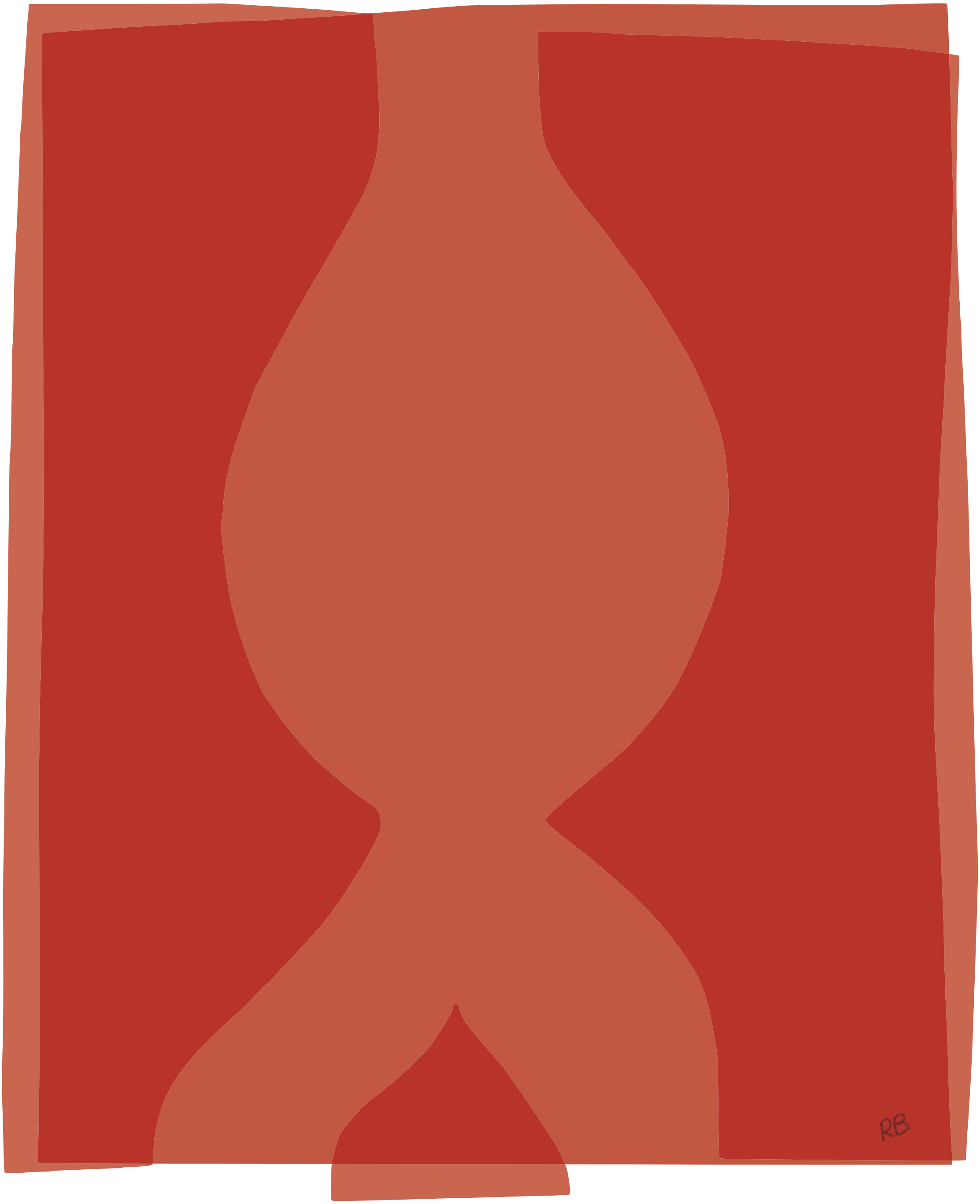
Elective Abdominal Aortic Aneurysm (AAA) repair: challenges remain

Bulder, R.M.A.



ELECTIVE ABDOMINAL AORTIC ANEURYSM REPAIR

THE CHALLENGES REMAIN

Stellingen behorende bij het proefschrift

Elective Abdominal Aortic Aneurysm (AAA) Repair: Challenges remain

1. AAA patiënten hebben een hoge excess mortaliteit na electieve repair, die niet gerelateerd lijkt te zijn aan het type procedure. (This thesis)

2. De excess mortaliteit van AAA patiënten lijkt grotendeels toe te schrijven aan cardiovasculaire oorzaken. Dit benadrukt de noodzaak van verder onderzoek naar cardiovasculaire pathogenese en de effectiviteit van cardiovasculair risicomanagement in de AAA populatie. (This thesis)

3. Het ernstige overlevingsnadeel van vrouwen onderstreept de noodzaak voor een meer vrouw-gerichte aanpak. (This thesis)

4. De klinische blik van de dokter en het perspectief van de patiënt zijn nog moeilijk te vangen in AAA onderzoek. (This thesis)

5. Large high-quality, well-performed observational studies could be complementary to randomized controlled trials to answer future research questions.

6. Qualitative research is a prerequisite of good quantitative research, particularly in areas that have received little previous investigation. (Pope BMJ 1995)

7. Reflectie is een valide onderzoeksdoel.

8. We should not accept the tenet that treating women for AAA is more problematic, when we do not fully understand how women's aneurysms and healthcare needs differ from those of men. (Pouncey EJVES 2021)

9. Simplicity isn't simple.

10. Het wad is een wereld waar de kortste weg tussen twee punten geen rechte lijn is. (Deen 2013) *Over de perikelen van promoveren*

11. Just do it. (Nike) *Iedere publicatie is een paar nikes waard*

Elective Abdominal Aortic Aneurysm (AAA) Repair:

Challenges remain

Ruth M.A. Bulder

ISBN	978-94-6510-284-9
Cover illustration and design	R.M.A. Bulder
Lay-out	Bregje Jaspers | www.ProefschriftOntwerp.nl
Printed by	ProefschriftMaken | www.proefschriftmaken.nl

Financial support by the Dutch Heart Foundation for publication of this thesis is gratefully acknowledged. ABN Amro, ChipSoft, Vaatchirurgie LUMC and HMC wetenschapsfonds are also gratefully acknowledged for the financial support for the printing of this thesis.

Elective Abdominal Aortic Aneurysm (AAA) Repair: Challenges remain

Proefschrift

Ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 5 november 2024
klokke 14:30 uur

door
Ruth M.A. Bulder

geboren te Groningen
in 1995

Promotor

Prof. dr. J.F. Hamming

Co-promotor

Dr. J.H.N. Lindeman

Leden promotiecommissie

Prof. dr. S. Mooijaart	
Prof. dr. R. Hultgren	Karolinska Instituut, Stockholm
Prof. dr. P.W.H.E Vriens	Elisabeth Tweesteden ziekenhuis, Tilburg
Dr. J.R. van der Vorst	
Prof. dr. F.A. Klok	

TABLE OF CONTENTS

Chapter 1

General introduction, objectives and outline of this thesis

1

INTRODUCTION

Elective abdominal aortic aneurysm (AAA) repair is a prophylactic procedure aiming to prolong patient life-expectancy by preventing aneurysm rupture (**Figure 1**).[1,2] Over the past 25 years, the landscape of AAA management underwent profound developments. Firstly, endovascular aneurysm repair (EVAR) has established itself as a more minimal invasive method of repair over traditional open repair. This, along with surgical ameliorations in general, resulted in a significant reduction of procedural mortality and thereby altered the surgical AAA population, including a broader spectrum of patients considered eligible for repair nowadays.[3] Secondly, the recognition of AAA patients as high cardiovascular risk patients, has led to a progressive implementation of cardiovascular risk management (CVRM).[4] Although AAA care has improved over the past decades, several controversies remain.

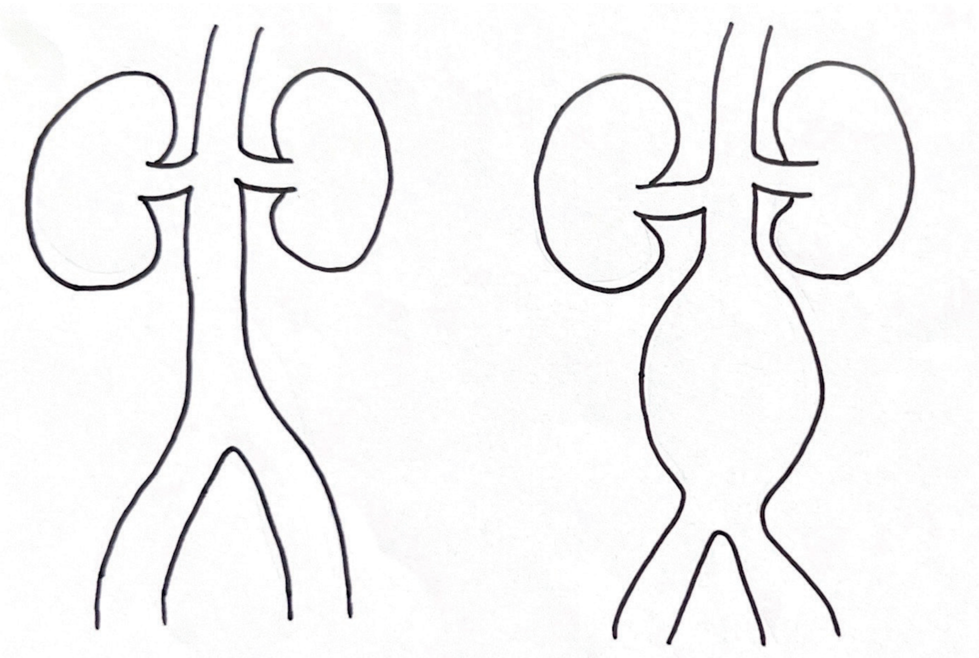


Figure 1. Abdominal aortic aneurysm (AAA)

An abdominal aortic aneurysm (AAA) is defined as an abnormal dilatation of the abdominal aorta of more than >150% compared to a normal adjacent diameter of the aorta. This is a life-threatening condition due to potential aneurysm rupture. In which case patients die due to hypovolemic shock (severe blood loss) if left untreated. To prevent aneurysm rupture, elective surgical repair is initiated.

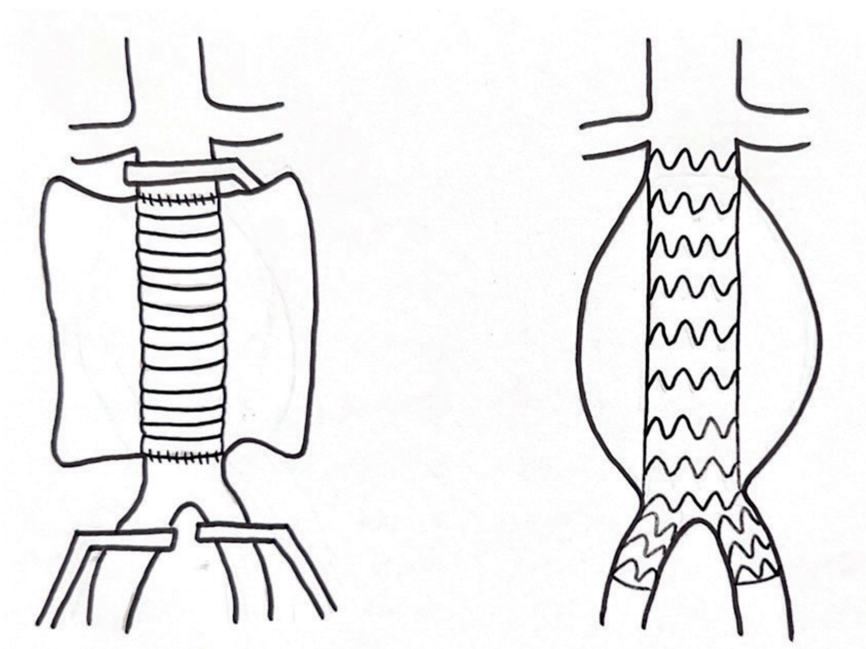


Figure 2. Elective AAA repair by open and endovascular repair
The primary options for elective AAA repair consist of either traditional open repair or endovascular aneurysm repair (EVAR). Currently, approximately 80% of AAAs are treated with EVAR.
Left: Open repair requires an incision along the midline of the entire abdomen. Thereafter, the aorta is clamped above and below the aneurysmal sac. The sac is opened and a tube graft is sewed into place to replace the aneurysmal sac.
Right: Endovascular aneurysm repair (EVAR) is a more minimal invasive method by entrance with a cathether in the groin. Thereafter a stentgraft (endograft) is placed in the aorta under X-ray guidance to seal off the aneurysm and exclude it from the blood circulation.

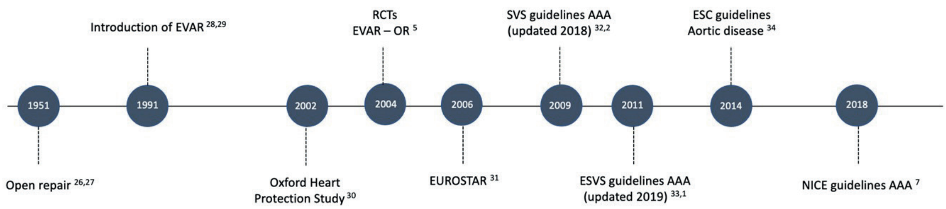


Figure 3. Developments in AAA management

Pitfalls in research: EVAR versus open repair

To date, EVAR has established itself as primary option for repair due to its significant lower short-term mortality compared to open repair. Nevertheless, an ongoing debate remains on whether EVAR should be the first choice of treatment due to concerns about its long-term durability.[5] Studies suggest that

EVAR associates with a higher long-term mortality and morbidity. In addition, its cost-effectiveness has been challenged.[6,7] These concerns are based on prospective trial data and retrospective research with both their own inherent limitations. To be more specific, trial data are based on the early EVAR era. As result, improvements in surgical technique and devices, hospital care, and follow-up (i.e. a more reticent attitude towards endoleaks) are not included. Also, due to strict inclusion criteria of patients in clinical trials, trial data do not represent the real-world patient population.[8] At last, trials are limited due to a low number of patients at risk, especially regarding long-term outcomes. Retrospective research, on the other hand, represents up-to-date real-world patient data. However, conclusions of retrospective research are likely to be interfered by confounding by indication, meaning that the type of repair is decided based on patient characteristics (**Figure 4**). To be more specific, the introduction of EVAR has lowered the threshold for repair. As result, older and more comorbid patients are considered eligible for repair nowadays, with EVAR as the preferred treatment in frailer patients. These patients are a priori at high risk for mortality and reinterventions. Therefore, a retrospective comparison of EVAR and open repair is challenging.

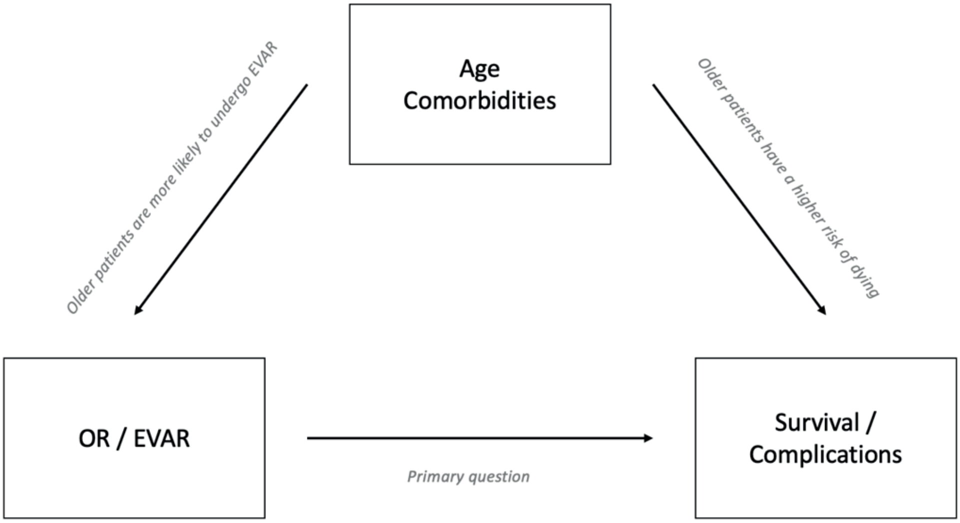


Figure 4. Confounding by indication

In an effort to minimize confounding by indication, alternative statistical approaches may offer a solution, such as pseudo-randomization (e.g. using time-frames as treatment allocation) and relative survival analysis. Relative survival analysis compares the survival of the patient population of interest with an age- sex- and year- matched general population. Consequently, it allows to evaluate the disease-specific excess mortality, while correcting for age- sex- and time-dependent differences.[9] The principle for relative survival calculations is shown in **Figure 5**.[10] A more practical/simplified explanation of relative survival is the following: ‘how the studied population is doing compared to what can be expected on the basis of a general population with a similar sex- and age- distribution throughout the corresponding years'.

Figure 5. Relative survival analysis

Poor long-term prognosis after successful elective repair

Application of relative survival analysis revealed a high long-term excess mortality of AAA patients after elective repair. This suggests that despite successful elimination of the rupture risk by elective repair (either with EVAR or open repair), AAA patients retain a high disease-specific long-term mortality. Hence, while the current focus of AAA repair is on rupture prevention, long-term mortality of AAA patient may seem largely independent of AAA rupture, and we therefore may overlook the real survival disadvantage of AAA patients.[11,12] The question remains as to what is causing the long-term mortality of AAA patients. Epidemiological studies show that the high long-term mortality may be primarily driven by a high cardiovascular risk accompanied with AAA disease.[13,14,15] Current cardiovascular guidelines recommend intensive CVRM, including lipid lowering medications, anti-hypertensive medication, and life-style advise (smoking cessation).[16,17,18] Thereby, improved surgical care, pre-operative optimization and the introduction of EVAR have lowered procedural mortality. Yet, it remains unknown whether, and if so, to what extent the developments in AAA care have translated into an improved life-expectancy of AAA patients. Particularly because these factors have simultaneously encouraged the treatment of older patients with greater comorbidity.

Sex-disparity in AAA repair: women's lives are at stake

While women are considered to be naturally protected against AAA, as only 15% of the AAA population is female, studies indicate a profoundly higher short- and long-term mortality for women compared to men.[19] The short-term mortality of female AAA patients is most pronounced with open repair, as mortality rates with EVAR are lower and more comparable to men.[20] Unfortunately, female patients are more frequently considered non-eligible for EVAR due to anatomical difficulties and are therefore more likely to undergo open repair. The high risk of undergoing open repair and subsequent high mortality rate have far reaching consequences. So far, insight in this high short-term mortality after elective open repair is missing. While there is a growing attention towards the inferior long-term mortality of female

AAA patients, the reason for the long-term sex-disparity remains unknown. Partly because, due to the higher prevalence of AAA in men, most evidence for the management of female AAA patients is based on studies underrepresenting women.

The patient perspective

A further knowledge gap in current AAA care is the inclusion of the patient perspective. To date, outcome parameters in AAA research have primary focused on mortality and morbidity. To improve outcomes of AAA care, especially considering the low procedural mortality rates, inclusion of the patient perspective is a most important aspect. Efforts to systematically include the patient perspective in medical research is reflected in the development of Core Outcome Sets (COS). COS are collections of key outcomes, including traditional outcomes as mortality and morbidity, but also the patient perspective.[21,22] In the process of developing the new European Society for Vascular Surgery guidelines on the management of AAA disease, it was articulated that outcomes considered important by vascular surgeons and/or researchers may substantially differ from that of the patient. Therefore, it called for the definition of COS to include the patient perspective in AAA research outcomes.[23] In general, the patient perspective is primarily evaluated through Quality of Life (QoL) as quantitative equivalent.[24] Associated with QoL are quantitative generic (e.g. SF-36 and EQ-5D) and disease-specific questionnaires. Generic questionnaires are applicable on a broad spectrum of diseases and allow for comparison between diseases and the general population. Disease-specific questionnaires are more specific to evaluate QoL of a certain patient group. A limitation of quantitative QoL scales is that they are based on questions defined by health professionals, which may not adequately reflect the patient perspective. To establish an in-dept understanding of the patient perspective, qualitative tools, including focus-groups and semi-structured interviews, are necessary.[25] In the AAA field, the patient perspective is mainly evaluated by quantitative QoL questionnaires. Considering that these questionnaires may not adequately reflect the patient perspective, the question arises whether these tools adequately reflect the patient perspective in AAA care and in turn can be used for the patient perspective of COS.

In conclusion, while AAA care has developed significantly over the past decades, several controversies and challenges remain. The aim of this thesis is to improve AAA care by quantifying the evidence for different treatment strategies (i.e. EVAR and open repair), and by evaluating several treatment outcomes. The first part of this thesis evaluates whether concerns about the long-term durability of EVAR are justified. Furthermore, it elaborates on the high long-term mortality after elective repair, and evaluates to what extent the developments in AAA care have impacted survival rates. It specifically addresses outcomes in women, as there exists a large knowledge deficit in this field. The second part of this thesis moves to other outcomes important in medical decision-making. It addresses the challenged cost-effectiveness of EVAR and investigates the current implementation of the patient perspective in AAA research outcomes.

OUTLINE OF THIS THESIS

PART I: AAA TREATMENT AND SURVIVAL

Concerns about the long-term survival of endovascular aneurysm repair (EVAR) have challenged the preference for EVAR as primary option for elective repair, and as such may have major consequences for current practice. However, these concerns are based on data impeded by the low generalizability of randomised controlled trials (RCTs) and confounding by indication i.e. asymmetrical medical decision-making based on patient characterises and patients' or surgeons' preferences, in retrospective research. In **Chapter 2** we performed a systematic review and meta-analysis evaluating the evidence of long-term survival after EVAR versus open repair. An impact of confounding by indication was minimized by a relative survival analysis and stratified analyses based on study type. Based on the relative survival analysis, it was shown that minimization of the rupture risk by elective repair still leaves patients at a high disease-specific long-term excess mortality. This questions the effectiveness of current AAA practice. Over the past decades the landscape of AAA management underwent profound developments i.e. the implementation of EVAR and cardiovascular risk management (CVRM). In **Chapter 3** and **Chapter 4** we evaluated whether, and if so to what extent, these developments impacted the survival of AAA patients following elective AAA repair. We further elaborated on the cause for this persisting high long-term excess mortality with a specific interest in possible age and sex-disparities. Studies show that women have both a higher long-term and procedural mortality risk. The high procedural mortality for women seems particularly related to a high mortality rate after elective open repair, as mortality rates with EVAR are lower and more comparable to men. Yet, women are at higher risk to undergo open repair as they are less often considered eligible for EVAR. Therefore, the high mortality after open repair has far reaching consequences. In order to improve medical-decision making and reduce mortality rates for women after elective open repair a first step is to understand the reason for this high procedural mortality. Therefore, in **Chapter 5** we evaluated the cause of death of female patients after elective open repair.

PART II: ASPECTS OF MEDICAL DECISION-MAKING

Besides mortality and morbidity outcomes, there are other outcomes important in medical decision-making. This includes, among others, the costs aspects and patient perspective. The cost-effectiveness of EVAR remains a debate. Yet, data used as rationale for this debate is impeded by time-dependent effect modification, confounding by indication and asymmetrical evaluation of outcomes. Therefore, in **Chapter 6** we evaluated costs of open repair versus EVAR, with minimization of these impeding factors.

Efforts to establish a more patient centred health care have led to an increasing integration of the patient perspective in medical decision making. This is reflected in the implementation of Core Outcome Sets (COS) for a variety of diseases. Considering AAA care, improvements in pre-operative patient selection, peri-operative care, and surgical technique (e.g. the introduction of EVAR) lowered procedural mortality and morbidity. As result, traditional outcome parameters such as procedural mortality and morbidity rates have become less discriminatory parameters to evaluate patient care. The question is whether the patient perspective is currently adequately reflected in AAA research and if recommendations can be made to implement these research outcomes in future research in the form of Aneurysm Core Outcome Sets (COS). **Chapter 7** consists of a scoping review comparing quantitative quality of life (QoL) tools and qualitative measurements of QoL of electively treated AAA patients.

PART III: SUMMARY AND FUTURE PERSPECTIVES

In the third and final part consists of the discussion and future perspectives (**Chapter 8**) and the summary (**Chapter 9**).

DATA SOURCES AND METHODS

	Study I (Chapter 2)	Study II (Chapter 3)	Study III (Chapter 4)	Study IV (Chapter 5)	Study V (Chapter 6)	Study VI (Chapter 7)
Study design	Systematic review and meta-analysis	Population-based, retrospective	Population based, retrospective	Cohort, retrospective	Cohort, retrospective	Scoping review
Data sources	Literature review	Swedish NPR, Cause of death registry	Dutch CBS (PR, HR, CDR, MR)	Hospital charts, DSAA	Hospital charts	Literature review
Population	Patients with elective AAA repair (EVAR – OR)	Patients with elective AAA repair	Patients with elective AAA repair	Female patients who died within <30 days after elective OR	Patients with elective AAA repair (EVAR – OR)	Patients with elective AAA repair
Number of patients	189 022	12 907	40 730	36	381	5981
Time period	1988 - 2015	2001 - 2015	1995 - 2017	2012 - 2019	1998 – 2000 2010 – 2012	1989 – 2013
Exposure	Elective OR versus EVAR	Elective AAA repair	Elective AAA repair	Elective OR	Elective OR versus EVAR	Elective AAA repair
Outcome	Survival	Time trends in incidence, survival, cause of death	Time trends in survival, competitive deaths	Cause of death	Costs (break-even point)	Patient perspective i.e. quality of life
Statistical method	Relative survival	Time-comparison, Relative survival	Time-comparison, Relative survival, Competing risk of death	Frequency distribution	IV analysis	Grounded theory

OR = open repair, EVAR = Endovascular Aneurysm Repair, NPR = National Patient Registry, CBS = Central Bureau of Statistics, PR = Person Registry, HR = Hospital Registry, CDR = Causes of Death Registry, MR = Medication Registry, IV analysis = instrumental variable analysis, DSAA = Dutch Surgical Aneurysm Audit.

REFERENCES

1. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kölbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines Committee, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholt JS, de Vega M, Vermassen F, Document Reviewers, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019;57:8-93.
2. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, Mastracci TM, Mell M, Murad MH, Nguyen LL, Oderich GS, Patel MS, Schermerhorn ML, Starnes BW. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018;67:2-77.
3. Pleumeekers HJ, Hoes AW, van der Does E, van Urk H, Hofman A, de Jong PT, Grobbee DE. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol. 199515;142:1291-1299.
4. Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022;146:e334-e482.
5. National Institute of Health and Care Excellence. Abdominal aortic aneurysm: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng156/chapter/Recommendations#monitoring- and-reducing-the-risk-of-rupture. [Accessed 24 June 2020].
6. Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM; EVAR-1, DREAM, OVER and ACE Trialists. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017;104:166-178.
7. Powell JT. Prophylactic Abdominal Aortic Aneurysm Repair? Open Repair Brings Early Pain but Later Gain. Eur J Vasc Endovasc Surg. 2016;52:719-720.
8. Paraskevas KI, de Borst GJ, Veith FJ. Why randomized controlled trials do not always reflect reality. J Vasc Surg. 2019;70:607-614.
9. Nelson CP, Lambert PC, Squire IB, Jones DR. Relative survival: what can cardiovascular disease learn from cancer? Eur Heart J. 2008;29:941-947.
10. Perme MP, Henderson R, Stare J. An approach to estimation in relative survival regression. Biostatistics. 2009;10:136-146.
11. Bath MF, Gokani VJ, Sidloff DA, Jones LR, Choke E, Sayers RD, Bown MJ. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015;102:866-872.
12. Tomee SM, Bulder RMA, Meijer CA, van Berkum I, Hinnen JW, Schoones J, Golledge J, Bastiaannet E, Matsumura JS, Hamming JF, Hultgren R, Lindeman JH. Excess mortality for abdominal aortic aneurysms and the potential of strict implementation of cardiovascular risk management. A multi-facetted study integrating meta-analysis-, national registry-, and PHAST and TEDY trial data. Eur J Vasc Endovasc Surg. 2022:S1078-5884(22)00805-X.

13. Goodney PP, Tavris D, Lucas FL, Gross T, Fisher ES, Finlayson SR. Causes of late mortality after endovascular and open surgical repair of infrarenal abdominal aortic aneurysms. J Vasc Surg. 2010;51:1340-1347.
14. Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis. Ann Vasc Surg. 2017;39:301-311.
15. Kaasenbrood L, Boekholdt SM, van der Graaf Y, Ray KK, Peters RJ, Kastelein JJ, Amarenco P, LaRosa JC, Cramer MJ, Westerink J, Kappelle LJ, de Borst GJ, Visseren FL. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134:1419-1429.
16. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kölbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines Committee, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholt JS, de Vega M, Vermassen F, Document Reviewers, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019;57:8-93.
17. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, Timaran CH, Upchurch GR Jr, Veith FJ. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50:880-896.
18. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873-2926.
19. Pouncey AL, David M, Morris RI, Ulug P, Martin G, Bicknell C, Powell JT. Editor's Choice - Systematic Review and Meta-Analysis of Sex Specific Differences in Adverse Events After Open and Endovascular Intact Abdominal Aortic Aneurysm Repair: Consistently Worse Outcomes for Women. Eur J Vasc Endovasc Surg. 2021;62:367-378.
20. Tomee SM, Lijftogt N, Vahl A, Hamming JF, Lindeman JHN. A registry-based rationale for discrete intervention thresholds for open and endovascular elective abdominal aortic aneurysm repair in female patients. J Vasc Surg. 2018;67:735-739.
21. Clarke M, Williamson PR. Core outcome sets and systematic reviews. Syst Rev. 2016;5:11.
22. COMET initiative. Core outcome measurements in effectiveness trials. Available at: https://www.comet-initiative.org/ [Accessed 14 February 2021].
23. Powell JT, Ambler GK, Svensjö S, Wanhainen A, Bown MJ. Beyond the AAA Guidelines: Core Outcome Sets to Make Life Better for Patients. Eur J Vasc Endovasc Surg. 2019;57:6-7.
24. Hamming JF, De Vries J. Measuring quality of life. Br J Surg. 2007;94:923-924.
25. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? Br J Cancer. 1988;57:109-112.
26. Freeman ME, Leeds FH: Vein inlay graft in the treatment of aneurysms and thrombosis of the abdominal aorta; a preliminary communication with report of 3 cases. Angiology 1951;2:579–587 072.

27. Dubost C, Allary M, Oeconomos N: (Treatment of aortic aneurysms; removal of the aneurysm; re-establishment of continuity by grafts of preserved human aorta.) Mem Acad Chir (Paris) 1951;77:381–383.
28. Volodos' NL, Shekhanin VE, Karpovich IP, Troian VI, Gur'ev Iu A: A self-fixing synthetic blood vessel endoprosthesis. (In Russian) Vestn Khir IM Grek 1986;137:123–125.
29. Parodi JC, Palmaz JC, Barone HD: Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5:491–499.
30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
31. Leurs LJ, Visser P, Laheij RJ, Buth J, Harris PL, Blankensteijn JD. Statin use is associated with reduced all-cause mortality after endovascular abdominal aortic aneurysm repair. Vascular. 2006;14:1-8.
32. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, Timaran CH, Upchurch GR Jr, Veith FJ. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50:880-896.
33. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, van Herwaarden JA, Holt PJ, van Keulen JW, Rantner B, Schlösser FJ, Setacci F, Ricco JB; European Society for Vascular Surgery. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41:S1-S58.
34. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873-2926.

PART I

AAA treatment and survival

Chapter 2

Meta-analysis of long-term survival after elective endovascular or open repair of abdominal aortic aneurysm

Ruth M.A. Bulder
Esther Bastiaannet
Jaap F. Hamming
Jan H.N. Lindeman

British Journal of Surgery 2019

ABSRACT

Background

Endovascular aneurysm repair (EVAR) has become the preferred strategy for elective repair of abdominal aortic aneurysm (AAA) for many patients. However, the superiority of the endovascular procedure has recently been challenged by reports of impaired long-term survival in patients who underwent EVAR. A systematic review of long-term survival following AAA repair was therefore undertaken.

Methods

A systematic review was performed according to PRISMA guidelines. Articles reporting short and/or long-term mortality of EVAR and open surgical repair (OSR) of AAA were identified. Pooled overall survival estimates (hazard ratios (HRs) with corresponding 95 % CI for EVAR versus OSR) were calculated using a random-effects model. Possible confounding owing to age differences between patients receiving EVAR or OSR was addressed by estimating relative survival.

Results

Some 53 studies were identified. The 30-day mortality rate was lower for EVAR compared with OSR: 1.16 (95 % CI 0.92 to 1.39) versus 3.27 (2.71 to 3.83) %. Long-term survival rates were similar for EVAR versus OSR (HRs 1.01, 1.00 and 0.98 for 3, 5 and 10years respectively; P= 0.721, P= 0.912 and P= 0.777). Correction of age inequality by means of relative survival analysis showed equal long-term survival: 0.94, 0.91 and 0.76 at 3, 5 and 10years for EVAR, and 0.96, 0.91 and 0.76 respectively for OSR.

Conclusion

Long-term overall survival rates were similar for EVAR and OSR. Available data do not allow extension beyond the 10-year survival window or analysis of specific subgroups.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has established itself as an important treatment option for patients with intact abdominal aortic aneurysm (AAA).[1] Nevertheless, the apparent superiority of EVAR has been challenged by studies raising concern about excess long-term mortality in patients who underwent EVAR.[2] These studies included the 15-year follow-up data from the EVAR 1 trial and more contemporaneous data from a single large German insurance company.[3,4] The latter authors reported reversal of the early survival benefit for elective EVAR after 1.5 years of follow-up, and impaired long-term survival of patients who received EVAR.[4] Others have reported worse 5-year survival after EVAR based on available data from RCTs and propensity cohort studies.[5] However, these data have limitations, including the use of older generations of stent-grafts, relatively small numbers of patients and the use of registry data.

A systematic evaluation of survival outcomes following elective EVAR and open surgical repair (OSR) was therefore undertaken to establish the relative survival estimates following either EVAR or OSR of intact AAA.

METHODS

Literature search and inclusion criteria

A systematic review of the literature between 1991 and 2018 was undertaken according to PRISMA guidelines.[6] Studies were identified using PubMed, Embase, Web of Science and Cochrane databases. Eligible studies included patients with an intact AAA treated by either EVAR or OSR. Studies that did not compare EVAR with OSR, studies that did not report 30-day mortality and those with follow-up of less than 3years were excluded, as were those that were not available as full text, and editorials, comments, letters and reviews. Sample size was not considered an exclusion criterion. No distinction was made between low-, medium- and high-risk patients because the definition among studies was too heterogeneous. The search was most recently updated on 17 March 2018 using a search strategy consisting of five search components (**Supplemental Appendix 1**).

The search strategy was based on the following hierarchy. The first and second components of the strategy consisted of AAA using all terms for abdominal aortic aneurysms. The third and fourth components comprised all terms for treatment by OSR or EVAR respectively. Two authors reviewed the titles and abstracts for eligibility. Full texts were reviewed when eligibility was either definite or unclear. Details of the search strategy are available in **Supplemental Appendix 1.**

Data extraction

The following information was extracted: year of publication, country of patient enrolment, start and end dates of patient recruitment, number of patients, mean age, percentage men, average time of follow-up and overall 30-day mortality rate when available. Patient survival was analyzed at the predefined endpoints 30 days, 3, 5 and 10 years. The 3-, 5-, 10- and 15-year survival rates were extracted from

Kaplan–Meier plots. In brief, the Kaplan–Meier graphs were magnified and printed on A3 paper. Lines were drawn on the tick marks of the x-axis (3, 5, 10 years) and y-axis (survival) from which the survival was retrieved. Some authors presented their results in multiple articles; only the most recent publication was included in the meta-analyses. The Cochrane Collaboration tool for assessing risk of bias was used to evaluate risk of bias and to assess study quality.[7]

Statistical analysis

Standard descriptive statistics were used to obtain baseline information. Meta-analyses were performed separately for all-cause 30-day mortality, and long-term survival. Odds ratios (ORs) with 95 % confidence intervals were calculated for 30-day mortality. When studies reported a mortality rate of zero, ORs were calculated by adding +1 to all cells in the 2×2 table. For studies reporting overall long-term survival, hazard ratios (HRs) for EVAR versus OSR were calculated with 95 % confidence intervals. HRs and confidence intervals for overall survival were than transformed to natural logarithms for meta-analyses. Pooled HRs for overall survival were estimated using the random-effects model of DerSimonian and Laird.[9]

Relative survival analysis was used to correct for possible age and sex differences for patients undergoing EVAR or OSR. In relative survival analysis, the survival of the cohort of interest (patients treated with EVAR or OSR) is compared with the expected survival of the matched general population. For each study, the expected survival was estimated on basis of life-tables from the Human Mortality Database. Life-tables were matched for age, sex, country of patient enrolment and year of operation of each study population.[10,11] Consequently, the expected survival was balanced for the sex ratio of the included studies. The difference between the two survival estimates (observed:expected, O:E) is assumed to reflect exposure-related deaths (mortality related to AAA treated by EVAR or OSR). This was presented as the O:E ratio.[12] O:E ratios can be used to compare mortality between individual patient populations with differences in age, sex and year of operation.[13,14] O:E ratios with 95 % confidence intervals were calculated and transformed to natural logarithms for meta-analyses. Pooled O:E ratios (relative survival) were estimated separately for EVAR and OSR, using the random-effects model of DerSimonian and Laird.[9] When studies reported a relative survival of more than 100 % (O:E ratio more than 1), the relative survival ratio was set at 1.

