAR) are applicable to endovascular treatment of PAA. First, the popliteal artery is smaller in diameter compared with the aorta, which can lead to a higher incidence of thrombosis and occlusion. Second, the popliteal artery is located in the flexible knee joint that can predispose to stent graft fracture and subsequent occlusion.

Analysis of our decision model indicated that GSVB remains the gold standard for treatment of aPAAs. PSA in the reference-case determined in 100% of the 10,000 simulations GSVB as preferred treatment, with an average of four months in perfect health as difference, which is the average for a complete group. It also confirms that elderly patients and patients with a very short life expectancy should probably not be treated at all. Based on current data, endovascular repair is indicated for high risk patients not suitable for open repair and for patients without suitable autologous vein. With the evolution of the endovascular procedures and associated increasing patency rates, they can be a feasible option for more patients in the near future.

Although the Markov model is performed with several different input variables, one limitation is that these variables rely on published data. If the input data change, the outcomes will change accordingly. Furthermore, we combined data from different articles and therefore data from different patients. This is a limitation of all decision models, and therefore extensive sensitivity analyses were performed to explore the effects of different assumptions concerning the input values to evaluate if these would change the outcomes of the model. Changing the basic assumptions over a wide range showed that did this not significantly change the outcomes. Another significant limitation is the lack of QoL-values and disease-specific mortality rates for patients with PAAs which required the use of data from patients with PAD, or patients with AAA. When we used a wide range for the QoL-values and disease-specific mortality rates, PSA showed that using either AAA or PAD values did not significantly change the outcomes of the model, because mortality rates and QoL-values were similarly applied to all treatment groups. Although costs and QALYs were slightly lower in the AAA-analysis, the overall outcomes are similar and the ratios between the treatment groups were similar, independent of data for PAD or AAA were used (Table V). Lastly, this model is based on data for men, because of lack of data for women with a PAA. Although PAA is typically a disease that is more prevalent in older men, we believe that the general results could apply to female patients as well.

Another issue is that the definition of patency is not uniformly described in different articles. We attempted to overcome this problem by retrieving primary and secondary patency rates of open and endovascular repair of PAAs from 35 articles to attenuate the effect of a single article. Other minor limitations include the fact that there is heterogeneity of PAA morphology (some patients have a diffuse pattern of arterial enlargement while others have more focal aneurysmal degeneration) and that this decision analysis model requires input from information that may not specifically address specific types of PAA. Additionally, no distinction was made between single stents or multiple stents, because most articles did not describe the number of stents used. We acknowledge that the use of one stent is the optimal situation. The hospitalization period of 4.3 days that was used for the stenting analysis seems quite long. However, in performing our analysis, we tried to be objective and used available published data, which likely included information from the beginning of the "learning curve". This is why we performed extensive sensitivity analysis on the hospitalization period for stenting and for GSVB over a wide range combined with a PSA and this did not significantly change the outcomes (Appendix Figure 6). The strength of PSA is that it can combine all the uncertainty around the variables at the same time. Our analysis showed that even if the hospitalization period for stenting would decrease to one day or less, GSVB has still lower costs and is cost-effective with regard to the "willingness to pay" threshold of $60,000/QALY. Despite these limitations, we feel that the information generated by this decision analysis is clinically relevant.

Decision analysis is a very useful tool when making important decisions in situations of uncertainty. Its strengths are to combine all the clinically relevant factors and not focus on one particular outcome. In an article assessing economic evaluation of endovascular and open treatment in patients with lower extremity PAD, the strengths of decision models are described. These include the analytic flexibility, the fact that all available information can be synthesized together and that all uncertainty in model inputs can be taken into account simultaneously, with PSA.[63] Although level 1 evidence was not available for PAA, we combined the best available literature and used PSA with wide ranges to assess the uncertainty around the variables used in the model. This decision model is especially designed as a clinical tool for the surgeon and determines the preferred treatment option for each unique patient. However, since costs are rising in healthcare worldwide, cost-effectiveness is also important to select the preferred treatment option. Our analysis indicates that stenting has lower expected QALYs and higher costs compared with GSVB. Furthermore, more reinterventions are necessary and a higher percentage of reinterventions are amputations. Nevertheless, if a suitable vein is not available, endovascular treatment is still preferred over OMT. A recent retrospective study, that assessed charges and total reinterventions of more than 2,000 Medicare patients with symptomatic and asymptomatic PAAs described similar results and showed that total costs are higher and more reinterventions are required in the endovascular group.[64]

It is important to know if it is beneficial for a patient with an aPAA to perform open or endovascular treatment and this decision analysis model helps to make a more contemplated decision. As shown above, patients with a life expectancy of less than 1.5 year, for example due to a recognized terminal condition, or elderly patients above 95 years are not indicated for intervention for aPAAs. This follows a logical explanation: it is not worth it for someone to undergo surgery for an asymptomatic disease, with all the complimentary morbidity, chance for earlier mortality and high costs if they can profit from the advantages for only a very short time. Furthermore, it is difficult to estimate a patient's life expectancy exactly, so this "1.5 year" is merely an overall estimate and serves as a guide when deciding on the appropriate choice of therapeutic options. Other analysis showed when 30-day perioperative mortality of open repair increases and reaches 6%, endovascular repair is the preferred treatment in most patients. Of course, this is very arbitrary and it is very difficult to define a patient as a "6% chance for perioperative mortality risk". To clarify this, we repeated the analysis with a relative risk (RR). It is easier to estimate a RR, or a risk-profile (e.g. low, medium or high-risk), for patients than an absolute risk. The analysis on perioperative mortality with RR was performed in two ways by first applying RR only to GSVB and then to both treatments. Both analyses show the same results and recommended bypass, even when RR was not applied to stenting and so one of the analyses was in advantage of the stenting group.

In all the studies, the most described risk factors are gender, presence of hypertension (present in 65% of the patients), diabetes (15%), smoking (35%) and cardiovascular status. For this patient group a weighted mean of 1.4% for perioperative mortality for open repair was defined. These risk factors are additive and will increase the risk profile and perioperative mortality. A complete analysis of contribution of all the separate risk factors to the perioperative mortality is beyond the scope of this paper. Furthermore, if PTFE bypass grafting, instead of GSVB, is performed and compared with stenting, stenting would be the preferred treatment option. This implies that patients without suitable autologous veins should be treated with an endovascular approach, irrespective of their risk profile.

Because of the lack of clear guidelines for treatment of aPAAs, decisions must be made at the patient level. Our decision analysis can be a good guideline for the treatment of patients with aPAAs. It also supports the general consensus that aPAAs that exceed 2 centimeter should be treated to prevent complications.

CONCLUSIONS

In conclusion, based on current data in the literature used in this decision analysis, GSVB is slightly preferred over stenting in the treatment of 65-year-old patients with asymptomatic PAAs. Stenting is accompanied by higher costs, less effectiveness and more reinterventions. However, those who are at higher risk for open repair or have no suitable autologous vein available should be considered as candidates for stenting. Very elderly patients and patients with a low life-expectancy should be treated with optimal medical management. Further improvement of endovascular techniques that increase the primary and secondary patency rates of stenting could make this the preferred initial therapy for more patients in the future.

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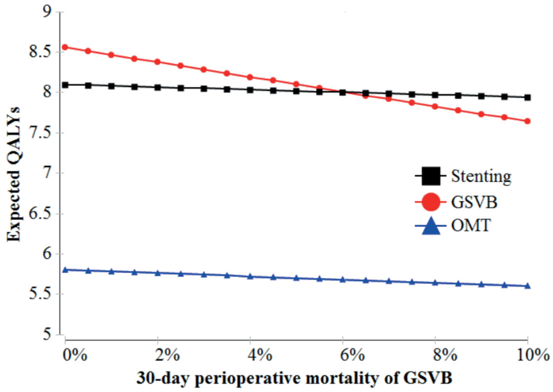
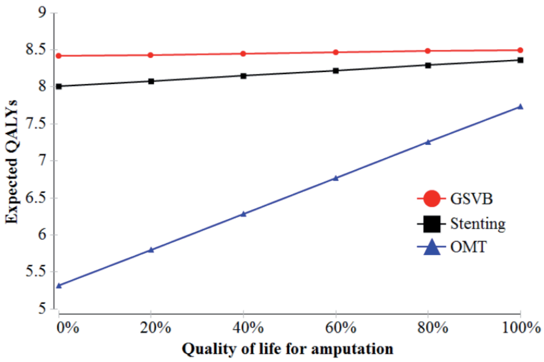
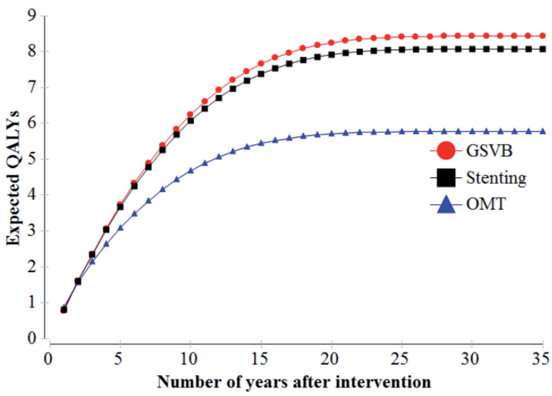
APPENDIX



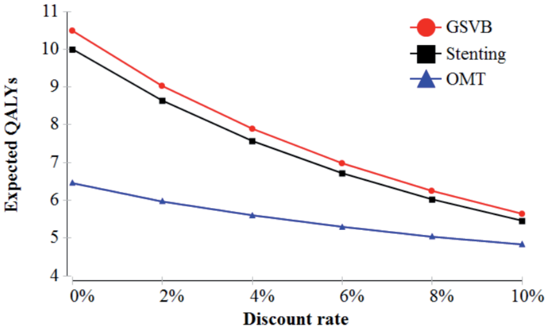
Appendix Figure 1 Total expected QALYs for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT per 30-day perioperative mortality. This figure depicts that expected QALYs for stenting are higher if 30-day perioperative mortality of GSVB increases to 6% (Reference-case: 65-year old men with aPAA). *QALYs*, quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.



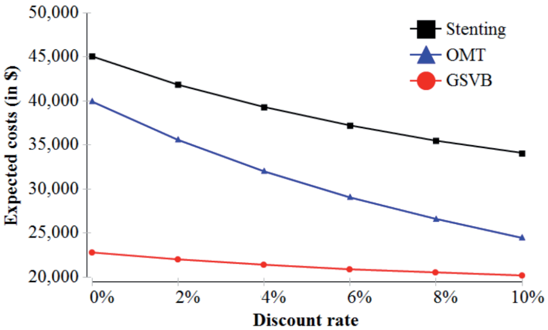
Appendix Figure 2 Total expected QALYs for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT per quality of life for amputation. This figure depicts that expected QALYs for GSVB are always higher than for stenting and OMT, and that the total QALYs for OMT are most affected by quality of life for amputation.
QALYs, quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.



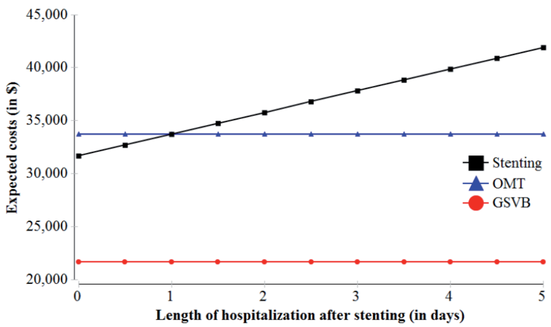
Appendix Figure 3 Total expected QALYs for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT if an unlimited number of PTAs were possible. This figure depicts that expected QALYs for GSVB (8.43, in reference-case 8.43), stenting (8.08, in reference-case 8.07) and OMT (5.76, in reference-case 5.77) are almost equal to the reference-case, if an unlimited number of PTAs were possible (Assumption in reference-case: only two PTAs possible after every intervention).
QALYs, quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment, *PTA*, percutaneous transluminal angioplasty.



Appendix Figure 4 Total expected QALYs for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT per discount rate. This figure depicts that expected QALYs for all treatments decrease if the discount rate is increased, but GSVB remains the preferred treatment option (Reference-case: 65-year old men with aPAA).
QALYs, quality-adjusted life years; *aPAA*, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.



Appendix Figure 5 Total expected costs (in $) for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT per discount rate. This figure depicts that expected costs for all treatments decrease if the discount rate is increased, but GSVB remains the least expensive treatment option (Reference-case: 65-year old men with aPAA).
aPAA, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.



Appendix Figure 6 Total expected costs for treatment of aPAAs in the reference-case patient for GSVB, stenting and OMT per length of hospitalization. This figure depicts that the expected costs for stenting are always higher than for GSVB, regardless of the length of hospitalization for stenting (Reference-case: 65-year old men with aPAA).
aPAA, asymptomatic popliteal artery aneurysms; *GSVB*, greater saphenous vein bypass; *stenting*, endovascular repair with covered stent; *OMT*, optimal medical treatment.

CHAPTER 11

A clinical decision model for selecting the most appropriate therapy for uncomplicated chronic dissections of the descending aorta

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ABSTRACT

Objective

The optimal treatment for patients with uncomplicated chronic Stanford type B aortic dissections (chTBAD) is still matter of debate.

Methods

A Markov decision-analysis model compared chTBAD patients treated with initial open surgical repair (OSR), thoracic endovascular aortic repair (TEVAR) and optimal medical therapy (OMT) followed by OSR or TEVAR if indicated during follow-up (OMT-OSR and OMT-TEVAR). Procedural risks, aortic growth and rupture rates, outcomes and quality of life-values were derived from best-available evidence in the literature. A chTBAD treatment strategy decision tool was developed, including the four key variables age, sex, surgical risk, and maximum initial aortic diameter. Primary outcome was quality-adjusted life years (QALYs).

Results

For the reference-patient cohort, 55-year-old men with chTBAD with a maximum aortic diameter of 5.0 cm, medium-risk for surgery and a threshold for surgery of 6.0 cm during follow-up, OSR yielded higher QALYs with 10.06 (95%CI: 9.52 – 10.56) QALYs, versus 9.92 (95%CI: 9.23 – 10.58) after TEVAR and 9.64 (95%CI: 9.38 – 9.88) and 9.40 (95%CI: 9.11 – 9.69) QALYs for OMT-OSR/ OMT-TEVAR. The difference between OSR and OMT-OSR is 0.42 QALYs (95%CI: 0.01 – 0.81), and between TEVAR and OMT-TEVAR: 0.52 (95%CI: 0.04 – 0.68). This showed that intervention is preferred over OMT. Change of the four variables resulted in change of preferred treatment. In general, OSR was the preferred treatment in younger patients with larger aortic diameter and in low-risk patients. TEVAR was preferred in elderly patients with large aortic diameter and if the aortic diameter threshold for repair decreases. OMT was the optimal therapy in high-risk patients, elderly patients or in patients with small aortic diameters.

Conclusions

This decision-analysis model shows that there is no "one size fits all" treatment for uncomplicated chTBAD. For the reference-patient cohort, intervention is preferred over OMT. Age is the most important deciding factor followed by initial aortic diameter. Immediate OSR is the preferred treatment option in younger patients with large initial aortic diameter and in low-risk patients. Immediate TEVAR is preferred in elderly patients with large initial aortic diameter and in patients with a lower threshold for surgery. OMT should be considered in high-risk patients, patients with small initial aortic diameters and in patients older than 80 years unless their initial aortic diameter exceeds 5.5cm. However, the differences in some patient groups are clinically insignificant, allowing a major role for patient preferences and hospital-specific considerations. This clinical decision model may guide chTBAD treatment.

INTRODUCTION

Aortic dissection is a potentially fatal condition with a mortality rate up to 30%.[1] Aortic dissections are usually arbitrarily classified after 14 days of symptoms as chronic dissections. Stanford type B dissections are defined as "limited to the descending aorta, and the intimal tear is usually within 2 to 5 cm of the left subclavian artery".[2]
The optimal treatment option for patients with an uncomplicated chronic type B aortic dissection (chTBAD) is controversial. Where the original debate had two positions, optimal medical therapy (OMT) with beta-blockers[3] and traditional open surgical repair (OSR),[4] a third treatment strategy, thoracic endovascular aortic repair (TEVAR), has been increasingly utilized during the last two decades. Good short-term results have been observed with relatively low peri-operative morbidity and mortality.[5-7] However, the reintervention rates after TEVAR are higher compared with traditional OSR, and aortic rupture occurs in approximately 1.5% of patients after TEVAR during their remaining lifetime.[8]
Unfortunately, no single treatment strategy is clearly preferential and Level 1 evidence regarding treatment specific outcomes is lacking. The INSTEAD trial was the first randomized study which compared TEVAR followed by OMT versus OMT only in patients with uncomplicated chTBAD. This study showed no significant difference in rupture, survival and reintervention after two years of follow-up.[9]
The primary goal of this article is to assess the effect of TEVAR, OSR and OMT on the quality-adjusted life years (QALYs) for specific groups of patients with uncomplicated chTBAD with a decision analysis model, synthesizing the best available evidence from the scientific literature. Secondary objective is to provide a treatment strategy decision tool for the surgeon, based on four patient characteristics: age, sex, initial aortic diameter and surgical risk-profile.