I2 statistics were used to estimate heterogeneity between studies.[15] An I2 value of more than 50 % was considered to indicate notable heterogeneity. Publication bias was assessed visually using funnel plots.[16] All analyses were performed using Stata/SE™ version 12.0 (StataCorp, College Station, Texas, USA).

RESULTS

Systematic review

Some 3061 articles were identified, of which 115 were selected and read in full. Eventually 53 studies fulfilled the inclusion criteria (**Figure 1**).[3,4,17–67] Among the 53 articles, there were four RCTs (8 %), 20 studies of administrative registries (38 %) and 29 cohort studies (55 %). Cohort studies were defined as studies of a selected group of patients (such as simple case series (retrospective or prospective) or clinical studies with or without a contemporaneous control group). Studies were labelled administrative if inclusion of patients was for administrative reasons (national or regional (quality) registries, or insurance data).

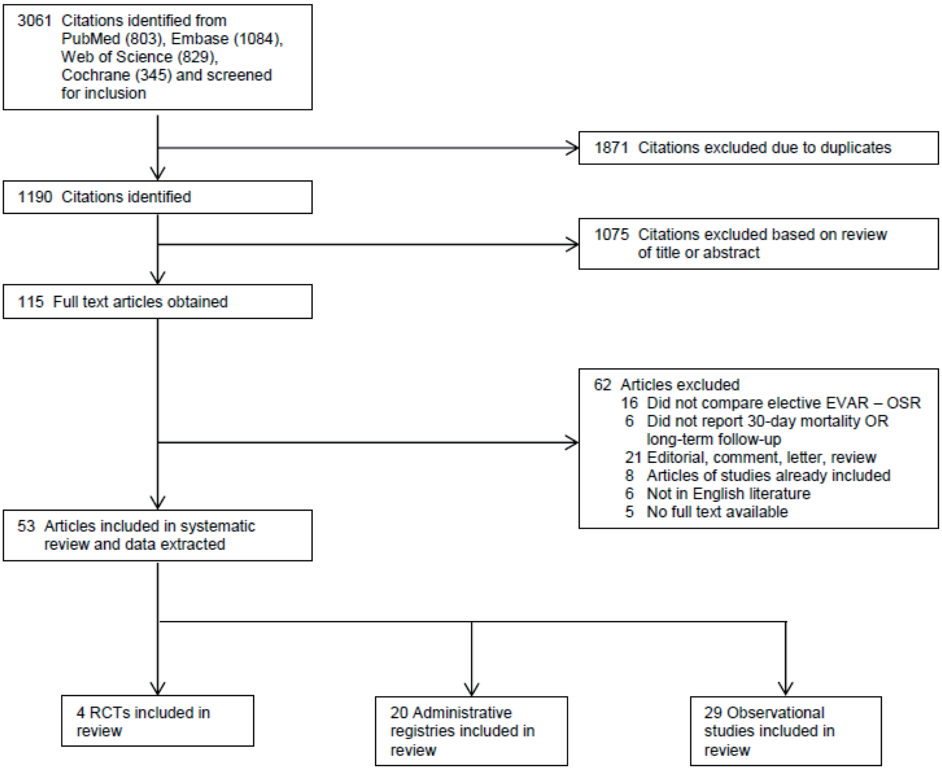


Figure 1. PRISMA diagram showing selection of articles for review

EVAR, endovascular aneurysm repair; OSR, open surgical repair.

All included studies were reviewed systematically and the findings are summarized in **Supplemental Table 1.** The review included a total of 189.022 patients: 102.053 treated with EVAR and 86.969 who had OSR; 2783 patients (1.5 %) were included in RCTs, 17.6071 (93.1 %) in administrative registries and 10168 (5.4 %) in cohort studies. All repairs were done between 1993 and 2015.
The mean age of patients across all studies was 73.8 years. Mean age of patients receiving EVAR or OSR was 71.7 and 71.9 years respectively in RCTs, 74.1 and 73.7 years in administrative registries, and 73.7 and 71.4 years in cohort studies. Some 81.1 % of all patients were men (82.4 % in the EVAR group and 79.5 % in the OSR group) (**Supplemental Table 1**). Only 11 of the 53 studies reported morphological selection criteria for EVAR.

Quality of studies
Risk of bias of the included studies was assessed according to the Cochrane criteria (**Supplemental Figure 1**).[7]
The main risk of bias in both administrative registries and cohort studies was confounding by indication, as the decision to perform EVAR or OSR was influenced by patient characteristics, patient's and surgeon's preferences, and other factors associated with the outcome that are possibly not captured in the data. The risk of bias was lowest in RCTs. However, RCTs are subject to strict inclusion and exclusion criteria, so their conclusions may not be directly generalizable to the clinical patient population.

Three studies that included Korean and/or Chinese patients were excluded from relative survival analysis because reliable life expectancy tables were not available.[42,52,61] Two studies that did not report the number of patients at risk in survival analysis were also excluded.[47,51] Overall, the number of excluded patients comprised 3.7 % of all reported patients.

Publication bias
Funnel plots for 30-day and 5-year survival did not show considerable asymmetry (**Supplemental Figure 2**). Hence, publication bias was not likely to be present among studies included in this analysis.

Short-term (30-day) mortality
Mortality at 30 days was reported in 51 studies (189.022 patients). The pooled 30-day mortality rate was 1.16 (95 % CI 0.92 to 1.39) % for EVAR and 3.27 (2.71 to 3.83) % for OSR. The pooled OR for 30-day mortality after OSR versus EVAR was 2.91 (95 % CI 2.55 to 3.32; $P < 0.001$) (Fig.S3, supporting information). Cohort studies and RCTs reported the lowest 30-day mortality rates. The total 30-day mortality rate was 2.06 (1.62 to 2.50) % for cohort studies and 1.99 (0.89 to 3.08) % for RCTs. Cohort studies also reported the lowest ORs for death after OSR versus EVAR (pooled OR 2.10, 1.56 to 2.84; $P < 0.001$), whereas RCTs had the highest ORs (pooled OR 3.25, 1.37 to 7.71; $P=0.007$). Administrative registries reported the highest 30-day mortality rates (pooled rate 2.40 (1.83 to 2.96) %) with a pooled OR of 3.09 (2.64 to 3.61; $P < 0.001$) (**Supplemental Table 2**).

Long-term survival

In total, 20 studies (108.078 patients) reported outcomes for 3 years of follow-up. The pooled HR for overall survival after EVAR versus OSR was 1.01 (95 % CI 0.95 to 1.08; P=0.721) (**Figure 2**). Significant heterogeneity was observed among all studies (I2=86.5 %, P<0.001), but heterogeneity decreased when analysis was undertaken by type of study. The pooled HR for survival after EVAR versus OSR was 1.08 (0.98 to 1.20; P=0.126) in administrative registries, 1.01 (0.93 to 1.10; P=0.798) in RCTs and 0.94 (0.88 to 1.00; P=0.069) in cohort studies.

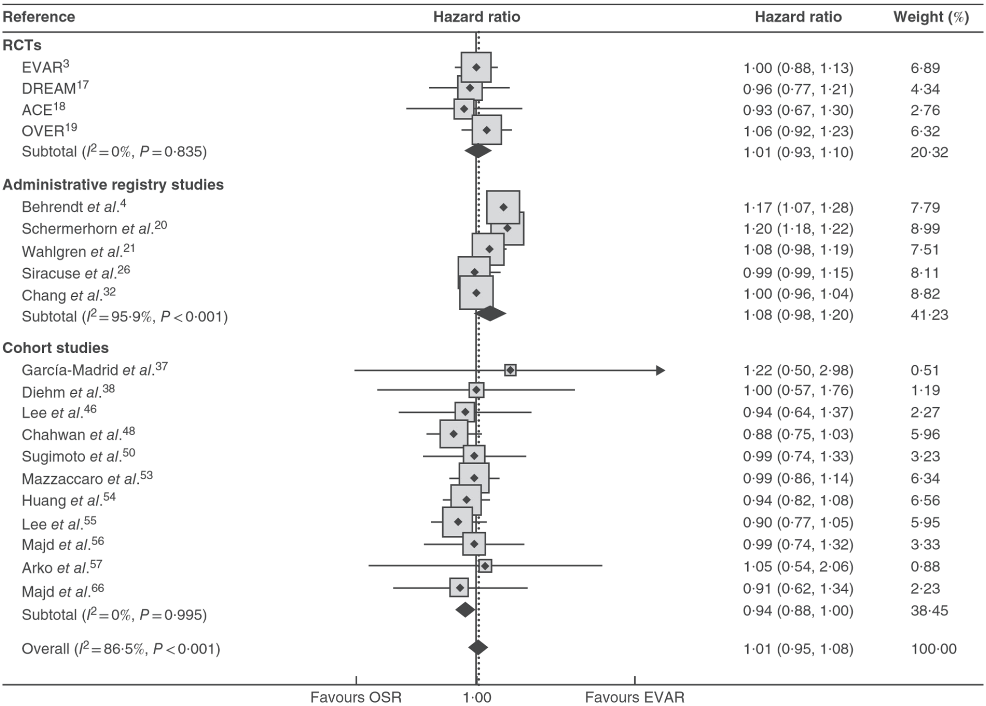


Figure 2. Forest plot of overall survival at 3 years after endovascular versus open repair of intact abdominal aortic aneurysms

Hazard ratios are shown with 95 per cent confidence intervals. A random-effects model was used for meta-analysis. EVAR, endovascular aneurysm repair; DREAM, Dutch Randomized Endovascular Aneurysm Management; OVER, Open Versus Endovascular Repair; OSR, open surgical repair.

Seventeen studies (124.665 patients) reported 5-year survival. The pooled HR for overall survival was 1.00 (0.98 to 1.02; P=0.912) (**Figure 3**). Heterogeneity was not detected (I2=0 %, P=0.947). RCTs and administrative registries had pooled HRs of 1.00 (0.91 to 1.10; P=0.970) and 1.00 (0.98 to 1.02; P=0.907) respectively. Cohort studies reported lower HRs than RCTs and administrative registries (pooled HR 0.96, 0.89 to 1.04; P=0.373).

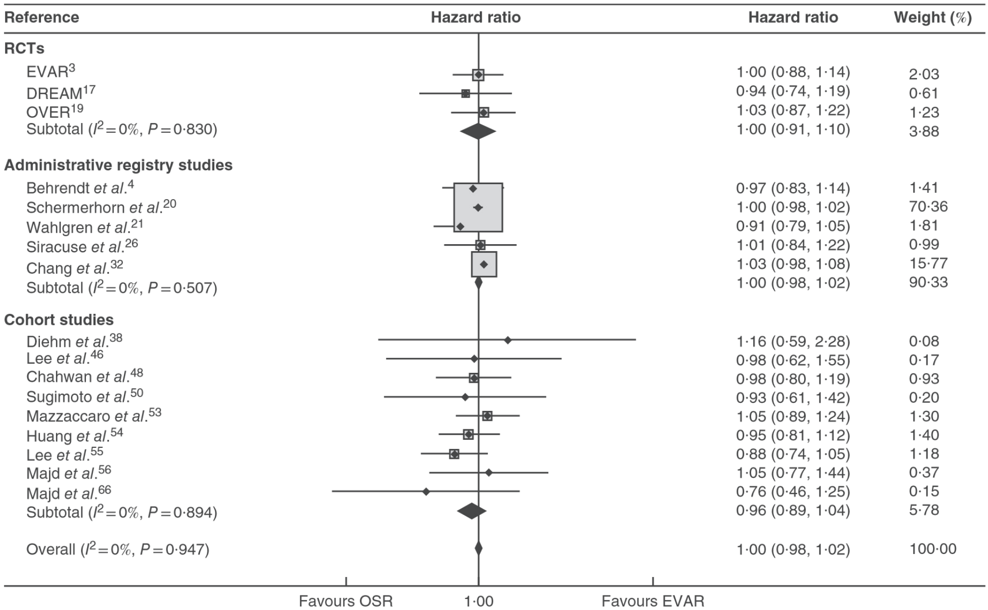


Figure 3. Forest plot of overall survival at 5 years after endovascular versus open repair of intact abdominal aortic aneurysms

Hazard ratios are shown with 95 per cent confidence intervals. A random-effects model was used for meta-analysis. EVAR, endovascular aneurysm repair; DREAM, Dutch Randomized Endovascular Aneurysm Management; OVER, Open Versus Endovascular Repair; OSR, open surgical repair.

Ten-year survival was reported by nine studies (10.233 patients). The pooled HR for overall survival was 0.98 (0.86 to 1.12; P=0.777) (**Figure 4**). No significant heterogeneity was detected (I2=14.2 %, P=0.315). The pooled HR was 1.04 (0.90 to 1.21; P=0.598) for RCTs and 0.91 (0.71 to 1.17; P=0.479) for cohort studies. Only one administrative registry reported 10 years of follow-up (HR 1.08, 0.57 to 2.06; P=0.813).

The EVAR 1 trial was the only study to report survival data after 15 years of follow-up, with an HR for survival after EVAR versus OSR of 0.60 (0.40 to 0.91).

Relative survival

Relative survival analysis was used to minimize the impact of age at repair as a confounder. The aggregated mean age at time of repair was 73.7years for EVAR and 71.4 years for OSR. Relative survival ratios are summarized in **Table 1** and FigsS4–S6 (supporting information). At all endpoints and for all study types, O:E survival ratios were similar for OSR and EVAR. They declined progressively with follow-up time, indicating impaired long-term disease-specific survival of patients with AAA.

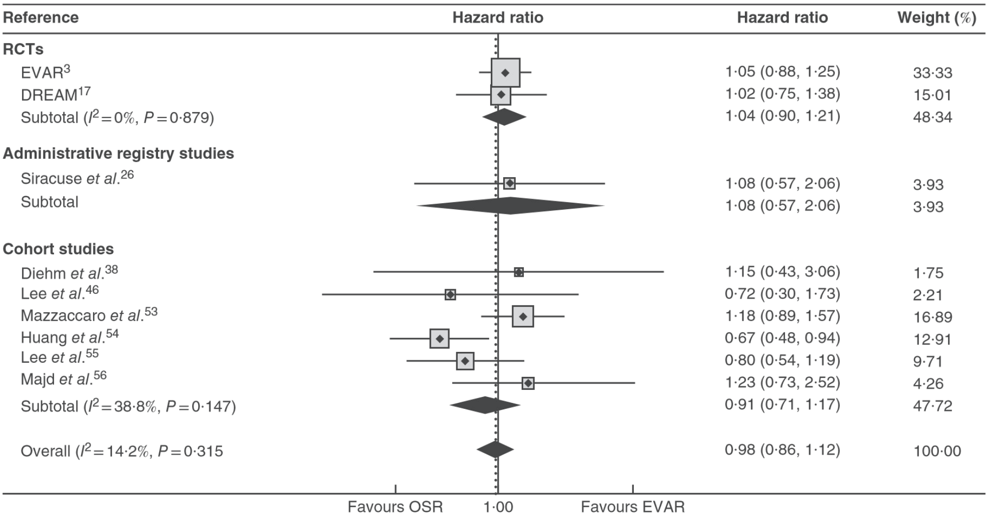


Figure 4. Forest plot of overall survival at 10years after endovascular versus open repair of intact abdominal aortic aneurysms

Hazard ratios are shown with 95 per cent confidence intervals. A random-effects model was used for meta-analysis. EVAR, endovascular aneurysm repair; DREAM, Dutch Randomized Endovascular Aneurysm Management; OVER, Open Versus Endovascular Repair; OSR, open surgical repair.

Table 1. Relative survival ratios (observed : expected survival) for endovascular and open surgical repair of intact abdominal aortic aneurysms

	3 years	5 years	10 years
EVAR	0.94 (0.92, 0.96)	0.91 (0.87, 0.94)	0.76 (0.67, 0.86)
OSR	0.96 (0.95, 0.98)	0.91 (0.88, 0.94)	0.76 (0.69, 0.85)

EVAR, endovascular aneurysm repair; OSR, open surgical repair.

DISCUSSION

This systematic review and meta-analysis has confirmed the superior 30-day survival after EVAR, and demonstrated equivalent long-term survival for EVAR and OSR at 3, 5 and 10 years of follow-up.

Concerns expressed about impaired long-term survival after EVAR have challenged the preference that some have for EVAR for elective repair, and as such may have major consequences for current practice. In this context, it is important to note that the conclusions are based on a small group of patients at risk, low generalizability of RCTs (low representation of women), and on age differences between OSR and EVAR cohorts.[2-4]

To address concerns with respect to a survival disadvantage for EVAR, a systematic review and meta-analysis based on the available survival outcome data was undertaken. Patient survival was analyzed at predefined endpoints of 30 days, 3, 5 and 10 years. Three-year survival rates were included as this was the most commonly reported long-term survival outcome. Apart from the EVAR 1 trial, no studies reported survival outcomes far beyond 10 years.[3]

Inclusion of different study types results in heterogeneity owing to factors such as inclusion/exclusion criteria of RCTs (reflected in the very low representation of women in the RCTs), asymmetrical medical decision-making, and possibly selective reporting in observational studies.[68,69] The number of included patients differed greatly among studies. Consequently, considerable heterogeneity was detected when all studies were pooled. Nonetheless, heterogeneity decreased significantly when analysis was performed by study design. Effect estimates were remarkably similar for all types of study, showing that heterogeneity does not influence the overall conclusions.

Conclusions based on observational studies are subject to confounding by indication, because the choice of treatment with EVAR or OSR (or no repair) is based on patient characteristics, and patient's and surgeon's preferences (asymmetrical medical decision-making). This is reflected in the age difference between patients having EVAR and those undergoing OSR in the cohort studies, indicative of the preference for EVAR in older patients. In this context, the absence of an age difference between patients undergoing EVAR or OSR in administrative registries may appear contradictory. A further evaluation showed that this absence reflects the dominance of the study of Schermerhorn and colleagues among the administrative studies.[20] This study was based on a propensity-matched design that included age as matching variable, thus obscuring any age differences between EVAR and OSR cohorts. Indeed, after exclusion of this study, an age difference was also noted for the administrative registries (72.7 years for EVAR versus 71.3 years for OSR).

Although it is not possible to correct for all aspects of asymmetrical decision-making, any impact of the age difference between EVAR and OSR groups can be minimized by relative survival analysis.[70] Relative survival is an accepted method to correct for differences in patient-specific characteristics (in particular age and sex) and to assess disease-specific mortality in the field of oncology, and the approach has recently also been applied in the cardiovascular field.[13,71] Relative survival analysis of patients in the cohort studies showed equivalent long-term survival after EVAR and OSR, indicating that age differences are indeed important confounders in survival analysis of patients with AAA. To illustrate the impact of medical decision-making on survival outcomes, the relative survival of patients considered unfit for OSR and who were followed in the EVAR 2 trial was also evaluated.[72] It was concluded that these patients had significantly worse survival than those included in the meta-analysis (**Supplemental Table 3**).

Relative survival data revealed a steady decline in overall O:E ratios from 3 to 10years after AAA repair. This shows that the impaired disease-specific survival of patients with AAA persists after successful aneurysm repair.[71,73] Although this might reflect the dominant role of smoking (history) in AAA disease, an evaluation by Ellis and colleagues suggested that smoking has only a minimal impact on disease-specific mortality for diseases commonly associated with excessive smoking.[74]

An alternative explanation is that the impaired long-term survival in patients with AAA relates to a higher incidence of neoplasms and, more importantly, to excess cardiovascular mortality in patients with AAA.[75,76] The latter calls for persistent awareness about cardiovascular risk management.
This evaluation has a number of limitations. The published data do not allow extension beyond the 10-year survival window as longer-term results are available only for the EVAR1 trial.[3] Moreover, because subgroup-specific data (women, younger patients, morphological characteristics of AAA) were not reported, a subanalysis could not be undertaken. A subanalysis for women is of particular importance as women have a higher mortality rate after OSR than men.[67] By the same token, women are more likely to present with more complex surgical accessibility and are often considered less optimal candidates for EVAR.[77]
Younger patients constitute another subgroup of particular interest, especially because they are generally considered to be at lower surgical risk, and are expected to have a longer life expectancy. It is conceivable that OSR is a better option for these patients, considering the lower reintervention rates and presumably superior graft durability after OSR.[3] However, Lederle and co-workers reported a lower mortality rate for young patients (aged less than 70years) who had EVAR.[19] Further results beyond 10 years, and with even younger patients are awaited.

The majority of data in this study is based on patients treated in the first decade following the introduction of EVAR. These patients presumably presented with less complex AAAs than those considered eligible for EVAR today. It is conceivable that the more complex devices currently employed for more hostile AAAs are more prone to failure, and this could translate into different long-term outcomes. To address this point, a time-dependent analysis was performed by ranking studies by median year of patient enrolment. This analysis showed that the conclusions of the present study were not influenced by time. Simultaneously, improved technology could lead to better durability of the devices, but data comparing individual devices have yet to be published.[78] The focus of this study was survival after EVAR and OSR. Efforts to analyse reintervention rates were compromised by missing data, and extreme non-uniformity and heterogeneity in defining and reporting reinterventions.

Although the relative survival analysis took age and sex differences into account, other patient characteristics that may influence the choice of treatment between EVAR and OSR could not be corrected for. Yet, asymmetrical medical decision-making as result of the higher intervention threshold for OSR presumably results in over-representation of 'healthier' patients in the OSR group. As such, conclusions from this meta-analysis may underestimate the benefit of EVAR.

REFERENCES

1. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M et al.; European Society for Vascular Surgery. Management of abdominal aortic aneurysms clinical practice guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg 2011; 41(Suppl 1): S1–S58.
2. Powell JT. Prophylactic abdominal aortic aneurysm repair? Open repair brings early pain but later gain. Eur J Vasc Endovasc Surg 2016;52:719–720.
3. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM; EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet 2016;388:2366–2374.
4. Behrendt CA, Sedrakyan A, Rieß HC, Heidemann F, Kölbel T, Petersen J et al. Short-term and long-term results of endovascular and open repair of abdominal aortic aneurysms in Germany. J Vasc Surg 2017; 66: 1704–1711.e3.
5. Takagi H, Ando T, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) group. Worse late-phase survival after elective endovascular than open surgical repair for intact abdominal aortic aneurysm. Int J Cardiol 2017;236:427–431.
6. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
7. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
8. Ruxton GB, Neuhäuser M, Freckleton R. Review of alternative approaches to calculation of a confidence interval for the odds ratio of a 2 × 2 contingency table. Methods Ecol Evol 2013; 4: 9–13.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139–145.
10. University of California, Berkeley. The Human Mortality Database. www.mortality.org [accessed 13 December 2017].
11. Max Planck Institute for Demographic Research. The Human Mortality Database. www.humanmortality.de [accessed 13 December 2017].
12. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol 2010; 39: 598–610.
13. Nelson CP, Lambert PC, Squire IB, Jones DR. Relative survival: what can cardiovascular disease learn from cancer? Eur Heart J 2008; 29: 941–947.
14. Rutherford MJ, Dickman PW, Lambert PC. Comparison of methods for calculating relative survival in population-based studies. Cancer Epidemiol 2012; 36: 16–21.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558.
16. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol 2014; 67: 897–903.
17. van Schaik TG, Yeung KK, Verhagen HJ, de Bruin JL, van Sambeek MRHM, Balm R et al.; DREAM trial participants. Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms. J Vasc Surg 2017; 66: 1379–1389.
18. Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P et al.; ACE trialists. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. J Vasc Surg 2011; 53: 1167–1173.e1.

19. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR et al.; OVER Veterans Affairs Cooperative Study Group. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012; 367: 1988–1997.
20. Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J et al. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. N Engl J Med 2015; 373: 328–338.
21. Wahlgren CM, Malmstedt J; Swedish Vascular Registry. Outcomes of endovascular abdominal aortic aneurysm repair compared with open surgical repair in high-risk patients: results from the Swedish Vascular Registry. J Vasc Surg 2008; 48: 1382–1388.
22. Siracuse JJ, Schermerhorn ML, Meltzer AJ, Eslami MH, Kalish JA, Rybin D et al.; Vascular Study Group of New England. Comparison of outcomes after endovascular and open repair of abdominal aortic aneurysms in low-risk patients. Br J Surg 2016; 103: 989–994.
23. Lee WA, Carter JW, Upchurch G, Seeger JM, Huber TS. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. J Vasc Surg 2004; 39: 491–496.
24. Bush RL, Johnson ML, Collins TC, Henderson WG, Khuri SF, Yu HJ et al. Open versus endovascular abdominal aortic aneurysm repair in VA hospitals. J Am Coll Surg 2006; 202:577–587.
25. Gupta PK, Ramanan B, Lynch TG, Gupta H, Fang X, Balters M et al. Endovascular repair of abdominal aortic aneurysm does not improve early survival versus open repair in patients younger than 60 years. Eur J Vasc Endovasc Surg 2012; 43: 506–512.
26. Siracuse JJ, Gill HL, Graham AR, Schneider DB, Connolly PH, Sedrakyan A et al. Comparative safety of endovascular and open surgical repair of abdominal aortic aneurysms in low-risk male patients. J Vasc Surg 2014; 60: 1154–1158.
27. Endicott KM, Emerson D, Amdur R, Macsata R. Functional status as a predictor of outcomes in open and endovascular abdominal aortic aneurysm repair. J Vasc Surg 2017; 65:40–45.
28. Johnson ON III, Sidawy AN, Scanlon JM, Walcott R, Arora S, Macsata RA et al. Impact of obesity on outcomes after open surgical and endovascular abdominal aortic aneurysm repair. J Am Coll Surg 2010; 210: 166–177.
29. Giles KA, Wyers MC, Pomposelli FB, Hamdan AD, Ching YA, Schermerhorn ML. The impact of body mass index on perioperative outcomes of open and endovascular abdominal aortic aneurysm repair from the National Surgical Quality Improvement Program, 2005–2007. J Vasc Surg 2010; 52: 1471–1477.
30. Locham S, Lee R, Nejim B, Dakour Aridi H, Malas M. Mortality after endovascular versus open repair of abdominal aortic aneurysm in the elderly. J Surg Res 2017; 215: 153–159.
31. Liang NL, Reitz KM, Makaroun MS, Malas MB, Tzeng E. Comparable perioperative mortality outcomes in younger patients undergoing elective open and endovascular abdominal aortic aneurysm repair. J Vasc Surg 2018; 67: 1404–1409.e2.
32. Chang DC, Parina RP, Wilson SE. Survival after endovascular vs open aortic aneurysm repairs. JAMA Surg 2015; 150: 1160–1166.
33. Jonker FH, Schlösser FJ, Dewan M, Huddle M, Sergi M, Indes JE et al. Abdominal aortic aneurysm repair in obese patients: improved outcome after endovascular treatment compared with open surgery. Vasc Endovascular Surg 2010; 44: 105–109.

34. Becquemin J, Bourriez A, D'Audiffret A, Zubilewicz T, Kobeiter H, Allaire E et al. Mid-term results of endovascular versus open repair for abdominal aortic aneurysm in patients anatomically suitable for endovascular repair. Eur J Vasc Endovasc Surg 2000; 19: 656–661.
35. Mehta M, Roddy SP, Darling RC III, Ozsvath KJ, Kreienberg PB, Paty PS et al. Infrarenal abdominal aortic aneurysm repair via endovascular versus open retroperitoneal approach. Ann Vasc Surg 2005; 19: 374–378.
36. Aarts F, van Sterkenburg S, Blankensteijn JD. Endovascular aneurysm repair versus open aneurysm repair: comparison of treatment outcome and procedure-related reintervention rate. Ann Vasc Surg 2005; 19: 699–704.
37. García-Madrid C, Josa M, Riambau V, Mestres CA, Muntaña J, Mulet J. Endovascular versus open surgical repair of abdominal aortic aneurysm: a comparison of early and intermediate results in patients suitable for both techniques. Eur J Vasc Endovasc Surg 2004; 28: 365–372.
38. Diehm N, Tsoukas AI, Katzen BT, Benenati JF, Baum S, Pena C et al. Matched-pair analysis of endovascular versus open surgical repair of abdominal aortic aneurysms in young patients at low risk. J Vasc Interv Radiol 2008; 19: 645–651.
39. Elkouri S, Gloviczki P, McKusick MA, Panneton JM, Andrews J, Bower TC et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. J Vasc Surg 2004; 39: 497–505.
40. Raval MV, Eskandari MK. Outcomes of elective abdominal aortic aneurysm repair among the elderly: endovascular versus open repair. Surgery 2012; 151: 245–260.
41. Hua HT, Cambria RP, Chuang SK, Stoner MC, Kwolek CJ, Rowell KS et al. Early outcomes of endovascular versus open abdominal aortic aneurysm repair in the National Surgical Quality Improvement Program-Private Sector (NSQIP-PS). J Vasc Surg 2005; 41: 382–389.
42. Bae M, Chung SW, Lee CW, Song S, Kim E, Kim CW. A comparative study of abdominal aortic aneurysm: endovascular aneurysm repair versus open repair. Korean J Thorac Cardiovasc Surg 2017; 50: 263–269.
43. Karmy-Jones R, Bloch R, Nicholls S. A comparison of endovascular repair versus open repair of abdominal aortic aneurysms in a community setting. Innovations (Phila) 2009; 4: 261–264.
44. Zhang CL, Song ZH, Wang F. Comparison of efficacy of endovascular aneurysm repair versus open surgical repair in middle/high-risk patients with abdominal aortic aneurysm. Am J Ther 2016; 23: e37–e43.
45. Gnus J, Ferenc S, Dziewiszek M, Rusiecki L, Witkiewicz W. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm in our own material in years 2002–2011. Adv Clin Exp Med 2015; 24: 475–479.
46. Lee K, Tang E, Dubois L, Power AH, DeRose G, Forbes TL. Durability and survival are similar after elective endovascular and open repair of abdominal aortic aneurysms in younger patients. J Vasc Surg 2015; 61: 636–641.
47. Paolini D, Chahwan S, Wojnarowski D, Pigott JP, LaPorte F, Comerota AJ. Elective endovascular and open repair of abdominal aortic aneurysms in octogenarians. J Vasc Surg 2008; 47: 924–927.
48. Chahwan S, Comerota AJ, Pigott JP, Scheuermann BW, Burrow J, Wojnarowski D. Elective treatment of abdominal aortic aneurysm with endovascular or open repair: the first decade. J Vasc Surg 2007; 45: 258–262.
49. Iannelli G, Monaco M, Di Tommaso L, Piscione F, Stassano P, Mainenti PP et al. Endovascular vs. open surgery of abdominal aortic aneurysm in high-risk patients: a single center experience. Thorac Cardiovasc Surg 2005; 53: 291–294.

50. Sugimoto M, Koyama A, Niimi K, Kodama A, Banno H, Komori K. Long-term comparison of endovascular and open repair of abdominal aortic aneurysms: retrospective analysis of matched cohorts with propensity score. Ann Vasc Surg 2017; 43: 96–103.
51. Jetty P, Hebert P, van Walraven C. Long-term outcomes and resource utilization of endovascular versus open repair of abdominal aortic aneurysms in Ontario. J Vasc Surg 2010; 51: 577–583.e1–e3.
52. Ren S, Fan X, Ye Z, Liu P. Long-term outcomes of endovascular repair versus open repair of abdominal aortic aneurysm. Ann Thorac Cardiovasc Surg 2012; 18: 222–227.
53. Mazzaccaro D, Nano G, Settembrini AM, Carmo M, Dallatana R, Salvati S et al. Open and endovascular elective treatment of abdominal aortic aneurysms: a real-world experience. Surg Today 2017; 47: 1347–1355.
54. Huang Y, Gloviczki P, Oderich GS, Duncan AA, Kalra M, Fleming MD et al. Outcome after open and endovascular repairs of abdominal aortic aneurysms in matched cohorts using propensity score modeling. J Vasc Surg 2015; 62: 304–311.e2.
55. Lee HG, Clair DG, Ouriel K. Ten-year comparison of all-cause mortality after endovascular or open repair of abdominal aortic aneurysms: a propensity score analysis. World J Surg 2013; 37: 680–687.
56. Majd P, Ahmad W, Becker I, Brunkwall JS. Ten-year single-center results of abdominal aortic aneurysm treatment: endovascular versus open repair. Ann Vasc Surg 2017; 44: 113–118.
57. Arko FR, Lee WA, Hill BB, Olcott C IV, Dalman RL, Harris EJ Jr et al. Aneurysm-related death: primary endpoint analysis for comparison of open and endovascular repair. J Vasc Surg 2002; 36: 297–304.
58. Arko FR, Hill BB, Reeves TR, Olcott C, Harris EJ, Fogarty TJ et al. Early and late functional outcome assessments following endovascular and open aneurysm repair. J Endovasc Ther 2003; 10: 2–9.
59. Hynes CF, Endicott KM, Iranmanesh S, Amdur RL, Macsata R. Reoperation rates after open and endovascular abdominal aortic aneurysm repairs. J Vasc Surg 2017; 65: 1323–1328.
60. Arko FR, Hill BB, Olcott C, Harris EJ Jr, Fogarty TJ, Zarins CK. Endovascular repair reduces early and late morbidity compared to open surgery for abdominal aortic aneurysm. J Endovasc Ther 2002; 9: 711–718.
61. Min SI, Min SK, Ahn S, Kim SM, Park D, Park T et al. Comparison of costs of endovascular repair versus open surgical repair for abdominal aortic aneurysm in Korea. J Korean Med Sci 2012; 27: 416–422.
62. Hicks CW, Black JH III, Arhuidese I, Asanova L, Qazi U, Perler BA et al. Mortality variability after endovascular versus open abdominal aortic aneurysm repair in a large tertiary vascular center using a Medicare-derived risk prediction model. J Vasc Surg 2015; 61: 291–297.
63. Hill BB, Wolf YG, Lee WA, Arko FR, Olcott C IV, Schubart PJ et al. Open versus endovascular AAA repair in patients who are morphological candidates for endovascular treatment. J Endovasc Ther 2002; 9: 255–261.
64. Handa N, Onohara T, Okamoto M, Yamamoto T, Shimoe Y, Okada M et al.; National Hospital Organization Network Study Group in Japan for Abdominal Aortic Aneurysm. Early outcomes of open abdominal repair versus endovascular repair for abdominal aortic aneurysm: report from national hospital organization network study in Japan. Ann Vasc Dis 2012; 5: 172–179.
65. Gouëffic Y, Becquemin JP, Desgranges P, Kobeiter H. Midterm survival after endovascular versus open repair of infrarenal aortic aneurysms. J Endovasc Ther 2005; 12: 47–57.
66. Majd P, Ahmad W, Galas N, Brunkwall JS. Patients older than 80 years can reach their normal life expectancy after abdominal aortic aneurysm repair: a comparison between endovascular aneurysm repair and open surgery. J Endovasc Ther 2018; 25: 247–251.

67. Tomee SM, Lijftogt N, Vahl A, Hamming JF, Lindeman JHN. A registry-based rationale for discrete intervention thresholds for open and endovascular elective abdominal aortic aneurysm repair in female patients. J Vasc Surg 2018; 67: 735–739.
68. Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994; 309: 1351–1355.
69. Glasziou PP, Sanders SL. Investigating causes of heterogeneity in systematic reviews. Stat Med 2002; 21: 1503–1511.
70. Perme MP, Henderson R, Stare J. An approach to estimation in relative survival regression. Biostatistics 2009; 10: 136–146.
71. Norman PE, Semmens JB, Lawrence-Brown MM. Long-term relative survival following surgery for abdominal aortic aneurysm: a review. Cardiovasc Surg 2001; 9: 219–224.
72. Sweeting MJ, Patel R, Powell JT, Greenhalgh RM; EVAR Trial Investigators. Endovascular repair of abdominal aortic aneurysm in patients physically ineligible for open repair: very long-term follow-up in the EVAR-2 randomized controlled trial. Ann Surg 2017; 266: 713–719.
73. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL et al.; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113: e463–e654.
74. Ellis L, Coleman MP, Rachet B. The impact of life tables adjusted for smoking on the socio-economic difference in net survival for laryngeal and lung cancer. Br J Cancer 2014; 111: 195–202.
75. Wang JC, Chien WC, Chung CH, Liao WI, Tsao CH, Wu YF et al. Increased risk of malignancy in patients with an aortic aneurysm: a nationwide population-based retrospective study. Oncotarget 2017; 9: 2829–2837.
76. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33: 1635–1701.
77. Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT; SWAN collaborators. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet 2017; 389: 2482–2491.

78. Arko FR III, Murphy EH, Boyes C, Nussbaum T, Lalka SG, Holleman J et al. Current status of endovascular aneurysm repair: 20 years of learning. Semin Vasc Surg 2012; 25: 131–135.

SUPPLEMENTAL MATERIAL

Supplemental Appendix 1. Search components literature search
("Aortic Aneurysm, Abdominal"[Mesh] OR "AAA"[tiab] OR (("Aneurysm"[Mesh] OR "Aneurysm"[Tw] OR "Aneurysms"[Tw]) AND ("Abdomen"[Mesh] OR "Abdominal Cavity"[Mesh] OR "Abdomen"[Tw] OR "Abdominal"[Tw] OR "Aorta, Abdominal"[Mesh] OR (("Aorta"[Tw] OR "Aortic"[Tw]) AND ("abdominal"[tw] OR "abdomen"[tw]))))) AND ("Endovascular Procedures"[majr] OR "Endovascular"[ti] OR "EVAR"[ti] OR "eEVAR"[ti] OR "Minimal invasive"[ti] OR "Minimally-invasive"[ti] OR "Minimally invasive"[ti] OR "Stentgraft"[ti] OR "Stent-graft"[ti]) AND ("Open"[ti] OR "OSR"[ti] OR "OAR"[ti] OR "OR"[ti] OR "OS"[ti])

Component 1: Abdominal aortic aneurysm
Component A: Aneurysm
"Aneurysm"[Mesh] OR "Aneurysm"[Tw] OR "Aneurysms"[Tw]

Component B: Abdominal
"Abdomen"[Mesh] OR "Abdominal Cavity"[Mesh] OR "Abdomen"[Tw] OR "Abdominal"[Tw]

Component C: Aortic
"Aorta"[Mesh] OR "Aorta"[Tw] OR "Aortic"[Tw]

Component 2: AAA
("Aortic Aneurysm, Abdominal"[Mesh] OR "AAA"[Tw])

Component 3: Endovascular aneurysm repair (EVAR)
("Endovascular Procedures"[Mesh] OR "Endovascular"[Tw] OR "EVAR"[Tw] OR "eEVAR"[Tw] OR "Minimal invasive"[Tw] OR "Minimally-invasive"[Tw] OR "Minimally invasive"[Tw] OR "Graft"[Tw] OR "Stentgraft"[Tw] OR "Stent-graft"[Tw])

Component 4: Open aneurysm repair (OR)
("Open"[Tw] OR "Surgical"[Tw] OR "OSR"[Tw] OR "OAR"[Tw] OR "OR"[Tw] OR "OS"[Tw])

Pubmed

("Aortic Aneurysm, Abdominal"[Mesh] OR "AAA"[tiab] OR (("Aneurysm"[Mesh] OR "Aneurysm"[Tw] OR "Aneurysms"[Tw]) AND ("Abdomen"[Mesh] OR "Abdominal Cavity"[Mesh] OR "Abdomen"[Tw] OR "Abdominal"[Tw] OR "Aorta, Abdominal"[Mesh] OR (("Aorta"[Tw] OR "Aortic"[Tw]) AND ("abdominal"[tw] OR "abdomen"[tw]))))) AND ("Endovascular Procedures"[majr] OR "Endovascular"[ti] OR "EVAR"[ti] OR "eEVAR"[ti] OR "Minimal invasive"[ti] OR "Minimally-invasive"[ti] OR "Minimally invasive"[ti] OR "Stentgraft"[ti] OR "Stent-graft"[ti]) AND ("Open"[ti] OR "OSR"[ti] OR "OAR"[ti] OR "OR"[ti] OR "OS"[ti])

17-03-2018: # referenties: 803

Embase

("Abdominal aorta aneurysm"/ OR "AAA".ti,ab. OR (("Aneurysm"/ OR "Aneurysm".mp. OR "Aneurysms".mp.) AND ("Abdomen"/ OR "Abdominal Cavity"/ OR "Abdomen".mp. OR "Abdominal".mp. OR "Abdominal aorta"/ OR (("Aorta".mp. OR "Aortic".mp.) AND ("abdominal".mp. OR "abdomen".mp.))))) AND (exp *"Endovascular surgery"/ OR "Endovascular".ti. OR "EVAR".ti. OR "eEVAR".ti. OR "Minimal invasive".ti. OR "Minimally-invasive".ti. OR "Minimally invasive".ti. OR "Stentgraft".ti. OR "Stent-graft".ti.) AND (*"open surgery"/ OR "Open".ti. OR "OSR".ti. OR "OAR".ti. OR "OR".ti. OR "OS".ti.)

17-03-2018: # referenties: 1084

Web of Science

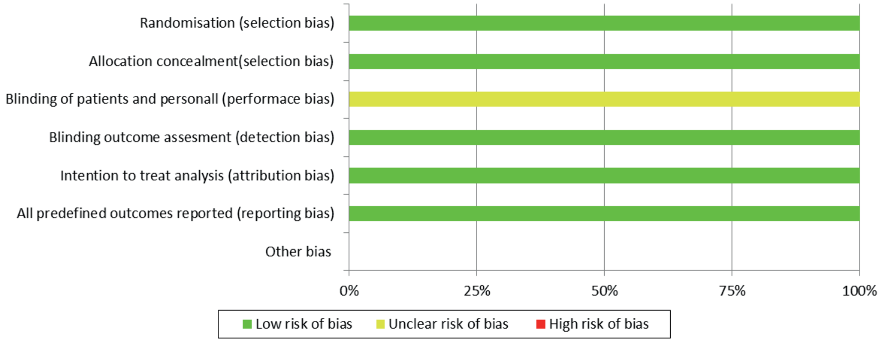
TS=("AAA" OR (("Aneurysm" OR "Aneurysms") AND ("Aorta" OR "Aortic") AND ("abdominal" OR "abdomen"))) AND TI=("Endovascular" OR "EVAR" OR "eEVAR" OR "Minimal invasive" OR "Minimally-invasive" OR "Minimally invasive" OR "Stentgraft" OR "Stent-graft") AND TI=("Open" OR "OSR" OR "OAR" OR "OR" OR "OS")

17-03-2018: # referenties: 829

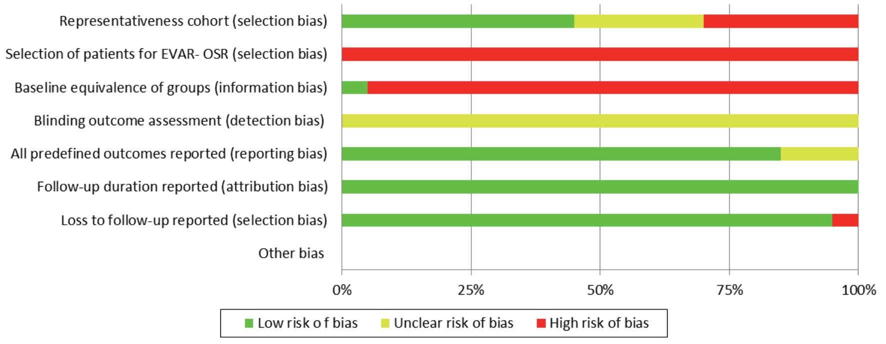
Cochrane

("AAA" OR (("Aneurysm" OR "Aneurysms") AND ("Aorta" OR "Aortic") AND ("abdominal" OR "abdomen"))) AND ("Endovascular" OR "EVAR" OR "eEVAR" OR "Minimal invasive" OR "Minimally-invasive" OR "Minimally invasive" OR "Stentgraft" OR "Stent-graft") AND ("Open" OR "OSR" OR "OAR" OR "OR" OR "OS")

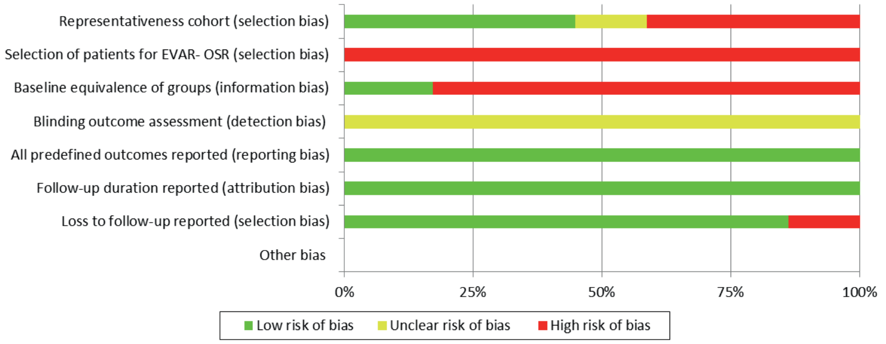
17-03-2018: # referenties: 345 (trials)



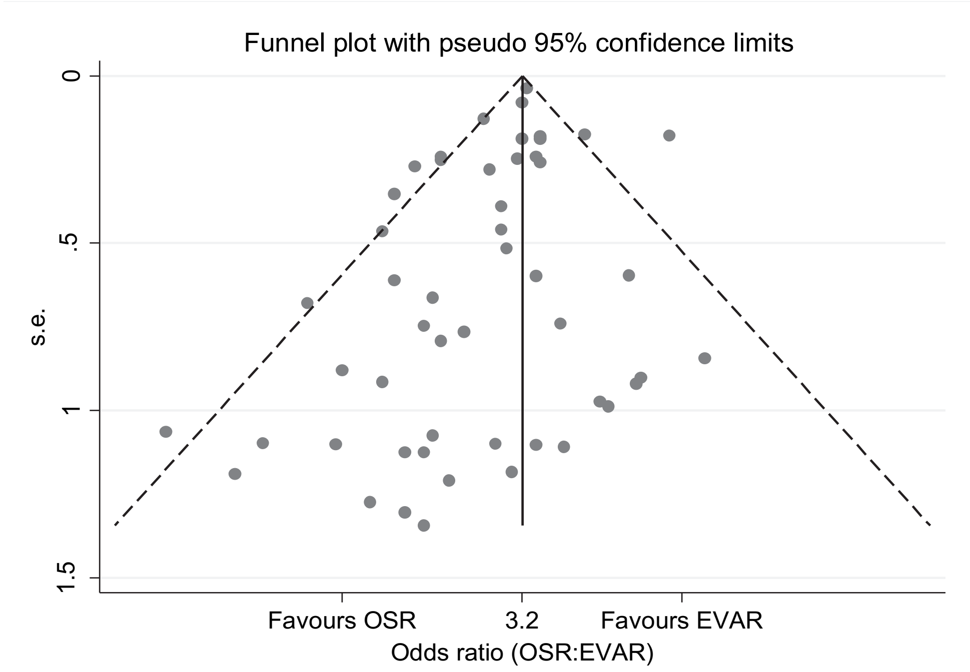
Supplemental Figure 1A. Risk of bias randomised controlled trials



Supplemental Figure 1B. Risk of bias administrative registries

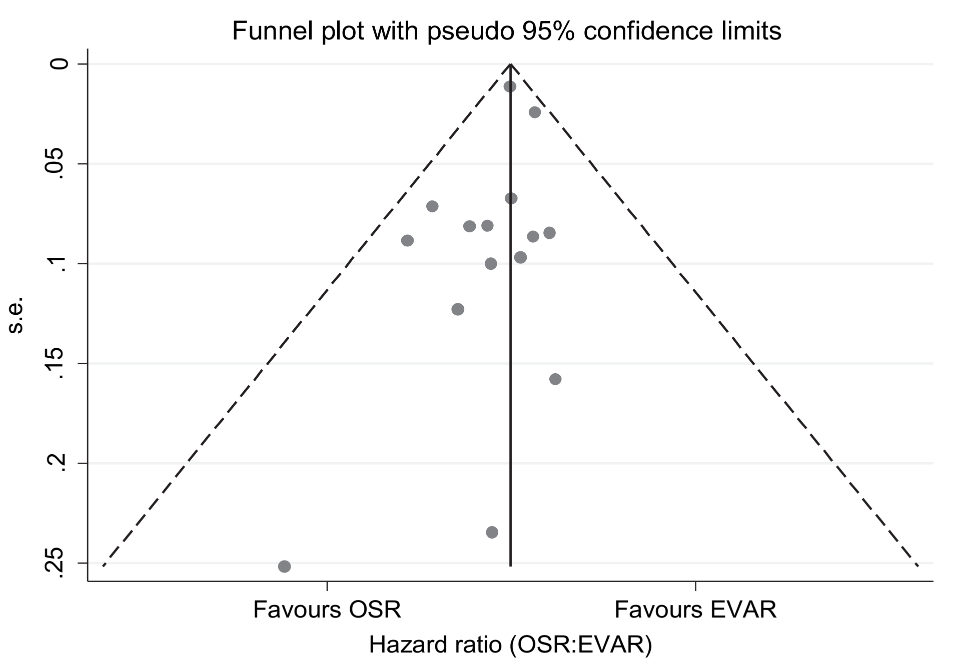


Supplemental Figure 1C. Risk of bias cohort studies



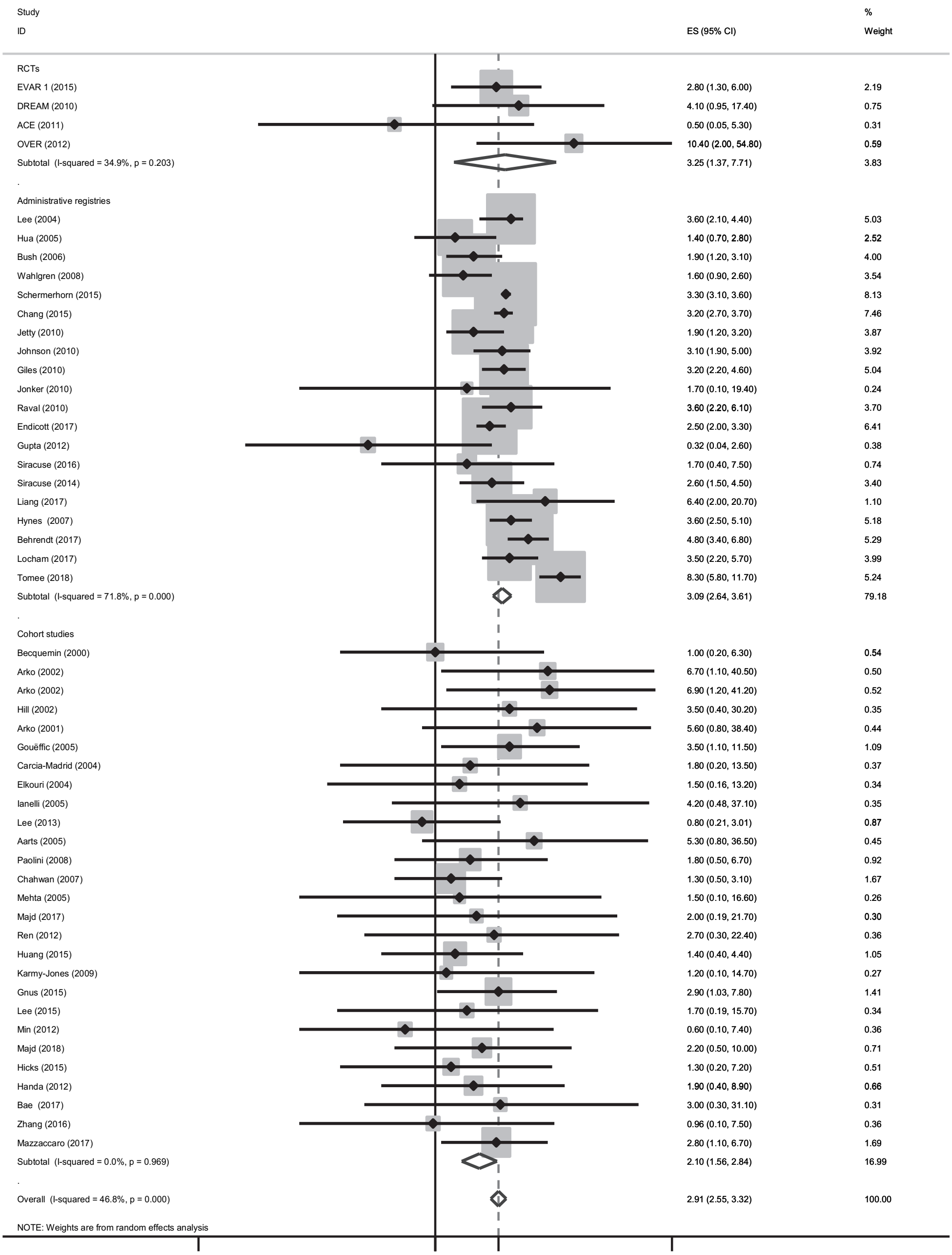
Supplemental Figure 2A. Funnel plot with pseudo 95% confidence interval for OR: mortality at 30-day open repair versus EVAR.

Funnelplot is based on fixed effect analysis, with an overall odds ratio of 3.2. Random effect analysis, performed in the meta-analysis estimates an odds ratio of 2.91. s.e. = standard error.

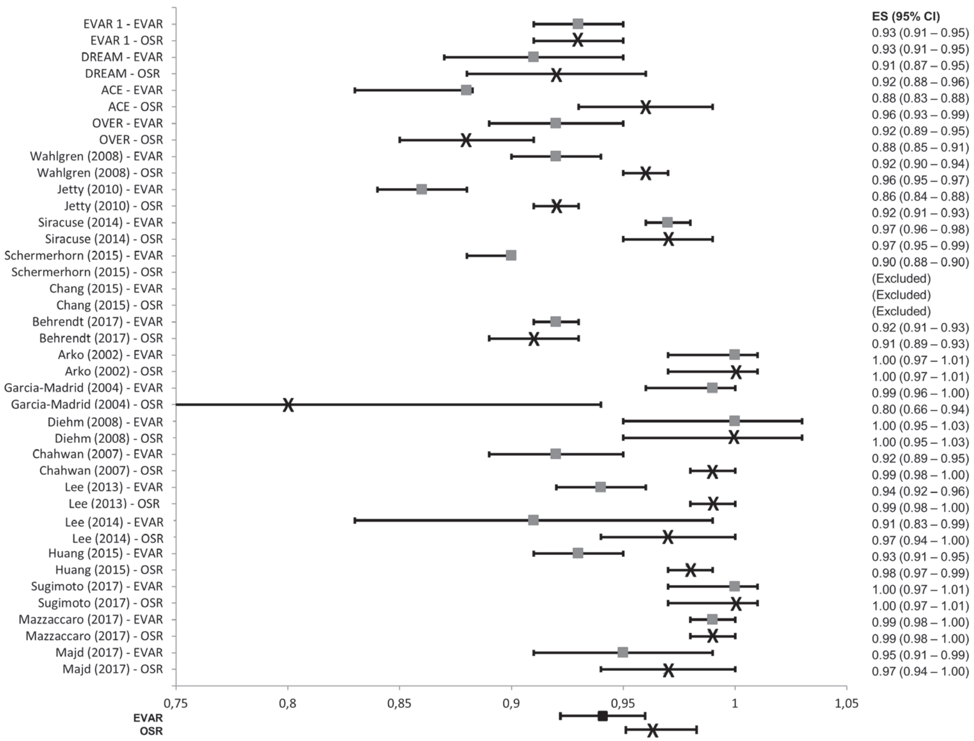


Supplemental Figure 2B. Funnel plot with pseudo 95% confidence interval for HR: mortality at 5 years open repair versus EVAR.

Funnelplot is based on fixed effect analysis. s.e. = standard error.

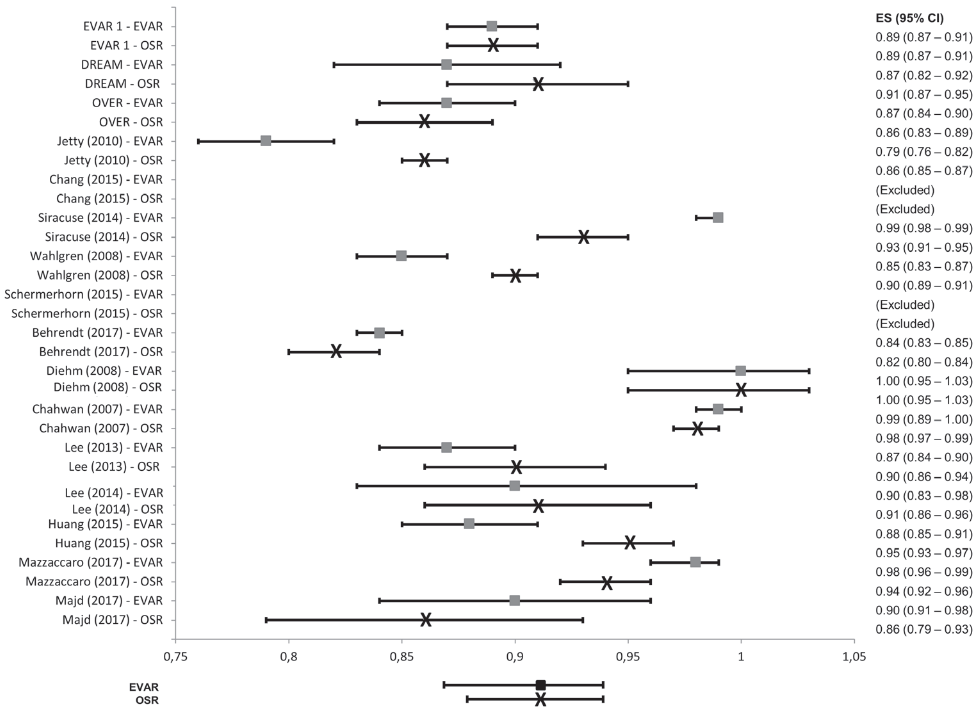


Supplemental Figure 3. Pooled Odds Ratio (open repair:EVAR) of observed mortality at 30-day/in-hospital



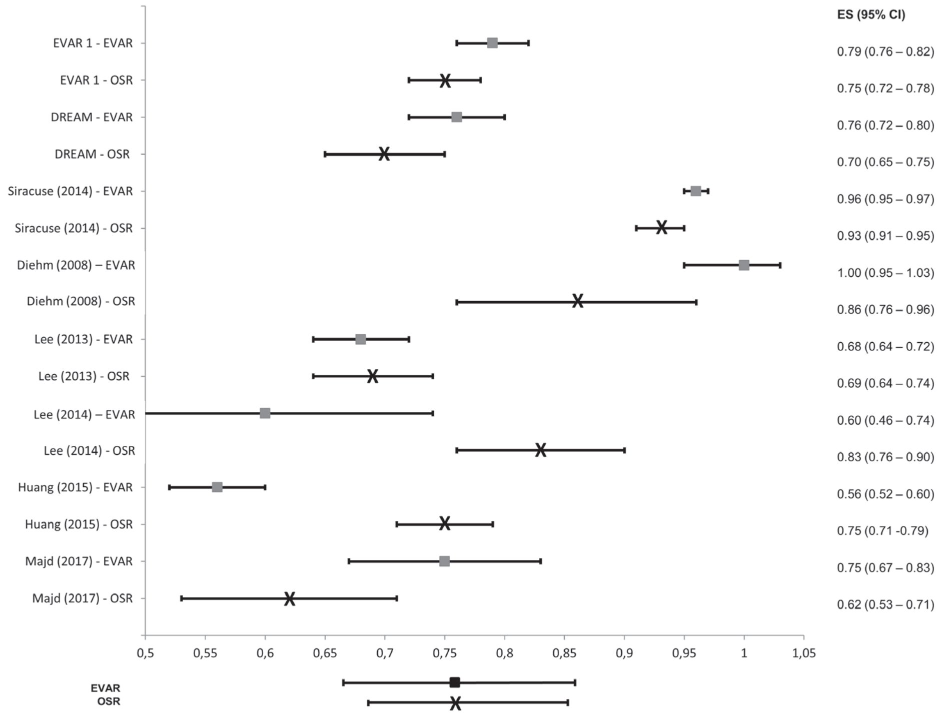
Supplemental Figure 4. 3-year relative survival for patients receiving EVAR (squares) or OSR (crosses).

Squares/crosses and confidence intervals below the X-axis indicate combined relative survival.



Supplemental Figure 5. 5-year relative survival for patients receiving EVAR (squares) or OSR (crosses).

Squares/crosses and confidence intervals below the X-axis indicate combined relative survival.



Supplemental Figure 6. 10-year relative survival for patients receiving EVAR (squares) or OSR (crosses).
Squares/crosses and confidence intervals below the X-axis indicate combined relative survival.

Supplemental Table 1. Review of included articles

Study	Study design	Country	Study period	Number of patents	% male	Age (mean) (sd)	Diameter AAA	30 – day	Observed survival	Relative survival
EVAR 1 (2015) [3]	RCT	United Kingdom	Sept, 1999 - Aug, 2004	EVAR: 626 OSR: 626	EVAR: 91 OSR: 91	EVAR: 74.2 (6.0) OSR: 74.0 (6.1)	EVAR: 6.5 OSR: 6.5	■	■	■
DREAM (2010) [17]	RCT	Netherlands/Belgium	Nov, 2000 - Dec, 2003	EVAR: 173 OSR: 178	EVAR: 93.1 OSR: 90.4	EVAR: 70.7 (6.6) OSR: 69.9 (6.8)	EVAR: 6.0 OSR: 6.0	■	■	■
ACE (2011) [18]	RCT	France	Mar, 2003 - Mar, 2008	EVAR: 150 OSR: 149	EVAR: 100 OSR: 98	EVAR: 68.7 (7.7) OSR: 70 (7.1)	EVAR: 5.5 OSR: 5.6	■	■	■
OVER (2012) [19]	RCT	United States	Oct, 2002 - Oct, 2008	EVAR: 444 OSR: 437	EVAR: 99.3 OSR: 99.5	EVAR: 69.6 (7.8) OSR: 70.5 (7.8)	EVAR: 5.7 OSR: 5.6	■	■	■
Behrendt (2017) [4]	Administrative registry	Germany	Oct, 2008 - Apr, 2015	EVAR: 3493 OSR: 1457	EVAR: 85.4 OSR: 82.8	EVAR: 74 OSR: 71	N.A.	■	■	■
Schermerhorn (2015) [20]	Administrative registry – PS	United States	Jan, 2001 - Dec, 2008	EVAR: 39.966 OSR: 39.966	EVAR: 77.7 OSR: 77.6	EVAR: 75.7 OSR: 75.5	N.A.	■	■	■
Wahlgren (2008) [21]	Administrative registry	Sweden	Jan, 2000 - Dec, 2006	EVAR: 1000 OSR: 2831	EVAR: 85 OSR: 83	EVAR: 75 (6) OSR: 73 (6)	N.A.	■	■	■
Siracuse (2016) [22]	Administrative registry	United States	2003 - 2014	EVAR: 1071 OSR: 476	EVAR: 100 OSR: 100	EVAR: 67.3 (5.7) OSR: 65.1 (6.3)	N.A.	■		
Lee (2004) [23]	Administrative registry	United States	Jan - Dec, 2001	EVAR: 4607 OSR: 2565	EVAR: 84.4 OSR: 78.1	EVAR: 73.4 (7.8) OSR: 71.9 (7.7)	N.A.	■		
Bush (2006) [24]	Administrative registry	United States	May, 2001 - Sep, 2003	EVAR: 717 OSR: 1187	EVAR: 99.6 OSR: 99.1	EVAR: 71.6 (7.8) OSR: 70.2 (7.9)	N.A.	■		
Gupta (2012) [25]	Administrative registry	United States	2007 - 2009	EVAR: 369 OSR: 282	EVAR: 90.8 OSR: 80.5	EVAR: 56 OSR: 56	N.A.	■		
Siracuse (2014) [26]	Administrative registry	United States	2007 - 2010	EVAR: 4068 OSR: 1459	EVAR: 100 OSR: 100	EVAR: 67 (6) OSR: 67 (6)	N.A.	■	■	■
Endicott (2017) [27]	Administrative registry	United States	2002 - 2010	EVAR: 4822 OSR: 4208	EVAR: - OSR: -	EVAR: - OSR: -	N.A.	■		
Johnson (2011) [28]	Administrative registry	United States	Jan, 2005 - Dec, 2006	EVAR: 1016 OSR: 1185	EVAR: - OSR: -	EVAR: - OSR: -	N.A.	■		
Giles (2010) [29]	Administrative registry	United States	2005 - 2007	EVAR: 3358 OSR: 2097	EVAR: 73.8 OSR: 82.8	EVAR: 71.5 (8.5) OSR: 74.1 (8.4)	N.A.	■		
Locham (2017) [30]	Administrative registry	United States	2011 - 2014	EVAR: 3869 OSR: 360	EVAR: 79.4 OSR: 68.9	EVAR: 78.4 (5.6) OSR: 76.8 (4.8)	N.A.	■		
Liang (2017) [31]	Administrative registry	United States	2003 - 2014	EVAR: 1928 OSR: 713	EVAR: 88 OSR: 85.3	EVAR: 62 OSR: 61	EVAR: 5.4 OSR: 5.5	■		

Supplemental Table 1. Continued

Chang (2015) [32]	Administrative registry	United States	2001 - 2009	EVAR: 12239 OSR: 11431	EVAR: 84.4 OSR: 77.5	EVAR: 75.1 OSR: 72.3	N.A.	■	■	■
Jonker (2010) [33]	Administrative registry	United States	Jan 2003 - Jan, 2008	EVAR: 25 OSR: 31	EVAR: 92 OSR: 97	EVAR: 75 (5.8) OSR: 67 (8.1)	N.A.	■		
Becquemin (2000) [34]	Administrative registry	France	Jan, 1995 - Mar, 1999	EVAR: 73 OSR: 107	EVAR: 94.3 OSR: 93.5	EVAR: 70 OSR: 69	N.A.	■		
Mehta (2005) [35]	Administrative registry	United States	Oct, 2001 - Apr, 2003	EVAR: 175 OSR: 232	EVAR: 85 OSR: 74	EVAR: 73 OSR: 73	N.A.	■		
Aarts (2005) [36]	Administrative registry	Netherlands	Oct, 1998 - Jan, 2004	EVAR: 99 OSR: 116	EVAR: 96 OSE: 87	EVAR: - OSR: -	EVAR:5.8 OSR: 6.0	■		
Garcia-Madrid (2004) [37]	Observational cohort	Spain	Mar, 1997 - Aug, 2000	EVAR: 53 OSR: 30	EVAR: 96.2 OSR: 93.3	EVAR: 73 OSR: 70	N.A.	■	■	■
Diehm (2008) [38]	Observational cohort – PS	United States	Apr, 1994 - Sept, 2005	EVAR: 25 OSR: 25	EVAR: 92 OSR: 92	EVAR: 62 (2.8) OSR: 59 (3.9)	EVAR: 5.0 OSR: 5.5		■	■
Elkouri (2004) [39]	Observational cohort	United States	Dec, 1999 - Dec, 2001	EVAR: 94 OSR: 261	EVAR: 90.4 OSR: 64.5	EVAR: 77 OSR: 73	EVAR: 5.7 OSR: 5.7	■		
Raval (2012) [40]	Administrative registry	United States	Jan, 2005 - Dec, 2008	EVAR: 1634 OSR: 391	EVAR: 79.4 OSR: 67.3	EVAR: >80 OSR: >80	N.A.	■		
Hua (2005) [41]	Administrative registry	United States	Jan, 2000 - Oct, 2003	EVAR: 460 OSR: 582	EVAR: 84.6 OSR: 79.6	EVAR: 74.0 OSR: 71.2	N.A.	■		
Bae (2017) [42]	Observational cohort	Korea	Jan, 2007 - Dec, 2014	EVAR: 58 OSR: 40	EVAR: 81.0 OSR: 62.5	EVAR: 71.4 (6.1) OSR: 66.9 (7.5)	EVAR: 6.1 OSR: 6.4	■		
Karmy-Jones (2009) [43]	Observational cohort	United States	Jan, 2007 - Dec, 2007	EVAR: 31 OSR: 12	EVAR: - OSR: -	EVAR: 71.6 (0.8) OSR: 66.1 (9)	EVAR: 5.7 OSR: 5.7	■		
Zhang (2016) [44]	Observational cohort	China	Jan, 2010 - Jan, 2014	EVAR: 28 OSR: 29	EVAR: 67.9 OSR: 72.4	EVAR: 69.9 (13.1) OSR: 67.3 (7.5)	EVAR: 6.9 OSR: 7.3	■		
Gnus (2015) [45]	Observational cohort	Poland	2002 - 2011	EVAR: 275 OSR: 743	EVAR: 88 OSR: 88	EVAR: 74 (6) OSR: 69 (6.7)	N.A.	■		
Lee (2014) [46]	Observational cohort	United Kingdom	Jan, 2000 - Dec, 2013	EVAR: 50 OSR: 119	EVAR: 92 OSR: 92	EVAR: 57.1 OSR: 56.6	EVAR: 5.6 OSR: 6.4	■	■	■
Paolini (2008) [47]	Observational cohort	United States	May, 1996 - Aug, 2006	EVAR: 81 OSR: 69	EVAR: 70.4 OSR: 69.9	EVAR: 83.7 (3.2) OSR: 83.2 (2.8)	EVAR: 5.8 OSR 6.2	■		
Chahwan (2007) [48]	Observational cohort	United States	Jun, 1996 - May, 2005	EVAR: 260 OSR: 417	EVAR: 79.6 OSR: 77.7	EVAR: 73.7 (7.6) OSR: 71.6 (7.9)	EVAR: 5.5 OSR: 6.1	■	■	■
Iannelli (2005) [49]	Observational cohort	Italy	Jan, 1998 - Jul, 2003	EVAR: 34 OSR: 28	EVAR: - OSR: -	EVAR: 75.3 (3.7) OSR: 72.5 (5.2)	N.A.	■		

Supplemental Table 1. Continued

Sugimoto (2017) [50]	Observational cohort - PS	Japan	Jun, 2007 - Oct, 2014	EVAR: 157 OSR: 157	EVAR: 86.6 OSR: 86.0	EVAR: 75 OSR: 74	EVAR: 5.3 OSR: 5.3		■	■
Jetty (2010) [51]	Administrative registry	Canada	Apr, 2002 - Mar, 2007	EVAR: 888 OSR: 5573	EVAR: 86.2 OSR: 80.3	EVAR: 76.0 OSR: 72.0	N.A.	■	■	■
Ren (2012) [52]	Observational cohort	China	Jan, 1998 - Dec, 2008	EVAR: 89 OSR: 136	EVAR: 80.9 OSR: 75.5	EVAR: 66.8 (8.8) OSR: 68.8 (9.5)	N.A.	■		
Mazzaccaro (2017) [53]	Observational cohort	Italy	Jan, 2000 - Dec, 2014	EVAR: 660 OSR: 452	EVAR: - OSR: -	EVAR: 73 OSR:71	EVAR: 5.3 OSR: 5.1	■	■	■
Huang (2015) [54]	Observational cohort - PS	United States	Jan, 2000 - Dec, 2011	EVAR: 558 OSR: 558	EVAR: 86 OSR: 86	EVAR: 74 (7.1) OSR: 72 (8.0)	EVAR: 5.7 OSR: 5.9	■	■	■
Lee (2013) [55]	Observational cohort - PS	United States	1996 - 2004	EVAR: 220 OSR: 220	EVAR: 81.4 OSR: 83.6	EVAR: 72.4 (8.3) OSR: 72.8 (7.6)	N.A.	■	■	■
Majd (2017) [56]	Observational cohort - PS	Germany	1998 - 2006	EVAR: 108 OSR: 108	EVAR: 98.1 OSR: 98.1	EVAR: 71.8 (6.8) OSR: 71.9 (6.8)	N.A.	■	■	■
Arko (2002) [57]	Observational cohort	United States	Jul, 1993 - Jun, 2000	EVAR: 174 OSR: 243	EVAR: 86 OSR: 83	EVAR: 73.5 (8.1) OSR: 73.4 (7.8)	N.A.	■	■	■
Arko (2003) [58]	Observational cohort	United States	Oct, 1996 - Jul, 2000	EVAR: 153 OSR: 141	EVAR: 83 OSR: 86	EVAR: 74.2 (7.9) OSR: 73.8 (7.2)	N.A.	■		
Hynes (2017) [59]	Observational cohort	United States	Oct, 2007 - Oct, 2013	EVAR: 5147 OSR: 1530	EVAR: 99 OSR: 99	EVAR: 71 (8) OSR: 68 (8)	EVAR: 5.8 OSR: 6.2	■		
Arko (2002) [60]	Observational cohort	United States	Jul, 1993 - May, 2000	EVAR: 200 OSR: 297	EVAR: 83 OSR: 58.9	EVAR: 73.6 (8.0) OSR: 73.4 (8.1)	EVAR: 5.7 OSR: 6.4	■		
Min (2012) [61]	Observational cohort	Korea	Jan, 2005 - Dec, 2009	EVAR: 26 OSR: 79	EVAR: 92.3 OSR: 86.1	EVAR: 75.0 (8.1) OSR: 70.3 (8.0)	EVAR: 5.7 OSR: 5.8	■		
Hicks (2015) [62]	Observational cohort	United States	Nov, 2003 - Aug, 2012	EVAR: 214 OSR: 83	EVAR: 80.8 OSR: 75.9	EVAR: 74.3 (0.54) OSR: 69.2 (0.86)	N.A.	■		
Hill (2002) [63]	Observational cohort	United States	Aug, 1995 - Nov, 1998	EVAR: 79 OSR: 70	EVAR: 86 OSR: 80	EVAR: 74 (8) OSR: 72 (8)	EVAR: 5.9 OSR: 5.9	■		
Handa (2012) [64]	Observational cohort	Japan	Jan, 2008 - Sept, 2010	EVAR: 259 OSR: 488	EVAR: 83 OSR: 81	EVAR: 77 (7) OSR: 74 (8)	N.A.	■		
Gouëffic (2005) [65]	Observational cohort	France	Jan, 1995 - Dec, 2001	EVAR: 209 OSR: 289	EVAR: 94 OSR: 94	EVAR: 71 (8) OSR: 69 (8)	N.A.	■		
Majd (2018) [66]	Observational cohort	Germany	1988 – 2015	EVAR: 131 OSR: 46	EVAR: 87 OSR: 76	EVAR: 83 OSR: 82	EVAR: 5.7 OSR: 6.6	■		
Tomee (2018) [67]	Administrative registry	The Netherlands	Jan, 2013 – Dec, 2015	EVAR: 5411 OSR: 1660	EVAR: 87.6 OSR: 81.8	EVAR: 73.7 OSR: 70.7	N.A.	■		

The squares (■) indicate that a study was included in a certain analysis.
PS = propensity cohort; N.A. = Not available

Supplemental Table 2. 30-day/in-hospital mortality rates of elective AAA repair

	Total mortality % (95% CI)	**Mortality EVAR** % (95% CI)	**Mortality OSR** % (95% CI)
All studies	2.29 (1.90 – 2.67)	1.16 (0.92 – 1.39)	3.27 (2.71 – 3.83)
RCTs	1.99 (0.89 – 3.08)	0.95 (0.07 – 1.84)	2.84 (0.92 – 4.76)
Administrative registries	2.40 (1.83 – 2.96)	1.36 (1.04 – 1.68)	3.73 (2.94 – 4.52)
Cohort studies	2.06 (1.62 – 2.50)	0.76 (0.47 – 1.06)	0.76 (0.47 – 1.06)

Supplemental Table 3. Relative survival of patients considered unfit for open repair, randomised to either EVAR or no intervention (EVAR 2 trial).