METHODS

Model and assumptions

A Markov cohort model was developed to simulate hypothetical cohorts of patients with chTBAD suitable for OSR and TEVAR, using TreeAge Pro 2012 (TreeAge Inc., Williamstown, MA, USA). A Markov model provides a convenient way of modeling prognosis for clinical problems with ongoing risk. The model assumes that the patient is always in one of a finite number of health states. All events are modeled as transitions from one health state to another. Each state is assigned a utility (quality-of-life (QoL) value), and the contribution of this QoL-value to the overall outcome depends on the length of time spent in the health state.[10]
Because of differences in natural history, patients with connective tissue disorders (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome etc.) were not considered. Four different treatment options were evaluated in this model: (1) immediate elective OSR or (2) TEVAR, (3) OMT followed by OSR (OMT-OSR) or (4) TEVAR (OMT-TEVAR), if required for later complications. Indications for intervention after OMT included an aorta diameter of 6.0 cm during follow-up, emergency repair for aortic rupture or other dissection-related complications requiring intervention. Additionally, treatment strategies were examined for use of different aortic diameter

thresholds for surgery during follow-up after OMT, including a threshold of 5.5 cm and 6.5 cm.[11] For the Markov decision analysis model, several different health states were defined for the four different treatment strategies of chTBAD. The transitions between the health states are shown in a simplified bubble-diagram in Figure 1. The model cycled in 1-year cycles and transitions between the health states were based on probabilities derived from an extensive search in the literature (Table I). A discount rate of 3% per year was used to discount future effectiveness.[12]

Patients in the first treatment group, immediate elective OSR, can start in five different initial health states after the initial intervention: "Good postoperative recovery after OSR", "Stroke after OSR", "Paraplegia after OSR", "Renal Failure after OSR" and "Dead". Stroke, paraplegia and renal failure were chosen because these are clinically the most relevant long-term morbidities after chTBAD repair.[13] Almost all the OSR cases were performed by direct aortic repair with posterolateral thoracotomy. Patients in the "Good postoperative" state could remain well without complications or could develop aortic or dissection-related complications, such as rupture, expanding dissection, recurrent pain or false aneurysms. These patients could die due to these complications, or stay alive. If they survived these acute complications, an emergency reintervention was required. Patients could subsequently recover well, die due to the reintervention, or develop long-term morbidity. For the patients in the "Stroke", "Paraplegia" and "Renal Failure" health-states, the same options were possible. However, we assumed that if a patient in one of these health-states suffered another complication which led to long-term morbidity, they transitioned to another health-state: "Multiple long-term morbidities". Once in this health-state, the health of the patient was decreased to a minimum and we assumed that a third long-term morbidity or complication would be equivalent to death.

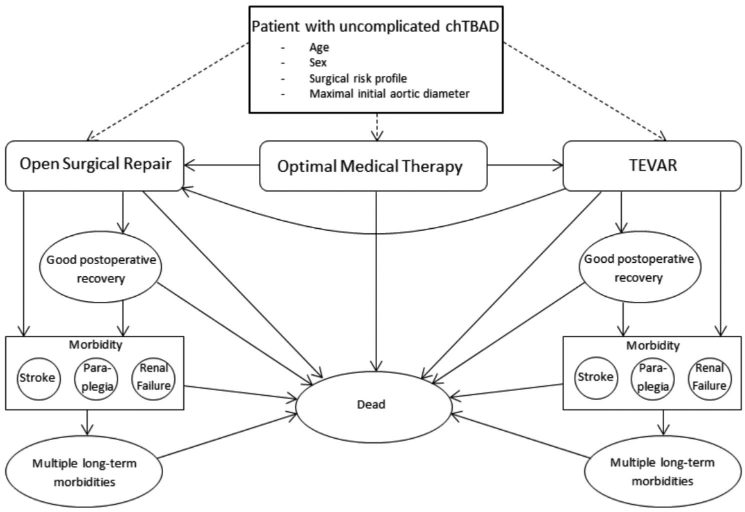

Figure 1 Simplified bubble diagram shows interaction between health states for treatment of chTBAD. Each health state has a possible transition to itself which is not shown in this figure for clarity of the figure. *chTBAD*, chronic type B aortic dissection; *TEVAR*, thoracic endovascular aortic repair.

Table I Reference-case probabilities and ranges for transitions to health states.

Variables	Reference-case	Range	References
Open surgical repair			
Technical success	95%	90% – 100%	4,21-24
Perioperative mortality rate	9.6%	5.0% – 15%	4,21-24
Perioperative complications OSR *	23%	15% – 25%	4,21-24
Stroke	5.8%	3.0% – 7.0%	4,21-24
Paraplegia	4.8%	3.0% – 6.0%	4,21-24
Renal failure	0.9%	0.5% – 3.0%	4,21-24
Other complications	11.5%	5.0% – 15%	4,21-24
Aortic complications †	2.1%	1.0% – 5.0%	4,21-24
Mortality after aortic complications	4.2%	3.0% – 6.0%	4,21-24
Need for reintervention	4.1%	3.0% – 15%	4,21-24
Rupture after OSR	0.2 %	0.1% – 1.5%	4,21-24
Mortality after rupture	50 %	20% – 80%	20
Perioperative mortality emergency intervention	19.8%	15% – 25%	4,21-24
Endovascular repair			
Technical success	89.9%	85% – 98%	5,7-9,25-30
Immediate conversion to OSR	0.4%	0.0% – 1.0%	6,8-10,12,32-36
Perioperative mortality rate	3.2%	1.0% – 10%	5,7-9,25-30
Perioperative complications endovascular repair*	19%	15% – 25%	5,7-9,25-30
Stroke	4.3%	3.0% – 6.0%	5,7-9,25-30
Paraplegia	0.8%	0.5% – 3.0%	5,7-9,25-30
Renal failure	2.6%	1.5% – 4.0%	5,7-9,25-30
Other minor complications	11.3%	5.0% – 15%	5,7-9,25-30
Aortic complications †	6.2%	3.0% – 10%	5,7-9,25-30
Mortality after aortic complications	5.1%	3.0% – 7.0%	5,7-9,25-30
Need for reintervention	14.3%	10% – 25%	5,7-9,25-30
Rupture after endovascular repair	1.2%	0.5% – 4.0%	5,7-9,25-30
Mortality after rupture	50%	20% – 80%	20
Perioperative mortality emergency intervention	19.8%	15% – 25%	5,7-9,25-30
Optimal medical therapy			
Mean growth male	1.2mm/y	0.0mm/y – 2.5mm/y	31-34
Mean growth female	3.3mm/y	0.0mm/y – 4.5mm/y	31-34
Average yearly rupture rate			
3.5 – 3.9 cm	0.1%	0.05% – 0.3%	32,34
4.0 – 4.9 cm	0.8%	0.5% – 2.0%	32,34
5.0 – 5.9 cm	1.9%	1.0% – 5.0%	32,34
≥ 6.0 cm	3.7%	2.0% – 10%	32,34

Table I continued

Variables	Reference-case	Range	References
Average yearly dissection rateΔ			
3.5 – 3.9 cm	2.2%	1.5% – 3.0%	32,34
4.0 – 4.9 cm	2.0%	1.5% – 3.0%	32,34
5.0 – 5.9 cm	2.9%	2.0% – 5.0%	32,34
≥ 6.0 cm	3.9%	2.5% – 10%	32,34
General variables			
SMR rate for chTBAD	Life-table	‡	14,24
Males	x1.97		
Females	x2.83		
Excess mortality rate for chTBAD + morbidity	Life-table	‡	14
Stroke	x3.62		16
Renal Failure	x3.2		17
Paraplegia	x4.9		18
Discount rate	3%	0% – 5%	12

* Perioperative mortality defined as 30-day mortality. † Aortic complications included extended or retrograde dissections, false aneurysms, and endoleaks. ‡ No range for standardized mortality rates and excess mortality of co-morbidities was used. Δ Dissection extension causing problems (e.g. malperfusion). *mm*, millimeter; *cm*, centimeter; *SMR*, standardized mortality rate; *chTBAD*, chronic type B aortic dissection; *OSR*, open surgical repair.

For the patients in the TEVAR-treatment group, the model structure was comparable with the OSR-treatment group, although there were some differences. For example, patients could develop an endoleak or retrograde dissection. Additionally, different probabilities for transitions between the different health states (e.g. risks of complications, aortic rupture rates) were used for the TEVAR-treatment group compared with the OSR-treatment group. Patients in the TEVAR and OSR-group received computed tomography (CT) follow-up every year.

Patients who started in the two conservative treatment groups received OMT and CT-follow-up every six months. Once the patient developed dissection-related complications (rupture, extended dissection, endoleak) or when the aortic diameter reached the threshold for surgery based on the size criteria, they required an emergency or elective intervention, respectively. Risk for dissection-related complications is dependent on the size of the aorta (Table I). Higher procedural risks were used for emergency repair compared with elective repair as reported in the literature. Once the patient underwent OSR or TEVAR, they moved to the health states of the OSR and TEVAR treatment group, as described above.

Mortality rates for men and women were obtained from the Mortality File from the Centers for Disease Control and Prevention.[14] In order to adjust mortality for the chTBAD, the patients were subjected to excess mortality for presence of chTBAD, independent of the treatment group. The excess mortality was modeled higher in female patients than for men, since female sex is an important risk factor for long-term mortality in patients with vascular disease.[15] Patients with long-term morbidities (stroke, renal failure and paraplegia) were subjected to a higher excess mortality, due to their reduced life expectancy.[16-18] To perform an analysis for low, medium and high-risk patients, mortality rates and perioperative mortality risk were adjusted by using a relative risk (RR). Risk-profiles included low-risk (RR=0.5), medium-risk (RR=1) and high-risk (RR=2). For example, a low-risk patient (RR = 0.5) had 50% less risk of death after both OSR and TEVAR in both elective and emergency settings compared with the average risks for each of these situations. Furthermore, the complication rate was similarly adjusted with the RR. The RR was tested over a wide range (0.5 – 5).

Open surgical repair, endovascular repair and optimal medical therapy

An extensive search was performed using the MEDLINE database with a language filter for English articles. The only articles that were considered eligible were those that described perioperative morbidity and mortality for both elective and emergency interventions, acute and long-term complications, technical success, rupture, dissection and reintervention rates, growth rates, rupture and dissection rates and importance of initial size of the aortic diameter of the descending aorta performed with OSR or TEVAR. Furthermore, studies were considered eligible if they (1) contained original data and (2) were comparative studies, large single-treatment studies (>10 patients), or described conservative management of chTBAD. All articles were subjected to critical appraisal as recommended by the Oxford Centre for Evidence Based Medicine.[19] The references of these articles were screened for any missing relevant articles. Outcomes retrieved from the 20 remaining articles were examined, evaluated for consistency, and integrated into a weighted mean. Furthermore, differences in natural course of the disease regarding aortic growth and mortality rates for men and women were determined in order to make the model specific for unique patient situations. The reference-case characteristics were equal to the characteristics of patient data retrieved from literature. All the rates, risks and probabilities were converted into annual probabilities and are shown in Table I.[4-8,20-34]

Quality of life and interventions

In order to calculate the expected QALYs, the number of cycles spent in each health state was multiplied by the QoL-value for the specific health states. A slightly higher QoL was used for patients who underwent repair than for patients treated with OMT based on documented evidence in the literature.[35,36] The QoL values for patients with long-term morbidities (stroke, paraplegia and/or renal failure) were reduced based on evidence from the literature regarding those specific morbidities.[37-39] For the interventions, disutilities or "tolls" were included. These disutilities were applied every time an intervention was required and were based on the average recovery time for these interventions (Table II). A wide range for all the QoL values was used to explore the effect of the assumptions.

Data analysis

The reference-case was a hypothetical cohort of 55-year-old men with an uncomplicated chTBAD with an initial aortic diameter of 5.0 cm and medium-risk for perioperative mortality. For patients undergoing medical therapy, a threshold for intervention during follow-up was a maximum aortic diameter exceeding 6.0 cm (Table III).

Table II Quality of life values and disutilities for interventions.

Health state or intervention	QoL value	Range tested	Reference
Good post-operative recovery	0.95	0.90 – 1.00	36
Conservative treated chTBAD	0.93	0.90 – 1.00	36
Renal Failure	0.49	0.40 – 0.55	37
Stroke	0.47	0.40 – 0.55	38
Paraplegia	0.45	0.40 – 0.55	39
Multiple morbidities *	0.20	0.10 – 0.30	Assumption
Dead	0.00		
OSR	-0.12	-0.15 – -0.09	Assumption
TEVAR	-0.05	-0.08 – -0.02	Assumption
Acute complication	-0.04	-0.06 – -0.02	Assumption

* Combination of two of the following co-morbidities: stroke, renal failure or paraplegia.
QoL, Quality of life; *chTBAD*, chronic type B aortic dissection; *OSR*, open surgical repair; *TEVAR*, thoracic endovascular aortic repair.

Table III Input variables for reference-case patient.

Parameter	Reference-case	Range
Sex	Male	Male / Female
Age (years)	55	50 – 100
Surgical risk category	Medium	Low – High
Initial aortic diameter (cm)	5.0	3.5 – 6.5
Threshold for intervention (cm)	≥ 6.0	5.5 – 6.5

cm, Centimeter.

Consistent with decision modeling practice, the treatment with the highest QALYs was considered the preferred treatment option for patients with chTBAD. A difference between two treatment strategies of less than 0.1 QALY, comparable with less than 1.5 months in perfect health, was considered to be clinically meaningless. After the reference-case analysis, deterministic one-way, two-way and three-way sensitivity analyses were performed to assess the influence of different patient and procedural characteristics. A probabilistic sensitivity analysis (PSA) was performed using 10,000 random samples to assess the uncertainty around the variable values using distributions of the values rather than deterministic values. PSA can test the robustness of the results of a model in the presence of uncertainty. PSA can also test the preferred treatment based on the frequency of the selection show the preferred treatment. Credibility intervals (CI) in Bayesian approaches are analogous to confidence intervals in frequentist statistics. Finally, a clinical decision tool for treatment of chTBAD was created in the form of a chart based on four patient characteristics: age, sex, maximum initial aortic diameter, and low/medium/high-risk for surgery.

RESULTS

Reference-case

The reference case was simulated in 10,000 patients. OSR was the preferred treatment in 87% of the samples for a 55-year-old male patient with an uncomplicated chTBAD and medium peri-operative mortality risk. The results of the analysis showed that this would result in 10.06 (95%CI: 9.52 – 10.56) QALYs after OSR, followed by 9.92 (95%CI: 9.23 – 10.58) QALYs after TEVAR, which is similar to a difference of two months in full health (95%CI: -0.21 – 0.47). OMT appeared to be less desirable for these patients with 9.64 (95%CI: 9.38 – 9.88, OMT-OSR; difference of 0.42 QALYs (95%CI: 0.01 – 0.81) comparable with 5.5 months in perfect health) and 9.40 QALYs (95%CI: 9.11 – 9.69, OMT-TEVAR), a difference of 0.66 QALYs (95%CI: 0.17 - 1.12) comparable with 8 months in perfect health).

Age

Age at the time of the decision was an important factor in determining the optimal treatment strategy as shown in Figure 2A and 2B. OSR is the preferred treatment until the age of 60 years, TEVAR is preferred for patients between 60 and 70 years old, and OMT should be considered after the age of 70 years for patients with medium peri-operative mortality risks. The difference between OMT-OSR and OMT-TEVAR was ≤0.01 QALY along the entire range when patients were age 70 or older. However, OMT as initial treatment strategy in patients 70 years or older resulted in QALYs comparable with an additional 2.5 months in full health compared with TEVAR, and nearly 6 months compared with initial OSR. Overall, age was the most important determinant for optimizing treatment decisions, because it most frequently caused a change in preferred treatment strategy, although the choice was also dependent on sex, health of the patient and initial maximum aortic diameter. The interaction between these four variables and the preferred treatment strategy for these patients is shown in Figure 3.

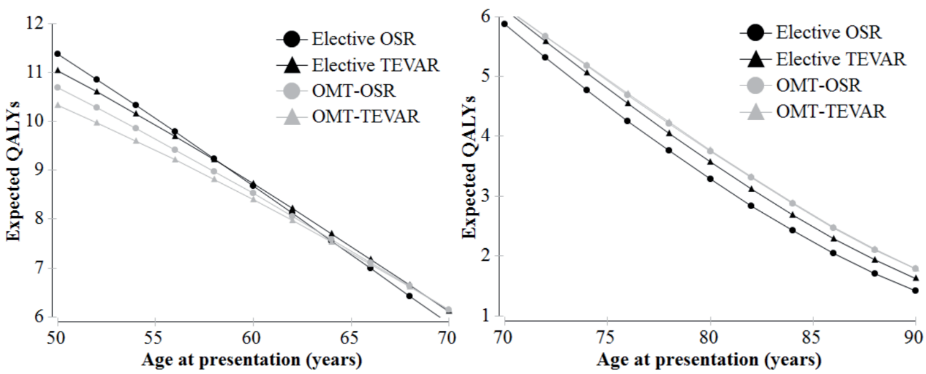

Figure 2 Total expected QALYs at age of presentation A, 50 – 70 years. B, 70 – 90 years. Thresholds indicate change in preferred treatment strategy: OSR ≤ 60y; 60y ≤ TEVAR ≤ 70y; and OMT ≥ 70y. * OMT-TEVAR and OMT-OSR are exactly equal in Figure 2B. *TEVAR*, Thoracic endovascular aortic repair; *QALYs*, quality-adjusted life years; *OSR*, open surgical repair; *OMT*, optimal medical therapy; *y*. year.