	3 years (95% CI)	**5 years** (95% CI)	**10 years** (95% CI)
EVAR	0.63 (0.56 – 0.70)	0.48 (0.41 – 0.55)	0.23 (0.17 – 0.29)
No intervention	0.62 (0.55 – 0.69)	0.41 (0.34 – 0. 48)	0.26 (0.20 – 0.32)

Chapter 3

Long-term prognosis after elective abdominal aortic aneurysm repair is poor in women and men: The challenges remain

Ruth M.A. Bulder
Mareia Talvitie
Esther Bastiaannet
Jaap F. Hamming
Rebecka Hultgren
Jan H.N. Lindeman

Annals of Surgery 2020

ABSTRACT

Objective

To evaluate the impact of changes in elective Abdominal Aortic Aneurysm (AAA) management on life-expectancy of AAA patients.

Background

Over the past decades AAA repair underwent substantial changes, that is, the introduction of EVAR and implementation of intensified cardiovascular risk management. The question rises to what extent these changes improved longevity of AAA patients.

Methods

National evaluation including all 12.907 (82.7% male) patients who underwent elective AAA repair between 2001 and 2015 in Sweden. The impact of changes in AAA management was established by a time-resolved analysis based on 3 timeframes: open repair dominated period (2001–2004, n = 2483), transition period (2005–2011, n = 6230), and EVAR-first strategy period (2012–2015, n = 4194). Relative survival was used to quantify AAA associated mortality, and to adjust for changes in life-expectancy.

Results

Relative survival of electively treated AAA patients was stable and persistently compromised [4-year relative survival and 95% confidence interval: 0.87 (0.85–0.89), 0.87 (0.86–0.88), 0.89 (0.86–0.91) for the 3 periods, respectively]. Particularly alarming is the severely compromised survival of female patients (4-year relative survival females 0.78, 0.80, 0.70 vs males 0.89, 0.89, 0.91, respectively). Cardiovascular mortality remained the main cause of death (51.0%, 47.2%, 47.9%) and the proportion cardiovascular disease over non-cardiovascular disease death was stable over time.

Conclusions

Changes in elective AAA management reduced short-term mortality, but failed to improve the profound long-term survival disadvantage of AAA patients. The persistent high (cardiovascular) mortality calls for further intensification of cardiovascular risk management, and a critical appraisal of the basis for the excess mortality of AAA patients.

INTRODUCTION

Although the impaired longevity of abdominal aortic aneurysm (AAA) patients is generally attributed to aneurysm rupture, the high mortality is also present in patients with small aneurysms, in whom the risk of rupture is negligible.[1-4] Besides, the relative high mortality persists after successful preventive repair for larger aneurysms.[5] This implies that AAA disease associates with a profound excess mortality risk independent of rupture. It has been suggested that this excess mortality relates to convergence of (cardiovascular) risk factors and frailty in AAA patients.[3,6]

Over the last 20 years, the landscape of AAA management underwent profound changes. The introduction and establishment of endovascular aneurysm repair (EVAR) resulted in a significantly reduced procedural mortality.[7] Moreover, the past decades are characterized by the broad implementation of intensified cardiovascular disease risk management (CVDRM) programs with the introduction of cholesterol-lowering strategies (statins),and increased awareness on the importance of blood pressure lowering and life-style modifications (smoking cessation), which has contributed to a lower cardiovascular event rate for the general cardiovascular population.[8–10]

The question arises whether, and if so, to what extent, the changes in AAA management (EVAR and CVDRM) improved longevity of AAA patients. To address this, a time-resolved analysis of patients who underwent elective AAA repair was performed based on the Swedish National Patient Registry. With its long-lasting registration, high validity, and highly accurate mortality data, this registry provides a unique opportunity to evaluate AAA repair epidemiology on national level.[11,12] To accurately estimate AAA-specific mortality, and to address putative alterations in life-expectancy due to demographic changes over time, a relative survival analysis was applied.

METHODS

Ethical Approval

This study was approved by the Regional Ethics Review Board in Stockholm and complies with the Declaration of Helsinki. For this population-based study, informed consent was not required, and the handling of data fulfils the requirements of the EU data protection laws.

Registry Data

All persons in Sweden are registered with an individual person specific identity number, which allows merging data on an individual level from different national registries.[13] The Swedish National Patient Registry (NPR) covers all hospital-associated care events and outpatient specialist care events based on the person-specific identity numbers in Sweden, a country with 9.8 million inhabitants in 2015. The NPR has a positive predictive value up to 96%.[11] All Swedish patients who underwent elective infrarenal AAA repair between 2001 and 2015 in 1 of the 30 hospitals that provide elective repair were identified through the Swedish NPR and the Cause of Death Registry.[12]

Data extraction was based on the first registered diagnosis (intact AAA, International Classification of Diseases-9 (ICD-9), and ICD-10 codes). This study only includes patients with elective AAA repair, patients with a diagnosis of ruptured AAA were excluded. Comorbidities included all registered diagnoses in the 5 years before the diagnosis AAA. Evaluated comorbidities were hypertension, hyperlipidaemia, heart disease, peripheral artery disease, stroke, chronic obstructive pulmonary disease, renal disease, diabetes, dementia, and thoracic aneurysm (IDC-9 and ICD-10 codes are provided in the **Supplemental Table 1**). Survival data were crossmatched with the Cause of Death Registry until December 31, 2016.

Time-resolved Analysis

To explore the possible impact of changes in AAA management overtime, that is, the implementation of EVAR and intensified CVDRM, 3 different timeframes, based on the proportion patients treated with OR versus EVAR, were defined and compared (see results).

Outcome Measures

The primary outcome was relative survival, which is the preferred method for estimating disease-specific outcomes in a population-based setting.[14–17] Relative survival analyses provide the opportunity to (1) quantify AAA-associated excess mortality and (2) to adjust for changes in life-expectancy (i.e. an altered age and sex distribution) due to demographic alterations over time.

Secondary outcome measures included short-term mortality and cause of death.

Statistical Analysis

All analyses were performed with Stata/SE, version 12.0 (StataCorp, College Station, TX). Normality was assessed by histograms. Continuous variables were expressed as means (+SD) or medians (+IQR) and compared using Student t-test or Mann-Whitney test. Categorical data were analyzed using the Chi-square test. A 2-sided P-value of <0.05 was considered statistically significant.

Relative survival was calculated by dividing the observed survival of the study population (i.e. electively treated AAA patients) and the expected survival of a general population (i.e. Swedish population) matched for age-, sex-, and year of operation.[18] Expected survival was retrieved from population life-tables.[19] A relative survival below 1 indicates that the survival of the study cohort is lower than expected on basis of the reference population.

Cox regression analysis was used to identify factors associated with 90-day and overall mortality. Each variable was tested for significance ($P < 0.1$) in a univariate analysis before entering into the multivariate model. Result are presented as hazard ratio (HR) and 95% confidence intervals (CIs).

A sensitivity analysis to address a possible impact of changes in patient frailty over time was performed by progressively excluding octogenarians from period 3 and determining the effect on the relative survival.

This study was conducted according to the STROBE guidelines for reporting of observational cohort studies in epidemiology.[20]

RESULTS

Changes in AAA Management

Time-related changes in AAA and cardiovascular risk management are illustrated in **Figure 1**. From 2001 until 2015, the proportion of AAA patients treated with EVAR steadily increased from 15.6% to 64.7%. In parallel, the use of statins increased from 20.3% in period 1 to 35.8% period 3 (P < 0.001).[21,22]

Three periods were defined based on proportions of treatments with OR versus EVAR. Period 1, with a dominance of open repair (2001–2004); period 2, which reflects a transition period from open repair to EVAR (2005–2011); and period 3, with an EVAR-first strategy (2012–2015) (**Figure 1**).

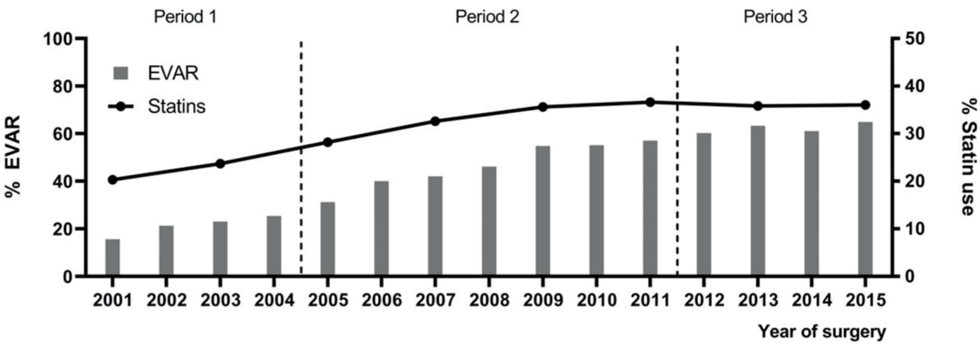


Figure 1. Developments in AAA management between 2001 and 2015. Percentage of EVAR procedures for patients with AAA repair and statin use for the general Swedish population.

Percentage of open repair = 100% - percentage of EVAR. AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

Patient Characteristics

A detailed overview of patient characteristics is shown in **Table 1**. In total, 12.907 (10.683 men (82.7%) and 2224 women (17.3%) underwent elective repair (OR period: n = 2483; transition period: n = 6230; EVAR period: n = 4194). The mean age at repair of patients increased from period 1 to period 3 (71.9 years to 72.8 years, P<0.001). Apart from a decrease in peripheral artery disease and stroke, the percentage of reported comorbidities increased over time (P<0.001).

Table 1. Patient Characteristics for All Patients Who Underwent Elective Infrarenal AAA Repair Between 2001 and 2015

	Period 1 (2001 – 2004)	**Period 2** (2005 – 2011)	**Period 3** (2012 – 2015)	Trend	**P-value**
Patient demographics					
All	2483	6230	4194		
OR (%)	1944 (78.3)	3243 (52.0)	1580 (37.7)	↓	<0.0001
EVAR (%)	539 (21.7)	2987 (48.0)	2614 (62.3)	↑	
Time from diagnosis AAA until surgery (months) (median + IQR)	4.4 (0 – 12.2)	7.8 (1.8 – 38.5)	17.2 (3.8 - 90.8)	↑	0.0001
Gender					0.140
Male (%)	2041 (82.2)	5131 (82.4)	3511 (83.7)	↑	
Female (%)	442 (17.8)	1099 (17.6)	683 (16.3)	↓	
Age (mean + SD)	71.9 (7.6)	72.5 (7.5)	72.8 (7.2)	↑	<0.0001
Comorbidity					
Hypertension (%)	666 (26.8)	2686 (43.1)	2091 (49.9)	↑	<0.0001
Hyperlipidaemia (%)	237 (9.5)	976 (15.7)	784 (18.7)	↑	<0.0001
Heart disease (%)	474 (19.1)	1640 (26.3)	1088 (26.0)	↑	<0.0001
PAD (%)	208 (8.3)	489 (7.9)	248 (5.9)	↓	<0.0001
Stroke (%)	175 (7.1)	439 (7.1)	241 (5.8)	↓	0.021
COPD (%)	190 (7.7)	701 (11.3)	494 (11.8)	↑	<0.0001
Renal disease (%)	62 (2.5)	242 (3.3)	138 (3.3)	↑	0.005
Diabetes (%)	177 (7.1)	630 (10.1)	525 (12.5)	↑	<0.0001
Dementia (%)	59 (2.4)	207 (3.3)	169 (4.0)	↑	0.001
TAA (%)	51 (2.1)	147 (2.4)	93 (2.2)	"	0.673

Data are presented as number of patients and percentage (%) unless indicated otherwise.
COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair; IQR, interquartile range; OR, open repair; PAD, peripheral artery disease; SD, standard deviation; TAA, thoracic aortic aneurysm.

Procedural Mortality (Short-term Survival)

Between period 1 to period 3 the overall procedural (90-day) mortality declined from 4.1% to 1.2% for OR, and from 1.9% to 0.9% for EVAR. The reduction was significant in men (P=0.001), but not for women (P=0.104) (**Table 2**).

Table 2. Crude procedural (90-day) mortality for all, male, and female patients per period

	Period 1		Period 2		Period 3		P-value
	Total	Death <90 days	Total	Death <90 days	Total	Death <90 days	
	n	n (% ; 95% CI)	n	n (% ; 95% CI)	n	n (% ; 95% CI)	
All							
Total	2483	103 (4.1; 3.4 – 5.0)	6230	129 (2.1; 1.7 – 2.5)	4194	50 (1.2; 0.9 – 1.6)	<0.0001
OR	1944	93 (4.8; 3.9 – 5.8)	3243	93 (2.9; 2.3 – 3.5)	1580	27 (1.7; 1.1 – 2.3)	<0.0001
EVAR	539	10 (1.9; 0.9 – 3.4)	2987	36 (1.2; 0.8 – 1.7)	2614	23 (0.9; 0.6 – 1.3)	0.124
Male							
Total	2041	82 (4.0; 3.2 – 4.9)	5131	95 (1.9; 1.5 – 2.3)	3511	33 (0.9; 0.6 – 1.3)	<0.0001
OR	1582	75 (4.7; 3.7 – 5.9)	2605	68 (2.6; 2.0 – 3.3)	1326	19 (1.4; 0.9 – 2,2)	<0.0001
EVAR	459	7 (1.5; 0.6 – 3.1)	2526	27 (1.1; 0.7 – 1.6)	2185	14 (0.6; 0.4 – 1.1)	0.117
Female							
Total	442	21 (4.8; 3.0 – 7.2)	1099	34 (3.1; 2.2 – 4.3)	683	17 (2.5; 1.5 – 4.0)	0.104
OR	362	18 (5.0; 3.0 – 7.7)	638	25 (3.9; 2.6 – 5.7)	254	8 (3.1; 1.0 – 5.3)	0.511
EVAR	80	3 (3.7; 0.8 – 10.6)	461	9 (2.0; 0.9 – 3.7)	429	9 (2.1; 1.0 – 3.9)	0.590

Data are presented as number of patients and percentage (%) with corresponding confidence interval. EVAR, endovascular aneurysm repair; OR, open repair.

Relative Survival (Long-term Survival)

Long-term survival of AAA patients was compared to the survival for the age- and sex-matched general population (relative survival). This analysis showed a stable, persistently impaired relative survival for electively treated AAA patients for all 3 periods (**Figure 2**). The 4 years relative survival was 0.87 (95% CI: 0.85–0.89), 0.87 (95% CI: 0.86–0.88), and 0.89 (95% CI: 0.86–0.91), for period 1, 2, and 3 respectively (n = 7845 patients). Ten-year survival could only be calculated for the first 2 periods because period 3 had a maximum follow-up of 4 years. The 10-year survival was 0.66 (95% CI: 0.63–0.70) for period 1, and 0.65 (95% CI: 0.62–0.69) for period 2 (n = 1778 patients).

Cause of Death

The cause of death distribution remained unchanged over the 3 periods (**Figure 3**). Cardiovascular mortality remained the main cause of death, accounting for 51.0%, 47.2%, 47.9% of the long-term mortality in respectively period 1, 2, and 3 (P=0.429). Neoplasm-related death was the second most common cause of death and was responsible for 23.5%, 25.2%, 21.7% of all long-term deaths (P=0.412).

Sex Differences

Female patients displayed a persistently more compromised relative survival (**Figure 2**). The 4-year relative survival for women was respectively: 0.78 (0.72–0.83), 0.80 (0.77–0.83), and 0.78 (0.68–.84) (mean, 95% CI), compared to 0.89 (0.87–0.91), 0.89 (0.87– 0.90), and 0.91 (0.88–0.94) for males for periods 1, 2, and 3. The increased mortality risk for women was confirmed by Cox regression [HR and 95% CI: 1.12 (1.04–1.20)] (**Supplemental Table 2**).

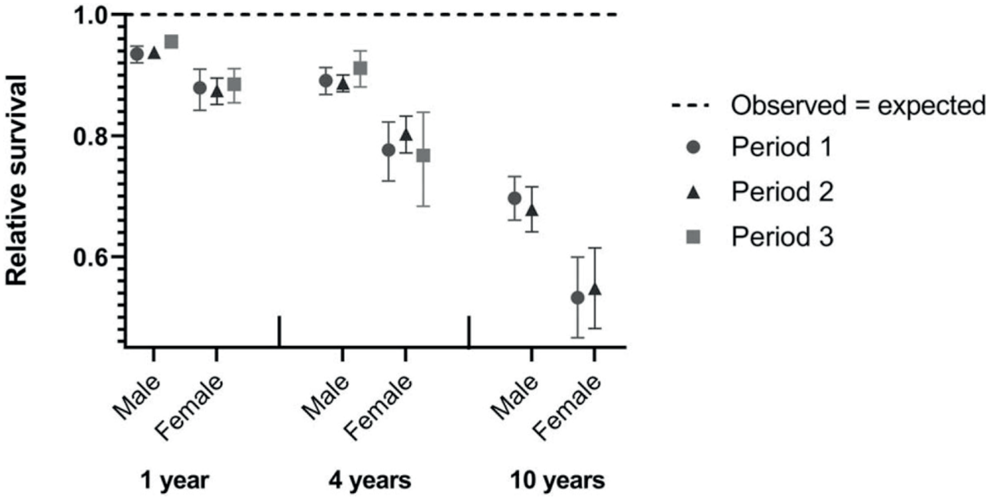


Figure 2. Relative survival for males and females for respectively period 1, period 2, and period 3 at 1, 4, 10 year survival.

Relative survival = observed survival (in study population): expected survival (for matched general Swedish population). 10 year survival data not available for period 3.

Sex-differences in survival persisted over time with a 10-year relative survival for women of 0.53 (0.47–0.60) in period 1 and 0.55 (0.48–0.62) in period 2 [males respectively: 0.70 (0.66–0.73) and 0.68 (0.64–0.72)]. Clear sex-differences were also observed for causes of death with cardiovascular causes more common in women (**Figure 3**).

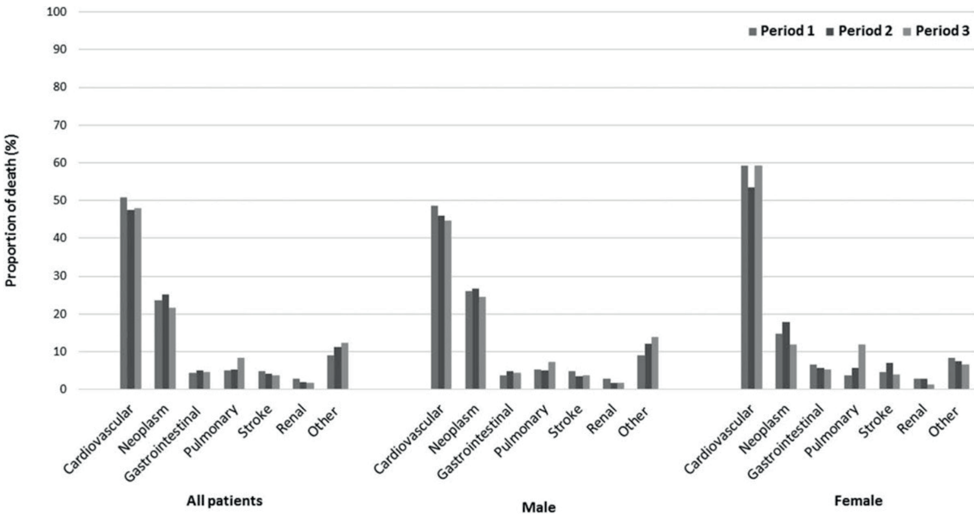


Figure 3. Long-term causes of death (proportions), including all patients who died after 90 days and within 4 year after elective infrarenal AAA repair.

AAA, abdominal aortic aneurysm.

Potential Bias Due to Change of Patient Selection Over Time

Although potential interference of population changes in age distribution and life-expectancy are covered by the relative survival analysis, conclusions of this time-resolved analysis are potentially interfered by changes in patient selection with a lower intervention threshold for EVAR and as a consequence, potentially more frail patients being repaired in the later time frames. Indeed, there was a small increase in age at repair [0.8 years for males (P=0.005) and 1.3 years for females (P=0.925)] over time, and a small increase in the proportion of male (but not female) octogenarians being treated in period 3 (19.6%) versus period 1 (15.7%) (P=0.002) (**Supplemental Figure 1**).

A trend towards a lower intervention threshold for frail patients was not supported by the stable (P=0.782) proportion of repaired/untreated women (conclusions with regard to men are interfered by the introduction of screening in 2006), and by the declining (males) or stable (females) procedural (90-day) mortality (P=0.000 and P=0.104, respectively) (**Table 2**).[23]

Because more direct measures for frailty were unavailable, a sensitivity analysis was performed to test whether conclusions would be impacted by a possible lower intervention threshold (and thus a higher proportion of frail patients) over time. Boundaries for this analysis were based on the proportion of octogenarians in period 3. **Supplemental Table 3** shows that progressive elimination of octogenarians did not influence the study conclusions.

DISCUSSION

This nationwide evaluation of survival after elective AAA repair over time shows improved short-term surgical outcomes, but a persistently, alarmingly poor long-term prognosis, in particular for women. These findings illustrate that major challenges remain in the context of AAA management.

This study applies a time-resolved design to evaluate whether the changes in AAA management in the last 2 decades improved outcomes.[24,25] Application of this approach was facilitated by the fact that the changes in AAA management, that is, the implementation of elective EVAR, and the implementation of intensified CVDRM occurred in well-defined time frames.[26] Therefore, 3 time frames were compared: a period with predominantly OR (period 1), a transition period (period 2), and a period with an EVAR-first strategy (period 3). Moreover, the study periods cover a time frame with increased awareness of the importance of CVDRM in high-risk patients, which is illustrated by the almost doubling of the proportion of patients on statins.[21,22,27] Relative survival analysis was applied to correct for alterations in population life-expectancy over time, and to approximate AAA-specific mortality. As mentioned, relative survival compares the observed survival of the study population (i.e. electively treated AAA patients) with the expected survival of an age-, sex-, year of operation and country-matched reference population (i.e. Swedish population). Therefore, relative survival approximates AAA specific survival.

The results of the present study showed clear improvements in surgical outcomes over the 3 time periods, with significant reductions in overall and OR related short-term mortality. A trend towards lower mortality was also suggested for EVAR. Yet, due to the low event rate the power to detect an effect is limited and significance was not reached. Lack of an effect of lower short-term mortality on the long term survival can be explained by the fact that the incidence of short term (1–2%) mortality dropped below the threshold to impact overall mortality. The equal age-corrected long-term survival for EVAR and OR underlines this phenomenon.[5,28]

The lagging long-term survival benefit could be explained by a change in patient selection over time. The introduction of EVAR, improved CVDRM, and better perioperative care has widened the spectrum of patients eligible for repair.[29] As result, conclusions might be interfered by more elderly and/or more frail patients considered eligible for repair in more recent years. Although the data do not fully exclude such an effect (there is a slight increase in the proportion of male octogenarians receiving repair), the proportion not screened (female) patients receiving repair versus not receiving repair remained stable over the full study period, whereas 90-day mortality, a strong surrogate for patient frailty actually declined.[23,30] To test whether, and if so to what extend conclusions with regard to the persistently impaired longevity would be influenced by a shift towards repair of more frail patients a sensitivity analysis was performed. This analysis showed that progressive elimination of octogenarians did not impact the conclusions of the study that long-term survival did not improve over time.
The lack of long-term survival benefit for the intensified CVDRM could reflect the phenomenon of competitive deaths, referring to the fact that preventing death from 1 disease (i.e. cardiovascular) exposes the patients to dying from another disease. This phenomenon would result in a shift of causes of death over time. Yet, the proportion of CVD did not decrease over time, while the proportion of non-CVD death did not increase. Consequently, the study observations do not relate to the phenomenon of competitive deaths. Alternatively, the stable relative survival could be attributed to AAA patients being undertreated for their cardiovascular risk factors.[31–33] In fact, more stringent therapeutic targets are set in recently revised guidelines for high-risk patients.[34] Nonetheless, it cannot be excluded that low therapy adherence biased the results leading to an underestimation of the possible beneficial effect of CVDRM, this emphasis the need for strict counseling.[35,36] A further point of concern is that AAA patients seem (relatively) resistant to classical CVDRM. An extensive report showed that the impact of lowering blood pressure on disease-free survival and life-years-lost is lower in AAA compared to other acute- and chronic cardiovascular diseases.[37] A possible explanation for this phenomenon is that AAA development reflects a high allostatic load, and thus flags a group of vulnerable patients. Moreover, this apparent inertness could also be a direct consequence increased cardiac afterload as result of loss of the Windkessel function in AAA disease.[38,39] This aspect is not resolved by AAA repair with a stiff aortic graft.

A particularly alarming signal is the profoundly compromised relative survival (0.5) of female AAA patients. This number is well below that reported for most malignancies.[40] The stable repaired/untreated ratio, stable procedural mortality, and stable mean diameter in annual SwedVasc reports do not support a shift towards accepting higher surgical risk patients or repair at lower diameters as underlying cause.[41]

Thus, a direct explanation for the persistent poor outcomes is missing. Potential explanations include the fact that although women are relatively protected from AAA, development of the disease in women may reflect a higher allostatic load and/or unfavorable genetic make-up in those who develop the disease, and thus an accumulation of risk factors for an impaired longevity.[42-44] Moreover, it is known that women are, even when correctly diagnosed, relatively untreated for their cardiovascular risk factors.[45] A final, more speculative aspect, is that the endovascular devices are ill designed for women as they are developed and optimized for the male anatomy. As a consequence, their dimensions could be suboptimalinwomen.[46,47] Support for the latter phenomenon stems from parallels in the incidence of EVAR and the reported incidence of AAA-related deaths in women (**Supplemental Figure 4**).

Limitations

The retrospective nature of the study and the use of registry data comes with inherent with design limitations, in particular, the cause of death registration. Due to the low autopsy rate (10.8% in 2016) the registry is prone to bias and misclassification, in particular to aspects such attribution of acute death to ruptured AAA.[48] Hence, interpretation of the cause of death must be done with caution. However, these limitations are not likely to influence the differences in of cause of death between men and women. Furthermore, there is a risk at reporting bias, as changes in reimbursement system and quality outcome assessment encourage registration of diagnosis.

It is unlikely that the conclusions of this study are interfered by a lack of power as this study had a high power to detect possible changes in patient survival [80% power to pick up a survival difference equivalent to a HR of 0.93 (95% CI: 0.91–0.94) for male patients and 0.85 (95% CI: 0.82–0.88) for female patients between period 1 and period 3].

CONCLUSION

Elective AAA management aims at preventing premature aneurysm-related death and prolonging survival of AAA patients. Over the past 2 decades changes in AAA management have clearly improved short-term outcomes and contributed to a broader spectrum of patients eligible for repair. Despite these short-term improvements there persists a profound overall long-term survival disadvantage of patients who undergo elective AAA repair, specifically in female patients. This suggests that overall mortality of AAA patients is not affected by type of procedure but rather by existing comorbidities. The persistent high (non-AAA related) long-term mortality calls for further intensification of cardiovascular risk management and a critical appraisal of the excess mortality of AAA patients.

REFERENCES

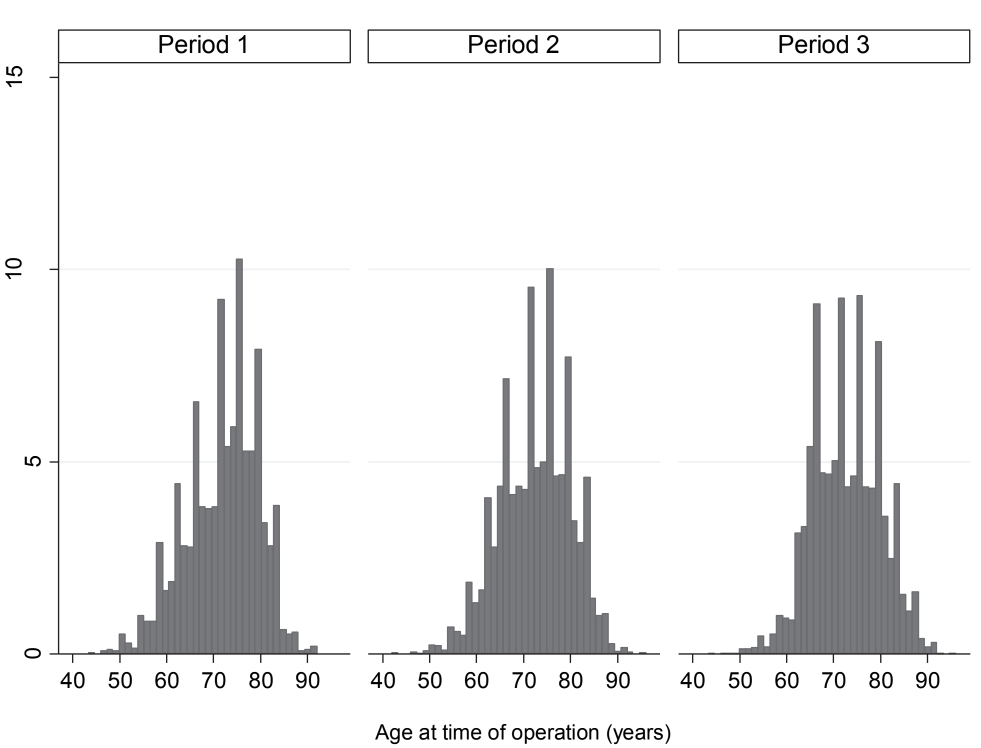
1. Rich N, Tucker LY, Okuhn S, et al. Long-term freedom from aneurysm-related mortality remains favorable after endovascular abdominal aortic aneurysm repair in a 15-year multicenter registry. J Vasc Surg. 2020;71:790–798.
2. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. Lancet. 2005;365:1577–1589.
3. Bath MF, Gokani VJ, Sidloff DA, et al. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015;102:866–872.
4. Freiberg MS, Arnold AM, Newman AB, et al. Abdominal aortic aneurysms, increasing infrarenal aortic diameter, and risk of total mortality and incident cardiovascular disease events: 10-year follow-up data from the Cardiovascular Health Study. Circulation. 2008;117:1010–1017.
5. Bulder RMA, Bastiaannet E, Hamming JF, et al. Meta-analysis of long-term survival after elective endovascular or open repair of abdominal aortic aneurysm. Br J Surg. 2019;106:523–533.
6. Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes indifferent arterial territories. J Cardiovasc Risk. 1994;1:333–339.
7. Wanhainen A, Verzini F, Van Herzeele I, et al. Editor's choice – European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. Eur J Vasc Endovasc Surg. 2019;57:8–93.
8. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315–2381.
9. Khashram M,Williman JA, Hider PN, et al. Management of modifiable vascular risk factors improves late survival following abdominal aortic aneurysm repair: a systematic review and meta-analysis. Ann Vasc Surg. 2017;39:301–311.
10. Eldrup N, Budtz-Lilly J, Laustsen J, et al. Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic aneurysms. J Vasc Surg. 2012;55:311–317.
11. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
12. Brooke HL, Talbaöck M, Hoörnblad J, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32:765–773.
13. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24:659–667.
14. Hu CY, Xing Y, Cormier JN, et al. Assessing the utility of cancer-registry processed cause of death in calculating cancer-specific survival. Cancer. 2013;119:1900–1907.
15. Hakulinen T, Seppaö K, Lambert PC. Choosing the relative survival method for cancer survival estimation. Eur J Cancer. 2011;47:2202–2210.
16. Nelson CP, Lambert PC, Squire IB, et al. Relative survival: what can cardiovascular disease learn from cancer? Eur Heart J. 2008;29:941–947.
17. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. IntJ Epidemiol. 2010;39:598–610. 18.

18. Rutherford MJ, Dickman PW, Lambert PC. Comparison of methods for calculating relative survival in population-based studies. Cancer Epidemiol. 2012;36:16–21.
19. V Shkolnikov, M Barbieri, J Wilmoth. Human Mortality Database [HDM website]. November 27, 2017. Available at: http://www.mortality.org or www.humanmortality.de. Accessed June 1, 2019.
20. MC Christen, STROBE Initiative Group. STROBE Statement [STROBE Statement website]. October 4, 2007. Available at: https://strobe-statement.org/index.php?id=available-checklists. Accessed October 22, 2019.
21. Szummer K, Wallentin L, Lindhagen L, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J. 2018;39:3766–3776.
22. SWEDHEART. SWEDHEART Annual Report. [SWEDHEART website]. Available at: https://www.ucr.uu.se/swedeheart/component/edocman/swedeheart-annual-report-2015-english-engelsk/viewdocument/923?Itemid=. Accessed February, 2020.
23. Zommorodi S, Leander K, Roy J, et al. Understanding abdominal aortic aneurysm epidemiology: socioeconomic position affects outcome. J Epidemiol Community Health. 2018;72:904–910.
24. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010;19:537–554.
25. Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. StatMed. 2014;33:2297–2340.
26. Smith ME, Andraska EA, Sutzko DC, et al. The decline of open abdominal aortic aneurysm surgery among individual training programs and vascular surgery trainees. J Vasc Surg. 2020;71:1371–1377.
27. Socialstryrelsen. National Swedish Prescribed Drug Registry (Lakemedelstatistik, Socialstyrelsen). Statiner inkl. Kombinationer. [Socialstyrelsen website]. Available at: https://sdb.socialstyrelsen.se/if_lak/val.aspx. Accessed September 11, 2019.
28. Powell JT, Sweeting MJ, Ulug P, et al. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017;104:166–178.
29. Chaikof EL, Brewster DC, Dalman RL, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50:880–896.
30. Hewitt J, Carter B, McCarthy K, et al. Frailty predicts mortality in all emergency surgical admissions regardless of age. An observational study. Age Ageing. 2019;48:388–394.
31. Allahyari A, Jernberg T, Hagstroöm E, et al. Application of the 2019ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study. Eur Heart J. 2020 [Epub ahead of print]. Available at: https://academic.oup.com/eurheartj/advance-article/doi/ 10.1093/eurheartj/ehaa034/5739477. Accessed May 10, 2020.
32. Saratzis A, Dattani N, Brown A, et al. Multi-centre study on cardiovascular risk management on patients undergoing AAA surveillance. Eur J Vasc Endovasc Surg. 2017;54:116–122.
33. Saratzis A, Jaspers NEM, Gwilym B, et al. Observational study of the medical management of patients with peripheral artery disease. Br J Surg. 2019;106:1168–1177.
34. Piepoli MF, Hoes AW, Agewall S, et al., ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies

and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315–2381.

35. Lemstra M, Blackburn D. Nonadherence to statin therapy: discontinuation after a single fill. Can J Cardiol. 2012;28:567–573.
36. Lin I, Sung J, Sanchez RJ, et al. Patterns of statin use in a real-world population of patients at high cardiovascular risk. JManagCareSpecPharm.2016;22:685–698. 37. 35.
37. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age specific associations in 1.25 million people. Lancet. 2014;383:1899–1911.
38. Westerhof N, Lankhaar JW, Westerhof BE. The arterial Windkessel. Med Biol Eng Comput. 2009;47:131–141.
39. Belz GG. Elastic properties and Windkessel function of the human aorta. Cardiovasc Drugs Ther. 1995;9:73–83.
40. National Cancer Control Indicators. 10-year Relative Survival [Australian Government Cancer Australia website]. February 2019. Available at: https:// ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/10-year-relativesurvival. Accessed February 27, 2020.
41. Annual Reports. Swedvasc, Swedish National Registry for Vascular Surgery [SwedVasc website]. Available at: https://www.ucr.uu.se/swedvasc/arsrapporter. Accessed May 9, 2020.
42. Lederle FA, Johnson GR, Wilson SE, et al. Abdominal aortic aneurysm in women. J Vasc Surg. 2001;34:122–126.
43. Scott RA, Bridgewater SG, Ashton HA. Randomized clinical trial of screening for 457 abdominal aortic aneurysm in women. Br J Surg. 2002;89:283–285.
44. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci. 1998;840:33–44.
45. Alabas OA, Gale CP, Hall M, et al. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. J Am Heart Assoc. 2017;6:e007123.
46. Grootenboer N, van Sambeek MR, Arends LR, et al. Systematic review and meta-analysis of sex differences in outcome after intervention for abdominal aortic aneurysm. Br J Surg. 2010;97:1169–1179.
47. Ulug P, Sweeting MJ, von Allmen RS, et al. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet. 2017;389:2482–2491.
48. European Health Information Gateway. Autopsy Rate for All Deaths [WorldHealth Organization website website]. 2020. Available at: https://gateway.euro.who.int/en/hfa-explorer/#xLZrZd7ntc. Accessed February 27, 2020.