Maximum initial aortic diameter (cm)

Age	Diameter	WOMEN Low-Risk	WOMEN Medium-Risk	WOMEN High-Risk	MEN Low-Risk	MEN Medium-Risk	MEN High-Risk	Diameter
50y	6.5	OSR	OSR	OSR/TEVAR	OSR	OSR	OSR/TEVAR	6.5
50y	6.0	OSR	OSR	OSR/TEVAR	OSR	OSR	OSR/TEVAR	6.0
50y	5.5	OSR	OSR	OSR/TEVAR	OSR	OSR	OSR/TEVAR	5.5
50y	5.0	OSR	OSR	OSR/TEVAR	OSR	OSR	OSR/TEVAR	5.0
50y	4.5	OSR	OSR	OSR/TEVAR	OSR	OSR	OMT	4.5
50y	4.0	OSR	OSR	OSR/TEVAR	OSR/OMT	OMT	OMT	4.0
50y	3.5	OSR	OSR	No diff	OMT	OMT	OMT	3.5
55y	6.5	OSR	OSR	TEVAR	OSR	OSR/TEVAR	TEVAR	6.5
55y	6.0	OSR	OSR	TEVAR	OSR	OSR/TEVAR	TEVAR	6.0
55y	5.5	OSR	OSR	TEVAR	OSR	OSR/TEVAR	TEVAR	5.5
55y	5.0	OSR	OSR	TEVAR	OSR	OSR/TEVAR	TEVAR	5.0
55y	4.5	OSR	OSR	TEVAR	OSR	OSR/OMT	OMT	4.5
55y	4.0	OSR	OSR	TEVAR	OMT	OMT	OMT	4.0
55y	3.5	OSR	OMT	OMT	OMT	OMT	OMT	3.5
60y	6.5	OSR	TEVAR	TEVAR	OSR	OSR/TEVAR	TEVAR	6.5
60y	6.0	OSR	TEVAR	TEVAR	OSR	OSR/TEVAR	TEVAR	6.0
60y	5.5	OSR	TEVAR	TEVAR	OSR	OSR/TEVAR	TEVAR	5.5
60y	5.0	OSR	TEVAR	TEVAR	OSR	OSR/TEVAR	TEVAR	5.0
60y	4.5	OSR	TEVAR	TEVAR	OSR	OSR/TEVAR	OMT	4.5
60y	4.0	OSR/OMT	TEVAR/OMT	TEVAR/OMT	OMT	OMT	OMT	4.0
60y	3.5	OMT	OMT	OMT	OMT	OMT	OMT	3.5
65y	6.5	OSR/TEVAR	TEVAR	TEVAR	OSR/TEVAR	TEVAR	TEVAR	6.5
65y	6.0	OSR/TEVAR	TEVAR	TEVAR	OSR/TEVAR	TEVAR	TEVAR	6.0
65y	5.5	OSR/TEVAR	TEVAR	TEVAR	OSR/TEVAR	TEVAR	TEVAR	5.5
65y	5.0	OSR/TEVAR	TEVAR	TEVAR	OSR/TEVAR	TEVAR	TEVAR/OMT	5.0
65y	4.5	OSR/TEVAR	TEVAR	TEVAR	OMT	OMT	OMT	4.5
65y	4.0	OSR/TEVAR	OMT	OMT	OMT	OMT	OMT	4.0
65y	3.5	OMT	OMT	OMT	OMT	OMT	OMT	3.5
70y	6.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.5
70y	6.0	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.0
70y	5.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	5.5
70y	5.0	TEVAR	TEVAR	TEVAR	No diff	TEVAR/OMT	OMT	5.0
70y	4.5	TEVAR	TEVAR	TEVAR	OMT	OMT	OMT	4.5
70y	4.0	OMT	OMT	OMT	OMT	OMT	OMT	4.0
70y	3.5	OMT	OMT	OMT	OMT	OMT	OMT	3.5
75y	6.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.5
75y	6.0	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.0
75y	5.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	5.5
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75y	4.5	TEVAR	OMT	OMT	OMT	OMT	OMT	4.5
75y	4.0	OMT	OMT	OMT	OMT	OMT	OMT	4.0
75y	3.5	OMT	OMT	OMT	OMT	OMT	OMT	3.5
80y	6.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.5
80y	6.0	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR	6.0
80y	5.5	TEVAR	TEVAR	TEVAR	TEVAR	TEVAR/OMT	TEVAR/OMT	5.5
80y	5.0	TEVAR/OMT	TEVAR/OMT	TEVAR/OMT	OMT	OMT	OMT	5.0
80y	4.5	OMT	OMT	OMT	OMT	OMT	OMT	4.5
80y	4.0	OMT	OMT	OMT	OMT	OMT	OMT	4.0
80y	3.5	OMT	OMT	OMT	OMT	OMT	OMT	3.5

OSR	Open surgical repair
OSR/TEVAR	Intervention: Open surgical repair or TEVAR
TEVAR	TEVAR
TEVAR/OMT	TEVAR or Optimal medical therapy
OMT	Optimal medical therapy
OSR/OMT	Open surgical repair or Optimal medical therapy

Figure 3 Treatment strategy decision chart. This tool indicates optimal treatment strategy on the basis of four basic characteristics: age, sex, surgical risk-profile and maximum initial aortic diameter. Two treatment strategies in the same cell (OSR/TEVAR, TEVAR/OMT and OSR/OMT) indicate a difference of less than two months in QALYs. ''No diff'' indicates a difference of less than two months for all the treatment groups. The dotted box is the reference-case. *TEVAR*, Thoracic endovascular aortic repair; *QALYs*, quality-adjusted life years; *OSR*, open surgical repair; *OMT*, optimal medical therapy.

Sex

For 55-year-old women, all other variables being equal, OSR would yield higher QALYs (9.05 QALYs; 95%CI: 8.61 – 9.45), compared with TEVAR (8.94 QALYs; 95%CI8.40 – 9.34). Difference between OSR and TEVAR was 0.11 (95%CI: -0.19 – 0.41) QALYs, and therefore this was a non-significant difference. Treating women with conservative management would diminish their life expectancy in full health with almost one year: OMT-TEVAR (8.30 QALYs; 95%CI: 8.04 – 8.56) and OMT-OSR (8.02 QALYs; 95%CI: 7.71 – 8.32). In comparison with male patients, female patients have in general 1.0 QALY less to live at the moment of the treatment decision for chTBAD, mainly due to the higher excess mortality associated with chTBAD in female patients.

Perioperative mortality risk

Sensitivity analysis of different categories of perioperative mortality risks in the same reference-case patient showed that initial TEVAR had the highest expected QALYs if the relative risk (RR) for perioperative mortality was increased to RR = 1.67. The benefit of TEVAR compared with OSR increased with higher RRs (Figure 4). For 75-year-old male patients, OMT was the optimal treatment strategy for all categories, including patients with low peri-operative mortality risks.

Maximum initial aortic diameter and threshold for surgery

Size of the initial aortic diameter was an important predictor of rupture and dissection. Therefore, a sensitivity analysis was performed on the initial maximum aortic diameter. Overall, patients with larger initial aortic diameters had more benefit from immediate intervention than patients with smaller aortic diameters. The impact of initial aortic diameter on optimal treatment strategy was supported by the outcomes for the range of maximum aortic diameter thresholds for intervention that we evaluated in the analysis (ranging from 3.5 cm to 6.5 cm). A patient with initial aortic diameter of 3.5 cm can expect 1.1 and 0.8 additional QALYs with initial OMT compared with immediate repair at the ages of 55 and 70 years, respectively. In contrast, patients with a very large initial aortic diameter (6.5 cm) should always be operated immediately which leads to an expected gain in QALYs of 1.1 (age of 55y) and 0.7 (age of 70y) compared with OMT (Figure 5).The outcomes for five different patient groups are shown in Table IV.

DISCUSSION

The current article presents a decision-analysis model which showed that there is no “one size fits all” treatment for uncomplicated chTBAD. Choice of optimal treatment strategy depends on several important factors, including age, sex, maximum aortic diameter and peri-operative mortality risks. Overall, the model showed that very old patients (≥ 80 years) should receive OMT, unless the initial aortic diameter exceeds 5.5 cm. Younger patients benefit more from immediate intervention, and particularly the peri-operative mortality risks (low, medium or high-risk) determine if OSR or TEVAR would be preferred. The SVS/AAVS medical comorbidity grading system can be used to categorize patients into the different risk-profiles. Initial aortic diameters ≤3.5 cm should generally be managed with OMT, independent of age of the patient.

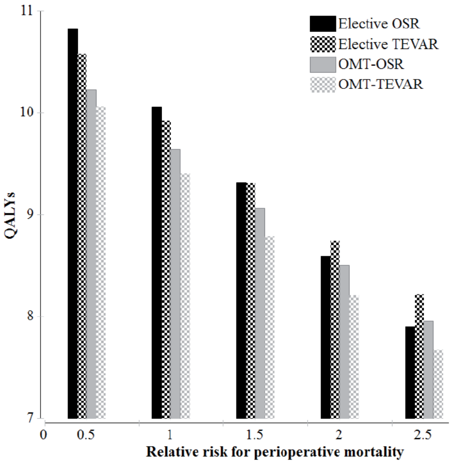

Figure 4 Total expected QALYs per risk-profile of reference-case patient (55-year-old man). Low-risk patient: Relative risk (RR) = 0.5; medium-risk: RR = 1.0; high-risk: RR = 2.0. Increase of the risk-profile of the patient shows a shift from OSR to TEVAR.
TEVAR, Thoracic endovascular aortic repair; *QALYs*, quality-adjusted life years; *OSR*, open surgical repair; *OMT*, optimal medical therapy.

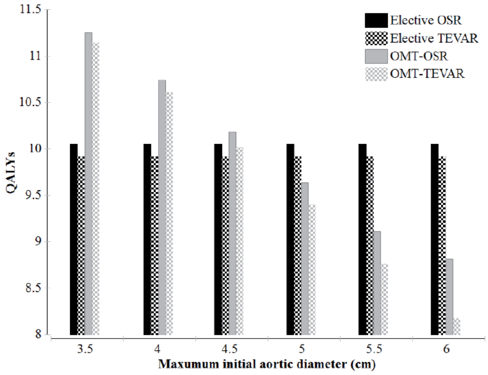

Figure 5 Total expected QALYs for maximum initial aortic size (in cm) of reference-case patient (55-year-old man with chTBAD). Increase of the maximum initial aortic diameter shows shift from optimal medical therapy to intervention as preferred strategy.
TEVAR, Thoracic endovascular aortic repair; *QALYs*, quality-adjusted life years; *cm*, centimeter; *chTBAD*, chronic type B aortic dissection; *OSR*, open surgical repair; *OMT*, optimal medical therapy.

Table IV Outcomes of different treatment strategies for five different patient-groups.

Reference case patient and changed parameter *	**Initial and changed variable**	**OSR †**	**TEVAR †**	**OMT-OSR †**	**OMT-TEVAR †**
Male, 55, medium-risk, aortic diameter: 5.0cm	n/a	10.06	9.92	9.64	9.40
Age	55y → 80y	3.28	3.57	3.75	3.77
Risk	Medium → High	8.59	8.74	8.41	8.12
Sex	Male → Female	9.05	8.94	8.30	8.02
Initial aortic diameter	5.0 cm → 3.5 cm	10.06	9.92	11.25	11.14

* Expected QALYs for the reference-case and subsequently for patients where the described parameter is changed compared to the reference case. Reference-case: 55-year-old, medium-risk, male patient with a chTBAD and aortic diameter of 5.0 cm.
† Outcomes are described in QALYS. Preferred treatment is printed in bold and underlined. A difference less than 0.1 QALYs is described as indifferent.
OSR, open surgical repair; *TEVAR*, thoracic endovascular aortic repair; *OMT-OSR*, optimal medical therapy followed by *OSR*; *OMT-TEVAR*, optimal medical therapy followed by TEVAR; *n/a*, not applicable; *y*, years; *cm*, centimeter; QALYs, quality-adjusted life years; *chTBAD*, chronic type B aortic dissection.

Interestingly, female patients benefit more from immediate interventions than male patients. This benefit is mainly due to the higher aortic growth rate in female patients, whereby women reach the threshold for intervention earlier than men do. Although this decision model can provide more insight in the preferred treatment for patients with chTBAD, several combinations of these variables give a difference in treatment strategies of less than two months and patient preference should play a major role in treatment decisions.

Decision analysis is an elegant method to study diseases that involve different health states, can progress, and transition requiring treatment or interventions. The strength of decision models is that one can perform a probabilistic sensitivity analysis by using a wide range of the variables instead of one fixed number, which is particularly useful in problems with uncertainty around the variables. Limitation of most of the clinical studies is that these studies mostly focus on one or two main outcomes, such as overall survival or adverse events. Although these are certainly highly important outcomes, one must not only focus on survival and adverse events. Other important factors, such as quality of life for long-term morbidities, rupture and dissection risks after more than five years and the risk-profile of the patient should also be taken into account. These data are lacking in most of these articles, although these results could highly affect the decision of treatment for a patient with a chTBAD.

This decision-analysis model considers all clinically relevant basic patient characteristics that should be taken into account before making a contemplated decision about the treatment. First, we assessed the variables which mostly influenced the decision: age, sex, peri-operative mortality risks, initial maximum aortic diameter and size-criteria for intervention during follow-up if OMT would initially be selected (threshold of 6.0 cm). The latter is not a fixed variable but a choice, based on general consensus in current clinical practice. Subsequently, we selected subgroups and performed analyses for all these subgroups. The outcomes in this model are fairly logical, and compatible with consensus that intervention should be avoided for small maximum initial aortic diameters and old patients, while interventions are more beneficial for larger maximum initial aortic diameters and younger patients. One of the goals of this study was to create a treatment strategy decision tool in the form of a chart, shown in Figure 3. This clinical decision model, requiring only basic patient characteristics, may guide treatment strategies for patients with chTBAD. However, since other factors, such as extent of the dissection, including its complexity, proximity to the origin of the left common carotid and subclavian arteries, the number of fenestrations and potential compromise of the visceral vasculature and aortoiliac bifurcations may be important determinants of whether TEVAR is feasible. Additionally, there will be patients who are no appropriate candidates for aortic surgery of any kind. Finally, there are patients in the OMT group who never have enlargement of the dissected aorta or complications during follow-up. Therefore, treatment should be tailored to the patient and a patient-specific approach should be performed.

Although decision analysis is a sophisticated method to synthesize the best-available evidence, this type of analysis has some limitations. In this particular setting, one of the limitations is that data were extracted from published articles and it was observed that reporting was subject to heterogeneity in terms of the array and detail for interventions, outcomes and the quality of reporting overall. Although the data are not consistent across the entire range of these papers, we tried to overcome this by checking for consistency and integrating the evidence

into weighted means. Furthermore, we explored the influence of the variables over wide ranges, based on results in literature.
Second, the growth rates of aortic diameters are difficult to predict and a wide range of yearly growth rates across patient groups has been described.[31-34] Furthermore, prediction of dissection-related complications is relatively complex, and only absolute aortic diameters were used in the analysis. In general, the faster the aortic diameter is expanding, the earlier the intervention should be performed. Patients who receive OMT should be followed every 6 months, and should be intervened on if a predefined threshold for intervention is reached, or when the aorta grows relatively fast (≥1 cm per year by consensus).[40] However, until the exact role of growth rates and dissection related complications are known, we should use currently available evidence to its fullest extent to optimize current treatment strategies.
QoL-values were obtained from published articles and QoL in conservative treated patients was reported lower than patients who received an intervention. However, sensitivity analysis on this showed that even if QoL for conservative treated patients was higher for patients who received an intervention, elective OSR and TEVAR were still preferred over OMT (Figure 6). This emphasizes the strength of this decision model. Finally, no QoL values have been published for the health state "Multiple Morbidities". This QoL value was assumed to be lower than for patients with one major morbidity, and tested over a wide range (0 – 1), which did not result in a change of conclusions since only a very small percentage of patients will end up in this health state.

Although several patient groups in the model had a difference of more than 1.0 QALYs, the small difference in QALYs for different treatment strategies for the reference-case cohort is noteworthy. How much does a difference of two months or less during long-term follow-up mean? Is it worth surgical or endovascular intervention and associated costs? Does this mean that there is no preferred strategy in these specific categories? This will also depend on patient preferences. However, sensitivity analysis of the tested variables showed a robust model, and did not significantly change the recommended treatment strategies. It is important to realize that a small difference in QALYs is an average for the group. Whereas some patients may have a small benefit, other patients may have a large benefit. A mean difference of 0.14 QALY/patient is 1,400 QALYs extra for a group of 10,000 patients, so 1,400 additional life years in perfect health for the whole group.

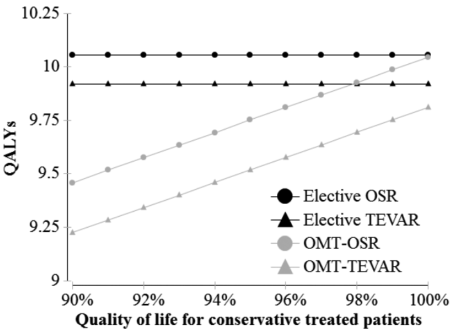

Figure 6 Total expected quality-adjusted life years (QALYs) for treatment of chronic type B aortic dissection in the reference-case patient (a 55-year-old man) with open surgical repair (OSR), thoracic endovascular aortic repair (TEVAR), and optimal medical therapy (OMT) per quality of life for conservative treated patients. Expected QALYs for OSR are always higher than for TEVAR and OMT, and only OMT is affected by QoL for conservative treatment.

Decision analysis is a powerful tool to distinguish preferred treatment strategies based on QALYs. Other decision-analysis studies on surgical topics show similar results with small differences between treatment strategies. Examples include evaluation of the benefit of carotid endarterectomy in asymptomatic patients compared with symptomatic patients with severe carotid artery stenosis (max <0.07 QALYs benefit) [41] and bare-metal versus drug-eluting stents in percutaneous coronary interventions (<0.014 QALYs).[42] Decision analysis is especially helpful for informed decisions in situations of uncertainty and high complexity and especially when randomized controlled trials are lacking. Furthermore, decision analysis is particularly useful when the difference in outcomes between strategies is small.

The purpose of this study was to design a decision tool which can be used to guide the surgeon in determining the preferred treatment option tailored to the individual patient with maximum number of QALYs as primary outcome. Therefore, no analysis of associated costs was performed. However, since healthcare costs are increasing nationwide, and political and societal focus on controlling health care costs are increasing, a cost-effectiveness analysis should be performed. Therefore, future studies should assess the total costs and cost-effectiveness of the currently proposed treatment strategies for chTBAD. The results of this model were based on the best-available evidence in literature and prospective evaluation of the model will be needed. However, since a higher level of evidence is currently lacking, and treatment decisions need to be made, this model, based on the best-available evidence could guide treatment decisions for patients with chronic descending thoracic aortic dissections.