SUPPLEMENTAL MATERIAL



Supplemental Figure 1. Age distribution per period.

Additional analyses: chi square on age distribution of patients <75 years – 75-59 years – >80 years against period 1 – period 2 - period 3 revealed a P=0.001.

Supplemental Table 1. ICD-codes and procedure codes used for identifying intact AAA, comorbidities, and procedures.

	ICD-9	ICD-10
Intact AAA	441D, 441E	I714
Hypertension		I109
Hyperlipedemia		E78X
Diabetes mellitus		E10 – E11X
Stroke		I61X, I63 – I64X, I69X
Ischemic heart disease		I24 – I25X
Chronic obstructive pulmonary disorder		J44X
Renal failure		N17 – N19X
Neoplasm		CXXX
Procedure codes		JAH00, PDA10, PDG10, PDG20, PDG21, PDG22, PDG23, PHD10, PHD21, PDQ10, PDQ21

Supplemental Table 2. **Multivariate cox regression analysis of 90-day and overall mortality, including all patients and stratified by gender.**

	90-day mortality HR (95% CI)	**P-value**	**Overall mortality** HR (95% CI)	**P-value**
All patients				
Type procedure (EVAR)	0.28 (0.24 – 0.33)	0.000	0.99 (0.93 – 1.05)	0.731
Sex (female)	1.44 (1.22 – 1.69)	0.000	1.12 (1.04 – 1.20)	0.002
Age	1.10 (1.09 – 1.11)	0.000	1.07 (1.07 – 1.08)	0.000
Ischemic heart disease	1.20 (1.02 – 1.43)	0.031	1.18 (1.11 – 1.26)	0.000
PAD	1.43 (1.13 – 1.81)	0.003	1.32 (1.20 – 1.45)	0.000
Stroke	1/73 (1.38 – 2.18)	0.000	1.46 (1.32 – 1.61)	0.000
TAA	1.67 (1.14 – 2.44)	0.008	1.70 (1.44 – 2.00)	0.000
Hypertension	0.94 (0.81 – 1.10)	0.464	0.98 (0.92 – 1.04)	0.438
Hyperlipidaemia	0.77 (0.61 – 0.97)	0.025	0.83 (0.76 – 0.92)	0.000
COPD	1.63 (1.34 – 1.98)	0.000	1.67 (1.54 – 1.81)	0.000
Dementia	1.78 (1.29 – 2.44)	0.000	1.79 (1.56 – 2.07)	0.000
Diabetes	1.34 (1.07 – 1.68)	0.000	1.29 (1.17 – 1.41)	0.000
Renal failure	1.64 (1.21 – 2.23)	0.002	1.88 (1.66 – 2.14)	0.000
Male patients				
Type procedure (EVAR)	0.25 (0.20 – 0.30)	0.000	0.99 (0.92 – 1.06)	0.762
Age	1.10 (1.09 – 1.12)	0.000	1.07 (1.06 – 1.08)	0.000
Female patients				
Type procedure (EVAR)	0.41 (0.30 – 0.56)	0.000	0.98 (0.85 – 1.12)	0.798
Age	1.09 (1.07 – 1.11)	0.000	1.07 (1.06 – 1.08)	0.000

EVAR, endovascular aneurysm repair; PAD, peripheral artery disease; TAA, thoracic aortic aneurysm; COPD, chronic obstructive pulmonary disease; HR, Hazard Ratio; 95% CI, 95% confidence interval

Supplemental Table 3. Sensitivity analysis of relative survival based on proportion of octogenarians (80 +) included in period 3.

	Period 1	**Period 2**	**Period 3**	**SENSITIVITY ANALYSIS**			
				75% (80+)	50% (80+)	25% (80+)	0% (80+)
1 year							
Male patients	0.94 (0.93 – 0.95)	0.94 (0.94 – 0.95)	0.96 (0.95 – 0.97)	0.96 (0.95 – 0.97)	0.96 (0.95 – 0.97)	0.96 (0.95 – 0.97)	0.96 (0.95 – 0.97)
Female patients	0.89 (0.85 – 0.92)	0.88 (0.86 – 0.90)	0.89 (0.86 – 0.92)	0.89 (0.86 – 0.92)	0.90 (0.87 – 0.92)	0.90 (0.86 – 0.92)	0.90 (0.87 – 0.93)
4 years							
Male patients	0.90 (0.87 – 0.92)	0.89 (0.88 – 0.91)	0.92 (0.88 – 0.94)	0.91 (0.88 – 0.94)	0.92 (0.89 – 0.94)	0.92 (0.89 – 0.95)	0.92 (0.89 – 0.95)
Female patients	0.78 (0.73 – 0.83)	0.81 (0.78 – 0.84)	0.77 (0.69 – 0.85)	0.76 (0.68 – 0.84)	0.78 (0.70 – 0.86)	0.77 (0.68 – 0.85)	0.77 (0.67 – 0.84)
10 years *							
Male patients	0.70 (0.66 – 0.74)	0.68 (0.64 – 0.72)	-	-	-	-	-
Female patients	0.54 (0.47 – 0.60)	0.55 (0.49 – 0.62)	-	-	-	-	-

* 10-years relative survival was not available for period 3 due to maximum follow-up of 4 years for this period.

Supplemental Table 4. Proportion of cause of death. Including all patients who died within 4 years following elective infrarenal AAA repair.

	Period 1 (2001 – 2004)	**Period 2** (2005 – 2011)	**Period 3** (2012 – 2015)
All patients			
	n = 588	n = 1219	n = 401
Cardiovascular	340 (57.8)	622 (51.0)	207 (51.6)
of which AAA related	143 (24.3)	257 (21.1)	87 (21.7)
Neoplasm	118 (20.1)	274 (22.5)	76 (20.0)
Gastrointestinal	26 (4.4)	65 (5.3)	16 (4.0)
Pulmonary	24 (4.1)	59 (4.9)	29 (8.2)
Stroke	24 (4.1)	48 (3.9)	13 (3.5)
Renal	13 (2.2)	21 (1.7)	6 (1.5)
Other	43 (7.3)	130 (10.7)	43 (11.2)
Male			
	n = 459	n = 972	n = 308
Cardiovascular	257 (56.0)	481 (49.5)	151 (49.0)
of which AAA related	109 (23.8)	189 (19.4)	55 (17.9)
Neoplasm	102 (22.2)	236 (24.3)	68 (22.1)
Gastrointestinal	18 (3.9)	48 (5.0)	12 (3.9)
Pulmonary	20 (4.4)	46 (4.7)	22 (7.1)
Stroke	18 (3.9)	32 (3.3)	11 (3.6)
Renal	10 (2.2)	15 (1.5)	5 (1.6)
Other	34 (7.4)	114 (11.7)	39 (12.7)
Female			
	n = 129	n = 247	n = 93
Cardiovascular	83 (59.3)	141 (57.1)	56 (60.2)
of which AAA related	34 (26.4)	68 (27.5)	32 (34.4)
Neoplasm	16 (12.4)	38 (15.4)	12 (12.9)
Gastrointestinal	7 (6.2)	17 (6.9)	4 (4.3)
Pulmonary	4 (3.1)	13 (5.3)	11 (11.8)
Stroke	5 (4.7)	16 (6.5)	3 (3.2)
Renal	3 (2.3)	6 (2.4)	1 (1.1)
Other	9 (7.0)	16 (6.5)	6 (6.5)

Data is presented as number of patients and percentage (%). AAA, abdominal aortic aneurysm.

Chapter 4

Persistent high long-term excess mortality after elective AAA repair especially in women: A large population-based study

Ruth M.A. Bulder
Joost R. van der Vorst
Jan van Schaik
Ajda Bedene
Willem M. Lijfering
Esther Bastiaannet
Jaap F. Hamming
Jan H.N. Lindeman

Annals of Surgery 2023

ABSTRACT

Objective

The aim of this time-trend analysis is to estimate long-term excess-mortality and associated cardiovascular risk for abdominal aortic aneurysm (AAA) patients after elective repair, while addressing the changes in AAA management and patient selection over time.

Background

Despite the intensification of endovascular aneurysm repair (EVAR) and cardiovascular risk management (CVRM), Swedish population data suggest that AAA patients retain a persistently high long-term mortality after elective repair. The question is whether this reflects sub-optimal treatment, a changing patient population over time, or a national phenomenon.

Methods

Nationwide time-trend analysis including 40730 patients (87% men) following elective AAA repair between 1995-2017. Three timeframes were compared, each reflecting changes in the use of EVAR and intensification of CVRM. Relative survival analyses were used to estimate disease-specific excess-mortality. Competing risk of death analysis evaluated the risk of cardiovascular versus non-cardiovascular death. Sensitivity analysis evaluated the impact of changes in patient selection over time.

Results

Short-term excess-mortality significantly improved over time. Long-term excess-mortality remained high with a doubled mortality risk for women (RER 1.87 (95%CI 1.73–2.02)). Excess-mortality did not differ between age-categories. The risk of cardiovascular versus non-cardiovascular death remained similar over time, with a higher risk of cardiovascular death for women. Changes in patient population (i.e. older and more comorbid patients in the latter period) marginally impacted excess-mortality (2%).

Conclusions

Despite changes in AAA care, patients retain a high long-term excess-mortality after elective repair with a persistent high cardiovascular mortality risk. In this a clear sex- but no age disparity stands out.

INTRODUCTION

A meta-analysis of long-term survival following elective abdominal aortic aneurysm (AAA) repair reports a persistently high excess mortality after repair.[1] Swedish population data imply a profound sex-difference and suggest that excess mortality has not improved over the last two decades. A notable finding considering the advances in surgical care such as the intensification of endovascular aneurysm repair (EVAR) and cardiovascular risk management (CVRM).[2]

Although the persistently compromised life-expectancy following elective AAA repair may imply that AAA patients are still sub optimally treated for their long-term mortality risk. It cannot be excluded that it reflects epidemiological changes in AAA care with more comorbid and/or older patients receiving repair in the current endovascular era.[3] Or that AAA disease may be associated with a residual mortality that is not fully amendable to CVRM. Finally, it cannot be excluded that the apparent lack of survival improvement observed in the Swedish population reflects a national phenomenon. The more so because a recent analysis of Danish population data implied improved survival and cardiovascular outcomes for AAA patients over time.[4,5]

The aim of this time-trend analysis is to evaluate long-term excess mortality and its associated cardiovascular risk for AAA patients after elective repair, while addressing the changes in AAA management (i.e. the increase in EVAR and CVRM) and epidemiological shifts (i.e. older and more comorbid patients) over time. Therefore, a relative survival analysis was used to estimate disease-specific excess mortality, as well as a competing risk of death analysis to evaluate the risk of cardiovascular versus non-cardiovascular death over time.

METHODS

Study population

Included patients underwent primary elective AAA repair in the Netherlands between 1995 and 2017.[6] Ruptured AAAs were excluded (**Supplemental Table 1**). Comorbidity burden was estimated through the Charlson Comorbidity Index (CCI) and included all diagnoses registered at the same moment as AAA repair.[7] Prescriptions for CVRM were extracted one year prior to repair to ensure preventive risk management (**Supplemental Table 1**). Date and cause of death were extracted until 31 December 2018 (**Supplemental Table 1**).[8] Three predefined periods were created, each reflecting clear contrasts in procedural an CVRM changes. In period 1 (1995-2000) open repair and rudimentary CVRM dominated; period 2 (2001-2011) was a transition period; and period 3 (2013-2017) saw an EVAR-first strategy and maximal implementation of CVRM.[9,10,11] A more detailed prescription of the methods and period choice is provided in the Supplemental Material.

Relative survival and competing risk of death analysis

Relative survival, rather than crude survival, was applied to 1) evaluate disease-specific mortality, and 2) to adjust for sex-, age- and time-related differences in life-expectancy.[12,13] A competing risk of death analysis was performed to estimate possible shifts in the risk of cardiovascular (CV) versus non-cardiovascular death over time.[14] Sensitivity analyses were performed to estimate the impact of changes in patient age and comorbidity burden on study conclusions. Further details are provided in the Supplemental Material.

Statistical analysis

All analyses were performed in SPSS, version 26 (IBM, Amsterdam) and Stata/SE, version 12.0 (StataCorp, College Station, TX, USA). Comparisons between groups were analysed using standard statistical methods. Relative survival reflects the ratio of the observed survival of the study population (i.e. electively treated AAA patients), and the expected survival of the matched (sex, age, and year of operation) general Dutch population.[12,13] A relative survival below 100% means that the disease-specific survival is lower than that of the reference population (i.e. excess mortality). Competing risk of death analyses were performed by estimating the cumulative incidence of CV death versus non-CV death (subdistribution hazard ratios, tested by Fine and Gray models).[14] A detailed description of the statistical analysis is provided in the Supplemental Material.

RESULTS

Time-trends in patient demographics

Between 1995 and 2017, 40730 patients (86.6% men) underwent elective AAA repair. Clear demographic changes occurred over time (**Table 1**), including an increase in the proportion of women (from 12.1 to 15.2%), and an approximately 2-years increase in mean age at repair (P<0.001). Moreover, the Charlson Comorbidity Index increased for men in all age categories, and for women in older age categories (70-74 and >80 years).

Table 1. Demographics of patients treated with elective AAA repair per period by sex and age

	Period 1 (1995 – 2000)	**Period 2** (2001 – 2011)	**Period 3** (2012 – 2017)	**P**
Elective repair, n (%)	11096	18731	10903	N.A.
Men	9749 (87.86)	16261 (86.81)	9247 (84.81)	
<65	2280 (20.55)	3117 (16.64)	1398 (12.82)	
65 – 70	2212 (19.94)	3165 (16.90)	1826 (16.75)	
71 – 74	2619 (23.60)	4113 (21.96)	2207 (20.24)	
75 – 79	1846 (16.64)	3702 (19.76)	2054 (18.84)	
> 80	792 (7.14)	2164 (11.55)	1762 (16.16)	

Table 1. Continued

Women	1347 (12.14)	2470 (13.19)	1656 (15.19)	
< 65	230 (2.07)	331 (1.77)	197 (1.81)	
65 – 70	240 (2.16)	388 (2.07)	280 (2.57)	
71 – 74	358 (3.23)	641 (3.42)	362 (3.32)	
75 – 79	332 (2.99)	659 (3.52)	431 (3.95)	
> 80	187 (1.69)	451(2.41)	386 (3.54)	
Age at time repair, mean (SD)	70.0 (7.5)	71.4 (7.7)	72.3 (7.7)	0.000
Men	69.7 (7.4)	71.2 (7.6)	72.4 (7.7)	0.000
<65	59.7 (4.2)	59.7 (4.1)	60.0 (3.8)	0.004
65 – 70	67.1 (1.4)	67.2 (1.4)	67.2 (1.4)	0.263
71 – 74	72.0 (1.4)	72.0 (1.4)	71.9 (1.4)	0.126
75 – 79	76.7 (1.4)	76.8 (1.4)	77.0 (1.4)	0.000
> 80	82.4 (2.3)	82.5 (2.4)	82.9 (2.6)	0.000
Women	71.7 (8.0)	72.8 (7.9)	73.6 (8.0)	0.000
< 65	58.9 (5.4)	58.9 (5.9)	59.1 (6.2)	0.944
65 – 70	67.2 (1.3)	67.1 (1.4)	67.3 (1.4)	0.079
71 – 74	72.1 (1.4)	72.1 (1.4)	72.1 (1.4)	0.987
75 – 79	76.9 (1.4)	76.9 (1.4)	76.9 (1.4)	0.730
> 80	83.0 (2.7)	82.9 (2.8)	83.1 (2.7)	0.369
CCI score, n (%)				
Men				
<65				0.001
0	1274 (55.9)	1687 (54.1)	821 (58.7)	
1	720 (31.6)	1061 (34.0)	379 (27.1)	
2	192 (8.4)	240 (7.7)	128 (9.2)	
>3	94 (4.1)	129 (4.1)	70 (5.0)	
65 – 70				0.000
0	1400 (51.3)	2088 (52.5)	1237 (54.0)	
1	923 (33.8)	1319 (33.2)	651 (28.4)	
2	252 (9.2)	331 (8.3)	248 (10.8)	
>3	154 (5.7)	238 (6.0)	157 (6.8)	
71 – 74				0.000
0	1037 (49.3)	1672 (50.6)	899 (51.7)	
1	698 (33.2)	1076 (32.6)	465 (26.7)	
2	227 (10.8)	306 (9.3)	220 (12.6)	
>3	140 (6.7)	248 (7.5)	156 (9.0)	
75 – 79				0.001
0	903 (48.9)	1888 (51.0)	1045 (50.9)	
1	597 (32.3)	1153 (31.2)	566 (27.6)	
2	208 (11.3)	365 (9.8)	260 (12.7)	

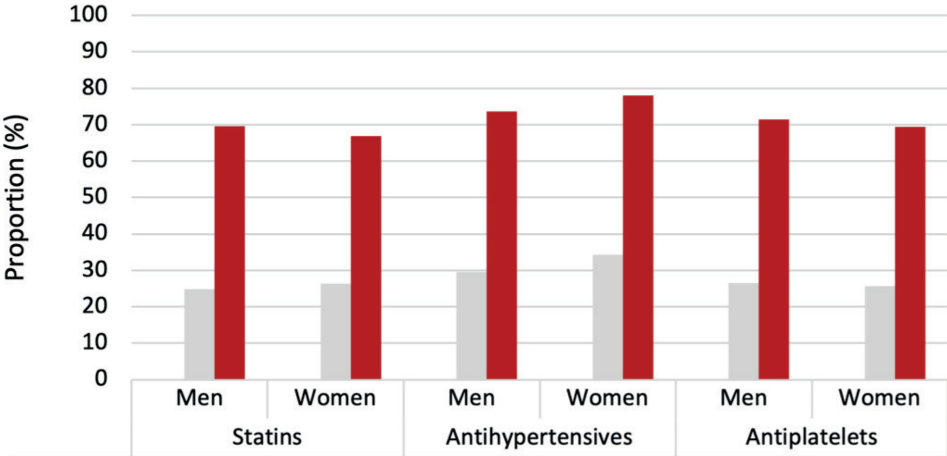
Table 1. Continued

>3	138 (7.5)	296 (8.0)	183 (8.9)	
> 80				0.000
0	352 (44.4)	1128 (52.1)	905 (51.4)	
1	280 (35.4)	664 (30.7)	464 (26.3)	
2	97 (12.2)	187 (8.6)	226 (12.8)	
>3	63 (8.0)	185 (8.6)	167 (9.5)	
Women				
<65				0.379
0	124 (53.9)	161 (48.6)	101 (51.3)	
1	78 (33.9)	130 (39.3)	62 (31.5)	
2	19 (8.3)	24 (7.3)	22 (11.2)	
>3	9 (3.9)	16 (4.8)	12 (6.1)	
65 – 70				0.142
0	153 (51.2)	239 (48.0)	169 (48.3)	
1	93 (31.1)	174 (35.0)	100 (28.6)	
2	30 (10.0)	56 (11.2)	45 (12.8)	
>3	23 (7.7)	29 (5.8)	36 (10.3)	
71 – 74				0.024
0	143 (47.8)	241 (45.4)	126 (43.2)	
1	111 (37.1)	199 (37.5)	90 (30.8)	
2	26 (8.7)	53 (10.0)	42 (14.4)	
>3	19 (6.4)	38 (7.2)	34 (11.6)	
75 – 79				0.077
0	153 (46.1)	316 (48.0)	210 (48.7)	
1	119 (35.8)	228 (34.6)	133 (30.9)	
2	42 (12.7)	65 (9.8)	41 (9.5)	
>3	18 (5.4)	50 (7.6)	47 (10.9)	
> 80				0.016
0	96 (51.3)	217 (48.1)	212 (54.9)	
1	58 (31.0)	154 (34.2)	86 (22.3)	
2	18 (9.6)	45 (10.0)	52 (13.5)	
>3	15 (8.0)	35 (7.7)	36 (9.3)	

Data are presented as number (proportions) unless indicated otherwise.
CCI indicates Charlson Comorbidity Index.

Time-trends in CVRM

Detailed information regarding medical CVRM was available for the years 2006–2017 and summarized in **Figure 1**. Over time, the proportion of patients with at least one CVRM prescription increased: statins from 24.8%-69.6% and 26.3%-66.9%, antihypertensive from 29.5%-73.7% and 34.3%-78.0%, and antiplatelets from 26.5%-71.3% and 25.6%-69.4%, for men and women respectively.



	Statins Men	Statins Women	Antihypertensives Men	Antihypertensives Women	Antiplatelets Men	Antiplatelets Women
Period 1						
Period 2	24,77	26,32	29,54	34,33	26,54	25,63
Period 3	69,58	66,85	73,67	77,96	71,34	69,44

Figure 1. Time trends of the implementation of pharmaceutical cardiovascular risk management, stratified by sex.

Time-trends in excess mortality (relative survival)

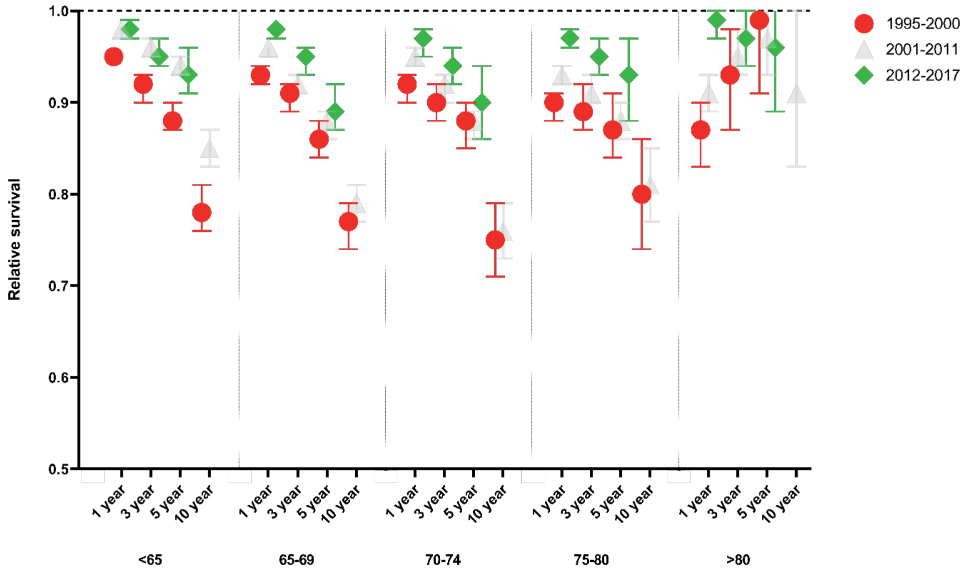
Short-term (1 year) relative survival improved for men, but not for women, over time. Long-term relative survival (3, 5, and 10 years) remained stably impaired over time, with a clear survival disadvantage for women (**Figure 2, Supplemental Table 2**). In fact, compared to men, women had a doubled mortality risk after correction for age and CCI scores (RER 1.87 (95%CI: 1.73–2.02). There were no differences in relative survival between age categories.

Time-trends in competing risk analysis of cardiovascular- versus non-cardiovascular death

Cause of death analysis implies a higher risk for cardiovascular death in the electively repaired AAA population compared to the general population (**Supplemental Figure 1**).

A competing risk analysis was performed to estimate the risk of cardiovascular versus non-cardiovascular mortality over time. This showed no change in cumulative incidence of cardiovascular versus non-cardiovascular death for all age categories and for both sexes over time. Throughout the first years after repair, the risk of cardiovascular death exceeded that of non-cardiovascular death. The dominance of cardiovascular death persisted for a longer time after surgery in women (to 6.5 years) than in men (to 3.5 years) (**Figure 3, Supplemental Table 3, Supplemental Figure 2**).

A



B

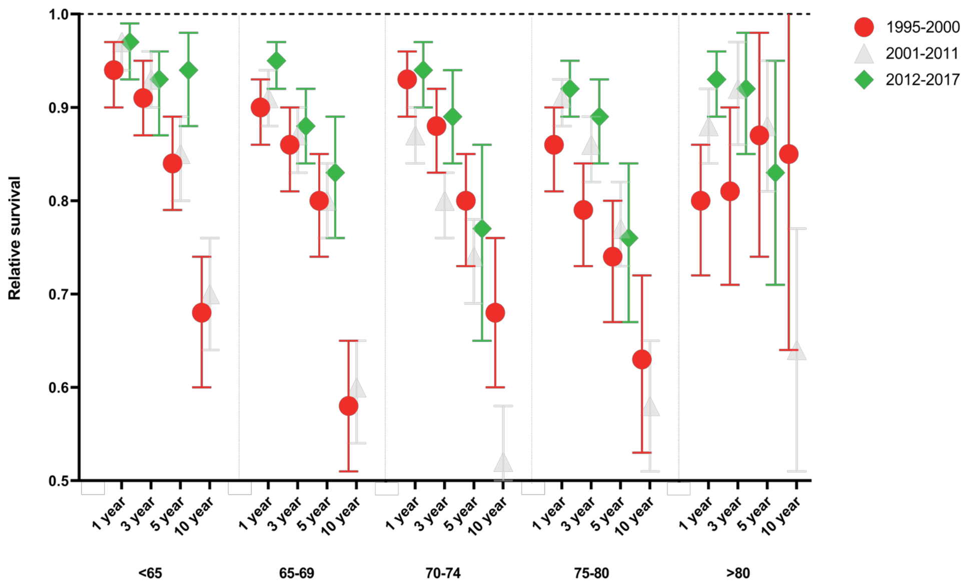


Figure 2. Relative survival (1, 3, 5, 10 years) for men (A) and women (B) stratified by age.

Note that 10-year RS could only be calculated for periods 1 and 2 due to the restricted follow-up in period 3.

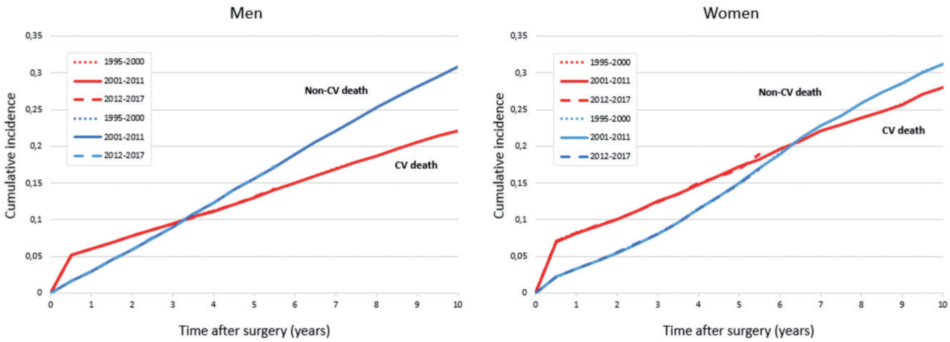


Figure 3. Cumulative incidence of cardiovascular vs. non-cardiovascular mortality over time stratified by sex.

The impact of changes in patient characteristics on study outcomes

From period 1 to 3, the mean age at time of repair increased with 2.7 years for men and 1.9 years for women (both P<0.001). Comorbidity scores increased for men in all age categories and for women in age categories 70-74 and >80 years. To estimate the impact of the lower repair threshold, resulting in an increase in the proportion of older and/or patients with greater comorbidity in the more recent time frame, stratified analyses by age, and sensitivity analyses addressing different degrees of comorbidity, were undertaken. Outcome comparison of age-categories showed similar survival rates and equal risks of cardiovascular death (**Figure 2, Supplemental Figure 2**). Sensitivity analyses addressing CCI showed a higher relative excess risk (RER) of death for patients with a higher CCI score, and a more pronounced impact of comorbidities on survival in older patients (**Supplemental Table 4**). Censoring all patients with a CCI score ≥3 receiving repair in period 3, implied a modest impact of changes in patient comorbidity on the relative survival (approximately 2%) for men (<65, 65-69, 75-80 years) and for younger women (<65 years) (**Table 2**).

Table 2. Sensitivity analysis. 5-years relative survival of entire patient cohort versus patient cohort with exclusion of patients with CCI>3.

	Period 1 (1995 – 2000)	**Period 3** (2012 – 2017)	
	Entire cohort	Entire cohort	Exclusion CCI >3
Men			
<65	0.88 (0.87 – 0.90)	0.93 (0.91 – 0.96)	0.94 (0.91 – 0.96)
65 – 70	0.86 (0.84 – 0.88)	0.89 (0.87 – 0.92)	0.92 (0.89 – 0.95)
71 – 74	0.88 (0.85 – 0.90)	0.90 (0.86 – 0.94)	0.93 (0.88 – 0.96)
75 – 79	0.87 (0.84 – 0.91)	0.93 (0.88 – 0.97)	0.95 (0.91 – 0.99)
> 80	0.99 (0.91 – 1.06)	0.96 (0.89 – 1.02)	1.00 (0.92 – 1.07)
Women			
< 65	0.84 (0.79 – 0.89)	0.94 (0.88 – 0.98)	0.95 (0.90 – 0.99)
65 – 70	0.80 (0.74 – 0.85)	0.83 (0.76 – 0.89)	0.86 (0.78 – 0.92)
71 – 74	0.80 (0.73 – 0.85)	0.77 (0.65 – 0.86)	0.79 (0.67 – 0.88)
75 – 79	0.74 (0.67 – 0.80)	0.76 (0.67 – 0.84)	0.79 (0.70 – 0.87)
> 80	0.85 (0.64 – 1.09)	0.83 (0.71 – 0.95)	0.88 (0.75 – 1.00)

Data represent relative survival with 95% CI.

DISCUSSION

In this 25-year nationwide study, short-term mortality after elective AAA repair was improved, as expected. Long-term mortality was stable, despite an aging patient population with increasing comorbidity. Long-term excess mortality, compared to a sex- and age- matched general population however, remained persistently high. The risk of cardiovascular death did not decrease over time despite intensification of pharmaceutical CVRM. A profound sex but no age-disparity stands out with a doubled excess mortality risk for women compared to men.

Despite improvements in short-term survival over time due to improvements in surgical outcomes, long-term survival remained persistently impaired. To put this in perspective, the excess mortality of elective AAA patients equals that, or is higher than, reported for most malignancies.[15] The absence of long-term survival benefit could be explained the gradual lowering of the threshold for repair, which resulted in older and more comorbid patients considered eligible for repair in the current era (chronological bias). In this study, this is reflected by an increase in Charlson Comorbidity Index (CCI), a doubling of the proportion of octogenarians, and a two-year increase in mean age at repair over the study period. The potential impact of these changes in patient selection over time was addressed by age stratified and sensitivity analyses. This showed that increased age did not correspond with lower survival. Associations were found between higher CCI scores and a higher risk of excess mortality (**Supplemental Table 4**). To evaluate the impact of higher CCI scores on the excess long-term mortality, a sensitivity analysis censoring all with a CCI ≥3 in period 3 was performed. This showed a marginal increase in relative survival of 2% (predominately men), yet relative survival remained severely impaired (**Table 2**). Therefore,

the persistently high excess mortality only marginally relates to an increase in comorbidity burden. The observation that there were no differences in excess mortality between age categories implies that the existence of an AAA reflects overall vulnerability, resulting in an univocally high mortality risk, regardless of whether a patient is 65 or 85 years old.
To gain a better understanding of possibly underlying causes for the excess long-term mortality, overall causes of death were evaluated. This implied a high cardiovascular cause of death (without AAA rupture) in the electively repaired AAA population (approximately 50%) compared to the general population. A result confirmed by other studies.[16] To evaluate to what extent intensification of CVRM over time influences the risk of cardiovascular mortality, a competing risk of death analysis was performed. Hypothetically, intensification of CVRM should decrease the risk for cardiovascular death, thereby exposing the patient to other competing mortality risks (e.g. malignancy), and thus potentially masking a beneficial effect of CVRM on overall survival. This analysis showed an unchanged cardiovascular mortality risk over time, as well as a particularly high cardiovascular risk for AAA patients in the first years after surgery. Therefore, it is suggested that the broader implementation of CVRM has a limited impact on cardiovascular mortality risk (on population level).

The apparent limited impact of CVRM on cardiovascular mortality risk may reflect a relative undertreatment of cardiovascular risk in electively repaired AAA patients. Despite consensus endorsing maximum CVRM in those patients, studies show that half of the AAA patients still do not receive optimal CVRM.[17,18] Moreover, AAA patients could be relatively resistant to traditional CVRM, as risk factors for AAA disease are different from traditional (atherosclerotic) cardiovascular risk factors.[19] The unchanged excess mortality could reflect the dominant role of smoking in AAA patients compared to the general population (**Supplemental Table 5**). Yet, prior research showed that the impact of smoking is minimal on disease-specific excess mortality for diseases highly associated with excessive smoking.[20] Alternatively, although the effectiveness of CVRM on non-fatal cardiovascular events has been firmly established, an effect on survival is unclear, as literature shows heterogenous results on the effect of cardiovascular medication of life-expectancy.[21,22]

This study showed a worrisome persistently high excess mortality for women. While inferior survival outcomes for women have been outlined previously, the basis for this sex-disparity remains unclear.[23,24,25] This study indicates that the disparity is not explained by a higher age of women at time of repair, as there were no significant survival differences between age categories. Alternative explanations include a higher allostatic load or comorbidity profile of women.[26] However, results of this study portray equal CCI scores for men and women, with an even lower effect size of CCI scores on survival in women (**Supplemental Table 4**). This is supported by a meta-analysis reporting fewer baseline comorbidities for women.[27] The high cardiovascular mortality of women, which persists for a longer time after surgery, point to the involvement of cardiovascular risk factors in the excess mortality for women. In this context, poorer profiles of female AAA patients are worrisome and suggest that women receive suboptimal treatment for their cardiovascular risk. This appears a general phenomenon because women, even when correctly diagnosed, are often undertreated for their cardiovascular risk factors.[28] Lastly, in contrast to men, the absence of a decline in tobacco use in women could explain the sex-dependent survival differences.[29]

Our data for the Dutch population confirm and extent Swedish population data, which showed a persistent impaired survival of AAA patients who underwent elective repair (**Supplemental Figure 3**).[2] This conclusion contrast with a recent Danish study, reporting a decrease in overall mortality and cardiovascular risk in patients diagnosed with AAA over time.[4] There are several explanations for this apparent discrepancy. First, the Danish study describes a heterogenous incomparable patient population that included both patients with either intact AAA or ruptured AAA, without mentioning surgery. Moreover, the follow-up in the Danish study was limited to 2 years, and therefore the improved survival of the Danish study population presumably reflects the improvements in short-term survival observed in the current study. Given the comparable excess mortality rates observed in both the Dutch and Swedish cohorts, it is unlikely that the persistently high excess-mortality reflects a national phenomenon.

Strengths and limitations

The first strength of this study is that is relies on a large nationwide registry, with a high reported validity (84–99%) and covers an extensive period of 25 years. A second strength is the fact that both the introduction of EVAR and CVRM occurred in well-defined timeframes. This facilitated our time-trend analysis. Availability of data from 1995 to 2017 allowed for comparison of a period with almost no EVAR and CVRM, with a period of EVAR-first strategy and extensive CVRM. Application of relative survival analyses allowed to estimate disease-specific excess mortality while accounting for the changes in patient characteristics over time (i.e. more female and older patients). As result of an ageing population and lower intervention threshold, a growing number of elderly patients is, and will be, considered eligible for AAA repair.[3] Age-differences exert important effects on survival comparisons, but are often not considered in (traditional) survival analysis. Older patients have a higher a priori risk of death. Therefore, comparing overall crude survival differences between younger and older patients introduces bias (immortal time bias).[30] Relative survival analysis, which corrects for age-differences in (a priori) life-expectancy, overcomes this. Furthermore, to the best of our knowledge, this is the first study to apply a competing risk analysis for cardiovascular mortality in AAA patients. As opposed to traditional survival analysis, competing risk analysis addresses the competitive nature of multiple causes to the same event. This study has some limitations inherent to the retrospective design and the use of registry data such as the quality of coding.[31,32] The use of general procedural codes prohibited a distinction between EVAR and open repair. However, long-term survival rates are reported to be similar for EVAR and open repair, and were not the focus of this study.[2,33] Cause of death registration is prone to bias and misclassification, hence interpretation of specific causes of death requires caution. Analyses of main categories of causes of death are less prone to misclassification. This study aimed to address time-dependent differences and it is unlikely that there are differences/bias in cause of death registration over time. Furthermore, stratification of results inevitably leads to a restricted number of patients and therefore larger 95% confidence intervals. This hampers the detection of more subtle differences in women. Lastly, while we were unable to demonstrate a benefit of CVRM on cardiovascular death, a potential benefit of CVRM on non-fatal cardiovascular events (prevention or postponement of myocardial infarction or stroke), was considered beyond the scope of this study.