CONCLUSIONS

This decision-analysis model shows that there is no "one size fits all" treatment for uncomplicated chronic type B aortic dissections. Age is the most important variable for determining preferred treatment, followed by initial aortic diameter. This clinical decision model can be used as a guide for the preferred treatment option for different patients with chTBAD.

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CHAPTER 12

Endovascular vs. Open repair of complicated acute type B aortic dissections

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ABSTRACT

Purpose

To assess the comparative effectiveness of thoracic endovascular aortic repair (TEVAR) vs. open surgical repair (OSR) of complicated acute type B aortic dissections (cABAD) using decision analysis.

Methods

A decision analysis comparing TEVAR and OSR for cABAD included variables extracted from the best-available evidence. Main outcomes were quality-adjusted life-years (QALYs), presented with the 95% confidence intervals (CI), and number of reinterventions over the remaining lifetime. Different clinical scenarios, including age, gender, and risk profile were analyzed. Parameter uncertainty was analyzed using probabilistic sensitivity analysis.

Results

In the reference case, a cohort of 55-year-old men, TEVAR was preferred over OSR: 7.07 QALYs (95% CI 6.77 to 7.38) vs. 6.34 QALYs (95% CI 6.04 to 6.66) for OSR. The difference of 0.73 QALYs (95% CI 0.29 to 1.17) is equal to 8.5 months in perfect health. TEVAR was more effective in all analyzed cases and age groups. Perioperative mortality was the most important variable affecting the difference between OSR and TEVAR, followed by the relative risk and percentage of aortic-related complications. Total expected reinterventions were 0.43/patient (TEVAR) and 0.35/patient (OSR).

Conclusion

The results of this decision model for the treatment of cABAD suggest that TEVAR is preferred over OSR. Although a higher number of reinterventions is expected, the total effectiveness of TEVAR is higher for all age groups. OSR should be reserved for patients whose aortic anatomy is unsuitable for endovascular repair.

INTRODUCTION

Acute aortic dissection of the descending aorta is a life-threatening condition with high morbidity and mortality. Acute dissection is diagnosed when clinical symptoms have started ≤14 days ago. Uncomplicated acute type B aortic dissection is usually managed by optimal medical therapy and close surveillance.[1,2] However, when complications such as (impending) aortic rupture, malperfusion (spinal, iliac, or visceral arteries), recurrent pain, refractory hypertension, hypotension, or shock are present, immediate intervention is required.[3,4]

Open surgical repair (OSR) has been the traditional treatment for complicated acute type B aortic dissection (cABAD) over the last decades, but it has been associated with high morbidity and mortality, the latter ranging from 17% to 40% in recently published studies.[5-7] However, thoracic endovascular aortic repair (TEVAR) has been increasingly utilized as a viable option and minimally invasive alternative to OSR to treat of acute aortic dissections.[7-9] Advantages of TEVAR include low perioperative morbidity and mortality, shorter hospitalization, and avoidance of cardiopulmonary bypass and aortic cross clamping. The early results after TEVAR for cABAD are promising[10]; however, long-term outcomes remain scarce, and no Level 1 evidence is available for the two major treatment modalities.

When randomized controlled trials are lacking, decision models are an excellent alternative to summarize, analyze, and compare the major therapeutic modalities for the treatment of cABAD. Furthermore, most publications report only one or two specific outcomes, but other important clinically relevant variables, including long-term morbidities (stroke, chronic renal failure, and paraplegia), aortic complications, number of reinterventions, and quality-of-life (QoL) measurements are less frequently reported. All these factors may play a major role in the decision making for individual patients with cABAD.

In this study, we used a decision model to investigate the outcomes of cABAD after TEVAR and OSR to gain insight regarding the effectiveness of these treatment modalities. The secondary objective was to determine threshold values for important variables, including age and risk profile, where there is a change of optimal treatment that identifies patient groups for whom TEVAR is preferred.

METHODS

A Markov cohort model was developed using TreeAge Pro 2013 (TreeAge Inc., Williamstown, MA, USA) to simulate hypothetical patient cohorts of 10,000 patients with cABAD. Markov models are employed to analyze the prognosis for clinical problems with rates and risks that change over time. In a Markov model, a patient is always in one of a finite number of discrete health states. All possibilities to move from one health state to another are modeled as transitions based on probabilities. Each of those states is assigned a QoL value (utility), and the contribution of this QoL value to the overall outcome of the different strategies depends on the time spent in the health state.[11] A simplified overview of our model for cABAD is depicted in Figure 1.

Complicated acute type B aortic dissection was defined as dissection with (impending) rupture, malperfusion, refractory hypertension, hypotension (<90 mmHg systolic), or shock.[4] Two types of interventions, OSR and TEVAR, were compared in this model, and outcomes were given in quality-adjusted life years (QALYs). QALYs were calculated by multiplying the time spent in a specific health state by the utility (QoL value) of that health state. Input variables including perioperative mortality, perioperative and long-term complications (stroke, paraplegia, renal failure, and minor complications), long-term aortic complications (rupture, endoleak, aortic expansion), reintervention rate, conversion from TEVAR to OSR, and mortality after rupture were extracted from a recently published meta-analysis (Table I).4 Input data not described in the published meta-analysis but necessary for the model were retrieved by performing additional analyses on all the articles used in the meta-analysis (Appendix).

Model and Assumptions

Hypothetical patients transitioned between 12 defined health states according to probabilities derived from the literature. The model cycled in 1-year intervals, with half cycle correction, until all patients were in the "dead" state. Patients started with an endovascular or open intervention for cABAD (Figure 1). Subsequent possibilities included postoperative mortality, uncomplicated postoperative recovery, and postoperative complications (stroke, paraplegia, chronic renal failure). For the TEVAR group, intraoperative conversion to OSR was possible. Patients who had an uncomplicated postoperative recovery could remain uncomplicated and well in subsequent years or they could develop aortic-related complications (rupture, expansion, endoleak). If they survived these aortic-related complications, they received an emergency intervention with accompanying risk for perioperative mortality.[12,13] If the initial intervention was complicated by stroke, chronic renal failure, or paraplegia, the same options were possible, although if a patient in one of these health states suffered another major complication that led to long-term morbidity, they transitioned to the "multiple long-term morbidities" health state. Once in this health state, the health of the patient was decreased to a minimum, with an associated decrease of the QoL value for this health state. To keep the model manageable, the assumption was made that a third long-term complication or morbidity would be equivalent to death.

Quality of Life

QoL values were assigned to all health states (Table II). QoL values were retrieved from published articles describing QoL after OSR and TEVAR. Patients reported better QoL after OSR compared with endovascular repair of the abdominal aorta after 1 year, and therefore the value for OSR was slightly higher compared with TEVAR at the end of the first year and was equal for both procedures after 1 year.[14,15] Furthermore, QoL for patients with stroke, chronic renal failure, and/or paraplegia was decreased based on reported QoL values in the literature.[16-19] Although there was no literature describing the QoL for patients with multiple major long-term complications, the QoL value was assumed to be even more decreased for a patient who suffered a second major morbidity/complication. A short-term disutility (a ''toll'') was incurred every time they underwent an intervention. This toll was higher for patients who underwent OSR compared with TEVAR, reflecting the longer postoperative period for patients in the OSR group.[14] For patients who developed acute complications, a small additional toll for their increased hospitalization period was included. All the QoL values and tolls were tested over a wide range with sensitivity analyses to assess the influence of the uncertainty around these values.

Table I Reference Case Probabilities and Ranges for Transitions to Health States for Treatment of cABAD.

Variable With References	Baseline Estimates Used in Analysis	Range Used in Sensitivity Analysis, %	Beta Distribution (Patients; Events)
OSR			
Perioperative (30-day) mortality rate[4]	17.5%	5–30	(1528; 268)
Perioperative complications			
Stroke[4]	5.9%	2–10	(1529; 90)
Paraplegia[4]	3.3%	2–10	(1529; 50)
Renal failuresS[4]	7.2%	2–10	(233; 17)
Other minor complications S[4]	60.5%	25–75	(1529; 926)
Aortic complications*[4]	36% / 5 year	32–42	†
Rupture after OSRS[4]	1.3%	0–5	(75; 1)
Mortality after rupture prior to intervention[12]	50%	0–100	(21,523; 10,331)
Perioperative death emergency intervention[13]	17.5%	5–50	(991; 173)
TEVAR			
Conversion to OSRS4	1.7%	0–5	(772; 13)
Perioperative (30-day) mortality rate[4]	10.2%	5–20	(2359; 241)
Perioperative complications			
Stroke[4]	4.9%	2–10	(2359; 115)
Paraplegia[4]	4.2%	2–10	(2359; 99)
Renal failureS[4]	4.8%	2–10	(422; 20)
Other minor complicationsS[4]	34.9%	25–75	(2359; 920)
Aortic complications*[4]	39% / 5 year	23–55	†
Rupture after TEVAR S[4]	2.4%	0–5	(585; 14)
Mortality after rupture prior to intervention[12]	50%	0–100	(21,523; 10,331)
Perioperative death emergency intervention[13]	10.8%	5–15	(991; 108)

cABAD, complicated acute type B aortic dissection; *OSR*, open surgical repair; *TEVAR*, thoracic endovascular aortic repair. * Aortic complications included extended dissections, false aneurysms, and endoleaks. † The complete given range was tested.

Mortality

Mortality data were obtained from the Centers for Disease Control and Prevention's mortality tables.[20] Since the mortality for patients with aortic dissection is higher compared with the general population, a disease-specific excess mortality was added to the mortality tables.[21] Additionally, disease-specific excess mortality was added to the mortality tables of the general population for patients with stroke, paraplegia, and chronic renal failure.[22-24] These excess mortalities were assumed to be constant over time. To perform an analysis for low, medium, and high-risk patients, perioperative mortality risks and rates of mortality were adjusted by using a relative risk (RR) ranging from 0.5 to 5. For example, we assumed that a low-risk patient (RR=0.5) had 50% less risk of dying after both TEVAR and OSR in both elective and emergency settings compared with the average risks for each of these situations. Furthermore, the complication rate was similarly adjusted with the RR.

Validation

To evaluate the validity of the model, the outcomes of the expected reintervention rates in the current study were compared with a published study describing the 5-year results and reintervention rates for endovascular repair of acute complicated type B aortic dissection.[25]

Data Analysis

The reference case was a cohort of 55-year-old men with cABAD. Patients accrued QALYs for each cycle they spent in one of the specific health states and accumulated QALYs until all patients were dead or had reached the age of 100 years. Consistent with general decision modeling practice, the treatment with the highest QALYs was considered the preferred treatment option for patients with cABAD. Subsequent to the reference case analysis, deterministic sensitivity analyses were performed to assess the influence of the input variables. A probabilistic sensitivity analysis (PSA) with Monte Carlo simulation was performed using 10,000 random samples to assess the uncertainty around the variables using distributions of the values rather than exact deterministic values. PSA can test the robustness of the results of a model in the presence of uncertainty. PSA can also test the preferred treatment based on the frequency selection of the preferred treatment. Mean outcomes were reported with their 95% credibility intervals (95% CI). Credibility intervals are also known as Bayesian confidence intervals, and the 95% CI in probabilistic sensitivity analysis indicates the range of outcomes that, conditional on the uncertainty in the inputs, can be expected in 95% of simulations. Beta distributions were

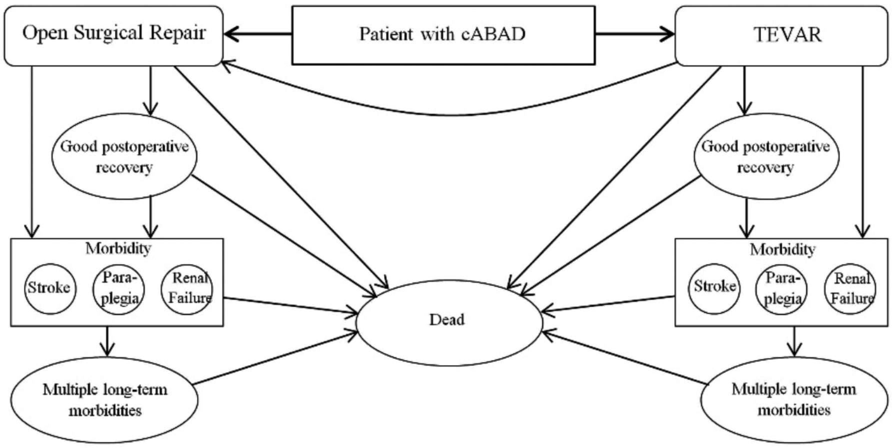

Figure 1 Multistate transition model for treatment of complicated acute type B aortic dissection (cABAD). *TEVAR*, thoracic endovascular aortic repair.

Table II Quality-of-Life (QoL) Values and Disutilities for Interventions.

Health state or intervention	QoL Value*	Range Tested
Good postoperative recovery OSR[14,15]	0.93	0.90 to 1.00
Good postoperative recovery TEVAR[14,15]	0.93	0.90 to 1.00
Stroke[16,19]	0.47	0.40 to 0.55
Renal failure[17,19]	0.49	0.40 to 0.55
Paraplegia[18,19]	0.45	0.40 to 0.60
Multiple morbidities† (assumption)	0.20	0.10 to 0.30
Dead	0.00	
OSR[14]	–0.12	–0.15 to –0.09
TEVAR[14]	–0.05	–0.08 to –0.02
Acute complication (assumption)	–0.03	–0.06 to –0.01

OSR, open surgical repair; *TEVAR*, thoracic endovascular aortic repair. * All QoL values are given in triangular distributions (most likely QoL min – max). † Combination of two of the following comorbidities: stroke, renal failure, or paraplegia.

used to model the probabilities of events, parameterized by the total number of patients and the number of patients with the event of interest. Triangular distributions were used for the utilities, parameterized by the best available minimum, maximum, and most likely value for these utilities. To take time preference into account, a discount rate of 3% per year was used to discount future effectiveness since life years in the near future were considered more valuable for patients than life years in the distant future.[26]

RESULTS

In the reference case of 55-year-old male patients, TEVAR was the preferred intervention for patients with cABAD. TEVAR yielded 7.07 QALYs (95% CI 6.77 to 7.38) vs. 6.34 QALYs (95% CI 6.04 to 6.66) for OSR. The difference of 0.73 QALYs (95% CI 0.29 to 1.17) is equal to 8.5 months in perfect health. A sensitivity analysis on age was performed and showed that TEVAR yielded higher QALYs for all age groups. The difference between TEVAR and OSR for 90-year-old patients was 0.21 QALYs (95% CI 0.13 to 0.29) and 0.78 QALYs (95% CI 0.29 to 1.27) for 50-year-old patients, always in favor of TEVAR.

A threshold analysis of the variables was performed to investigate at what point this would result in a change of preferred intervention from TEVAR to OSR. Thresholds were found for the following variables: relative risk of mortality and morbidity, perioperative mortality, conversion to OSR, aortic complications and stroke, renal failure, and paraplegia after TEVAR. Preferred treatment was not influenced by age: TEVAR yielded higher QALYs for all age groups (Figure 2). For some of the variables, a threshold was found when tested over a wide range, but it was unlikely that this variable would increase or decrease to this threshold value. For example, if the perioperative mortality for OSR decreased by 50%, OSR would be favored over TEVAR, given that the mortality for TEVAR would remain the same. Also, if the aortic-related complications (rupture, device-related complications, reinterventions, endograft migration, collapse, and/or endoleaks) after TEVAR would increase to 53% after 5 years, OSR would be favored as well. The reference case values and threshold values are shown in Table III. Subsequently, an analysis of the influence of these variables was performed (Figure 3); here, the influence of perioperative mortality of OSR and TEVAR were the most important variables for the difference in QALYs between OSR and TEVAR, followed by the relative risk of mortality and morbidity and aortic complications after intervention. The influence of the discount rate and age was not significant and the importance of conversion to OSR on the total expected QALYs was <0.10 QALYs difference if this was tested over a wide range (0%–10%). Since the perioperative mortality for OSR and TEVAR were the most important variables, a 2-way sensitivity analysis was performed on these variables (Figure 4). If the perioperative mortality for OSR and TEVAR was almost equal, there was no difference between these treatment modalities as reflected by the QALYs. Only if the perioperative mortality for TEVAR was higher compared with OSR, all other variables being equal, did OSR outweigh TEVAR as the best treatment option.

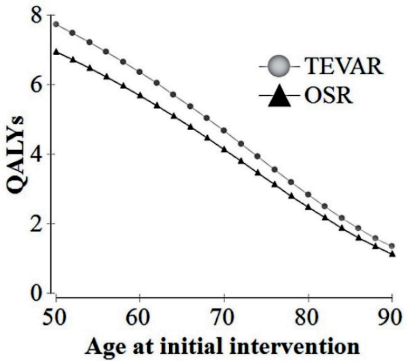

Figure 2 Total expected quality-adjusted life years (QALYs) for open surgical repair (OSR) and thoracic endovascular aortic repair (TEVAR) depending on the age of initial intervention of complicated acute type B aortic dissection (cABAD) for the reference case patient (55-year-old men). See the Results section for further details.