CONCLUSION

Although improvements in surgical care resulted in a significantly lower short-term mortality and broadened the spectrum of patients eligible for repair, AAA patients, especially women, retain a high long-term excess mortality risk. Despite the intensification of CVRM, the cardiovascular mortality risk remains the primary cause of death. The persistently high excess mortality appears largely independent of changes in patient selection. Future studies should focus on high sex-dependent excess mortality, and strategies to reduce accompanied comorbidity risks.

REFERENCES

1. Bulder RMA, Bastiaannet E, Hamming JF, et al. Meta-analysis of long-term survival after elective endovascular or open repair of abdominal aortic aneurysm. Br J Surg. 2019;106:523-533.
2. Bulder RMA, Talvitie M, Bastiaannet E, et al. Long-term Prognosis After Elective Abdominal Aortic Aneurysm Repair is Poor in Women and Men: The Challenges Remain. Ann Surg. 2020;272:773-778.
3. Pleumeekers HJ, Hoes AW, van der Does E, et al. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol. 1995;142:1291-1299.
4. Nicolajsen CW, Søgaard M, Eldrup N, et al. Temporal trends in abdominal aortic aneurysmal disease: a nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy. Eur J Prev Cardiol. 2022;29:1957-1964.
5. Trenner M, Haller B, Storck M, et al. Trends in Patient Safety of Intact Abdominal Aortic Aneurysm Repair: German Registry Data on 36,594 Procedures. Eur J Vasc Endovasc Surg. 2017;53:641-647.
6. Central Bureau of Statistics. Microdata: zelf onderzoek doen [in Dutch]. https://www.cbs.nl/nl-nl/onze-diensten/maatwerk-en-microdata/microdata-zelf-onderzoek-doen
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.
8. Mackenbach JP, Van Duyne WM, Kelson MC. Certification and coding of two underlying causes of death in The Netherlands and other countries of the European Community. J Epidemiol Community Health. 1984;41:156-160.
9. Prinssen M, Buskens E, Blankensteijn J. The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial. Background, design and methods. The Journal of cardiovascular surgery. 2002;43:379-84.
10. Gezondheidsraad. Bevolkingsonderzoek naar aneurysma van de abdominal aorta (AAA) [in Dutch]. 2019. Available at: file:///Users/ruthbulder/Downloads/kernadvies+Bevolkingsonderzoek+naar+aneurysma+van+de+abdominale+aorta+AAA.pdf (data downloaded on [15-03-2021])
11. Dutch Surgical Aneurysm Audit database. Data available for 2013 – 2019.
12. Rutherford MJ, Dickman PW, Lambert PC. Comparison of methods for calculating relative survival in population-based studies. Cancer Epidemiol. 2012;36:16-21.
13. Human Mortality Database. University of California BU, and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on [06-09-2022]).
14. de Glas NA, Kiderlen M, Vandenbroucke JP, de Craen AJ, Portielje JE, van de Velde CJ, Liefers GJ, Bastiaannet E, Le Cessie S. Performing Survival Analyses in the Presence of Competing Risks: A Clinical Example in Older Breast Cancer Patients. J Natl Cancer Inst. 2015;108:djv366.
15. Dinmohamed AG, Lemmens VEPP, de Hingh IHJT, et al. Relative survival in early-stage cancers in the Netherlands: a population-based study. J Hematol Oncol. 2020;13:49-52.
16. Goodney PP, Tavris D, Lucas FL, et al. Causes of late mortality after endovascular and open surgical repair of infrarenal abdominal aortic aneurysms. J Vasc Surg. 2010;51:1340-1347.
17. Robertson L, Atallah E, Stansby G. Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm. Cochrane Database Syst Rev. 2017;1:CD010447.
18. Bath MF, Gokani VJ, Sidloff DA, et al. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015;102:866-872.

19. Raffort J, Lareyre F, Clément M, et al. Diabetes and aortic aneurysm: current state of the art. Cardiovasc Res. 2018;114:1702-1713.
20. Ellis L, Coleman MP, Rachet B. The impact of life tables adjusted for smoking on the socio-economic difference in net survival for laryngeal and lung cancer. Br J Cancer 2014;111:195–202.
21. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A, Braunwald E, Giugliano RP, Sabatine MS. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2020 Nov 21;396(10263):1637-1643.
22. Risum Ø, Sandven I, Sundhagen JO, Abdelnoor M. Editor's Choice - Effect of Statins on Total Mortality in Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2021 Jan;61(1):114-120.
23. Pouncey AL, Powell JT. Womens lives at stake: Women Suffer Disproportionately After Abdominal Aortic Aneurysm Repair, So What Can We Do About It? Eur J Vasc Endovasc Surg. 2021;62:1-3.
24. Pouncey AL, David M, Morris RI, et al. Editor's Choice - Systematic Review and Meta-Analysis of Sex Specific Differences in Adverse Events After Open and Endovascular Intact Abdominal Aortic Aneurysm Repair: Consistently Worse Outcomes for Women. Eur J Vasc Endovasc Surg. 2021;62:367-378.
25. Talvitie M, Stenman M, Roy J, et al. Sex Differences in Rupture Risk and Mortality in Untreated Patients With Intact Abdominal Aortic Aneurysms. J Am Heart Assoc. 2021;10:e019592.
26. Hultgren R, Larsson E, Wahlgren CM, et al. Female and elderly abdominal aortic aneurysm patients more commonly have concurrent thoracic aortic aneurysm. Ann Vasc Surg. 2012;26:918-923.
27. Tedjawirja VN, de Wit MCJ, Balm R, et al. Differences in Comorbidities Between Women and Men Treated with Elective Repair for Abdominal Aortic Aneurysms: A Systematic Review and Meta-Analysis. Ann Vasc Surg. 2021;76:330-341.
28. Driscoll A, Beauchamp A, Lyubomirsky G, et al. Suboptimal management of cardiovascular risk factors in coronary heart disease patients in primary care occurs particularly in women. Intern Med J. 2011;41:730-736.
29. Nelissen BG, Herwaarden JA, Pasterkamp G, et al. Shifting abdominal aortic aneurysm mortality trends in The Netherlands. J Vasc Surg. 2015;61:642-647.
30. Pilleron S, Maringe C, Morris EJA, et al. Immortal time bias in older vs younger age groups: a simulation study with application to a population-based cohort of patients with colon cancer. MedRxiv. 2022.
31. Paas GR, Veenhuizen KC. Research on the Validity of the LMR [in Dutch]. Utrecht, The Netherlands: Prismant; 2022.
32. De Bruin A, Kardaun JWPF, Gast A, et. al. Record linkage of hospital discharge register with population register: Experiences at Statistics Netherlands. Stat J UN Econ Comm Eur. 2004;21:23-32.

SUPPLEMENTAL MATERIAL

Supplemental Appendix 1. Detailed description of methods

Data sources

Data was obtained from national Dutch registries which were accessed through Statistics Netherlands: the Population Register (PR), Hospital Discharge Register (HDR), Medication Register (MR), and Cause of Death Register (CDR).[1] The PR contains baseline data of all residents in the Netherlands. The HDR contains data on hospitalisations, including admission- and discharge dates, diagnosis, and (surgical) procedures. The MR includes data of medication prescribed in hospitals and dispensed from outpatient or community pharmacies or in care homes. The CDR registers date of death, and causes of death based on death certificates.[2]

All registers include an individual person- and admission- specific identification number assigned to each resident in the Netherlands, which allows data merging on individual patient level from the different registries.

Data governance

All linkages and analyses were performed in a secured data environment of Statistics Netherlands. The data handling was completely anonymized, and in full agreement with privacy legislation in the Netherlands. According to the Dutch law, approval from an independent ethics committee is not required for registry-based studies in which specific individuals cannot be identified. This study was conducted according to the STROBE guidelines for reporting of observational cohort studies in epidemiology.[3]

Patient population

All patients who underwent elective abdominal aortic aneurysm repair between 1995 and 2017 were identified through the Hospital Discharge Register (HDR). Patients were included with a first registered hospitalization with a primary diagnosis of intact AAA (ICD-9: 441E or ICD10: I174) and subsequent AAA repair (CCV/CBV/ZA codes: **Supplemental Table 1**). Patients with a diagnosis of ruptured AAA (ICD-9: 441D or ICD10: I173) or no procedural code were excluded. Comorbidities included all diagnosis (ICD-9 and ICD-10) registered during the same hospital admission as AAA repair. The comorbidity burden was estimated through the Charlson Comorbidity Index (CCI). The CCI is a weighted score of comorbidities ranging from 0 (no comorbidities) to 6 (extensive comorbidities).[4,5,6] Before 2005 and after 2014 registration in the HDR was mandatory, but voluntary for the 2005-2013 interval. As result, the number of participating hospitals in the HDR transiently declined between 2005-2014. The estimated proportion of missing cases carried from 5 to 25 per cent between 2005-2014. Missing cases are considered missing at random, and are therefore not likely to influence results. In 2012 there was a transition in registrations, as such there is no data available for this year.

Prescriptions for cardiovascular risk management were extracted from the MR based on ATC4 codes (**Supplemental Table 1**). To ensure that prescriptions represented secondary CVRM prescriptions, data was extracted one year prior to the elective repair.

Mortality data was obtained from the CDR until 31 December 2018.

Time-trends

Three predefined time periods, each reflecting clear contrasts in procedural and CVRM characteristics were created. A first period (1: 1995-2000), dominated by open repair and rudimentary pharmaceutical CVRM; a second period (2: 2001-2011), reflecting the transition from open repair to EVAR and progressive implementation of CVRM; and a third period (3: 2013-2017), with an EVAR-first strategy and full implementation of CVRM. Up to 1994 no EVARs were performed in the Netherlands. From 1995 to 2017 the proportion of EVAR gradually increased from 1.2% to 80%.[7,8,9] The proportion of CVRM significantly increased from 2006 until 2017 (P = 0.000). The proportion of patients with at least one CVRM prescription increased: statins from 24.8%-69.6% and 26.3%-66.9%, antihypertensive from 29.5%-73.7% and 34.3%-78.0%, and antiplatelets from 26.5%-71.3% and 25.6%-69.4%, for men and women respectively.

Outcomes: relative survival and competing risks of death

The primary outcomes included time-trends in 1- 3- 5- and 10- year(s) relative survival rate(s). Relative survival, rather than crude survival, was chosen to 1) evaluate the disease-specific mortality, and 2) to adjust for sex-, age and time-dependent differences in life-expectancy.[10,11]

While relative survival provides an estimate of disease-specific survival, and corrects for changes in demographics, it is a relative measure with the absolute impact being determined by the disease-specific *and* population (background) mortality. As a more tangible illustration of the disease-specific mortality remaining after successful AAA repair, Supplemental Table 2 was included to summarize the actual observed and expected 5-years mortality, as well as the excess mortality rates.

Secondary outcomes included time-trends in cause of death distribution and a competing risk analysis for cardiovascular versus non-cardiovascular death. Causes of death were determined based on ICD-9 and ICD-10 codes (Supplemental Table 1). A competing risk-of-death analysis was performed in order to estimate the risk of cardiovascular death (CV) in the presence of non-CV death.[12] This aspect was considered relevant since changes in intensity of CVRM potentially altered the cardiovascular mortality risk. Hypothetically, implementation of CVRM could lead to a decrease of the cardiovascular mortality, thereby exposing the patient to other (competing) mortality risks and masking a potential beneficial effect of CVRM on overall mortality.

Sensitivity analysis

To estimate the potential impact of changes in patient frailty on study conclusions, two sensitivity analyses were performed. Firstly, differences between older and younger patients were evaluated. Secondly, a generalized mixed model (GLM) was applied in order to estimate the impact of comorbidities (CCI index) on relative survival.

Statistical analysis

All analyses were performed with SPSS, version 26 (IBM, Amsterdam) and Stata/SE, version 12.0 (StataCorp, College Station, TX, USA). Normality was assessed by histograms. Continuous variables were expressed as means (+SD) or medians (+IQR) and compared using Student's t-test or Mann-Whitney test. Categorical data were expressed as proportions and analysed using the chi-square test. A two-sided p-value of <0.05 was considered statistically significant.

Relative survival was calculated as the ratio of observed survival of the study population (i.e. electively treated AAA patients) and the expected survival of the matched (age, sex, and year of operation) general Dutch population.[11] Population life-tables were used to estimate the expected survival.[13] A relative survival below 100% means that the disease-specific survival is lower than expected for the reference population. The relative excess risk (RER) of death was estimated by a multivariate generalized linear model (GLM) with a Poisson distribution based on collapsed relative survival data on specific survival end-points.

Competing risk analyses were performed by estimating the cumulative incidence of CV death throughout 10 years follow-up with non-CV death as competing risk. Cumulative incidence as percentages with corresponding 95% CIs were reported for 1, 3, 5, and 10 years. Subdistribution hazard ratios were reported with 95% CIs to allow for statistical testing (Fine and Gray models).

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Codes used for data extraction of patient inclusion, cardiovascular prescriptions, and causes of death.

DIAGNOSIS	
ICD-9 codes	
AAA	441E
ICD-10 codes	
AAA	I174
PROCEDURE	
CVV codes	
	883656 883653 539995 539990 539985 539980 539595 539590 539575 539570 538338 538337 538336 538335 538334 538333 538332 538331 538330 31311 31319 31318 31310 3313 539525 31390 538541 31313 883603 538241883606 31380 538090 538540 538090 538540 538541 538244 88368 538242 538040
CBV codes	
	388932A 333556E333556D 333556C 333555B 333555A 333539B 333539BA 333533B 333533A 333532F 333532E 333532D 333532C 333532B 333532A 333530R 333530Q 333530P 333530N 333530M 333530K 333530J 333530H 333530G 333530C 333530A 333154B 333154A 333153Y 333153X 333153R 333153Q 333153M 333153L 388922 385332 380020 333558 333556 333555 333553 333539 333538 333537 333536 333535 333534 333533 333532 190302 080930 033699 033562 033561 033560 033559 033555 033554 033521 033520
ZA codes	
	190302 080930 080822 080821 080823 033562 33561 033560 033559 033558 033557 033556 033555 033554 033521 033520
MEDICATION	
ATC code	
Statins	C10A C10B
Antihypertensive	C02K C02L C02N C03A C03B C03C C03D C03E C03X C07A C07B C07C C07D C07E C07F C08C C08D C08E C08G C09A C09B C09C C09D C09X C04A
Antiplatelets	B01A
CAUSES OF DEATH	
ICD-9 codes	
Cardiovascular	39, 40, 41, 42, 43, 44, 45
Respiratory	46, 47, 48, 49, 50, 51
Digestive	52, 53, 54, 55, 56, 57
Malign neoplasm	14, 15, 16, 17, 19, 20
Renal	58, 59, 60, 61, 62
Nervous system	32, 33, 34, 35, 36, 37, 38
Other	All other
ICD-10 codes	
Cardiovascular	I
Respiratory	J

Supplemental Table 1. Continued

Digestive	K
Malign neoplasm	M
Renal	N
Nervous system	G
Other	All other

Supplemental Table 2. Excess mortality of AAA patients undergoing elective repair between 1995 – 2017, stratified by men (A) and women (B) and age categories.
A

		< 65			**65 - 69**			**70 - 74**			**75 - 79**			**> 80**		
Men		Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
1 year	N	2280	3117	1398	2729	3976	2293	2102	3302	1740	1846	3702	2054	792	2164	1762
	Observed mortality	141	100	44	261	254	96	254	276	108	302	434	156	185	394	192
	Expected mortality	26,2	28,7	12	68,2	78,4	39,7	85,5	106,9	49,5	111,1	187,6	97,2	78,6	196,5	166,3
	Excess mortality (O-E)	114,8	71,3	32	192,8	175,6	56,3	168,5	169,1	58,5	190,9	246,4	58,8	106,4	197,5	25,7
	Excess mortality %	5,04	2,29	2,29	7,06	4,42	2,46	8,02	5,12	3,36	10,34	6,66	2,86	13,43	9,13	1,46
	Excess mortality rate	5,38	3,48	3,67	3,83	3,24	2,42	2,97	2,58	2,18	2,72	2,31	1,60	2,35	2,01	1,15
3 year	N	2073	2959	1060	2364	3579	1674	1743	2863	1175	1421	3057	1386	547	1641	1081
	Observed mortality	62	66	15	93	155	51	107	158	50	101	239	85	55	175	129
	Expected mortality	28,9	32,2	9,5	73,2	83,9	30,4	88,5	113	37,3	111,7	194,3	72,2	75,3	191,4	106,5
	Excess mortality (O-E)	33,1	33,8	5,5	19,8	71,1	20,6	18,5	45	12,7	-10,7	44,7	12,8	-20,3	-16,4	22,5
	Excess mortality %	1,60	1,14	0,52	0,84	1,99	1,23	1,06	1,57	1,08	-0,75	1,46	0,92	-3,71	-1,00	2,08
	Excess mortality rate	2,15	2,05	1,58	1,27	1,85	1,68	1,21	1,40	1,34	0,90	1,23	1,18	0,73	0,91	1,21
5 year	N	1949	2823	447	2150	3253	674	1512	2551	465	1199	2566	495	434	1305	341
	Observed mortality	71	56	8	140	161	26	97	198	26	127	229	26	58	179	39
	Expected mortality	31,5	36	4,1	76,9	90,6	12,2	90,3	119,1	15,1	109,2	195,3	26,6	69,7	178,8	33,2
	Excess mortality (O-E)	39,5	20	3,9	63,1	70,4	13,8	6,7	78,9	10,9	17,8	33,7	-0,6	-11,7	0,2	5,8
	Excess mortality %	2,03	0,71	0,87	2,93	2,16	2,05	0,44	3,09	2,34	1,48	1,31	-0,12	-2,70	0,02	1,70
	Excess mortality rate	2,25	1,56	1,95	1,82	1,78	2,13	1,07	1,66	1,72	1,16	1,17	0,98	0,83	1,00	1,17
10 year	N	1587	2031	-	1524	2051	-	921	1393	-	623	1200	-	191	394	-
	Observed mortality	79	69	-	106	132	-	99	134	-	90	154	-	32	68	-
	Expected mortality	34,9	38,7	-	77	91,9	-	78,6	106,6	-	82,3	139	-	44,2	78,2	-
	Excess mortality (O-E)	44,1	30,3	-	29	40,1	-	20,4	27,4	-	7,7	15	-	-12,2	-10,2	-
	Excess mortality %	2,78	1,49	-	1,90	1,96	-	2,21	1,97	-	1,24	1,25	-	-6,39	-2,59	-
	Excess mortality rate	2,26	1,78	-	1,38	1,44	-	1,26	1,26	-	1,09	1,11	-	0,72	0,87	-

B

Women		< 65			65 - 69			70 - 74			75 - 79			> 80		
		Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
1 year	N	230	331	197	299	498	350	2102	3302	1740	332	659	431	187	451	386
	Observed mortality	15	12	7	33	48	22	254	276	108	57	79	45	50	81	51
	Expected mortality	1,4	1,9	1,1	3,7	5,2	3,5	85,5	106,9	49,5	10,4	19	11,3	11,9	27,4	24
	Excess mortality (O-E)	13,6	10,1	5,9	29,3	42,8	18,5	168,5	169,1	58,5	46,6	60	33,7	38,1	53,6	27
	Excess mortality %	5,91	3,05	2,99	9,80	8,59	5,29	8,02	5,12	3,36	14,04	9,10	7,82	20,37	11,88	6,99
	Excess mortality rate	10,7	6,3	6,4	8,9	9,2	6,3	3,0	2,6	2,2	5,5	4,2	4,0	4,2	3,0	2,1
3 year	N	209	310	143	255	440	235	1743	2863	1175	250	549	290	130	349	242
	Observed mortality	3	7	4	8	23	11	107	158	50	19	39	18	15	23	21
	Expected mortality	1,6	2	0,8	4,1	5,7	2,5	88,5	113	37,3	11,1	20,8	8,7	12,4	29,8	17,1
	Excess mortality (O-E)	1,4	5	3,2	3,9	17,3	8,5	18,5	45	12,7	7,9	18,2	9,3	2,6	-6,8	3,9
	Excess mortality %	0,67	1,61	2,24	1,53	3,93	3,62	1,06	1,57	1,08	3,16	3,32	3,21	2,00	-1,95	1,61
	Excess mortality rate	1,88	3,50	5,00	1,95	4,04	4,40	1,21	1,40	1,34	1,71	1,88	2,07	1,21	0,77	1,23
5 year	N	194	289	62	237	393	75	1512	2551	465	213	465	104	112	290	77
	Observed mortality	7	17	0	18	20	1	97	198	26	19	48	11	15	36	8
	Expected mortality	1,7	2,1	0,3	4,5	6,1	0,9	90,3	119,1	15,1	11,9	21,8	3,3	13,2	30,1	5,5
	Excess mortality (O-E)	5,3	14,9	-0,3	13,5	13,9	0,1	6,7	78,9	10,9	7,1	26,2	7,7	1,8	5,9	2,5
	Excess mortality %	2,73	5,16	-0,48	5,70	3,54	0,13	0,44	3,09	2,34	3,33	5,63	7,40	1,61	2,03	3,25
	Excess mortality rate	4,12	8,10	0,00	4,00	3,28	1,11	1,07	1,66	1,72	1,60	2,20	3,33	1,14	1,20	1,45
10 year	N	151	189	-	157	232	-	921	1393	-	130	205	-	47	93	-
	Observed mortality	9	8	-	17	24	-	99	134	-	20	26	-	6	22	-
	Expected mortality	1,8	2,1	-	4,5	5,6	-	78,6	106,6	-	11,9	16,8	-	8,7	13,8	-
	Excess mortality (O-E)	7,2	5,9	-	12,5	18,4	-	20,4	27,4	-	8,1	9,2	-	-2,7	8,2	-
	Excess mortality %	4,77	3,12	-	7,96	7,93	-	2,21	1,97	-	6,23	4,49	-	-5,74	8,82	-
	Excess mortality rate	5,00	3,81	-	3,78	4,29	-	1,26	1,26	-	1,68	1,55	-	0,69	1,59	-

Supplemental Table 3. Cumulative incidence of cardiovascular death, with non-cardiovascular death as competing risk, per period. Stratified by age. A: men B: women.

A

	Period 1 (1995 – 2000)	**Period 2** (2001 – 2011)	**Period 3** (2012 – 2017)
All			
1 year	6.09 (5.84 – 6.34)	6.09 (5.84 – 6.34)	6.09 (5.85 – 6.35)
3 years	9.49 (9.18 – 9.80)	9.49 (9.18 – 9.80)	9.50 (9.19 – 9.81)
5 years	13.02 (12.70 – 13.43)	13.06 (12.69 – 13.43)	13.10 (12.73 – 13.47)
10 years	22.14 (21.66 – 22.62)	22.13 (21.65 – 22.62)	-
< 65 years			
1 year	6.07 (5.82 – 6.32)	6.13 (5.88 – 6.38)	6.08 (5.84 – 6.34)
3 years	9.47 (9.16 – 9.78)	9.41 (9.10 – 9.72)	9.45 (9.14 – 9.76)
5 years	13.01 (12.65 – 13.38)	13.11 (12.75 – 13.48)	-
10 years	22.14 (21.66 – 22.62)	22.21 (21.73 – 22.70)	-
65 - 69 years			
1 year	6.11 (5.86 – 6.36)	6.08 (5.84 – 6.34)	6.06 (5.81 – 6.31)
3 years	9.52 (9.22 – 9.84)	9.49 (9.18 – 9.80)	9.43 (9.12 – 9.74)
5 years	13.05 (12.69 – 13.42)	13.05 (12.69 – 13.42)	-
10 years	22.17 (21.69 – 22.66)	22.13 (21.65 – 22.62)	-
70 - 74 years			
1 year	6.08 (5.83 – 6.33)	6.13 (5.89 – 6.39)	6.10 (5.85 – 6.35)
3 years	9.49 (9.18 – 9.80)	9.48 (9.17 – 9.79)	9.82 (9.51 – 10.14)
5 years	13.06 (12.70 – 13.43)	13.06 (12.69 – 13.42)	-
10 years	22.14 (21.66 – 22.63)	22.16 (21.68 – 22.64)	-
75 – 79 years			
1 year	6.09 (5.84 – 6.34)	6.08 (5.83 – 6.33)	6.05 (5.81 – 6.30)
3 years	9.51 (9.20 – 9.82)	9.49 (9.18 – 9.80)	9.55 (9.24 – 9.86)
5 years	13.06 (12.70 – 13.43)	13.08 (12.72 – 13.45)	-
10 years	22.11 (21.63 – 22.60)	22.12 (21.64 – 22.61)	-
> 80 years			
1 year	6.15 (5.91 – 6.41)	6.09 (5.84 – 6.34)	6.09 (5.85 – 6.35)
3 years	9.51 (9.20 – 9.82)	9.50 (9.20 – 9.81)	9.50 (9.19 – 9.81)
5 years	13.05 (12.69 – 13.42)	13.10 (12.73 – 13.47)	-
10 years	22.12 (21.64 – 22.61)	22.30 (21.82 – 22.79)	-

B

	Period 1 (1995 – 2000)	**Period 2** (2001 – 2011)	**Period 3** (2012 – 2017)
All			
1 year	8.24 (7.53 – 8.99)	8.19 (7.48 – 8.93)	8.17 (7.46 – 8.91)
3 years	12.49 (11.62 – 13.40)	12.45 (11.58 – 13.35)	12.47 (11.60 – 13.37)
5 years	17.14 (16.10 – 18.21)	17.22 (16.18 – 18.28)	16.86 (15.84 – 17.92)
10 years	28.01 (26.67 – 29.38)	27.99 (26.64 – 29.34)	-
< 65 years			
1 year	8.06 (7.36 – 8.80)	8.84 (8.10 – 9.60)	9.46 (8.70 – 10.25)
3 years	12.30 (11.43 – 13.20)	12.66 (11.78 – 13.58)	11.56 (10.72 – 12.43)
5 years	16.48 (15.46 – 17.52)	16.21 (15.20 – 17.24)	-
10 years	28.02 (26.67 – 29.38)	28.30 (26.95 – 29.67)	-
65 - 69 years			
1 year	8.55 (7.83 – 9.31)	8.20 (7.50 – 8.95)	8.50 (7.78 – 9.26)
3 years	12.60 (11.72 – 13.51)	12.34 (11.47 – 13.24)	12.10 (11.25 – 13.00)
5 years	17.04 (16.01 – 18.10)	16.89 (15.86 – 17.95)	-
10 years	28.71 (27.35 – 30.09)	27.92 (26.58 – 29.28)	-
70 - 74 years			
1 year	8.41 (7.69 – 9.16)	8.26 (7.55 – 9.01)	9.38 (8.63 – 10.17)
3 years	12.60 (11.72 – 13.51)	12.45 (11.58 – 13.35)	12.47 (11.60 – 13.37)
5 years	17.07 (16.03 – 18.13)	17.24 (16.20 – 18.31)	-
10 years	28.14 (26.79 – 29.50)	27.95 (26.61 – 29.31)	-
75 – 79 years			
1 year	8.24 (7.53 – 8.99)	8.22 (7.51 – 8.97)	8.17 (7.46 – 8.91)
3 years	12.49 (11.62 – 13.40)	12.64 (11.76 – 13.55)	12.68 (11.80 – 13.60)
5 years	16.94 (15.91 – 18.00)	17.22 (16.18 – 18.28)	-
10 years	28.36 (27.01 – 29.73)	27.99 (26.64 – 29.34)	-
> 80 years			
1 year	7.93 (7.23 – 8.66)	8.19 (7.48 – 8.93)	8.41 (7.69 – 9.16)
3 years	12.43 (11.55 – 13.33)	12.53 (11.66 – 13.44)	12.53 (11.66 – 13.44)
5 years	17.14 (16.10 – 18.21)	17.27 (16.22 – 18.33)	-
10 years	28.39 (27.04 – 29.76)	27.67 (26.33 – 29.02)	-

Supplemental Table 4. Generalized mixed model. Effect of Charlson Comorbidity Index (CCI) on relative survival.

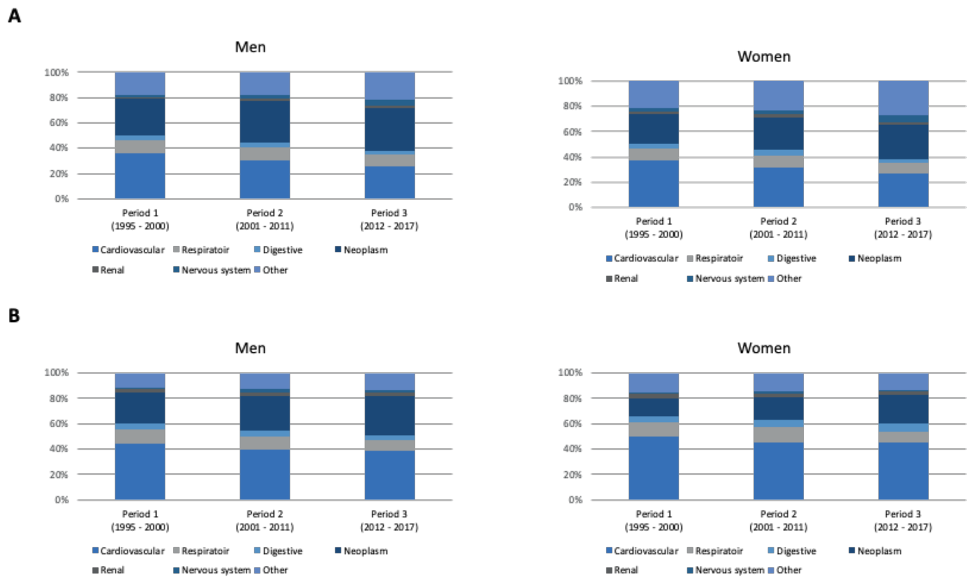
	CCI 1	CCI 2	CCI > 3
Men			
<65	1.43 (1.17 – 1.76)	2.75 (2.15 – 3.52)	5.55 (4.34 – 7.10)
65 – 70	1.52 (1.24 – 1.85)	2.68 (2.13 – 3.38)	6.07 (4.93 – 7.47)
71 – 74	1.99 (1.53 – 2.59)	3.55 (2.68 – 4.71)	5.45 (4.16 – 7.16)
75 – 79	2.82 (1.93 – 4.12)	5.67 (3.84 – 8.37)	11.81 (8.16 – 17.09)
> 80	5.61 (2.46 – 12.78)	11.05 (4.79 – 25.48)	23.39 (10.31 – 53.05)
Women			
< 65	1.19 (0.82 – 1.74)	1.93 (1.11 – 3.33)	5.16 (3.08 – 8.64)
65 – 70	1.16 (0.86 – 1.59)	2.01 (1.39 – 2.90)	4.92 (3.45 – 7.00)
71 – 74	1.38 (1.01 – 1.89)	2.52 (1.73 – 3.67)	2.71 (1.79 – 4.10)
75 – 79	1.67 (1.18 – 2.37)	2.35 (1.53 – 3.61)	5.08 (3.41 – 7.57)
> 80	2.73 (1.45 – 5.13)	4.14 (2.06 – 8.32)	8.63 (4.54 – 16.39)

Odds ratio (OR) with 95% CIs. CCI 0 is reference.

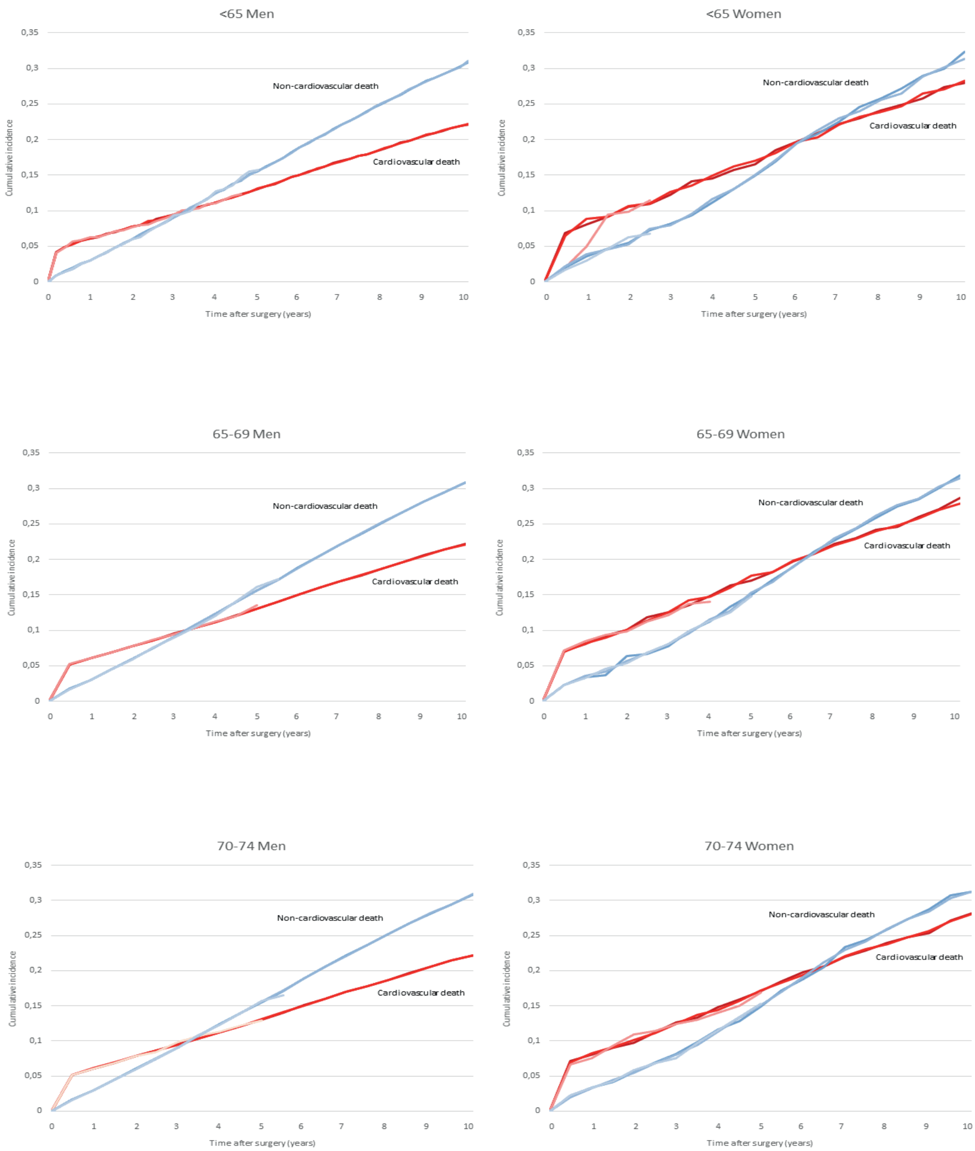
Supplemental Table 5. Smoking habits of the general population in the Netherlands between 1995 – 2017.

Year	Proportion of smokers
1995	35.9
1996	36.0
1997	35.8
1998	34.7
1999	34.0
2000	32.7
2001	34.7
2002	33.7
2003	32.2
2004	31.1
2005	31.1
2006	31.1
2007	29.3
2008	29.0
2009	28.4
2010	26.8
2011	26.8
2012	24.4
2013	24.4
2014	25.4
2015	26.0

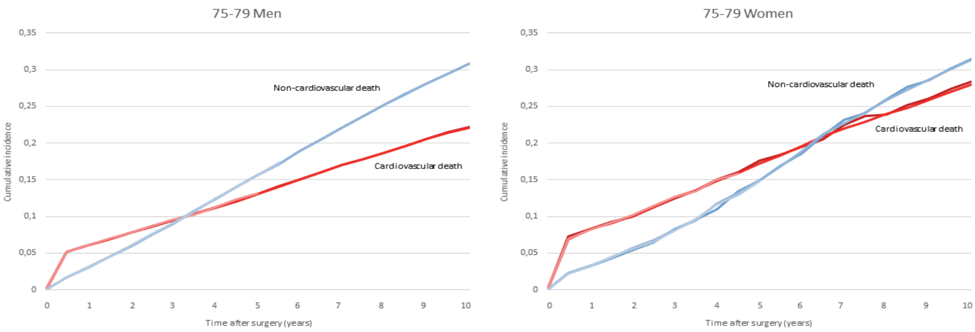
Statline data for the general Dutch population.[14] Data for the AAA population was not available.