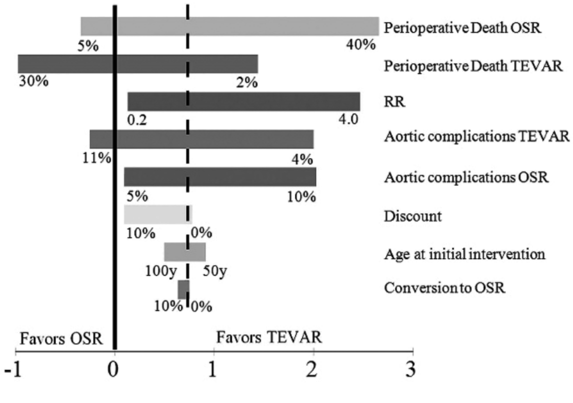

Figure 3 Tornado diagram for the influence of the variables in the decision model. The tornado diagram shows the influence of the variables on the difference between open surgical repair (OSR) and thoracic endovascular aortic repair (TEVAR). The dashed line indicates the difference in the reference-case analysis (0.73 QALYs); the black line indicates the indifference point between OSR and TEVAR. The broader the bar, the more influence the variable has on the difference. The range tested is shown in the figure. *QALYs*, quality-adjusted life years; *RR*, relative risk for mortality and morbidity.

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Table III Threshold Values That Shift the Preferred Intervention to OSR

Variable	Reference Case Value	Threshold Value
Age, y	55	No change
Relative risk	1	0.04
Perioperative mortality TEVAR	10.2%	18.7%
Perioperative mortality OSR	17.5%	9.0%
Conversion to OSR	1.7%	64.5%
Aortic complications TEVAR	39% / 5 years	53% / 5 years
Aortic complications OSR	36% / 5 years	24% / 5 years
Renal failure TEVAR	4.8%	18.1%
Stroke TEVAR	4.9%	17.4%
Paraplegia TEVAR	4.2%	15.5%
Discount	3.0%	No change

OSR, open surgical repair; *TEVAR*, thoracic endovascular aortic repair.

An analysis was performed on the expected reinterventions. Average of expected reinterventions for a 55-year-old man with cABAD was 0.43 for patients in the TEVAR group and 0.35 for patients in the OSR group. Almost 50% of the reinterventions were performed in the first 5 years after initial intervention. The reintervention rate was also used as validation of the model and showed that the reintervention rate for patients treated with TEVAR after 5 years is 22% in our study compared with 26% previously reported.[25]

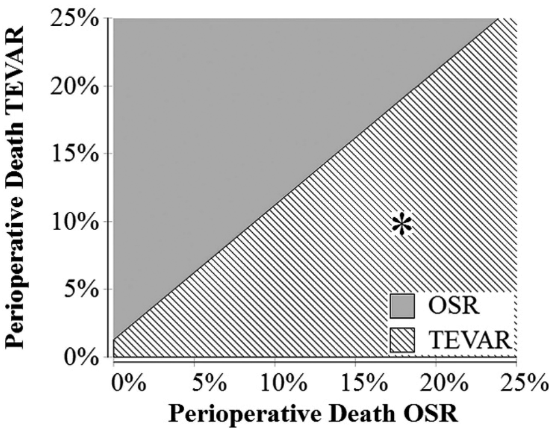

Figure 4 Effect of perioperative mortality of open surgical repair (OSR) and thoracic endovascular aortic repair (TEVAR) on the preferred treatment option for complicated acute type B aortic dissection for the reference case (55-year-old men). In the gray region of graph, OSR is favored over TEVAR, in the striped region TEVAR is the preferred intervention. The asterisk indicates the reference case analysis (perioperative mortality for OSR 17.5% and for 10.2% TEVAR).

DISCUSSION

In this study, the effectiveness of the two major treatment modalities for patients with cABAD was assessed. The results of this clinical decision model, based on the best-available current evidence in the literature, suggest that TEVAR has higher effectiveness compared with traditional open repair for all age groups. The most important variable that influences the difference is the higher perioperative mortality of patients in the OSR group. Although more reinterventions are expected for patients in the TEVAR group, the advantage of lower perioperative mortality of TEVAR outweighs the disadvantage of more reinterventions and related potential additional morbidity and mortality for the TEVAR group.

Decisions based solely on one or two clinical parameters can be misleading and would favor the minimally invasive treatment over the more complicated open procedure. Most articles that present data on short-term results, including perioperative morbidity and mortality, base their conclusions purely on these parameters and conclude that TEVAR is better. Furthermore, not only are the short-term morbidity and mortality of importance for clinical decisions, but also the long-term complications, number of reinterventions, and QoL after the intervention, especially in the case of possible major morbidities (e.g., chronic renal failure, stroke, paraplegia), when the QoL is decreased.

This clinical decision model, which integrates measures of outcome, suggests that TEVAR should be the initial treatment of choice in many cases of cABAD, although there are still exceptions, e.g., patients with aortic anatomy unsuitable for endovascular repair. Additionally, decision models are able to combine all the relevant published studies regarding the topic of interest, which increases the strength of the results and conclusions due to the higher number of patients and decreased uncertainty around the variables.

When randomized controlled trials are lacking, decision models are an excellent alternative to summarize, analyze, and compare the major treatment modalities for the treatment of cABAD. However, there are some limitations to any decision analysis study. Decision models are hypothetical, and the variables in many models, including ours, are based on probabilities published in the literature. Since no Level 1 evidence is available, the presented model is based on data from large case series with only a few articles describing a comparison between the two treatment modalities. Case series are subject to selection bias, and reporting in different articles was subject to heterogeneity. However, the strength of decision models is that one can perform a probabilistic sensitivity analysis by using a wide range of variables instead of basing the decision on one fixed number, which is particularly useful in problems with uncertainty around the variables. The presented results are robust and not sensitive for changes over a wide range of the evaluated variables.

The difference in QALYs seems small, but it is important to recognize that this small difference in QALYs is an average for the entire group. Whereas a large number of patients may experience a small benefit, a small number of patients may have a large benefit. Compared with other results from decision models in vascular surgery, the difference of 0.73 QALYs (8.5 months in perfect health) is actually very large and mainly because of the highly fatal nature of this disease and associated interventions. Previously reported differences in decision analysis models in vascular surgery include a difference of 0.36 QALYs for 65-year-old patients with asymptomatic popliteal artery aneurysms (greater saphenous vein bypass vs. endovascular repair with covered stents),[27] an evaluation of the benefit of carotid endarterectomy in asymptomatic patients compared with symptomatic patients with severe carotid artery stenosis (max <0.07 QALYs benefit),[28] and 0.14 QALYs for 55-year-old patients with chronic type B aortic dissection (TEVAR vs. OSR).[29]

Another limitation is the omission of conservative or optimal medical treatment as a management strategy. However, there are only a few reports with a small number of patients describing the results of conservative management for the treatment of cABAD.[5,6] These results report a high perioperative morbidity and mortality resulting in the general consensus that conservative management should be applied only to patients unsuitable for open and endovascular repair. Therefore, we felt it was unnecessary to evaluate this treatment option in this decision model. Furthermore, given the lack of published data for conservative management for cABAD, the results for this treatment option would be very unreliable, with considerable uncertainty around the variables used for patients treated with conservative management and, as described above, there is general consensus that complicated cases [(impending) aortic rupture, malperfusion (spinal, iliac, or visceral arteries), recurrent pain, refractory hypertension, hypotension (<90 mmHg systolic) or shock] should be treated.[4,30]

Furthermore, as with all decision analysis models, assumptions have to be made to keep the model tractable. For example, the assumption was made that a third long-term morbidity or complication would be equivalent to death. This assumption was tested by changing the structure of the model such that an infinite number of reinterventions and major morbidities were possible. Since only a small percentage of patients ended up with the possibility of three or more major morbidities, testing this assumption resulted in a change of <0.01 QALYs for the difference between OSR and TEVAR (still 0.73 QALYs difference in favor of TEVAR). Another assumption was made regarding the QoL values for patients with multiple morbidities and acute complications. However, these assumptions affected both treatment options similarly and were tested over a wide range (QoL 0–1) and did not affect the general consensus or the average difference between the two outcomes.

Finally, this decision model used male patients for the reference case. Women with aortic dissection die more frequently than men (OR 1.4, $p=0.04$), and surgical outcome is worse in women than men.[31] However, this will affect the results similarly for OSR and TEVAR in women, and although the expected QALYs will be lower, the overall conclusions are likely to be applicable to both men and women.

To our knowledge, no one has constructed a decision model for the treatment of cABAD. As described above, most articles assess only one or two clinical outcomes and base their conclusions on these results. The strength of decision models is that it can combine all the clinically relevant factors affecting the outcome and base the conclusions on these combined outcomes. An increasing trend of using decision analysis models can be seen during the most recent years in cardiovascular surgical and interventional radiological journals because it provides an elegant method to study vascular diseases if Level 1 evidence is lacking.

Data from the International Registry of Acute Aortic Dissection (IRAD) indicate that nearly 30% of cABAD patients undergoing open repair for malperfusion or impending rupture die within 30 days. Furthermore, the IRAD study demonstrated an ~20% composite neurological morbidity and a renal failure rate close to 18%.[5] These events are significantly lower if treated with TEVAR and could represent a significant advance in the treatment of this pathology.[30] However, reintervention rates are higher in patients treated with TEVAR, which could play a major role in decisions made while caring for cABAD patients.[25,32] The strength of the study we present is that all clinically relevant data are combined and evaluated with one validated outcome measurement: QALYs.[32]

The results of this decision analysis model are clear, and there is a significant difference between the two treatment options. The next question is what new studies could add. A well conducted randomized controlled trial comparing TEVAR and OSR could finally provide Level 1 evidence and could be valuable for this field, although the superiority of TEVAR is shown in multiple case series.[7,13,30] This decision model focused specifically on the effectiveness of the two major treatment modalities. No costs were included since the main objective was to assess the effectiveness so that the optimal treatment strategy can be tailored to the patient. However, Narayan and colleagues[33] described that there was no significant difference in overall hospitalization costs for the treatment of descending thoracic aortic pathologies. In a study on the cost-effectiveness for treatment of abdominal aortic aneurysms, endovascular aneurysm repair was cost-effective in almost 100% of the cases compared with open repair.[34] A cost-effectiveness analysis can be performed in the future to further evaluate these results and to assess if costs are within acceptable limits from a societal perspective. Furthermore, new techniques for the treatment of cABAD, including the chimney technique, which has been described as a feasible option for the treatment of acute descending aortic pathologies[35] have not yet been reported in larger series. No long-term results have been reported, but the existing data could be part of decision models for cABAD in the future.

CONCLUSION

The results of this decision model for the treatment of cABAD suggest that TEVAR is preferred over OSR. Although a higher number of reinterventions is expected, the overall effectiveness for TEVAR is higher for all age groups, independent of the risk profile of the patient. OSR should be performed when the patient's aortic anatomy is not suitable for endovascular repair. Although the results in this decision model are clear, the treatment strategy should be tailored to the individual patient.

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APPENDIX – SUPPLEMENTAL REFERENCES

OSR

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TEVAR

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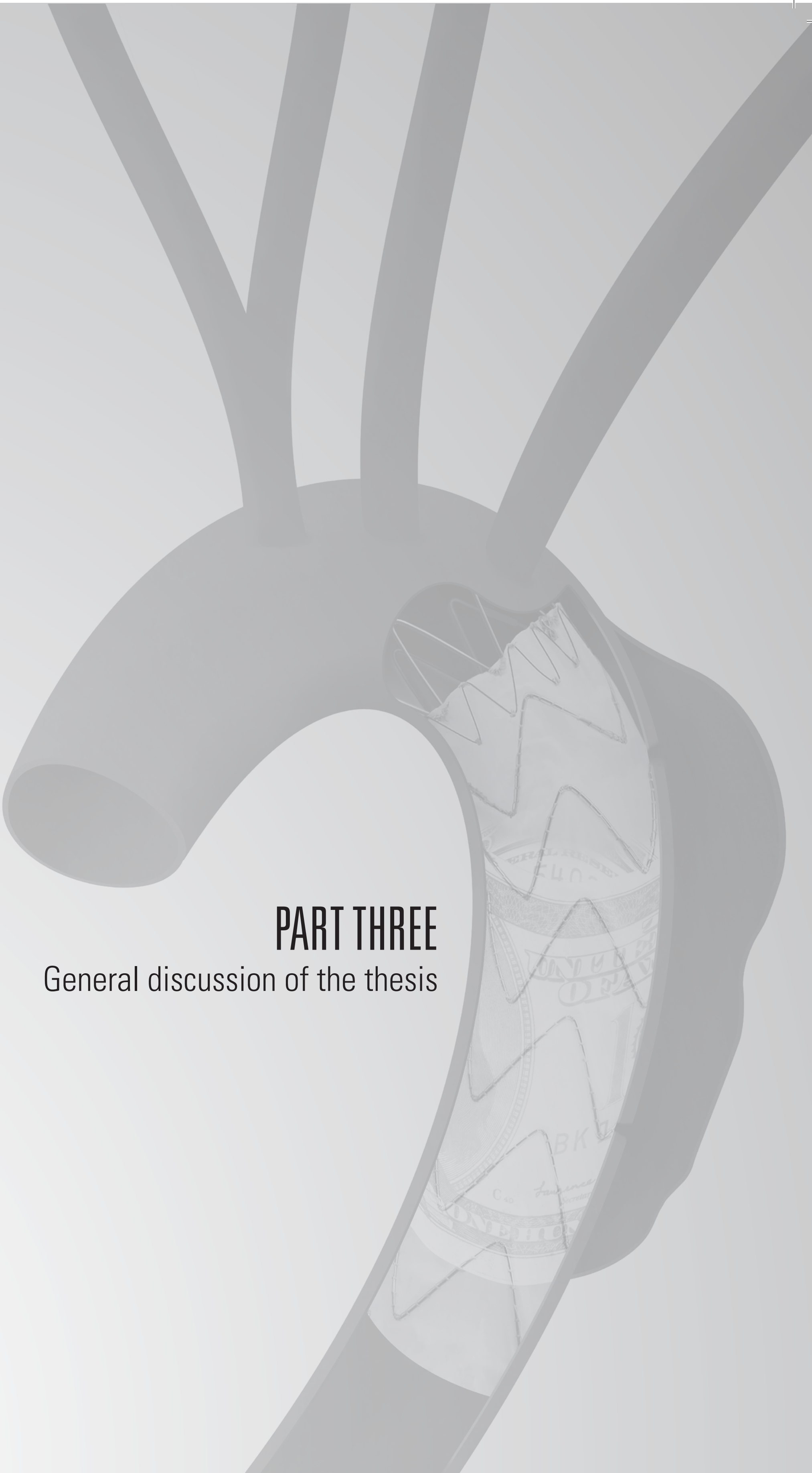

PART THREE

General discussion of the thesis

CHAPTER 13

Summary and general discussion

Improvements in techniques and devices in the vascular surgical field are numerous. The most important change in the last decades is the switch towards the endovascular solution of pathologies that involve vascular surgical interventions.[1-3] Over a period of seven years, there has been an increase of 422% reported for endovascular procedures performed by vascular surgery trainees, while the number of open procedures has decreased by 17.1%.This trend is still continuing.[4] Currently, around 75% of all cases performed by vascular surgeons are done by endovascular means.[5] Increase of the number of surgical interventions is accompanied by an increase in the use of endovascular devices. One has only to look at the *Endovascular Today Buyer's guide* of the last couple of years to see the increase in the huge number of available endovascular devices in Europe and the United States. The evolution of endovascular devices and interventions has undeniably led to a decrease in perioperative morbidity and mortality and improving the health of the patient should always be the number one priority of a physician. However, with the ever increasing health care expenditures, the costs of the new devices and interventions are also relevant.[6] Between 1950 and 2012, real gross domestic product (GDP) per capita in the United States grew at an average of 2.0%, while real national health care expenditures per capita grew at 4.4% per year, which is a difference of 2.4% per year. Growth of the national health care expenditures per capita with the same rate as in the last 50 years will result in health care absorbing more than 20% of the GDP in less than 10 years and 30% in 2040.[7] Currently, the bulk of medical procedure payments go to hospitals and device manufactures and not to physicians.[8] A recently published study reported that stent grafts for endovascular aortic repair (EVAR) account for 52% of all allocated technical costs.[9] EVAR is currently associated with negative operating margins. It is reported that the trend of increasing health care costs is potentially unsustainable for hospitals.[9] Additionally, vascular surgeons are largely unaware of the pricing variation among devices and respective vendors. Better awareness of vendor price differentials may lead to better negotiation on the device pricing and potentially price reduction of endovascular devices.[9,10] In summary, the endovascular revolution has led to a better effect, but sometimes also to significantly higher costs.

A decade ago, studies already investigated the cost-effectiveness of open and endovascular repair of abdominal aortic aneurysms (AAAs).[11-15] In some instances, improvement of an endovascular device led to a minimal improvement in health, while the increase in costs was huge. Nevertheless, minimally invasive procedures led to a shorter hospital stay, which decreased the total costs. Thus, there was a clear trade-off in open versus endovascular repair in both costs and effectiveness. In general, endovascular repair is associated with lower perioperative morbidity and mortality and a shorter hospital stay, while in the long run more reinterventions are required when compared to open repair. Moreover, there are undeniably higher procedure and device related costs for endovascular repair. Therefore, it is important to critically evaluate the effect and costs of new endovascular devices before these are implemented in the surgical armamentarium. Is this increase in the health of the patient worth the higher costs? In other words, do we get value for money?

In PART ONE of this thesis, several new endovascular devices and techniques were discussed. In **Chapter 2** the short-term results of the chimney technique were evaluated. The aim of this study was to provide insight into the safety, applicability, and outcomes of thoracic endovascular aortic repair (TEVAR) with the chimney graft technique. The chimney graft technique involves placement of a stent or stent-graft parallel to the main aortic stent-graft to extend the proximal or distal sealing zone while maintaining side branch patency.[16,17] The advantage of the chimney technique is that readily available, on-the-shelf stents can be used. Custom-made, single-branched, or multi-branched aortic stent grafts can also be used, but these devices are expensive and are not applicable in time-sensitive settings.[18] All original data regarding the chimney technique in patients treated with TEVAR were systematically reviewed. In total, 94 patients were included in this review, the largest collection describing outcomes of the chimney technique until now. In almost 75% of all patients, this was performed in the elective setting and in the remaining 25% in the emergency setting; there was no difference in technical success. However, endoleaks remain the Achilles' heel of the chimney technique and occurred in almost one fifth of all patients, with type Ia being most frequently reported. The placement of the chimney graft along the thoracic endograft increases the risk for type Ia endoleaks by creating gutters next to the chimney graft and affecting a good proximal seal, which can potentially lead to non-resolving type Ia endoleak.[19] Nevertheless, TEVAR with the chimney technique is considered a viable treatment option and may expand treatment strategies for patients with challenging thoracic aortic pathology and anatomy in the emergent and elective setting. As described in the introduction of this thesis, and shown in **Chapter 2**, new endovascular techniques and devices will also lead to new problems and complications, such as endoleaks. This gives manufacturers the opportunity to invent new devices to prevent or treat these complications. One of these new devices, the Aptus HeliFX EndoAnchors received clearance from the U.S. Food and Drug Administration (FDA) in November 2011. Since the availability of the EndoAnchors, several in vitro and smaller in vivo studies have shown EndoAnchors to be a feasible and safe treatment option for primary or secondary procedures to prevent or treat complications after thoracic or abdominal aortic stent graft placement.[20-22] In **Chapter 3** we reported the use of Aptus HeliFX EndoAnchors for endovascular treatment of a proximal type I endoleak after previous EVAR of a giant 12 x 11 cm ruptured AAA. Because of the highly angulated neck and close position of the endograft to the renal arteries, placement of a proximal extension cuff was contra-indicated; therefore, the endoleak was treated with an alternative approach using the Aptus HeliFX EndoAnchors, successfully placing them circumferentially on the proximal site of the endograft. This successfully treated the endoleak by excluding the aneurysm sac from the circulation and follow-up after 3 months showed no residual type I endoleak. This case showed that placement of EndoAnchors can serve as a viable treatment option for proximal type I endoleaks after failed EVAR for ruptured AAAs.

Preferred treatment of another life-threatening event, ruptured descending thoracic aortic aneurysm (rDTAA), has also moved towards endovascular therapy. In the last decade, TEVAR has evolved to become a viable option and is now considered to be the preferred treatment for rDTAAs.[23] Successful treatment of rDTAAs requires a multidisciplinary approach especially during critical moments such as induction, moment of aortic occlusion and placement of the aortic stent-graft. In **Chapter 4** the surgical and anesthetic considerations for the endovascular treatment of rDTAAs were discussed alongside the new opportunities and new challenges faced by surgeons and anesthesiologists. The main focus of research in the last couple of years, not only in the field of vascular surgery but also in other specialties, was centered around the treatment of such pathologies and the prevention of the devastating spinal cord injury and paraplegia which can occur.[24,25] It has been shown that the use of a proactive spinal cord protection protocol could decrease the rates of paraplegia.[26] In order to improve the outcomes of TEVAR for rDTAA, close communication between the anesthesiologist and the surgeon and a thorough understanding of the events during the procedure are mandatory.

In the first Chapters, major endovascular interventions were discussed. The question which arises is: Is open surgical repair in vascular surgery outdated and never the preferred treatment? Several different factors affect this, including the type and extent of the disease and on the type and risk-profile of the patient. Open surgical repair has not been relegated to history and in some cases open surgical repair is still required and/or preferred. In **Chapter 5**, we reported a case of successful open surgical repair of a giant 6 x 7 cm superior mesenteric artery aneurysm (SMAA). Endovascular repair of giant aneurysms is difficult, since coiling and stenting cannot guarantee complete exclusion of the aneurysmal sac from the blood flow, and the risk of rupture remains.[27] Additionally, the best treatment for splanchnic aneurysms is not clear and open repair is a good option, especially since open repair of visceral artery aneurysms is less invasive than surgical repair of thoracic or abdominal aortic aneurysms. SMAAs are the third most common splanchnic aneurysms, but account for only 5.5% of all splanchnic aneurysms. With more than 60% of all splanchnic aneurysms, splenic artery aneurysms (SAAs) are by far the most common.[28] In **Chapter 6**, the short and long-term outcomes of the three most used treatment options for SAA (open repair, endovascular repair and conservative management) were systematically retrieved from the literature. A meta-analysis of the 1,321 patients was performed which showed that the 30-day mortality of open repair was significantly higher than that of endovascular treatment. A larger number of patients treated with endovascular treatment, however, required reinterventions compared to open repair and conservative management. The only difference in baseline characteristics and co-morbidities between the open and endovascular groups was the number of ruptured aneurysms. In general, endovascular repair of SAA has better short-term results compared to open repair, but open repair is associated with fewer late complications and reinterventions during follow-up. Conservatively treated patients showed a higher, late aneurysm-related mortality rate. These patients were usually older, had smaller aneurysm sizes and fewer symptoms and ruptures compared to patients in the two interventional groups. Not surprisingly, ruptured SAAs are predictors of a significantly higher perioperative mortality compared to non-ruptured aneurysms.

These results can be interpreted as descriptive results, but it is still unclear which treatment is best for which patient. Therefore, in PART TWO of this thesis, we aimed to create treatment strategy decision tools based on, variables such as age, gender and risk-profile and whether these interventions are cost-effective or not. In **Chapter 7**, the value of decision analysis, decision models and cost-effectiveness analyses, with a special focus on surgical research was explained and discussed. The number of decision models and theoretical cost-effectiveness analyses is increasing, and hence it is important for surgeons to understand these studies. Many surgeons consider these decision models as a 'black box'.[29] We considered it our task to make surgeons familiar with this type of analysis and therefore we created a step-by-step guide explaining how to perform a decision analysis. It is not necessary that every surgeon can perform decision analysis, but a basic understanding would be required to keep up with future research. In Chapters **8 – 12**, we evaluated several vascular diseases with decision analysis, including chronic and acute type B aortic dissections, chronic mesenteric ischemia (CMI), popliteal artery aneurysms (PAAs) and SAAs.

In **Chapter 8 – 10**, the cost-effectiveness of CMI (**Chapter 8**), SAAs (**Chapter 9**) and PAAs (**Chapter 10**) was evaluated. Similar to treatment of other vascular diseases, endovascular revascularization has surpassed open revascularization for the treatment of CMI, and since 2002 endovascular revascularization has been performed more frequently than open revascularization.[30] The cost-effectiveness of these two major treatment modalities was evaluated in the initial reference-case cohort of 65-year-old female patients in **Chapter 8**. Female patients were chosen because 70% to 80% of all patients with CMI are women and 65 years is the average age at intervention.[31] Subsequently, several different clinical scenarios were also evaluated. This model showed that female and male patients with CMI refractory to conservative management could be best treated by endovascular means, based on the higher effect and lower costs compared with surgical repair, making it both more effective and cost-saving. It also showed that the younger the patient, the larger the difference in QALYs between open and endovascular repair, and the higher the benefit of endovascular repair. Interestingly, patients treated with endovascular repair could expect up to five times more reinterventions, but this did not lead to higher costs. Endovascular revascularization was only more expensive for patients younger than 60 years old, however, since the incremental cost-effectiveness ratio (ICER, the difference in costs of the two strategies, divided by the difference in effect of the two strategies) was less than the willingness-to-pay threshold (WTP, the amount that society is willing to pay for one year in perfect health), endovascular repair was still considered cost-effective.

Another intervention on the visceral vessels was discussed in **Chapter 9**, where the cost-effectiveness of open, endovascular repair and conservative management for SAAs was evaluated. 55-year old female patients were chosen for the reference-case. Endovascular repair had higher effectiveness and lower costs compared with open repair once more and a substantial mean difference of more than ten months in perfect health was shown. Conservative management was less costly, but also less effective compared with endovascular repair. Since the ICER of endovascular repair vs. conservative management was less than the WTP, endovascular repair was considered cost-effective, independent of the gender and risk-profile of the patient. Older patients should be considered for conservative management, based on the high costs in relation to the very small gain in health, when treated with endovascular treatment. Finally, a flowchart for clinical decision-making was developed, which could also be used for shared decision-making with the patient. Shared decision-making is increasingly important and tools like these can be used in delivering patient-centered care. If a decision is shared, there is a greater chance that it will increase patient satisfaction, and can potentially lead to a quicker recovery.[32] The fact that open repair is not completely obsolete is shown in **Chapter 10**, where the treatment options for asymptomatic popliteal artery aneurysms were evaluated in a clinical decision model. Aneurysms are typically found in older men, with a male:female ratio up to 30:1, and with a mean age at time of diagnosis of 65 years, and therefore 65-year-old men were chosen as reference-case.[33] PAAs are the second most common arterial aneurysms after AAAs and account for 75% to 80% of all peripheral aneurysms, although the incidence is still <0.1%.[34] An intervention on the peripheral arteries is generally considered less invasive than an intervention on the visceral arteries, described in the previous two chapters. The aim of the presented study was to assess the cost-effectiveness and preferred treatment options (stenting, greater saphenous vein bypass (GSVB) and optimal medical therapy (OMT)) for PAAs using decision analysis. In general, the analysis showed that intervention was preferred over OMT. GSVB treatment for these patients results in slightly higher QALYs (4 months in perfect health) compared with stent placement. Furthermore, costs are higher for stenting vs. GSVB and more reinterventions were required after stenting, making GSVB the preferred strategy for all outcomes considered. Patients who are at high risk for open repair, if the 5-year primary patency rates of stenting increase and patients without suitable vein should be considered as candidates for endovascular repair. For very old patients and patients with a very short life expectancy, OMT yields higher effectiveness. Further improvement of endovascular techniques that increase patency rates of endovascular stents could make this the preferred therapy for more patients in the future. This study emphasized that treatment options in vascular surgery are not "one size fits all" treatments, but variables such as age, gender and risk-profile play a major role in choosing the best treatment.

Another example of clinical decision making in the era of personalized medicine was reported in **Chapter 11**. In this chapter the three most utilized treatment strategies for the treatment of chronic type B aortic dissection (conservative management, open repair and endovascular repair) were evaluated. In this study, we had a special focus on the effectiveness of the three treatment strategies, since the choice of treatment depends on several variables. A treatment strategy decision tool was developed, including four basic patient characteristics (age, sex, surgical risk, and maximum initial aortic diameter). The outcomes of this decision-analysis model showed that there is no "one size fits all" treatment for uncomplicated chronic type B dissections. A change of the four variables resulted in a change of preferred treatment. Age is the most important deciding factor, followed by initial aortic diameter. Immediate open surgical repair (OSR) is the preferred treatment option in younger patients with a large initial aortic diameter and in low-risk patients. Immediate TEVAR is preferred in elderly patients with a large initial aortic diameter. OMT should be considered in high-risk patients, in patients with small initial aortic diameters, and in patients aged >80 years, unless they have a large initial aortic diameter (>5.5 cm). However, the differences in some patient groups were clinically insignificant, allowing a major role for patient preferences and hospital specific considerations. The tool developed and presented in this study model may guide chTBAD treatment and could play a major role in shared decision-making.

In case the aortic dissection is complicated by (impending) aortic rupture, malperfusion (spinal, iliac, or visceral arteries), recurrent pain, refractory hypertension, hypotension or shock, it is a life-threatening condition with high morbidity and mortality, and immediate intervention is required.[35,36] There is a clear trade-off in making the decision for the best treatment. TEVAR is associated with lower perioperative morbidity and mortality, but has higher reintervention rates. Despite this trade-off, the results of the study presented in **Chapter 12** were straightforward and suggested that TEVAR was preferred over open repair. Although a higher number of reinterventions was expected, the total effectiveness of TEVAR was higher for all age groups. Open surgical repair should be reserved for patients whose aortic anatomy is unsuitable for endovascular repair.

The five previously discussed chapters showed that although endovascular management is very often the best treatment option, it is not the preferred management in all vascular diseases. Additionally, the best treatment option depends on the type of disease, but more importantly, on the “type” of patient. Age, gender, risk-profile, aortic diameter: several factors have a huge impact on treatment strategy. Furthermore, as discussed previously, healthcare costs are still increasing, and treatment decisions should be made with the view of keeping costs in control. Therefore, it is important to optimize personalized management and cost-effectiveness in vascular surgery.

FUTURE PERSPECTIVES

This thesis discussed new endovascular techniques and devices, evaluated the cost-effectiveness of these new endovascular interventions and guided vascular surgery treatment towards more personalized management. The studies performed in this thesis showed that there is no “one size fits all” treatment in vascular surgery, and demonstrated that several patient-specific characteristics have impact on the effect of the intervention, the costs and the expected reinterventions. Therefore, these patient characteristics should influence the decision of type of treatment.

The type of methodology employed in this research thesis, decision analysis, is currently a hot topic in medical research, and the number of studies utilizing these decision models is constantly increasing. For diseases with a low incidence and prevalence it is difficult to perform a well-conducted randomized controlled trial. In case Level 1 evidence is lacking, other types of research should provide the necessary information. The strength of decision models is that they can combine several studies and integrate different types of input variables, and even if there is some uncertainty around the input variables, the best management option can still be determined. Additionally, not only outcomes such as perioperative mortality and complications can be analyzed, but also quality of life, costs and expected reinterventions, which play a major role in determining the preferred treatment option. With decision models, one can select the preferred treatment based on the expected effect of the treatment interventions for specific patient groups which could play a major role in the era towards personalized management. One comment on decision modelling is that the difference between treatment strategies is sometimes small, and that a difference of, for example, three months is not relevant. However, even if the difference is small, a decision has to be made. Additionally, the difference is the mean for the whole group, so where some patients have a small benefit, others may have a substantial benefit.

The progress of and decision analysis is still evolving and more and more modelling techniques are reported and important. One of these new techniques nowadays is value of information analysis. Since more and more research is performed, tons of information is accumulated, and more information usually means more evidence and less uncertainty in decision models. However, performing more research to decrease uncertainty is justified only if the expected benefit to future patients exceeds the cost of performing the research, especially with the ever increasing healthcare costs in mind. Therefore, it is essential to know how much future research can contribute in optimal decision making. Value of information analysis estimates the expected benefit of obtaining more information through future research, but is not the actual value of future research, since prediction of future research is impossible. Instead, the value of information is the expected value of future research. Value of information analysis is performed to determine whether future research is justified and to guide the design of a new study. The new study is performed, and the information obtained is incorporated into the model. This process is repeated over and over until the cost of the future studies are higher than the benefit from obtaining more information. Besides this, creating decision models can also detect gaps in surgical research. When creating a model, and no or almost none information is available this creates a new research topic.

Outcomes of decision models are also increasingly used for communication with the patient. A study of thoughts of surgeons on shared decision-making (SDM) showed that ninety-one per cent of the clinicians agreed with the concept of SDM.[37] Shared decision-making is increasingly important and several tools can be used for patient-centered care, for example with an easy to use treatment strategy decision chart. If a decision is shared, there is a greater chance that it will increase patient satisfaction, and can potentially lead to a quicker recovery.[38] Additionally, outcomes of decision models can be made available to the public and integrated in web-based tools and mobile applications. Patients searching for information on the internet can easily fill in their variables and see their preferred treatment options. However, these options are still in its infancy and can and should not replace the contact between the patient and the clinician.

Second, we as physicians can, and should, play a major role in decreasing the costs of healthcare worldwide. If a treatment has a very small health benefit, but brings a large increase in costs with it, should we implement it? The physician should always do what is best for the patient, but can we do this no matter what the costs? This is an ethical question, and there is no obvious right or wrong and multiple books can be written about this topic. However, using these models, we as physicians can bend the curve of the increasing costs due to the expensive endovascular devices. If we can show in several studies that the minimal increase in effect is not worth the high costs of the endovascular devices, unless the costs of the endovascular devices will be decreased, we may convince the manufacturer to decreases the cost of endovascular devices. In this way, we can make the new endovascular devices more affordable and at least try to control health care costs worldwide. As discussed previously, the costs of the endovascular devices are higher than all the other technical costs combined.[9] Future studies should focus on the evaluation of less expensive endovascular devices. It is my goal to optimize the personalized management in vascular surgery while simultaneously optimizing cost-effectiveness, so that we all benefit from the new endovascular techniques and devices.