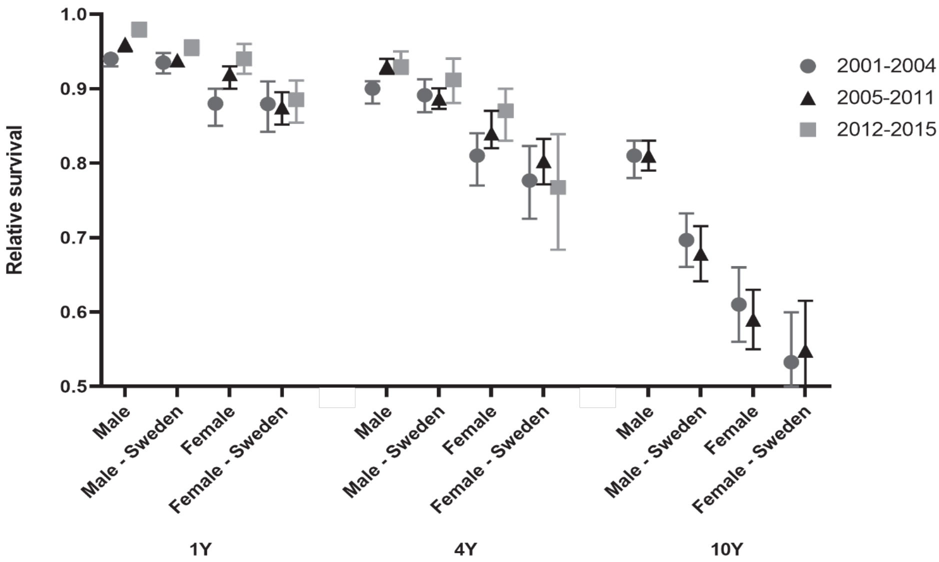
Supplemental Figure 1. Cause of death distribution between 1995 – 2017 of AAA patients (A) versus the general population (B) by sex.



Supplemental Figure 2. Cumulative incidence of cardiovascular versus non-cardiovascular mortality over time (1995 – 2017) stratified by sex and age.



Supplemental Figure 2. Continued



Supplemental Figure 3. Comparison between Dutch and Swedish population of Relative survival (RS) of patients after elective AAA repair between 2001 – 2015 by male and female at 1, 4, and 10 years.

REFERENCES

1. Central Bureau of Statistics. Microdata: zelf onderzoek doen [in Dutch]. https://www.cbs.nl/nl-nl/onze-diensten/maatwerk-en-microdata/microdata-zelf-onderzoek-doen
2. Mackenbach JP, Van Duyne WM, Kelson MC. Certification and coding of two underlying causes of death in The Netherlands and other countries of the European Community. J Epidemiol Community Health. 1987;41:156-160.
3. von Elm E, Altman DG, Egger M, et. al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453-1457.
4. Charlson ME, Pompei P, Ales KL, et. al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.
5. Quan H, Li B, Couris CM, et. al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676-682.
6. Radovanovic D, Seifert B, Urban P, et. al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. Heart. 2014;100:288-294.
7. Prinssen M, Buskens E, Blankensteijn J. The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial. Background, design and methods. The Journal of cardiovascular surgery. 2002;43:379-84.
8. Gezondheidsraad. Bevolkingsonderzoek naar aneurysma van de abdominal aorta (AAA) [in Dutch]. 2019. Available at: file:///Users/ruthbulder/Downloads/kernadvies+Bevolkingsonderzoek +naar+aneurysma+van+de+abdominale+aorta+AAA.pdf (data downloaded on [15-03-2021])
9. Dutch Surgical Aneurysm Audit database. Data available for 2013 – 2019.
10. Bastiaannet E, Liefers GJ, de Craen AJ, et. al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat. 2010;124:801-807.
11. Rutherford MJ, Dickman PW, Lambert PC. Comparison of methods for calculating relative survival in population-based studies. Cancer Epidemiol. 2012;36:16-21.
12. de Glas NA, Kiderlen M, Vandenbroucke JP, et. al. Performing Survival Analyses in the Presence of Competing Risks: A Clinical Example in Older Breast Cancer Patients. J Natl Cancer Inst. 2015;108:djv366.
13. Human Mortality Database. University of California BU, and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on [06-09-2022]).
14. Statline. Gezondheid, leefstijl, zorggebruik en -aanbod, doodsoorzaken; vanaf 1900 [in Dutch]. Available at https://opendata.cbs.nl/#/CBS/nl/dataset/37852/table?searchKeywords=stoppen%20met%20roken (data downloaded on [24-04-2023]).

Chapter 5

Hypothesis of the high mortality of female patients following elective open abdominal aortic aneurysm repair

Ruth M.A. Bulder
Victoria N. Tedjawirja
Jaap F. Hamming
Mark J. Koelemay
Ron Balm
Jan H.N. Lindeman
Study group collaborators

European Journal of Vascular and Endovascular Surgery 2022

ABSRACT

Background

The excess mortality of female patients after elective abdominal aortic aneurysm (AAA) repair in part relates to the short-term mortality of open repair (30-days mortality: 8.0% vs. 4.0% in males). This high mortality after open repair has far reaching consequences because female patients are at higher risk to undergo open repair due to a higher rate of unsuitability for EVAR. An explanation for the high excess procedural mortality for women after elective open repair is missing. This study evaluates the cause of female-sex associated mortality of elective open aneurysm repair.

Methods

This nationwide evaluation based on the Dutch Surgical Aneurysm Audit (DSAA) and an in-dept evaluation of patient records between 2013-2019 identified all patients who were registered in the DSAA as a female patient who died within 30-days or in-hospital following elective open AAA repair (n = 48). After identification of cases local hospitals were contacted to provide detailed information concerning each case.

Results

In total 36 female patients with a median age of 75 (IQR: 71-78) years were included. The median aneurysm diameter at time of repair was 55 (51-63) mm. Most patients had an infrarenal aneurysm (58%). The other cases were juxtarenal (39%) or suprarenal (3%). Main cause of death was intestinal ischemia (44%). Other causes included myocardial infarction (17%), trombo-embolic events (8%), and iatrogenic injuries (6%). Aneurysm diameter and age were similar for surviving and deceased female patients.

Conclusion

This nationwide explorative analysis characterizes intestinal ischemia as the main contributor to the excess mortality after elective open aneurysm repair in women. This conclusion calls for the evaluation of strategies aimed at minimizing the risk of postoperative intestinal ischemia.

INTRODUCTION

Abdominal aortic aneurysm (AAA) disease is associated with a clear sex disparity with worse short- and long-term mortality in women.[1,2] The high short-term mortality essentially relates to a high mortality following elective open repair as the mortality rates for endovascular aneurysm repair (EVAR) are lower.[1,3] Because female patients are often considered non-eligible for EVAR, they are more likely to undergo open repair. To date, insight into the high procedural morality rate after open repair is missing. This exploratory, nationwide study evaluated the causes of death for all women who died following elective open repair.

METHODS

The study was approved by the Leiden University Medical Centre ethics committee (G18.123) and participating centres, and was performed according to the STROBE guidelines.

This retrospective evaluation included all women who died within 30days/inhospital following primary elective open AAA repair in The Netherlands (2013-2019). Patients were identified through the Dutch Surgical Aneurysm Audit (DSAA) (https://dica.nl/dsaa/home).

Because data registration, including causes of death, is limited in the DSAA, patients records were all re-evaluated in order to obtain detailed information. Two researchers (R.B., V.T.) extracted data using a prespecified data extraction form (available upon request). Causes of death were centrally re-evaluated by senior clinicians. Analyses were performed with Stata/SE, version 12.0 (StataCorp, College Station, TX). Student's t test and the Mann-Whitney U rank test were applied for parametric or non-parametric data, and chi-squared or the Fisher exact test for categorical data. A p value < 0.05 was considered statistically significant.

RESULTS

Thirty-six women with a median age of 75 (interquartile range [IQR] 71 - 78) years were identified. Patients had an infrarenal (58%), juxtarenal (39%), or suprarenal (3%) aneurysm. Median repair diameter was 55 (IQR 51 - 63) mm (**Table 1**). Reference data for the full Dutch elective repair cohort are provided at https://dica.nl/dsaa/home. Age and aneurysm diameter were similar for surviving and deceased female patients. Women were older, repaired at smaller diameters, and more frequently required suprarenal clamping than men. There were no differences in aneurysm location.

The median time to death was seven (IQR 2 - 11) days. The main cause of death was intestinal ischaemia (44%). The diagnosis of intestinal ischaemia was based on laparotomy (n=9), colonoscopy (n=2), autopsy (n=2), computed tomography (n=2), or clinical presentation (n=1). Intestinal ischaemia mainly presented in the left colon (63%). Apart from higher intra-operative blood loss (P=0.027) in patients with intestinal ischaemia, patient or procedural characteristics were similar for deceased patients with and without intestinal ischaemia (**Table 1**).

Table 1. Characteristics of female patients who died postoperatively after elective open AAA repair, with subgroup analysis of female patients who with and without intestinal ischemia.

	All patients (n = 36)	Intestinal ischemia - (n = 20)	Intestinal ischemia + (n = 16)	*p* [a]
Age, median (IQR), years	75 (71 – 78)	72 (71 – 78)	75 (71 – 78)	0.78
Comorbidities, No (%)				
Myocardial infarction	11 (31)	6 (30)	5 (31)	>0.99
PAD	9 (25)	3 (15)	6 (38)	0.15
Stroke	4 (11)	3 (15)	1 (6)	0.61
COPD	18 (50)	11 (55)	7 (44)	0.74
Diabetes mellitus	5 (14)	3 (15)	2 (13)	>0.99
Smoker, No (%)	18 (50)	13 (65)	5 (31)	0.09
Location AAA, No (%) Infrarenal – Juxtarenal – suprarenal	21 (58) - 14 (39) - 1 (3)	12 (60) - 7 (35) - 1 (5)	9 (57) - 7 (44) - 0 (0)	
Diameter AAA, median (IQR), mm	55 (51 – 63)	56 (51 – 61)	55 (52 – 61)	0.74
Type of graft (bifurcated), No (%)	13 (36)	8 (40)	5 (31)	0.73
Duration of surgery, median (IQR), min	222 (181 – 256)	222 (190 – 249)	221 (172 – 285)	0.90
Duration of proximal clamping, median (IQR), min	43 (32 – 78)	42 (32 – 75)	52 (31 – 100)	0.77
Proximal clamping place, No (%) Infrarenal – suprarenal	18 (50) - 18 (50)	10 (50) - 10 (50)	8 (50) - 8 (50)	>0.99
Blood loss, median (IQR), cc	2000 (1400 – 3000)	1500 (1300 – 2200)	2650 (2150 – 4615)	0.03
Cause of death, No (%)				
Intestinal ischemia	16 (44)	-	-	
Myocardial infarction	6 (17)	-	-	
Trombo-embolic event	3 (8)	-	-	
Iatrogenic injury	4 (6)	-	-	

* Other causes of death included: pneumonia (3%), acute tubular necrosis (3%), limb ischemia (3%), cardiogenic shock (3%), massive bleeding (3%), encephalopathy (3%), cardiac asthma (3%), not able to ween (3%), occlusion of prothesis (3%). Median time between primary repair and death was 7 days (IQR: 2 – 11).

[a] P value indicates differences between patients with and without intestinal ischemia.

DISCUSSION

This exploratory study identifies intestinal ischaemia as the main contributor to cause of death (44%) in women dying after elective open AAA repair. This observation aligns with earlier reports identifying female sex as an independent risk factor for intestinal ischaemia after elective open repair.[5]

Currently, there is no definite explanation for the high incidence of intestinal ischaemia in women, and for its association with open repair. Possible hypotheses include patient selection, procedural aspects, and anatomical differences.[1] By virtue of the limitations of EVAR, open repair is performed in a selection of patients with more complex anatomy.[4] Additionally, smaller vessel diameters and a higher incidence of suprarenal clamping may predispose women to (intestinal) hypoperfusion during open repair.[4] A further aspect is the female predisposition for chronic mesenteric ischaemia, and their presumed less adequate mesenteric collateral network.[5] Consequently, it could be argued that ligation of the inferior mesenteric artery (IMA) during open repair is less adequately compensated for in women.[5] However, this hypothesis is challenged by registry data showing absent excess short term mortality following EVAR, a procedure during which the IMA is also occluded.[3] This absent excess mortality contrasts with conclusions from a recent meta-analysis, a disparity possibly reflecting use of more contemporary data.[2] Consequently, the cause(s) of intestinal ischaemia is/are probably multifactorial and more complex. Aspects to consider include sex specific differences in the microvasculature, with increased incidences of non-obstructive vascular disease, i.e., non-ST elevated myocardial infarction and non-obstructive intestinal ischaemia in women; and the "selection effect" with incident AAA disease identifying a population of biologically more vulnerable women.[1]

Considering that the decision of elective repair reflects a tradeoff between rupture risk and procedural risk, the high mortality after open repair implies that a more dynamic intervention threshold is indicated for women.[1] Further, potential benefits of pre- and/or per-operative mesenteric evaluation, and/or re-implantation of the IMA merit consideration.

This study is limited by a small number of patients, inherent to the low incidence of AAA in women and the size of the Dutch population. Due to the exploratory nature of the study, a male reference population was not included. Yet, other reports show a lower incidence of intestinal ischaemia in men (28%).[5]

Concluding, it is hypothesised that intestinal ischaemia is the main contributor to high mortality after elective open aneurysm repair in women. This calls for further exploration and evaluation of strategies aiming to minimise the risk of post-operative intestinal ischaemia.

REFERENCES

1. Pouncey AL, Powell JT. Women's lives matter: women suffer disproportionately after abdominal aortic aneurysm repair, so what can we do about it? J Vasc Surg 2021;62:1e3.
2. Pouncey AL, David M, Morris RI, Ulug P, Martin G, Bicknell C, et al. Editor's Choice e Systematic review and meta-analysis of sex specific differences in adverse events after open and endovascular intact abdominal aortic aneurysm repair: consistently worse outcomes for women. Eur J Vasc Endovasc Surg 2021;62:367e78.
3. Tomee SM, Lijftogt N, Vahl A, Hamming JF, Lindeman JHN. A registry-based rationale for discrete intervention thresholds for open and endovascular elective abdominal aortic aneurysm repair in female patients. J Vasc Surg 2018;67:735e9.
4. Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT, on behalf of the SWAN collaborators. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet 2017;389:2482e91.
5. Ultee KH, Zettervall SL, Soden PA, Darling J, Bertges DJ, Verhagen HJ, et al. Incidence of and risk factors for bowel ischemia after abdominal aortic aneurysm repair. J Vasc Surg 2016;64: 1384e91.

PART II
Aspects of medical decision-making

Chapter 6

A systemic evaluation of the costs of elective EVAR and open abdominal aortic aneurysm repair Implies cost equivalence

Ruth M.A. Bulder
Daniël Eefting
Patrick W.H.E. Vriens
Robert B. van Tongeren
Jon S. Matsumara
Wilbert B. van den Hout
Jaap F. Hamming
Jan H.N. Lindeman

European Journal of Vascular and Endovascular Surgery 2020

ABSRACT

Background

The suggested high costs of endovascular aneurysm repair (EVAR) hamper the choice of insurance companies and financial regulators for EVAR as the primary option for elective abdominal aortic aneurysm (AAA) repair. However, arguments used in this debate are impeded by time related aspects such as effect modification and the introduction of confounding by indication, and by asymmetric evaluation of outcomes. Therefore, a re-evaluation minimizing the impact of these interferences was considered.

Methods

A comparative analysis was performed evaluating a period of exclusive open repair (OR; 1998-2000) and a period of established EVAR (2010-2012). Data from four hospitals in The Netherlands were collected to estimate resource use. Actual costs were estimated by benchmark cost prices and a literature review. Costs are reported at 2019 prices. A break even approach, defining the costs for an endovascular device at which cost equivalence for EVAR and OR is achieved, was applied to cope with the large variation in endovascular device costs.

Results

One hundred and eighty-six patients who underwent elective AAA repair between 1998 and 2000 (OR period) and 195 patients between 2010 and 2012 (EVAR period) were compared. Cost equivalence for OR and EVAR was reached at a break even price for an endovascular device of €13.190. The main cost difference reflected the longer duration of hospital stay (ward and Intensive Care Unit) of OR (€11.644). Re-intervention rates were similar for OR (24.2%) and EVAR (24.6%) (P=0.92).

Conclusion

Cost equivalence for EVAR and OR occurs at a device cost of €13 000 for EVAR. Hence, for most routine repairs, EVAR is not costlier than OR until at least the five year follow up.

INTRODUCTION

Owing to its profoundly lower procedural morbidity and superior 30 day mortality, endovascular aneurysm repair (EVAR) has become the preferred strategy for elective abdominal aortic aneurysm (AAA) repair.[1] However, the literature suggests that EVAR comes with higher device costs and higher re-intervention rates.[2] As a consequence, the cost effectiveness of EVAR is being challenged and, on this basis, the preference for EVAR as the primary option for elective AAA repair is disputed.[3]

Yet, conclusions regarding the costs of EVAR vs. open repair (OR) are potentially affected by time related aspects, such as effect modification and the emergence of confounding by indication, and by an asymmetric evaluation of outcomes (see **Table 1** for definitions and examples). In fact, all prospective (trial based) cost (effectiveness) studies are based on devices and medical decision making from the early EVAR era.[4] Therefore the time related positive impact of procedural changes (i.e. improved devices and delivery systems, imaging modalities, and surgical experience), as well as changes in follow up, such as a more reticent attitude towards endoleaks are ignored. However, interpretation of more recent (retrospective) analyses is affected by decreasing OR volume, resulting in loss of surgical routine, and by the emergence of asymmetric medical decision making (confounding by indication, **Table 1**), in which the type of repair is essentially dictated by the patient's characteristics, for example EVAR is preferred in more frail patients.[5,6]

While time related aspects of effect modification and confounding by indication could be resolved in a randomised controlled trial, such a trial would most likely be considered unethical in the current timeframe with an established position and preference for EVAR. An alternative strategy is a comparative analysis of representative intervals. This analysis compares two periods: an open repair period (1998-2000) and EVAR period (2010-2012). The 1998-2000 period reflects a timeframe with standard OR and minimal interference of competitive medical decision making with EVAR. The 2010-2012 period reflects a timeframe with well established (and as first choice of repair) EVAR (i.e. established devices and surgical experience, and developed follow up policies). This period also allowed for a five year follow up.

Procedural costs were recalculated in order to reflect the actual (2019) costs. Device costs are the main determinant of the overall costs for EVAR, yet considering the broad spectrum of devices available, and the fact that actual per device costs are highly negotiable, it was difficult to assign a uniform per unit price.[7] To address these aspects, a break even approach was considered appropriate; therefore, the price for an EVAR device at which cost equivalence for EVAR and open repair was reached was estimated and reported.

Table 1. Explanation of terms used in the article

Term	Definition	Example
Time-dependent effect modification	The association between the exposure and outcome depends on a third variable i.e. alterations in care over time.	- Improved surgical experience with EVAR - Loss of surgical routine with open repair - Improvements of endovascular devices - Altered follow-up after EVAR (more reticent attitude towards endoleaks)
Confounding by indication	Asymmetrical decision-making i.e. the choice of repair (OR/EVAR) is based on and influenced by patient characteristics.	- The introduction of EVAR lowered the threshold for repair; as result more frail and older patients are being treated by EVAR, whereas some advise OR in younger/fit patients.
Asymmetrical evaluation of outcomes	Biased evaluation of outcomes in published studies.	- Strong focus on graft-related re-interventions in studies evaluating EVAR

EVAR, endovascular aneurysm repair; OR, open repair.

METHODS

Ethical approval

The medical ethical committee of Leiden University Medical Centre reviewed the study protocol (G18.126). The boards of the individual study centres all granted approval.

Data collection

This study includes all consecutive patients who underwent primary, elective AAA repair, in either the OR (1998-2000) or EVAR (2010-2012) period. Exclusion criteria were emergency repair, thoracic AAA, suprarenal AAA or need for suprarenal clamping, mycotic/inflammatory AAA, and previous aortic repair. Patients were identified from hospital registry data of four hospitals in the Netherlands (one university hospital and three non-academic teaching hospitals). Patient and procedural data were retrieved from medical records. Re-interventions were defined as any procedure related to the primary OR or EVAR.

Outcome

The aim of this study was to compare costs associated with OR and EVAR. Patient outcomes were not considered, as would be the case in a cost effectiveness analysis. Instead, a break even point for EVAR device costs was calculated as the point at which the costs of OR equalled those of EVAR. The primary end point was the break even point for OR and EVAR. This point reflects the costs of an endovascular device at which cost equivalence for EVAR and OR is reached.

Unit costs, viz. the total expenditure associated with the separate aspects of AAA repair, were defined on the basis of the registered benchmark costs for the Dutch hospitals, and a systematic literature search.[8,9,10] Procedural costs included operating room use, graft (OR), cell saver, and length of stay on the surgical ward and Intensive Care Unit (ICU). Operating room costs included all direct and indirect costs, calculated as costs per minute of operating time. Surgical ward and ICU costs reflected both direct and indirect costs and were calculated on a daily basis.

Follow up costs included both regular follow up (postoperative consultations and imaging) and follow up associated with complications. Regular follow up was based on the 2011 European Society for Vascular Surgery (ESVS) guidelines.[11] For patients who underwent EVAR, this included one computed tomography angiogram at 12 months, and yearly duplex ultrasounds and plain radiographs thereafter; for patients who underwent OR, it included a duplex ultrasound at three months, six months, one year, and optional at three years. Costs of complications included all costs related to reinterventions, which were defined as any procedure related to the primary EVAR or OR, including graft related reinterventions, abdominal wall hernias, bowel obstructions, wound dehiscences, thrombosis, and so on. Re-intervention costs were estimated in the same manner as the costs of the primary intervention. All costs were converted to the 2019 price level using the Consumer Price Index.[12] Costs per unit estimates are provided in **Table 2**.

Costs of AAA surveillance programmes or pre-operative screening were not included, as these are extremely heterogeneous owing to the timing of diagnosis and not influenced by the type of AAA repair.

Table 2. Composition of Dutch costs (in 2019 euros*) with the USA costs (in 2019 euros) as reference

	Netherlands	United States
Operating room/min	22 [11]	36 [26]
Ward/day	548 [12]	1012 [27]
ICU/day	1678 [12]	1988 [27]
Graft OR	663 [13]	1434 [28]
Graft EVAR	-	-
Cellsaver	172 [14]	232 [28]
CT Abdomen	171 [12]	574 [29]
CTA aorta	346 [12]	
Ultrasound Abdomen	86 [12]	121 [29]
X-Ray	46 [12]	28 [29]
Postoperative consult	96 [12]	105 [30]

ICU, intensive care unit; OR, open repair; EVAR, endovascular aneurysm repair; CT, computed tomography; CTA, computed tomography angiography.

* All costs were converted to the 2019 price level using the Consumer Price Index.[12]

Statistical analysis

The normality of data was assessed by histograms. Continuous variables were expressed as means ("standard deviation) or medians (interquartile range [IQR]) and compared using the Student's t test or the Mann-Whitney U test. Categorical data were analysed using the chi square test. A p value of $< .05$ was considered statistically significant. All analyses were conducted with SPSS version 26 (IBM, Armonk, NY, USA).

RESULTS

Study population

This study is based on an evaluation of all elective AAA repairs performed between 1998 and 2000 (OR) or between 2010 and 2012 (EVAR), with 186 patients having open repair and 195 patients EVAR in the respective periods. Baseline patient characteristics are shown in **Table 3**. The proportion of active smokers was higher in the OR group (P<0.001). The proportion of diabetic patients (P<0.001) and patients on statins (P<0.001) was higher in the EVAR group.

Primary AAA repair (OR e EVAR)

Table 4 shows that OR was associated with a slightly longer duration of surgery (P<0.001), a longer ICU stay (P<0.001), and a longer stay on the surgical ward (P<0.001). The number of post-operative consultations was similar for the two groups (P=0.32), but imaging was more common after EVAR (P<0.001). Primary repair related resource use is summarised in **Table 4**.

Re-interventions

The relative and absolute number of repair related reinterventions for the five year follow up period was similar. In fact, 24.2% (total re-interventions, n = 81) of the OR patients and 24.6% (total re-interventions, n = 85) of the EVAR patients underwent at least one repair related re- intervention (P=0.92). There was a clear difference in the nature and timing of re-interventions with a median reintervention time of one month (IQR 0-17 months) in the OR group and 23 months (IQR 4-37.5 months) in the EVAR group (P<0.001). Re-interventions in the EVAR group were mainly graft related (EVAR, n = 67 vs. n = 1 in the OR group; P<0.001). Surgery related re-interventions (including wound complications, incisional hernias, re-laparotomies, and gastro-intestinal complications) were more prevalent in the OR group (OR, n = 80 vs. EVAR, n = 18; P<0.001). A detailed overview of all repair related re-interventions is provided in **Table 5**.

Costs

Mean costs (2019 prices) of the initial hospital admission, graft, and follow up are presented in **Table 4**. Overall costs after five years for OR were €20.041 and for EVAR €6.576 (excluding the device costs). Mean costs of re-interventions for OR were €5.907 per re-intervention (€2.572 per elective OR); re-intervention costs for EVAR were €5.953 (€2.595 per elective EVAR) (P=1.00). **Table 6** provides a summary of the re-intervention costs.

Table 3. Characteristics of 381 patients treated by open (OR) vs. endovascular aneurysm repair (EVAR) in The Netherlands in 1998-2000 and 2010-2012, respectively

	Open repair n = 186	EVAR n = 195	P-value
Age - years	70.6 ± 7.6	72.1 ± 8.0	0.71
Gender			0.63
Male	158 (84.9)	169 (86.7)	
Female	28 (15.1)	26 (13.3)	
Diameter AAA (mm), median (IQR)	57.5 (52.0 – 65.0)	57.0 (55.0 – 61.0)	0.81
missing	16	5	
ASA classification			0.82
ASA 1	10 (5.4)	11 (5.6)	
ASA 2	108 (58.1)	120 (61.5)	
ASA 3	53 (28.5)	62 (31.8)	
ASA 4	0 (0)	1 (0.5)	
missing	15	1	
Smoking status			< 0.001
Yes	57 (30.6)	48 (24.6)	
No	66 (35.5)	128 (65.6)	
Not known	63 (33.9)	19 (9.7)	
Diabetes mellitus	11 (6.4)	31 (16.0)	0.004
missing	15	1	
COPD	41 (23.8)	46 (23.7)	0.98
missing	14	1	
Hypertension	111 (73.0)	129 (75.0)	0.61
missing	34	12	
Hyperlipidaemia	68 (47.6)	76 (44.2)	0.55
missing	43	23	
Medication use			
Statins	42 (38.2)	117 (68.8)	< 0.001
missing	76	25	
Antihypertensive	55 (50.5)	87 (50.9)	0.95
missing	77	24	

Data are presented as n (%) or mean ± standard deviation unless stated otherwise.
IQR, interquartile range; AAA, abdominal aortic aneurysm; ASA, American Society for Anesthesiologists; COPD, chronic obstructive pulmonary disease.

Table 4. Mean costs (in euros) of primary procedures for 186 open (OR) or 195 endovascular (EVAR) abdominal aortic aneurysm repairs in The Netherlands

		Open repair n = 186		**EVAR n = 195**		**Difference OR - EVAR (€)**
	Unit costs (€)	Resource use	Total costs (€)	Resource use	Total costs (€)	
Surgery						
OR time (min)	22	183	4026	127	2794	1232
Cell saver	172	1	172	0	0	172
Device *	663	1	663	0	0	663*
Hospital stay						
ICU (days)	1678	4.1	6880	0	0	6880
Ward (days)	548	13.8	7562	4.7	2576	4987
Follow-up						
CTA	346	0	0	1	346	- 346
Ultrasound	86	3	258	5	430	- 172
X-ray	46	0	0	1	46	- 46
Consult	96	5	480	4	384	96
Total*			20.041		6576	13.466*

Data are presented as mean costs in euros. There were no missing data regarding primary outcomes. ICU, intensive care unit.

* Costs of the EVAR device are not included here. Threshold costs are calculated in the break even point analysis.

Table 5. Re-interventions after 186 open repair (OR) and 195 EVAR for a five year follow up in The Netherlands

	OR (n = 186)	**EVAR** (n = 195)	**P-value**
Patients with reinterventions	45 (24.2)	48 (24.6)	0.92
Total number of reinterventions	81	85	
Total graft related	1	67	<0.001
Endoleak	0 (0)	39 (45.9)	
Migration	1 (1.2)	2 (2.4)	
Occlusion/stenosis	0 (0)	23 (27.1)	
Other	0 (0)	3 (3.5) *	
Total non graft related	80	18	<0.001
Relaparatomy	14 (17.3)	0 (0)	
Wound complication	17 (21.0)	8 (9.4)	
Incisional hernia	16 (19.8)	0 (0)	
RAAA	1 (1.2)	0 (0)	
AAA spurium	1 (1.2)	2 (2.4)	
Bleeding	1 (1.2)	1 (1.2)	
Embolism/thrombus	4 (4.9)	3 (3.5)	
Limb/amputation	7 (8.6)	1 (1.2)	
Gastro-intestinal	9 (11.1)	0 (0)	
Fistula	3 (3.7)	0 (0)	
Other **	7 (8.6) **	3 (3.5) ***	

Data are presented as n (%). RAAA, ruptured abdominal aortic aneurysm.

* Dissection stent graft, infection stent graft, proximal anastomotic abdominal aortic aneurysm.
** Infection, neurological complications, tracheotomy, inserting renal graft.
*** Removal peel away sheet, abscess, infection.

Table 6. Costs of the 166 re-interventions in the five years following 186 elective open repairs (OR) or 195 endovascular aneurysm repairs (EVAR) in The Netherlands

		Open repair n = 186		**EVAR n = 195**		**Difference OR - EVAR (€)**
	Unit costs (€)	Resource use	Total costs (€)	Resource use	Total costs (€)	
Surgery						
OR time (min)	22	73	1606	51	1122	484
Hospital stay						
ICU (days)	1678	0.8	1342	1.2	2014	- 672
Ward (days)	548	5.4	2959	4.7	2576	- 242
CTA	346	0	0	0.7	242	242
Total*			5907		5953	- 46

Data are presented as costs in euros. ICU, intensive care unit.
* The p value for total costs of open repair vs. EVAR re-intervention is 1.0.

6

Break even point and sensitivity analyses

Considering the costs of both primary repair and reinterventions after five years of follow up, the break even point for cost equivalence of OR and EVAR is established at €13.466. The impact of variations in ICU and hospital stay on the break even point were addressed in a sensitivity analysis (**Table 7**). Boundaries were based on different scenarios reflecting various days at the ICU and ward.

Table 7. Sensitivity analysis: impact of hospital and intensive care unit (ICU) stay on the break even point (device costs for endovascular aneurysm repair [EVAR] and open repair (OR) of abdominal aortic aneurysm)

ICU days (OR)	Ward days (OR)											
	3	4	5	6	7	8	9	10	11	12	13	14
EVAR one day admission ward												
1	4 320	4 868	5 416	5 964	6 512	7 060	7 608	8 156	8 704	9 252	9 800	10 348
2	5 998	6 546	7 094	7 642	8 190	8 738	9 286	9 834	10 382	10 930	11 478	12 026
3	7 676	8 224	8 772	9 320	9 868	1 0416	10 964	11 512	12 060	12 608	13 156	13 704
4	9 354	9 902	10 450	10 998	11 546	12 094	12 642	13 190	13 738	14 286	14 834	15 382
5	11 032	11 580	12 128	12 676	13 224	13 772	14 320	14 868	15 416	15 964	16 512	17 060
EVAR two days admission ward												
1	3 772	4 320	4 868	5 416	5 964	6 512	7 060	7 608	8 156	8 704	9 252	9 800
2	5 450	5 998	6 546	7 094	7 642	8 190	8 738	9 286	9 834	10 382	10 930	11 478
3	7 128	7 676	8 224	8 772	9 320	9 868	10 416	10 964	11 512	12 060	12 608	13 156
4	8 806	9 354	9 902	10 450	10 998	11 546	12 094	12 642	13 190	13 738	14 286	14 834
5	10 484	11 032	11 580	12 128	12 676	13 224	13 772	14 320	14 868	15 416	15 964	16 512
EVAR three days admission ward												
1	3 224	3 772	4 320	4 868	5 416	5 964	6 512	7 060	7 608	8 156	8 704	9 252
2	4 902	5 539	6 087	6 635	7 183	7 731	8 279	8 827	9 375	9 923	10 471	11 019
3	6 580	7 306	7 854	8 402	8 950	9 498	10 046	10 594	11 142	11 690	12 238	12 786
4	8 258	9 073	9 621	10 169	10 717	11 265	11 813	12 361	12 909	13 457	14 005	14 553
5	9 936	10 840	11 388	11 936	12 484	13 032	13 580	14 128	14 676	15 224	15 772	16 320
EVAR four days admission ward												
1	2 676	3 224	3 772	4 320	4 868	5 416	5 964	6 512	7 060	7 608	8 156	8 704
2	4 354	4 902	5 450	5 998	6 546	7 094	7 642	8 190	8 738	9 286	9 834	10 382
3	6 032	6 580	7 128	7 676	8 224	8 772	9 320	9 868	10 416	10 964	11 512	12 060
4	7 710	8 258	8 806	9 354	9 902	10 450	10 998	11 546	12 094	12 642	13 190	13 738
5	9 388	9 936	10 484	11 032	11 580	12 128	12 676	13 224	13 772	14 320	14 868	15 416
EVAR five days admission ward												
1	2 128	2 676	3 224	3 772	4 320	4 868	5 416	5 964	6 512	7 060	76 08	8 156
2	3 806	4 354	4 902	5 450	5 998	6 546	7 094	7 642	8 190	8 738	9 286	9 834
3	5 484	6 032	6 580	7 128	7 676	8 224	8 772	9 320	9 868	10 416	10 964	11 512
4	7 162	7 710	8 258	8 806	9 354	9 902	10 450*	10 998	11 546	12 094	12 642	13 190†
5	8 840	9 388	9 936	10 484	11 032	11 580	12 128	12 676	13 224	13 772	14 320	14 868

Each part of the table represents the subsequent number of days (1, 2, 3, 4, 5) on the ward for EVAR patients. The first column represents the number of days at the ward for OR patients. The following columns present the number of days on the ICU for OR patients. With these numbers, alterations in hospital stay can be simulated, i.e. if EVAR patients stay four days on the ward and OR patients three days on the ICU and 11 days on the ward, this is visualised in the "EVAR four days admission ward" part of the table, on the third row below and in the column for 11 ward days.

* Primary analysis break even point equals 13.466 (equals 13.190 when based on integer days on ward and ICU).

** Shorter ward stay (nine days) for OR = 10.450d (= adjusted decrease in hospital stay of open repair [factor 0.67] for the Dutch situation).

DISCUSSION

The total costs of EVAR remain a matter of debate. In fact, the presumed higher costs of EVAR are one of the mainstays of the current National Institute of Health and Care Excellence (NICE) guideline recommendation to refrain from EVAR for elective repair.[3] Specifically, the concept states that "the total cost per patient associated with EVAR is higher, and it is expected to generate fewer QALYs per patient".[3] However, these conclusions are based on the current literature, which is potentially prone to time related aspects such as effect modification and the introduction of confounding by indication, and asymmetric evaluation of outcomes (**Table 1**). In order to reduce these time related aspects a comparative analysis of two time periods, i.e., an open repair period (1998-2000) and an EVAR period (2010-2012), was performed. Conclusions from this analysis show that cost equivalence for OR and EVAR is established at an EVAR device cost level of approximately €13.000. This break even point reflects the mean of the reported prices for an endovascular device (€6.249-25.425).[7,13,14] As such, it is concluded that for device costs up to €13 000, the total costs per patient associated with EVAR are lower than for OR.

So far, several studies reviewed costs of OR vs. EVAR. A detailed evaluation based on the EndoVascular Aneurysm Repair (EVAR-1) trial data concluded that EVAR was not cost effective over the lifetime.[15] With the exception of the Anevrysme de l'aorte abdominale, Chirurgie vs. Endoprothese (ACE) trial, similar conclusions were reached by the other prospective (trial based) analyses, which all concluded that while initial hospitalisation costs with EVAR were lower, the costs significantly increased over time.[4,16] Conclusions from real world cost analyses, however, were less unanimous, and reported EVAR to be more costly, as well as cost effective.[9,17,18] In the light of the contrasting conclusions and the large variation in cohorts and outcomes, authors of a meta-analysis concluded that costs cannot be employed as an instrument to choose between the methods of AAA repair.[19]

Contrasting conclusions concerning the overall costs of EVAR and OR largely relate to the fact that the interpretation of available studies is interfered by time related aspects (i.e. effect modification, and the introduction of confounding), and by an asymmetric evaluation of outcomes (**Table 1**). So far, these aspects have not been addressed. Aspects of time related effect modification may profoundly impact any conclusions with respect to procedural costs. Since its introduction, the EVAR procedure has been thoroughly optimised. A new generation of devices and delivery systems, more experienced teams, a less intense follow up, and a more conservative approach towards type II endoleaks may all reduce the costs associated with of EVAR.[1,20] In parallel, the broad implementation of EVAR comes with a profound reduction in the number of, and thus experience with open procedures.[1] This may potentially negatively impact the efficacy and outcomes of OR (and consequently result in higher procedural costs). Further interference results from confounding by indication. The implementation of EVAR as an option for AAA repair introduced confounding by indication, in which the preferred choice of repair is dictated by patient characteristics. This is reflected in the preference for EVAR in older and frail patients. As a consequence, EVAR and OR groups are not comparable in the current timeframe.