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CHAPTER 14

Summary in Dutch - Nederlandse samenvatting

De laatste twee decennia is er een grote toename in chirurgisch onderzoek geweest en enorme vooruitgang in de vaatchirurgie. De belangrijkste verandering die is opgetreden binnen de vaatchirurgie is de shift van open chirurgische behandelingen naar een minimaal invasieve benadering, de endovasculaire behandeling. Bij endovasculaire behandeling wordt er vaak een klein buisje (stent) geplaatst in een bloedvat zodat deze goed open blijft (in het geval van atherosclerose, vaatvernauwing) of zodat het vat niet nog verder verwijdt als gevolg van een verwijding van een bloedvat (aneurysma), met als gevolg dat de kans op een scheur (ruptuur) niet nog verder toeneemt.
Deze shift naar endovasculaire behandeling heeft plaatsgevonden in de grote vaatchirurgische interventies, bijvoorbeeld de verandering van open chirurgische behandeling van abdominale aorta aneurysmata (AAA) naar endovasculaire aorta reparatie (EVAR) en in de kleinere vaatchirurgische ingrepen, waar het plaatsen van een stent en percutane transluminale angioplastiek (PTA) momenteel een belangrijke rol spelen in de behandeling van perifere arteriële vaatziekten. Ondertussen blijven nieuwe endovasculaire technieken en instrumenten zich ontwikkelen. Dit is een goede, positieve en noodzakelijke ontwikkeling, maar de toename van het aantal technieken en instrumenten gaat ook gepaard met een toename aan keuzes, beslissingen en kosten. Vragen die hierbij opkomen zijn bijvoorbeeld: voegen al deze nieuwe instrumenten wel wat toe aan de gezondheid van de patiënt? En is de verbetering die wordt bereikt, welke soms erg gering is, de toename in kosten van deze nieuwe technieken en instrumenten wel waard? Daarnaast brengen nieuwe technieken ook nieuwe complicaties met zich mee. Een voorbeeld hiervan is de "endoleak", voor het eerst beschreven in 1996. Bij een endoleak stroomt het bloed langs de geplaatste stent het aneurysma in, bij een EVAR bijvoorbeeld. Met het toenemende gebruik van de nieuwe "chimney techniek" bijvoorbeeld, is er ook een toename van het aantal endoleaks. Vervolgens is daar weer een nieuwe endovasculaire oplossing voor ontwikkeld om het aantal endoleaks te verlagen. Dit zal later in deze samenvatting worden beschreven.
Ten aanzien van de onderzoeken van chirurgische interventies geldt dat de meeste onderzoeken het effect van de behandeling op de gezondheid van de patiënt evalueren. Echter beschrijven de meeste studies de vroege morbiditeit en mortaliteit en evalueren zij bijvoorbeeld niet de kwaliteit van leven van de patiënt, voor, gedurende en na de behandeling. Dit is echter een zeer belangrijke determinant om te bepalen of een behandeling succesvol is. Afgezien van de kwaliteit van leven, zijn ook de kosten zeer belangrijk. Namelijk omdat bij een kleine winst in de gezondheid, maar een grote toename van de kosten, men zich kan afvragen of de nieuwe behandeling het dan wel waard is, als er al een kwalitatief vergelijkbare, maar goedkopere behandeling beschikbaar is.
Gezien het feit dat veel van de vasculaire aandoeningen een lage incidentie en prevalentie hebben, zijn gerandomiseerde gecontroleerde onderzoeken (RCTs) zeldzaam en beschikken we niet over Level I evidence. Omdat deze RCTs erg kostbaar en tijdrovend zijn is het nog maar de vraag of deze in de toekomst wel uitgevoerd zullen worden. Het vergelijken van de uitkomsten van verschillende behandelingen voor vasculaire aandoeningen blijft echter nog steeds noodzakelijk. Voor het evalueren van deze verschillende behandelingsopties kunnen beslismodellen worden gebruikt. Beslismodellen maken het mogelijk om verschillende studies te combineren en verschillende variabelen te integreren waardoor ze een goede methode

vormen om vasculaire aandoeningen te bestuderen, in het geval dat Level-1-Evidence ontbreekt. Het doel van de onderzoeken beschreven in dit proefschrift was om de kosteneffectiviteit van diverse behandelingsopties te evalueren en de optimale behandeling te selecteren voor verschillende klinische patiëntengroepen voor een aantal vaatchirurgische aandoeningen, met behulp van beslismodellen.

Over een periode van zeven jaar, is er een toename van 422% gerapporteerd van endovasculaire procedures uitgevoerd door vaatchirurgische opleidingsassistenten, terwijl het aantal open chirurgische procedures is gedaald met 17,1%. Deze trend zet momenteel nog steeds door. Verhoging van het aantal chirurgische ingrepen gaat gepaard met een toename van het gebruik van endovasculaire instrumenten. Deze evolutie van endovasculaire interventies heeft onmiskenbaar geleid tot een daling van vroege morbiditeit en sterfte, en verbetering van de gezondheid van de patiënt is altijd prioriteit nummer één van de chirurg. Echter, met de steeds toenemende kosten in de gezondheidszorg worden de kosten van de nieuwe endovasculaire instrumenten en interventies ook relevant. Tussen 1950 en 2012, groeide het bruto binnenlands product (BBP) per hoofd van de bevolking in de Verenigde Staten met een gemiddelde van 2,0%, terwijl de nationale uitgaven voor gezondheidszorg per hoofd van de bevolking groeiden met 4,4% per jaar. Indien de groei van de nationale uitgaven voor gezondheidszorg per hoofd van de bevolking met dezelfde snelheid blijft groeien als in de afgelopen 50 jaar, dan zal de gezondheidszorg meer dan 20% van het BBP zijn in minder dan 10 jaar en 30% in 2040. Momenteel gaat het grootste deel van de kosten van vaatchirurgisch procedures naar de producenten van de vaatchirurgische instrumenten. Een onlangs gepubliceerde studie beschreef dat stentgrafts voor endovasculaire aorta reparatie (EVAR) goed zijn voor 52% van alle technische kosten tijdens dit soort operaties. Ter vergelijking, de kosten voor stentgrafts zijn driemaal zo hoog als de kosten voor het gebruik van de operatiekamer, die bij behandelingen waarbij geen stentgrafts worden gebruikt de grootste kostenpost is. Er is gerapporteerd dat deze trend van stijgende kosten in de gezondheidszorg op den duur niet meer vol te houden zal zijn voor ziekenhuizen. Daarnaast is gebleken dat vaatchirurgen zich grotendeels onbewust zijn van de prijsverschillen tussen endovasculaire instrumenten van verschillende producenten. Beter besef van prijsverschillen kan leiden tot een betere onderhandelingspositie en een mogelijke prijsverlaging van endovasculaire instrumenten.

Samenvattend heeft de endovasculaire revolutie geleid tot een betere uitkomst, maar soms ook tot aanzienlijk hogere kosten. In sommige gevallen leidt verbetering van een endovasculaire interventie tot een minimale verbetering van de gezondheid, terwijl de kostenstijging soms enorm is. Echter zorgen minimaal invasieve procedures wel voor een kortere opnameduur, waarin de totale kosten lager zijn. Er is dus een duidelijke afweging voor open versus endovasculaire behandeling in zowel de kosten en effectiviteit. In het algemeen wordt endovasculaire behandeling geassocieerd met een lagere perioperatieve morbiditeit en mortaliteit en een kortere ziekenhuisopname periode, terwijl op de lange termijn meer reïnterventies nodig zijn in vergelijking met open chirurgische interventie. Bovendien zijn er hogere procedure gerelateerde kosten voor endovasculaire behandeling. Daarom is het belangrijk om het effect en de kosten van nieuwe endovasculaire instrumenten kritisch te evalueren alvorens deze in het chirurgische instrumentarium op te nemen. Is de toename in het effect van de gezondheid van de patiënt de hogere kosten waard? Met andere woorden, krijgen we waar voor ons geld?

In DEEL EEN van dit proefschrift zijn verschillende nieuwe endovasculaire instrumenten en technieken besproken. In **Hoofdstuk 2** werden de korte termijn resultaten van de chimney (schoorsteen) techniek geëvalueerd. Het doel van deze studie was om inzicht te krijgen in de veiligheid, toepasbaarheid en uitkomsten van thoracale endovasculaire aorta reparatie (TEVAR) met de chimney techniek. De chimney techniek houdt in dat er een kleinere stent wordt geplaatst, parallel aan de aorta stent graft, zodat de proximale en distale sealing zone (bovenste en onderste afsluit gebied) verlengd kan worden terwijl de zijtakken van de aorta voorzien blijven van bloedtoevoer. (Figure1) Het voordeel van de chimney techniek is dat beschikbare stents, direct gebruikt kunnen worden. Speciaal op maat gemaakte, stentgrafts met vaste zijtakken kunnen ook gebruikt worden, maar deze multi-branched aortic stentgrafts zijn kostbaar en niet te gebruiken in acute situaties. In deze studie werden alle originele data over TEVAR in combinatie met de chimney techniek systematisch verzameld en geanalyseerd. In totaal werden data van 94 patiënten verzameld, waarmee dit de grootste collectie patiënten tot op heden is. Bijna 75% van de patiënten werd geopereerd tijdens een geplande operatie en de overige 25% tijdens spoedoperaties, maar er werd geen verschil in technisch succes gezien. De meest voorkomende complicatie was de endoleak, die bij ongeveer 1 op de 5 behandelde patiënten optrad, waarvan het merendeel uiteindelijk spontaan herstelde. Mede hierdoor wordt de chimney techniek beschouwd als een goede behandeloptie en is het een toevoeging aan de behandelstrategieën voor patiënten met een uitdagende thoracale aorta pathologie of anatomie, tijdens electieve of spoedoperaties.

Zoals eerder beschreven leiden nieuwe interventies soms ook tot nieuwe problemen en complicaties, zoals endoleaks. Dit geeft producenten de mogelijkheid om nieuwe endovasculaire instrumenten te ontwikkelen die deze complicaties kunnen voorkomen of behandelen. Een voorbeeld hiervan zijn de Aptus HeliFX EndoAnchors. In **Hoofdstuk 3** werd een casus gerapporteerd van een patiënt die behandeld werd met deze EndoAnchors vanwege een endoleak na EVAR voor een gigantische 12 x 11 cm geruptureerd AAA. Het endoleak werd succesvol behandeld en na (een follow-up van) 3 maanden waren er geen tekenen van een endoleak meer te bekennen. Deze casus laat zien dat endovasculaire behandeling met de EndoAnchors een goede behandeloptie is voor endoleaks na een EVAR voor geruptureerde AAAs.

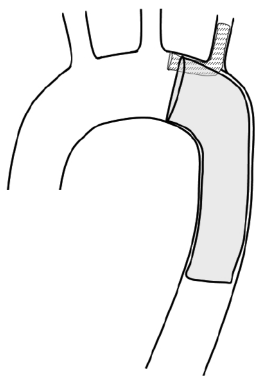

Figure 1 De chimney techniek houdt in dat er een kleinere stent wordt geplaatst, parallel aan de aorta stent graft, zodat de proximale en distale sealing zone (bovenste en onderste afsluit gebied) verlengd kan worden terwijl de zijtakken van de aorta voorzien blijven van bloedtoevoer.

De optimale behandeling voor een andere levensbedreigende aandoening, de gerupturеerde aneurysmata van de thoracale aorta descendens (rDTAA), bestaat tegenwoordig ook uit een endovasculaire behandeling. In het laatste decennium heeft TEVAR zich ontwikkeld tot een goede en betrouwbare behandel optie voor rDTAAs. Succesvolle behandeling van rDTAAs vereist een multidisciplinaire aanpak, voornamelijk gedurende de kritische momenten, zoals inductie en plaatsing van de stent graft. In **Hoofdstuk 4** werden de chirurgische en anesthetische overwegingen voor de endovasculaire behandeling van rDTAAs bediscussieerd, mede als de nieuwe mogelijkheden en uitdagingen waarmee chirurgen en anesthesiologen worden geconfronteerd. De belangrijkste focus van onderzoek op dit gebied in de afgelopen jaren, was het voorkomen van dwarslaesies en paraplegie welke kunnen optreden tijdens endovasculaire behandeling van gerupturеerde aneurysmata. Het is aangetoond dat het gebruik van een "proactief ruggenmerg-bescherming protocol" de incidentie van paraplegie kan verminderen. Om de uitkomsten van TEVAR voor rDTAA te verbeteren is nauwe communicatie tussen de anesthesist en de chirurg noodzakelijk.
In de eerste paar hoofdstukken zijn voornamelijk de grotere vaatchirurgische ingrepen besproken. Hierbij komt endovasculaire behandeling vaak beter naar voren wanneer vergeleken met open behandeling. De vraag is dan ook: Is de periode van open chirurgische behandeling voor vaatchirurgische ziekten dan volledig verleden tijd?
Er zijn verschillende factoren die op deze kwestie invloed hebben, onder andere het type en de uitgebreidheid van de ziekte maar ook de karakteristieken en het risicoprofiel van de patiënt. Uiteraard is open chirurgische behandeling niet geheel achterhaald, in sommige casussen is deze benadering zelfs noodzakelijk, dan wel de behandeling van voorkeur. In **Hoofdstuk 5** is een casus besproken van een patiënt met een gigantisch 6 x 7 cm aneurysma van de arteria mesenterica superior. Endovasculaire behandeling van deze grotere aneurysmata is lastig aangezien stenten of coilen geen garantie geven op complete exclusie van de aneurysmazak van de bloedcirculatie waardoor het risico op ruptuur aanwezig blijft. Aneurysmata van de arteria mesenterica superior zijn de op twee na meest voorkomende aneurysmata van de splanchnische vaten en zijn verantwoordelijk voor 5.5% van alle splanchnische aneurysmata. Met meer dan 60% van alle splanchnische aneurysmata is de arteria lienalis het meest aangedane bloedvat. In **Hoofdstuk 6** werden de korte en lange termijn resultaten gerapporteerd van de drie meest gebruikte behandelopties voor aneurysmata van de arteria lienalis (open, endovasculaire en conservatieve behandeling). Deze resultaten werden systematisch verkregen uit de literatuur wat leidde tot de grootste verzameling van data over uitkomsten na behandeling van aneurysmata van de arteria lienalis wereldwijd. Er werd een meta-analyse van de 1.321 geïncludeerde patiënten uitgevoerd welke liet zien dat de 30-dagen mortaliteit na open behandeling significant hoger was dan na endovasculaire behandeling. Echter hadden wel meer patiënten die endovasculair behandeld werden een reïnterventie nodig vergeleken met patiënten die open of conservatief behandeld waren. Het enige verschil in baseline karakteristieken en co-morbiditeiten tussen de open en endovasculaire groep, was het aantal gerupturеerde aneurysmata, wat hoger was in de open groep. In het algemeen gold dat patiënten die endovasculair behandeld waren betere korte termijn resultaten hadden, maar bij open chirurgische behandeling waren er minder late complicaties en minder reïnterventies. Conservatief behandelde patiënten hadden een hogere aneurysma-gerelateerde sterfte. Deze patiënten waren ook ouder, hadden kleine

aneurysmata en minder symptomen en rupturen vergeleken met patiënten in de andere twee groepen. Niet verrassend was dat geruptureerde aneurysmata voorspellend waren voor een significant hogere perioperatieve mortaliteit vergeleken met niet-geruptureerde aneurysmata.

Hoewel deze resultaten aangeven dat endovasculaire behandeling minder risicovol is, is het nog niet geheel duidelijk voor welke (groep) patiënten, welke behandeling de voorkeur heeft. Daarom was het doel van DEEL TWEE van dit proefschrift om beslistabellen voor behandeling te creëren, gebaseerd op onder andere variabelen als leeftijd, geslacht en risico profiel. In **Hoofdstuk 7** is de waarde van beslismodellen en kosteneffectiviteitsanalyses besproken, met een speciaal focus op chirurgisch onderzoek. Het aantal wetenschappelijke publicaties dat gebruik maakt van beslismodellen neemt toe en daarom is het belangrijk voor chirurgen om deze studies te begrijpen. We hebben een overzicht gemaakt van de belangrijkste termen en begrippen die voorkomen in studies met beslismodellen en een "step-by-step" gids gecreëerd waardoor chirurgen deze studies gemakkelijker kunnen begrijpen. Het is niet noodzakelijk dat iedereen dit soort studies kan uitvoeren, maar wel om ze te begrijpen en zo op de hoogte te blijven van toekomstig chirurgisch onderzoek. In **Hoofdstukken 8 – 12** zijn verschillende vaatchirurgische aandoeningen geëvalueerd met behulp van beslismodellen.
In **Hoofdstuk 8 – 10** werd de kosteneffectiviteit van de behandelingen voor chronische mesenteriale ischemie (CMI), aneurysmata van de arteria lienalis en van de arteria poplitea geëvalueerd.
Endovasculaire revascularisatie (EV) heeft open revascularisatie voorbij gestreefd als behandeling van voorkeur van CMI en wordt sinds 2002 vaker uitgevoerd dan open behandeling (OR). De kosteneffectiviteit van de twee belangrijkste behandelmethoden voor CMI werd geëvalueerd in **Hoofdstuk 8**. Dit model liet zien dat mannelijke en vrouwelijk patiënten met CMI het best endovasculair behandeld kunnen worden, gebaseerd op het hogere effect en de lagere kosten vergeleken met open revascularisatie. Het liet ook zien dat, hoe jonger de patiënt, hoe groter het verschil is in effectiviteit tussen EV en OR, in het voordeel van EV. Interessant was dat patiënten die endovasculair behandeld werden tot vijf keer meer reïnterventies konden verwachten, maar dat dit niet leidde tot hogere kosten in vergelijking met OR. EV was wel kostbaarder voor patiënten jonger dan 60 jaar, echter was het incremental cost-effectiveness ratio (ICER, het verschil in kosten van de twee strategieën gedeeld door het verschil in effect van de twee strategieën) lager dan de willingness-to-pay (WTP, het bedrag dat de samenleving bereid is om te betalen voor één jaar in perfecte gezondheid). Hierdoor werd endovasculaire behandeling nog steeds beschouwd als kosteneffectief.
Een andere interventie voor de viscerale arteriën werd beschreven in **Hoofdstuk 9**, waar de kosteneffectiviteit van open, endovasculaire en conservatieve behandeling voor aneurysmata van de arteria lienalis geëvalueerd werd. Hieruit bleek ook dat endovasculaire behandeling de optimale behandeling was, gebaseerd op de lagere kosten en hogere effectiviteit, die een gemiddeld verschil liet zien van tien maanden tussen open en endovasculaire behandeling. Conservatieve behandeling was minder kostbaar, maar ook minder effectief vergeleken met endovasculaire behandeling. Gezien het feit dat de ICER lager was dan de WTP werd endovasculaire behandeling ook hier beschouwd als kosteneffectief, onafhankelijk van het geslacht en risicoprofiel van de patiënt. Voor oudere patiënten zou conservatieve behandeling

overwogen moeten worden, vanwege de hoge kosten in combinatie met de kleine winst in effectiviteit wanneer endovasculair behandeld werd. Uiteindelijk werd er een flowchart ontwikkeld voor klinische besluitvorming welke gebruikt kan worden voor gedeelde besluitvorming (shared decision-making) met de patiënt. Gedeelde besluitvorming is in toenemende mate belangrijk en dit soort stroomschema's kunnen hier uitstekend bij helpen. Het is gebleken dat als een beslissing gedeeld wordt tussen behandelaar en patiënt, de kans toeneemt dat de patiënt tevreden is en het herstel mogelijk sneller verloopt.

Het feit dat open behandeling niet geheel achterhaald is, werd beschreven in **Hoofdstuk 10** waarin de behandelopties voor patiënten met asymptomatische aneurysmata van de arteria poplitea (PAAs) werden geëvalueerd met behulp van een klinisch beslismodel. PAAs zijn de op één na meest voorkomende arteriële aneurysmata na AAAs en zijn verantwoordelijk voor 75% tot 80% van alle perifere aneurysmata, hoewel de incidentie nog steeds minder dan 0.1% is. Interventies aan de perifere vaten worden over het algemeen beschouwd als minder invasief vergeleken met een interventie aan de viscerale arteriën. Het doel van deze studie was om de kosteneffectiviteit en optimale behandeling voor de drie meest gebruikte behandelingsstrategieën te evalueren: endovasculaire behandeling (stenting), bypass met de vena saphena magna (GSVB) of optimale medicamenteuze therapie (OMT). Dit beslismodel liet zien dat opereren effectiever is vergleken met OMT. GSVB resulteerde in hogere effectiviteit (verschil van vier maanden in perfecte gezondheid) vergeleken met stenting. Daarbij waren de kosten voor stenting hoger en waren er meer reïnterventies noodzakelijk, vergeleken met GSVB, waardoor GSVB de optimale behandeling bleek te zijn qua gezondheidswinst en kosteneffectiviteit. Bij patiënten die een hoog risicoprofiel hebben, patiënten waarbij geen geschikte vene beschikbaar is, en indien de 5-jaars patency rates van stenting toeneemt, moet endovasculaire behandeling met stentplaatsing worden overwogen. Bij zeer oude patiënten en patiënten met een korte levensverwachting is OMT effectiever. Deze studie liet dus ook zien dat er binnen de vaatchirurgie geen "one size fits all" behandelingen bestaan, maar dat variabelen als leeftijd, geslacht en risicoprofiel ook een zeer belangrijke rol spelen in het selecteren van de optimale behandeling.

Een ander voorbeeld van klinische besluitvorming in het tijdperk van gepersonaliseerde geneeskunde werd besproken in **Hoofdstuk 11**. In dit hoofdstuk werden de drie meest gebruikte behandelingsstrategieën voor chronisch type B aorta dissecties (conservatieve behandeling (OMT), open behandeling en TEVAR) geëvalueerd. In deze studie lag de focus in het bijzonder op de effectiviteit, omdat de keuze voor type behandeling afhankelijk is van verschillende variabelen. Een behandeling beslistabel werd ontwikkeld, gebaseerd op vier basis patiënten karakteristieken. De uitkomsten van dit model lieten zien dat er geen "one size fits all" behandeling bestaat voor ongecompliceerde chronische type B aorta dissecties. Namelijk, een verandering in één van de variabelen resulteerde ook in verandering van optimale behandeling. Leeftijd was de belangrijkste beslisfactor, gevolgd door de initiële diameter van de aorta. Onmiddellijke open behandeling was de behandeling van voorkeur in jongere patiënten met een grote initiële aorta diameter en in laag-risico patiënten. Onmiddellijke interventie met TEVAR was de optimale behandeling in oudere patiënten en voor patiënten met grotere initiële aorta diameters. OMT zou moeten worden overwogen in hoog-risico patiënten, in patiënten met kleine aorta diameters en in patiënten ouder dan 80 jaar, behalve als zij een aorta diameter van meer dan 5.5 cm hebben. De verschillen tussen behandelingen in sommige patiëntgroepen waren echter niet significant waardoor er ook een belangrijke rol is weggelegd voor voorkeur van de patiënt en ziekenhuis-gerelateerde overwegingen. Het ontwikkelde beslismodel dat gepresenteerd werd in dit onderzoek kan de richting voor de behandelingsstrategie voor chronisch type B aorta dissecties helpen bepalen en kan een belangrijke rol spelen in shared decision-making.

In het geval dat de aorta dissectie samengaat met een aorta ruptuur, malperfusie, terugkerende pijn, refractaire hypertensie, hypotensie of shock, wordt de aorta dissectie beschouwd als een gecompliceerde dissectie. Gecompliceerde acute dissectie van de aorta descendens is een levensbedreigende aandoening met hoge morbiditeit en mortaliteit, en onmiddellijke interventie is dan ook noodzakelijk. Er is een duidelijke afweging die gemaakt moet worden tijdens de beslissing voor type behandeling: TEVAR wordt geassocieerd met lagere perioperatieve morbiditeit en mortaliteit, maar heeft hogere reïnterventie rates vergeleken met open chirurgische behandeling. Ondanks deze afweging laten de resultaten, die gepresenteerd zijn in **Hoofdstuk 12**, duidelijk zien dat de optimale behandeling voor gecompliceerde acute dissecties van de aorta descendens TEVAR is. Hoewel een hoger aantal reïnterventies te verwachten was voor patiënten die behandeld waren met TEVAR, was TEVAR effectiever voor alle leeftijdsgroepen. Open chirurgische behandeling moet gereserveerd worden voor patiënten van wie de aorta anatomie ongeschikt is voor endovasculaire behandeling.

De vijf zojuist besproken hoofdstukken lieten zien dat endovasculaire behandeling niet voor alle vaatchirurgische aandoeningen de behandeling van voorkeur is. Daarnaast is behandeling van voorkeur niet alleen afhankelijk van het type ziekte, maar ook van het "type" patiënt. Leeftijd, geslacht, risicoprofiel, aorta diameter: verschillende factoren hebben een belangrijke impact op de behandelingsstrategie. Bovendien nemen de kosten in de gezondheidszorg nog steeds toe en zou de keuze voor behandeling genomen moeten worden met het oog op het binnen de perken houden van de kosten. Daarom is het belangrijk om gepersonaliseerde behandeling en kosteneffectiviteit binnen de vaatchirurgie te optimaliseren.

TOEKOMST PERSPECTIEVEN

In dit proefschrift werden nieuwe endovasculaire technieken en systemen besproken, de kosteneffectiviteit van deze nieuwe endovasculaire interventies geëvalueerd en heeft vaatchirurgische behandelingen richting een meer gepersonaliseerde behandeling gestuurd. De uitgevoerde onderzoeken die beschreven zijn in dit proefschrift laten zien dat er geen "one size fits all" behandeling bestaat binnen de vaatchirurgie en hebben gedemonstreerd dat verschillende patiënt-specifieke karakteristieken impact hebben op het effect van de interventie, de kosten en de te verwachten reïnterventies.

Het type onderzoeksmethode wat gebruikt is in dit proefschrift, decision analysis (beslissingsanalyse), is momenteel een hot topic in medisch onderzoek en het aantal studies waarin deze methode wordt gebruikt neemt momenteel toe. Voor aandoeningen met een lage incidentie en prevalentie is het uitvoeren van een goed georganiseerde en gerandomiseerde studie lastig en kostbaar. In het geval dat er geen Level-1-evidence is, kunnen andere onderzoekstechnieken de nodige informatie geven. De kracht van beslismodellen is dat ze verschillende studies kunnen combineren en verschillende variabelen kunnen integreren en dat, zelfs in het geval van onzekerheid rondom de inputvariabelen, de uitkomsten zeker kunnen zijn. Verder worden niet alleen uitkomsten zoals perioperatieve morbiditeit en mortaliteit meegenomen, maar ook kwaliteit van leven, kosten en het te verwachten aantal reïnterventies, welke alle een zeer belangrijke rol spelen in het bepalen van de behandeling van voorkeur. Met beslismodellen kan men de optimale behandeling bepalen op het te verwachten effect van de verschillende interventies voor specifieke patiëntengroepen en deze beslismodellen kunnen dan ook een zeer belangrijke rol gaan spelen in het tijdperk van meer gepersonaliseerde geneeskunde. De vooruitgang van de verschillende technieken van decision analysis is nog steeds aan de gang en meerdere modelleer technieken worden beschreven en zijn belangrijk. Eén van deze modernere technieken die tegenwoordig vaak wordt toegepast is "value of information" analyse. Omdat meer en meer onderzoek wordt uitgevoerd, wordt er heel veel informatie verzameld. Meer informatie betekent normaal gesproken meer bewijs en minder onzekerheid. Meer onderzoek doen om de onzekerheid te verlagen is echter alleen verantwoord indien het voordeel voor toekomstige patiënten hoger is dan de kosten van het uitvoeren van onderzoek, helemaal als we de toenemende kosten in de gezondheidszorg in gedachten hebben. Daarom is het essentieel om te weten hoeveel toekomstig onderzoek kan bijdragen aan het bepalen van de optimale behandeling. Value of information analysis wordt uitgevoerd om te bepalen of toekomstig onderzoek te rechtvaardigen is en om te helpen creëren van toekomstige studies. Verder kunnen beslismodellen gaten in chirurgisch onderzoek detecteren. Indien een model gecreëerd wordt en geen, of bijna geen informatie is beschikbaar, creëert dit een nieuw onderwerp van onderzoek.

Uitkomsten van beslismodellen worden ook in toenemende mate gebruikt voor communicatie met de patiënt. Uit studies is gebleken dat meer dan 90% van alle clinici het eens is dat shared-decision making (SDM) kan bijdragen aan een betere communicatie met de patiënt. SDM is in toenemende mate belangrijk en verschillende hulpmiddelen kunnen gebruikt worden om behandelingen en beslissingen met de patiënt te bespreken. Indien een behandeling besproken en gedeeld wordt met de patiënt, is de kans groter dat de patiënt tevreden zal zijn, wat mogelijk kan leiden tot een kortere herstelperiode. Daarnaast kunnen uitkomsten van beslismodellen publiekelijk beschikbaar gemaakt worden en geïntegreerd worden in online-hulpmiddelen en apps voor mobiele telefoons. Deze technieken staan echter nog in de kinderschoenen en moeten absoluut niet het contact tussen de arts en patiënt verminderen.

Ten tweede, wij als clinici kunnen en moeten wereldwijd een belangrijke rol spelen in het verlagen van de kosten in de gezondheidszorg. Wij moeten ons afvragen of een behandeling die tot een relatief kleine klinische vooruitgang leidt, maar torenhoge kosten met zich meebrengt, dan wel geïmplementeerd moeten worden? Clinici doen altijd wat het beste is voor de patiënt, maar moeten we dit blijven doen, hoe hoog de kosten ook zijn? Dit is een ethische kwestie en er bestaat geen goed of fout antwoord. Echter, door middel van het gebruik van beslismodellen kunnen wij als clinici de stijgende trend van de kosten in de gezondheidszorg doorbreken. Als verschillende studies laten zien dat het minimale effect van de endovasculaire systemen, de hoge prijs die hier voor betaald moet worden niet waard is, tenzij producenten de kosten van de stents verlagen, kunnen we nieuwe endovasculaire systemen betaalbaarder maken en op zijn minst de gezondheidszorgkosten wereldwijd proberen te verlagen. Zoals eerder besproken

zijn de kosten van endovasculaire systemen hoger dan alle andere technische kosten gecombineerd. Daarom zouden toekomstige studies zich voornamelijk moeten focussen op het evalueren van minder dure endovasculaire systemen.
Het is mijn doel om de gepersonaliseerde behandeling in de vaatchirurgie optimaal te maken en tegelijkertijd de kosteneffectiviteit van de behandelingen te optimaliseren, zodat iedereen kan profiteren van nieuwe endovasculaire technieken en instrumenten.

CHAPTER 15

Review Committee

Acknowledgements - Dankwoord

List of Publications & Presentations

Curriculum Vitae

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PUBLICATIONS

Van Waes OJ, Van Lieshout EM, **Hogendoorn W**, Halm JA, Vermeulen J. Treatment of penetrating trauma of the extremities: ten years' experience at a Dutch level 1 trauma center. *Scandinavian journal of trauma, resuscitation and emergency medicine* 2013;21:2.

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Hogendoorn W, Hunink MGM, Schlösser FJV, Moll FL, Sumpio BE, Muhs BE. A Clinical Decision Model for Selecting the Most Appropriate Therapy for Uncomplicated Chronic Dissections of the Descending Aorta. *Journal of Vascular Surgery*. Epub ahead of print: March 7, 2014.

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Hogendoorn W, Hunink MGM, Schlösser FJV, Moll FL, Sumpio BE, Muhs BE. Endovascular vs. Open Repair of Complicated Acute Type B Aortic Dissections. *Journal of Endovascular Therapy. In press.*

Hogendoorn W, Lavida A, Hunink MGM, Moll FL, Geroulakos G, Muhs BE, Sumpio BE. A Systematic Review and Meta-Analysis of Open Repair, Endovascular Repair and Conservative Management of True Splenic Artery Aneurysms. *Submitted to Journal of Vascular Surgery.*

Hogendoorn W, Moll FL, Sumpio BE, Hunink MGM. Clinical Decision Modeling and Cost-Effectiveness Analysis in Surgical Research. *Submitted to Annals of Surgery.*

Hogendoorn W, Lavida A, Hunink MGM, Moll FL, Geroulakos G, Muhs BE, Sumpio BE. Cost-Effectiveness of Endovascular Repair, Open Repair and Conservative Management of Splenic Artery Aneurysms. *Submitted to Journal of Vascular Surgery.*

PRESENTATIONS

Feb 2013 **"Medical Decision Making and Decision Analysis in Vascular Surgery"**
Seminars in Surgical Research, *Yale University, New Haven, CT, USA*

Apr 2013 **"Beslismodel voor open operatie versus endovasculaire behandeling in patiënten met een asymptomatisch aneurysma van de arteria poplitea"**
(in Dutch) Vascular Days (Vaatdagen), *Noordwijkerhout, the Netherlands*

Oct 2013 **"Reintervention and Cost-Effectiveness after Endovascular versus Open Popliteal Artery Aneurysm Repair"**
2013 Annual Clinical Congress, American College of Surgeons, *Washington, DC, USA*

Nov 2013 **"Successful Treatment of a Proximal Type I Endoleak with HeliFX EndoAnchors after Previous Endovascular Aneurysm Repair of a Ruptured Abdominal Aortic Aneurysm"**
International College of Angiology, 55th Annual World Congress, *New Haven, CT, USA*

Jan 2014 **"Optimizing Treatment for Chronic Mesenteric Ischemia: A Comparison of Open and Endovascular Repair in a Clinical Decision Model"**
38th Annual Meeting, Southern Association for Vascular Surgery, *Palm Beach, FL, USA*

Feb 2014 **"Evaluating New Endovascular Devices and Techniques for Vascular Surgical Diseases with Decision Analysis"**
Yale University Seminars in Surgical Research, *Yale University, New Haven, CT, USA*

Mar 2014 **"Optimalisatie van de behandeling van chronische mesenteriale ischemie: Vergelijking van open & endovasculaire behandeling in een klinisch beslismodel"** (in Dutch) Vascular Days (Vaatdagen), *Noordwijkerhout, the Netherlands*

May 2014 **"Bestaat er een "one size fits all" behandeling voor patiënten met ongecompliceerde chronische dissecties van de aorta descendens?"** (in Dutch) NVVH Chirurgendagen, *Veldhoven, the Netherlands*

June 2014 **"Cost-Effectiveness Analysis of the Treatment of Splenic Artery Aneurysms"**
15th Biennial European Meeting, Society for Medical Decision Making, *Antwerp, Belgium*

June 2014 **"Kosteneffectiviteit van de behandeling van aneurysmata van de arteria lienalis."** (in Dutch) Vascular Rounds Midden-Nederlands, *UMC Utrecht, Utrecht*

COURSES

2012 – 2013 **Cost-Effectiveness Analysis and Decision Making**
School of Public Health, *Yale University, New Haven, CT, USA*

March 2013 **Advanced Topics in Decision-making in Medicine**
Clinical Epidemiology Winter Programme, *Netherlands Institute of Health Science, Rotterdam, the Netherlands*

TEACHING ACTIVITIES

Jul/Aug 2013 **Teaching Assistant**, Methods for Decision Making in Medicine, Clinical Effectiveness Summer Program Course for Medical Doctors. *Harvard School of Public Health, Boston, MA, USA*

CURRICULUM VITAE

Wouter Hogendoorn, MD was born on November 27, 1984 in Zeist, the Netherlands. After graduating from the Montessori Lyceum Herman Jordan in Zeist, he entered the Erasmus University Rotterdam School of Medicine in 2005. During Medical School, he spent a few months in Macha, Choma District, Zambia for a research fellowship at the Macha Hospital and conducted research at the department of Traumatology, Erasmus MC, Rotterdam.

After completing his medical degree in May 2012, he was invited by Prof. Dr. Frans L. Moll (promotor), Dr. Bauer E. Sumpio (co-promotor) and Dr. Bart E. Muhs (co-promotor) to perform PhD research at the section of Vascular Surgery at Yale University School of Medicine in New Haven, Connecticut, USA. The main focus of his research was optimizing personalized management and cost-effectiveness in Vascular Surgery, which is presented in this thesis. During his PhD research period, he started working with Prof. Dr. M.G. Myriam Hunink (promotor) from the Erasmus Medical Center, Rotterdam, the Netherlands and Harvard School of Public Health, Boston, Massachusetts, USA. Wouter spent the summer of 2013 in Boston, where he was teaching assistant at the Harvard School of Public Health, Boston, USA to assist Prof. dr. Hunink with the course Methods for Decision Making in Medicine. During his research fellowship in the United States, Wouter presented his work at numerous prestigious meetings, including the American College of Surgeons, the Southern Association for Vascular Surgery, the Vascular Days, the Society for Medical Decision Making and Chirurgendagen. In August 2014, Wouter started with clinical work at the surgery department of the Maasstad Ziekenhuis, Rotterdam, the Netherlands. He will defend his PhD thesis "Optimizing Personalized Management and Cost-Effectiveness in Vascular Surgery" at the University of Utrecht on September 23, 2014.