A further, so far ignored, aspect in cost analyses is the asymmetric evaluation of outcomes. While OR is generally considered a final solution, there has always been awareness on the need for post-procedural surveillance with EVAR. This has resulted in an intensified follow up after EVAR, as well as awareness of re-interventions. These contrasting attitudes are reflected in an asymmetric evaluation of re-intervention costs after EVAR or OR. In fact, most studies fail to systematically include re-interventions related to OR.[21,22] As a consequence, the reported higher incidence of re-interventions after EVAR may reflect underestimation of the number of interventions following OR.

A final limitation of the available reports is that the included prices of an endovascular device in these studies reflect list prices, and not the actual, negotiated costs paid by individual hospitals. This latter aspect may greatly impact conclusions as device costs are the primary determinant of EVAR related costs.

In order to reduce the impact of time related aspects, it was decided to do a comparative cost analysis for elective infrarenal AAA repair based on a comparison of two representative intervals. A period of almost exclusive OR and a period of preferred and established EVAR. Complex EVAR procedures (suprarenal and pararenal AAAs) were excluded as these reflect an extremely heterogeneous group of patients and procedures. The two timeframes showed broadly similar baseline characteristics (American Society of Anesthesiologists' classification and age) for patients receiving OR or EVAR. Asymmetric evaluation of repair related re-interventions was avoided by a systematic evaluation of all re-interventions related to the primary procedure in the five years after the primary repair. Although the evaluation indicated clear differences in the type of re-intervention, it was concluded that the overall number of procedure related re-interventions was similar for EVAR and OR.

Performance and the interpretation of cost analyses are interfered by the complex cost structures of health systems and the lack of transparency. In order to minimise this interference, benchmark costs for Dutch hospital costs were applied, as these are probably the best reflection of the actual costs for the Netherlands.[8] As cost structures may not directly translate to other countries/health systems, reference costs for the USA are included in **Table 2**.[23-28]

Based on the data in this evaluation, cost equivalence for OR and EVAR is reached at approximately €13.000 for an endovascular device. This estimate reflects the mean of prices for endovascular devices reported in the literature (€6.249 - €25.425).[7,13,14] Yet, conclusions are obviously influenced by the devices used, individual pricing agreements between hospitals and suppliers, and days spent in the ICU and on the ward. The latter aspect was addressed in a sensitivity analysis (**Table 7**), which allows for an individualised estimation of the break even point for cost equivalence.

Note that conclusions regarding cost equivalence are exclusively based on actual procedural and re-intervention costs, and that aspects of formal cost effectiveness analysis, such as differences in procedural mortality and utility, are not included in the analysis. From the patient's perspective, EVAR comes with a number of advantages, including a substantially lower procedural morbidity and mortality, aspects that are of particular relevance for elderly patients, and should be taken into account in considerations of cost effectiveness.[29-32] Moreover, decisions regarding follow up in this evaluation reflected the 2011 ESVS guidelines. Implementation of the current guidelines, advising that patients with an adequate seal and no type II endoleaks (30% - 60% of patients) do not require imaging up to five years, would result in a break even point that further favours EVAR (€13.552 - €13.914).

Altogether, it could be argued that from a cost effectiveness perspective, the break even point for EVAR is well above €13.000 for an EVAR device. Consequently, in contrast to the conclusions of the NICE guidelines, most EVAR procedures will generate more quality adjusted life years per patient than OR.[3]

Limitations

As the OR period represents patients from 1998 to 2000 it is unclear to what extent the costs of OR (procedural costs, and ICU and ward stay) are influenced by current reductions in OR volume (and thus team skills) on one hand, and technical improvements on the other hand. Average ICU and ward times declined between 1998 and 2010.[33] Therefore, the cost of OR could be overestimated. The potential impact of these aspects is illustrated by a sensitivity analysis (**Table 7**). Note that this sensitivity analysis does not include underlying causes of altered hospital stay. This reflects a general model and should not be used for individual decision making. It is concluded that even with a shorter hospital stay of open repair, EVAR remains cost equivalent.

A further aspect not addressed in this study is that the lower threshold with EVAR may result in AAA repair in patients whose surgical treatment would have been withheld in the OR era.[20] This may result in the inclusion of more frail patients in the 2010-2012 period. Although it could be argued that this phenomenon would actually favour EVAR, it may also result in the treatment of patients who will not live long enough to benefit from the repair. This latter aspect will obviously negatively impact the cost effectiveness of EVAR.

Finally, the data were collected retrospectively. As a consequence, the analysis is influenced by time related aspects such as the organisation of patient records. Follow up in this study was limited to five years. Thus, reinterventions beyond five years are not included. However, it is considered unlikely that this affects the conclusions of this evaluation, the more so as a considerable number of complications of OR present more than five years after primary repair.

The data did not allow for specific subgroup analyses. Such an analysis would be particularly relevant for women as female patients have a higher 30 day mortality with OR than men (8.0% vs 4.3%).[34] As this sex specific mortality is not observed for EVAR it is highly unlikely that different conclusions would be reached for women.

CONCLUSION

Results from this cost analysis study show that cost equivalence for EVAR and OR occurs at a device costs of €13.000. Hence, for most routine repairs EVAR is not costlier than OR until at least five years of follow up.

REFERENCES

1. Arko FR, Murphy EH, Boyes C, Nussbaum T, Lalka SG, Holleman J, et al. Current status of endovascular aneurysm repair: 20 years of learning. Semin Vasc Surg 2012;25:131e5.
2. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev 2014;1:CD004178.
3. National Institute of Health and Care Excellence. Abdominal aortic aneurysm: diagnosis and management. Available at: https://www.nice. org.uk/guidance/ng156/chapter/Recommendations#monitoringand-reducing-the-risk-of-rupture. [Accessed 24 June 2020].
4. Epstein D, Sculpher MJ, Powell JT, Thompson SG, Brown LC, Greenhalgh RM. Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic aneurysm based on four randomized clinical trials. Br J Surg 2014;101:623e31.
5. Zettervall SL, Schermerhorn ML, Soden PA, McCallum JC, Shean KE, Deery SE, et al. The effect of surgeon and hospital volume on mortality after open and endovascular repair of abdominal aortic aneurysms. J Vasc Surg 2017;65:626e34.
6. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg 2009;50:880e96.
7. Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, et al. Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model. Health Technol Assess 2009;13:1e315.
8. Portal performation. Available at: https://portal.performation.com. [Accessed 13 February 2020].
9. Burgers LT, Vahl AC, Severens JL, Wiersema AM, Cuypers PW, Verhagen HJ, et al. Cost-effectiveness of elective endovascular aneurysm repair versus open surgical repair of abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2016;52:29e40.
10. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Pöll RG, Onstenk R, et al. Patient blood management in elective total hip- and knee-replacement surgery (Part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology 2014;120:839e51.
11. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's choice - European society for vascular surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. Eur J Vasc Endovasc Surg 2019;57:8e93.
12. CBS. StatLine e consumentenprijzen; Prijsindex. 2015. Available at: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83131ned/table?ts¼1560106575807. [Accessed 13 February 2019].
13. Berghmans JCH, Lübke T, Brunkwall JS. A cost calculation of EVAR and FEVAR procedures at a European academic hospital. Ann Vasc Surg 2019;54:205e14.
14. Lemmon GW, Neal D, DeMartino RR, Schneider JR, Singh T, Kraiss L, et al. Variation in hospital costs and reimbursement for endovascular aneurysm repair: a Vascular Quality Initiative pilot project. J Vasc Surg 2017;66:1073e82.
15. Patel R, Powell JT, Sweeting MJ, Epstein DM, Barrett JK, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) randomised controlled trials: long-term follow-up and costeffectiveness analysis. Health Technol Assess 2018;22:1e132.

16. Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P, et al. ACE trialists. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. J Vasc Surg 2011;53:1167e73.
17. Dua A, Kuy S, Lee CJ, Upchurch Jr GR, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. J Vasc Surg 2014;59:1512e7.
18. Gupta AK, Alshaikh HN, Dakour-Aridi H, King RW, Brothers TE, Malas MB. Real-world cost analysis of endovascular repair versus open repair in patients with nonruptured abdominal aortic aneurysms. J Vasc Surg 2020;7:432e43.
19. van Bochove CA, Burgers LT, Vahl AC, Birnie E, van Schothorst MG, Redekop WK. Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm. J Vasc Surg 2016;63:827e38.
20. Tadros RO, Faries PL, Ellozy SH, Lookstein RA, Vouyouka AG, Schrier R, et al. The impact of stent graft evolution on the results of endovascular abdominal aortic aneurysm repair. J Vasc Surg 2014;59:1518e27.
21. Curl GR, Faggioli GL, Stella A, D'Addato M, Ricotta JJ. Aneurysmal change at or above the proximal anastomosis after infrarenal aortic grafting. J Vasc Surg 1992;16:855e9.
22. Hagino RT, Taylor SM, Fujitani RM, Mills JL. Proximal anastomotic failure following infrarenal aortic reconstruction: late development of true aneurysms, pseudoaneurysms, and occlusive disease. Ann Vasc Surg 1993;7:8e13.
23. Childers CP, Maggard-Gibbons M. Understanding costs of care in the operating room. JAMA Surg 2018;153:e176233.
24. Stroupe KT, Lederle FA, Matsumura JS, Kyriakides TC, Jonk YC, Ge L, et al. Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm in the OVER trial. J Vasc Surg 2012;56:901e9.
25. Matsumura JS, Stroupe KT, Lederle FA, Kyriakides TC, Ge L, Freischlag JA, et al. Costs of repair of abdominal aortic aneurysm with different devices in a multicenter randomized trial. J Vasc Surg 2015;61:59e65.
26. Waters JR, Meier HH, Waters JH. An economic analysis of costs associated with development of a cell salvage program. Anesth Analg 2007;104:869e75.
27. Hengge UR, Wallerand A, Stutzki A, Kockel N. Cost-effectiveness of reduced follow-up in malignant melanoma. J Dtsch Dermatol Ges 2007;5:898e907.
28. Lubitz CC, Kong CY, McMahon PM, Daniels GH, Chen Y, Economopoulos KP, et al. Annual financial impact of welldifferentiated thyroid cancer care in the United States. Cancer 2014;120:1345e52.
29. Bulder RMA, Bastiaannet E, Hamming JF, Lindeman JHN. Metaanalysis of long-term survival after elective endovascular or open repair of abdominal aortic aneurysm. Br J Surg 2019;106: 523e33.
30. Arko FR, Hill BB, Reeves TR, Olcott C, Harris EJ, Fogarty TJ, et al. Early and late functional outcome assessments following endovascular and open aneurysm repair. J Endovasc Ther 2003;10:2e9.
31. Williamson WK, Nicoloff AD, Taylor Jr LM, Moneta GL, Landry GJ, Porter JM. Functional outcome after open repair of abdominal aortic aneurysm. J Vasc Surg 2001;33:913e20.
32. Lennings CJ. Optimism, satisfaction and time perspective in the elderly. Int J Aging Hum Dev 2000;51:167e81.
33. CBS. StatLine e gezondheid, leefstijl, zorggebruik eneaanbod, doodsoorzaken; vanaf 1900. Available at: https:// opendata.cbs.nl/ statline/#/CBS/nl/dataset/37852/table?ts¼1581606736291. [Accessed 11 November 2019].
34. Tomee SM, Lijftogt N, Vahl A, Hamming JF, Lindeman JHN. A registry-based rationale for discrete intervention thresholds for open and endovascular elective abdominal aortic aneurysm repair in female patients. J Vasc Surg 2018;67:735e9.

6

Chapter 7

Towards patient centred outcomes for elective abdominal aortic aneurysm repair: A scoping review of quality of life scales

Ruth M.A. Bulder
Jaap F. Hamming
Jan van Schaik
Jan H.N. Lindeman

European Journal of Vascular and Endovascular Surgery 2021

ABSRACT

Background

In order to better incorporate the patient's perspective in medical decision making, core outcome sets (COS) are being defined. In the field of abdominal aortic aneurysm (AAA), efforts to capture the patient's perspective focus on generic quantitative quality of life (QoL) scales. The question arises whether these quantitative scales adequately reflect the patient's perspective on QoL, and whether they can be included in the QoL aspect of COS. A scoping review of QoL assessment in the context of elective AAA repair was undertaken.

Methods

A scoping review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. Articles reporting QoL assessment in the context of elective AAA repair were identified. Quantitative studies (i.e. traditional QoL scales) were aligned (triangulation approach) with qualitative studies (i.e. patient perspective) to identify parallels and discrepancies. Mean Short Form 36 item survey (SF-36) scores were pooled using a random effects model to evaluate sensitivity to change. Data Sources: PubMed, Embase, Web of Science, and the Cochrane Library.

Results

Thirty-three studies were identified, of which 29 (88%) were quantitative and four (12%) qualitative. The 33 studies reported a total of 54 quantitative QoL scales; the most frequently used were the generic SF-36 (16 studies) and five dimension EuroQol (EQ-5D; eight studies). Aneurysm specific scales were reported by one study. The generic quantitative scales showed poor alignment with the patient's perspective. The aneurysm specific scales better aligned but missed "concerns regarding symptoms" and "the impact of possible outcomes/ complications". "Self control and decision making", which was brought forward by patients in qualitative studies, was not captured in any of the current scales.

Conclusion

There is no established tool that fully captures all aspects of the patient's perspective appropriate for a COS for elective AAA repair. In order to fulfil the need for a COS for the management of, AAA disease, a more comprehensive overview of the patient's perspective is required.

INTRODUCTION

Efforts to establish more patient centred health care have led to the increasing integration of the patient's perspective in medical decision making. To achieve this, disease specific core outcome sets (COSs) are defined together with patients for a wide range of diseases.[1,2] It is recommended that COSs are reported in all studies concerning a specific patient cohort in order to allow for systematic evaluation of study outcomes.[3,4]

In the process of developing the new European Society for Vascular Surgery guidelines on the management of abdominal aortic aneurysms (AAAs), it was discovered that outcomes considered important by vascular surgeons may substantially differ from the patient's perspective on treatment outcomes.[5,6] In order to better incorporate the patient's perspective, the vascular society called for definition of a COS for the management of AAA disease.[7] COSs are collections of key outcomes, such as mortality, morbidity, and the patient's perspective.[7] The focus of this study was on the patient's perspective in the context of elective AAA repair.

Studies addressing the patient's perspective generally rely on "quality of life" (QoL) as a quantitative equivalent. This umbrella term includes concepts such as QoL, health related QoL, or health status.[8] Underlying these concepts are generic and disease specific (quantitative) questionnaires. Generic questionnaires, such as the Short Form 36 item survey (SF-36) and five dimensional EuroQol (EQ-5D), are applicable across a broad variety of diseases, and allow for comparison across patient groups, as well as with the general population.[9] Disease specific questionnaires provide more detail and allow for a more focussed evaluation.[10] It is generally recommended that both generic and disease specific questionnaires are used to best evaluate the QoL of a patient cohort.[10] A limitation of quantitative scales is that they are based on questions defined by health professionals, which may not reflect the patient's perspective. Moreover, quantitative scales provide limited information and do not allow for an in depth examination of the patient's view.[11] To better assess the patient's perspective, qualitative research (semi-structured interviews and focus groups) is needed.[12]

In the field of AAAs, most studies addressing the patient's perspective on treatment outcomes rely on quantitative QoL questionnaires.[13-15] With the knowledge that quantitative QoL scales do not, or only partially, capture the patient's perspective, the question arises whether current QoL scales adequately reflect the perspective of patients with AAA, and can be included in the QoL aspect of a COS for AAA. To address this question a scoping review was performed. Unlike a (regular) systematic review that addresses one specific question, a scoping review broadly identifies and maps all the available evidence to inform practice.[16] The aim of this review was to (1) summarise the available reports of QoL assessment in elective AAA repair; (2) evaluate possible discrepancies between established (quantitative) QoL questionnaires and qualitative research (patient's perspective); and (3) estimate the sensitivity of QoL scales to changes in QoL in the context of elective AAA management.

METHODS

Literature search

This review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (**Supplemental Appendix 1**).[17,18] The study protocol uses the methodological framework proposed by Arksey and O'Malley and additional recommendations made by Levac.[19-22] The study protocol is available upon request from the corresponding author. Studies were identified through a systematic search in PubMed, Embase, Web of Science, and the Cochrane Library (updated 25 January 2021). The search strategy was based on QoL/ patient perceptions and AAA (**Supplementary Appendix 2**).

Study inclusion

The review included all studies reporting QoL in the context of elective open AAA repair or endovascular aneurysm repair (EVAR). Studies that exclusively focussed on patients with small AAAs (< 5.5 cm); patients under surveillance; or studies that exclusively evaluated pre-operative QoL were excluded, as were studies that focussed on ruptured AAA, thoracic abdominal aneurysm, or aortic dissection. Letters, comments, reviews, or studies not available as full texts were also excluded. Studies evaluating cost effectiveness by estimation of quality adjusted life years (QALYs) were also excluded, because QALYs are based on mortality and reintervention rates, rather than patient reported outcomes (PROs). Two authors (R.B. and J.L.) reviewed the results of the search strategy. Titles and abstracts were reviewed for eligibility. When eligibility was uncertain or unclear, the full texts were reviewed.

Data extraction

Data concerning year of publication, years of patient inclusion, number of included patients, patient characteristics (age and sex), treatment by open repair or EVAR, and timing of follow up were collected for all study types. For quantitative studies, data extraction included type of QoL assessment tool(s), timing of QoL assessment, and key results. For qualitative studies data extraction included method of data collection (interview or focus groups), and key results. Data extraction was done by three independent researchers (R.B., J.L., and J.S.).

Quality assessment

Owing to the heterogeneity of study design the quality of quantitative studies was assessed by a descriptive review (age, sex, patient background, and responsiveness rate) (**Table 1**). The Critical Appraisal Skills Programme (CASP) qualitative research checklist was used to evaluate the methodological quality of qualitative studies.[23] Quality assessment was done by three independent researchers (R.B., J.L., and J.S.). In line with the guidelines for scoping reviews, the methodological quality of studies was not included in the analysis.[21]

Table 1. Review articles reporting quality of life (QoL) assessment in elective abdominal aortic aneurysm (AAA) repair

Author (year)	Years of inclusion	Type of repair	Male/Female (n)	Age (y) Median (IQR) Mean (± SD)	Quality of Life tool	Attention for reinterventions	Follow-up time points	Type of study	Response rate (%)	Patient characteristics
QUANTITATIVE RESEARCH										
Magee (1992) [29]	1998 – 1999	OR	78/8	71 (48 – 84)	Rosser index	-	Pre-op, 30 (18-42) mo	P Single	80%	-
Sandstrom (1996) [30]	1993 – 1994	OR	16/6	69 (49 – 81)	SIP HI	-	6-12 mo	P Single	100%	-
Mangione (1997) [31]	1990 – 1993	OR	78/17	72 ± 8	SF-36	-	Pre-op, 1, 6, 12 mo	P Single	86%	No differences responders – no responders
Hennessy (1998) [32]	*	OR	11/3	71 (56 – 88)	Rosser index HSCL GHQ	-	13 (3-28) mo	R Single	-	-
Perkins (1998) [33]	*	OR	50/9	74 (51 – 83)	SF-36 Rosser index	-	Pre-op, 6 w, 3 mo, 6 mo	P Multi	95%	-
Lloyd (2000) [34]	*	EVAR - OR	EVAR: 34/0 OR: 48/0	EVAR: 73 (59 – 82) OR: 73 (59 – 86)	SF-36	-	Pre-op, 6 mo	P Single	-	-
Malina (2000) [35]	1997 – 1998	EVAR – OR	EVAR: 17/4 OR 16/5	EVAR: 74 (53 – 81) OR: 74 (46 – 80)	NHP score	-	Pre-op, 5, 30, 90 d	P Single	100%	-
Aquino (2001) [36]	1997 – 1999	EVAR – OR	EVAR: 23/2 OR: 19/7	EVAR: 71 ± 2 OR: 70 ± 6	SF-36	-	Pre-op, 1, 4, 8, >52 w	P Single	100%	100% Caucasian (EVAR) 96% Caucasian (OR)
Ballard (2004) [37]	2000 – 2003	EVAR – OR	EVAR: 20/2 OR: 81/26	EVAR: 77 (51 – 87) OR: 72 (33 – 89)	SF-12	-	Pre-op, 3 w, 4 mo, 1 y	P Single	100%	-
Lottman (2004) [38]	1996 – 1999	EVAR – OR	EVAR: 54/3 OR: 16/3	EVAR: 69 (52 – 82) OR: 68 (52 – 81)	SF-36 EQ-5D	-	Pre-op, 1, 3 mo	RCT Multi	95%	-

Table 1. Continued

Soulez (2005) [39]	1998 – 2002	EVAR – OR	EVAR: 19/1 OR: 20/0	EVAR: 70 ± 6 OR: 71 ± 7	SF-36 Karnofsky score Pain scale	-	Pre-op, 1, 3, 6, 12, 18, 24 mo, 24, 48 h, 7, 30 d (pain scale)	RCT Single	-	-
Vogel (2005) [40]	1998 – 2003	EVAR – OR	EVAR: 80/12 OR: 86/40	EVAR: 72 ± 0.7 OR: 71 ± 0.7	SF-36	-	Pre-op, 2 w – 3 mo + 3-12 mo	P Single	70%	-
Aljabri (2006) [41]	*	EVAR – OR	EVAR: 37/6 OR: 25/8	EVAR: 76 ± 7 OR: 67 ± 9	SF-36	-	Pre-op, 1 w, 1 mo, 6 mo	P Multi	100%	88% self-dependent (EVAR) 97% self-dependent (OR)
Kurz (2010) [42]	1997 – 2003	EVAR	<80y: 213/19 >80y: 31/7	<80y: 70 (43 – 79) >80y: 83 (80 – 93)	NHP score	-	55 (29-78) mo (<80) 34 (4-71) mo (>80)	P Single	96% - 53%	
Ehlers (2011) [43]	1989 – 2007	OR	327/0	72 ± 5	SF-12 EQ-5D EQ-VAS	-	5 ± 3.5 y	R Registry	87%	No differences responders – no responders. Except time since surgery (shorter in responders)
Khan (2011) [44]	2006 – 2008	EVAR – OR	EVAR: 17/4 OR: 86/16	EVAR: 78 ± 1 OR: 74 ± 7	Study specific questionnaire (based on: review + focus group)	-	23 (6-40) mo	P Registry	89%	-
Kisis (2012) [45]	2008 – 2010	EVAR – OR	EVAR: 17/3 OR: 16/4	EVAR: 78 ± 1 OR: 74 ± 7	SF-36	-	Pre-op, 1 mo, 1 y	P Single	100%	
Hinterseher (2013) [46]	1995 – 2006	EVAR – OR	EVAR: 47 OR: 98	EVAR: 71 (68 – 92) OR: 69 (52 – 86)	WHOQOL-BREF SF-36	-	30 (4-53) mo (EVAR) 67 (18-153) mo (OR)	R Single	76%	-
Mouawad (2013) [47]	*	EVAR – OR	EVAR: 18/2 OR: 14/1	EVAR: 71 ± 8 OR: 69 ± 4	SF-36	-	Pre-op, 30 d, 90 d, 1 y	P Single	75%	75% married (EVAR) 87% married (OR)
Pol (2014) [48]	2009 – 2011	EVAR	<80y: 880/93 >80y: 250/40	<80y: 70 ± 7 >80y: 83 ± 3	EQ-5D	-	Pre-op, 1 w, 30 d	R Registry	96%	-

Table 1. Continued

Tocher (2013) [49]	*	OR	19/3	69 (58 – 80)	Pain score Interview (pain expectations)	-	Pre-op, 0, 24, 48, 96 h	P Single	-	-
De Bruin (2016) [50]	1999 – 2002	EVAR – OR	EVAR: 161/12 OR: 161/17	EVAR: 71 ± 7 OR: 70 ± 7	SF-36 EQ-5D	-	Pre-op, 3 w, 6 w, 3 mo, 6 mo, 12 mo + every 6 mo until 5 y	RCT Multi	90%	-
Peach (2016) [51]	*	EVAR – OR	EVAR: 89/14 OR: 67/2	EVAR: 77 (61 – 96) OR: 73 (60 – 90)	Aneurysm DQoL Aneurysm SRQ Aneurysm TSQ	-	6, 12, >12 mo	R Multi	66%	-
Kato (2017) [52]	2011 – 2013	EVAR – OR	EVAR: 24/1 OR: 28/2	EVAR: 76 ± 8 OR: 73 ± 8	SF-36	-	Pre-op, 1, 3, 6, 12 mo	P Single	100%	Patients with additional surgical procedures were excluded
Dijkstra (2019) [53]	2009 – 2011	EVAR	Endoleak: 175/22 No endoleak: 803/90	Endoleak: 74 ± 8 No endoleaks: 73 ± 8	EQ-5D	Yes	Baseline, 1 y	R Registry	-	Patients with concomitant or another type (I/III) of endoleak were excluded
Pettersson (2019) [54]	*	EVAR – OR	EVAR: 32/4 OR: 31/9	EVAR: 75 (65 – 85) OR: 68 (52 – 80)	SOC-questionnaire Malina's 5 6ESQ	-	1 mo, 1 y, 2 y	P Single	84%	-
EVAR 2 [55]	1999 – 2003	EVAR – No repair	EVAR: 141/25 No repair: 147/25	EVAR: 77 ± 6 No repair: 76 ± 7	SF-36 EQ-5D	-	1, 3, 12 mo (EVAR), 2, 4, 13 mo (no repair)	RCT Multi	96%	Patients who are considered non eligible for open repair
Lederle (2012) [56]	2002 – 2008	EVAR – OR	EVAR: 441/3 OR: 435/2	EVAR: 0 ± 8 OR: 71 ± 8	SF-36 EQ-5D IIEF-5	-	6 mo, 30 d, 12 mo + every year until 8 y	RCT Multi	67% - 85%	87% Caucasian (EVAR) 87% Caucasian (OR)

7

Table 1. Continued

EVAR 1 [57]	1999 – 2003	EVAR - OR	EVAR: 494/49 OR: 489/50	EVAR: 74 ± 6 OR: 74 ± 6	SF-36 EQ-5D	-	Pre-op, 0-3 mo, 3-12 mo, 12-24 mo	RCT Multi	99%	100% Caucasian (EVAR) 100% Caucasian (OR)
QUALITATIVE RESEARCH										
Dubois (2014) [58]	*	EVAR – OR	EVAR: 18/0 OR: 18/0	72 (58 – 85)	Focus group	Yes	2 – 12 mo	P Single	34%	Patients primarily declined due to difficulty travelling to the hospital
Lee (2017) [59]	*	EVAR – OR	EVAR: 31/0 OR: 21/0		Focus group → questionnaire	Yes	Experience of perioperative and postoperative care (1 y)	P Registry + Single	32%	-
Letterstal (2010) [60]	2005	OR	6/4	73 (55 – 83)	Semi-structured interviews	-	<3 mo	P Single	100%	-
Peach (2016) [61]	Before 2016	EVAR – OR	EVAR:28/1 OR: 6/2	EVAR: 73 (61 – 88) OR: 75 (65 – 86)	Focus groups	-	6 (2-13) mo (EVAR) 8 (3-20) mo (OR)	P Single	-	-

Data are presented as n, median interquartile range, or mean ± standard deviation, unless stated otherwise. OR, open repair; EVAR, endovascular aneurysm repair; SIP, Sickness Impact Profile; HI, Health index; SF-36, Short Form 36-item survey; HSCL, Hopkins Symptom Checklist; GHQ, General Health Questionnaire; NHP, Nottingham Health Profile; SF-12, Short Form 12-item survey; EQ-5D, EuroQoL 5D; EQ-VAS, EuroQoL visual analogue scale; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire – BREF; Aneurysm DQoL, Aneurysm-Dependent Quality of Life; Aneurysm SRQ, Aneurysm Symptom Rating Questionnaire; Aneurysm TSQ, Aneurysm Treatment Satisfaction Questionnaire; SF-8, Short Form 8-item survey; SOC, Sense of Coherence; ESQ, Experience of Service Questionnaire; IIEF=5, International Index of Erectile Function – 5; P, prospective study; R, retrospective study; RCT, randomized controlled trial; Single, single center study; Multi, multi center study.

If sex of patients was not specified, it was assumed that sex was 100% male.

***** Year of inclusion not stated in the article.

Outcome assessment

The primary outcomes were (1) identification of quantitative QoL scales and their outcomes; and (2) comparison between items included in quantitative QoL scales and items emerging in qualitative research. Secondary outcomes included average follow up duration, and outcomes with respect to follow up. Mean QoL scores were pooled at predefined time points: pre-operative, one, six, 12, and 24 months after intervention

To explore outcomes emerging from qualitative research, qualitative studies were analysed in several phases. Firstly, key findings were sorted by their original themes and subthemes (**Supplementary Appendix 3**). Secondly, similar findings were identified and sorted into common themes and subthemes using the framework analysis (**Supplementary Appendix 4**).[24] The findings were compared with the original texts to confirm that the correct meaning was comprehended.

To evaluate the alignment between qualitative and quantitative studies, items that emerged from the qualitative synthesis were mapped against items from quantitative studies. A triangulation approach was used to evaluate whether the items overlapped (+), partially overlapped (+/-), or did not overlap (-).[25,26]

Three authors (R.B. [PhD student], J.L. [vascular researcher], and J.S. [vascular surgeon]) independently extracted and analysed the data. When the researchers disagreed, outcomes were discussed and consensus on the findings was reached.

Statistical analysis

Mean QoL scores of quantitative questionnaires were pooled using a random effects model of DerSimonian and Laird.27 Heterogeneity was assessed by I2 statistics.28 All analyses were performed with Stata/SE, version 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Literature search

The literature search identified 4446 non-identical articles, of which 2921 were excluded after title review. Eighty-eight abstracts and 47 full texts were read to assess eligibility. The final review included 33 articles that reported aspects of the QoL of patients with AAA who underwent elective repair (**Figure 1**).

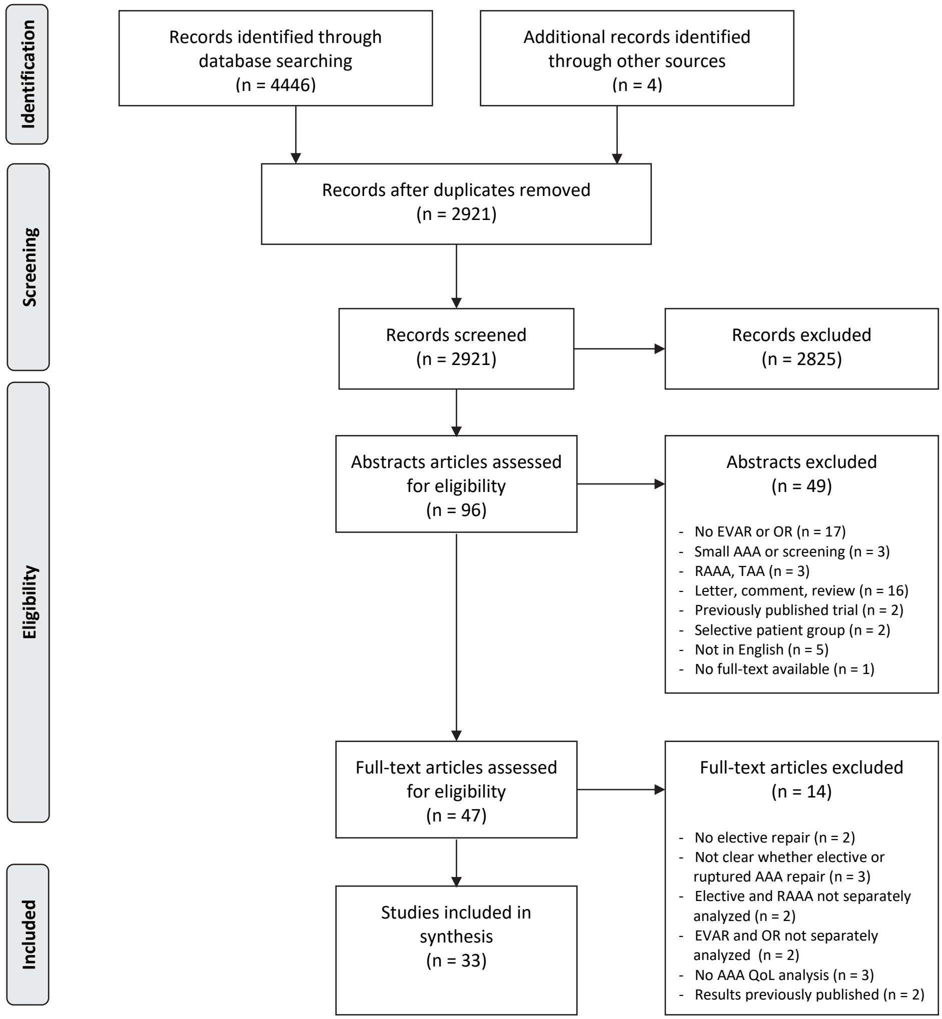


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews (PRISMA- ScR) flow diagram for literature search to identify studies on quality of life (QoL) assessment in elective abdominal aortic aneurysm (AAA) repair

EVAR, endovascular aneurysm repair; OR, open repair; RAAA, ruptured AAA; TAA, thoracic aortic aneurysm.

Study characteristics

Of the 33 articles, 29 (88%) were quantitative studies and four (12%) were qualitative studies. Most studies included both EVAR and open repair (OR) patients. Eight studies exclusively included OR patients, and four studies focussed on EVAR patients. An overview of included articles can be found in **Table 1**.29-61 In total, this review included data for 7223 patients: 2610 treated by OR and 4613 by EVAR. All patients were included between 1989 and 2013. Patient age ranged from 67 to 83 years (OR group: 67 - 83 years; EVAR group: 69 - 78 years). The proportion of males was 91% in both the OR and EVAR groups. The median follow up was one year. Only one study reported a follow up period of > 6 years (**Figure 2**). The overall quality of qualitative studies was good (**Supplementary Table 1**). The methodology of studies reporting quantitative QoL measurements varied. Descriptive data regarding the patient population and response rate are reported in **Table 2**.

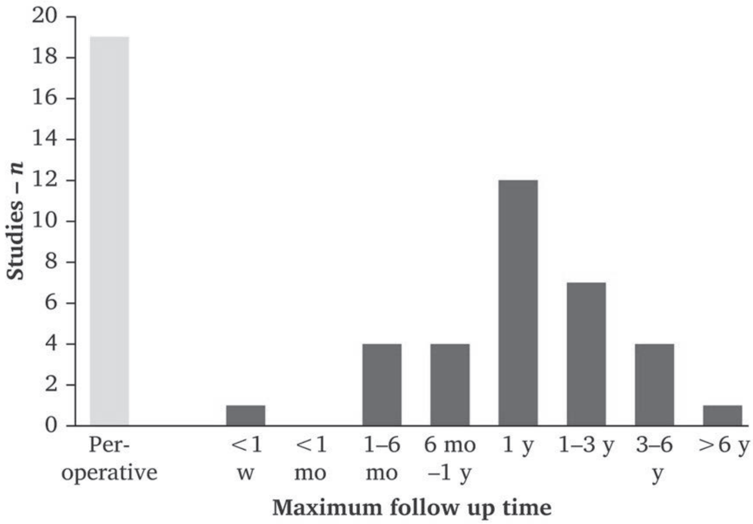


Figure 2. Number of studies reporting on pre-operative quality of life assessment and maximum follow up time after elective abdominal aortic aneurysm repair

Table 2. Items from qualitative research categorised in six main themes and their alignment in the generic, quantitative quality of life questionnaires in assessment for elective abdominal aortic aneurysm (AAA) repair

	GENERIC		AAA-SPECIFIC		
Aspects emerging from qualitative research	**SF-36**	**EQ-5D**	**Aneurysm DQoL**	**Aneurysm SRQ**	**Aneurysm TSQ**
Functional outcomes					
Recovery time	-	-	-	-	-
Being able to go home	-	-	-	-	-
Being able to work	-	+/-	+	-	-
Financial implications	-	-	+	-	-
Energy	+	-	+	-	-
Restrictions of activity	+	+	+	-	-
Self-care/dependence on others	+	+	+	-	-
Sex life	-	-	+	-	-
Household tasks	+/-	-	+	-	-
Able to go on holiday	-	-	+	-	-
(Physical) symptoms					
Pain	+	+	-	+	-
Leg numbness	-	-	-	+	-
Problems walking	+	+	-	+	-
Loss of appetite	-	-	-	+	-
Weight loss/gain	-	-	-	+	-
Urination problems	-	-	-	+	-
Bowel problems	-	-	-	+	-
Nausea	-	-	-	+	-
Lethargy	+	-	-	+	-
General weakness	-	-	-	+	-
Tiredness	+	-	-	+	-
Sleep/sleeping disturbances	-	-	-	+	-
(Night) sweats	-	-	-	+	-
Fever	-	-	-	+	-
Bruising	-	-	-	+	-
Swelling	-	-	-	+	-
Headaches	-	-	-	+	-
Wound problems	-	-	-	+	-
Psychological outcomes					
Concerns about outcomes/complications	-	-	-	-	-
Concerns about symptoms	-	-	-	-	-
Anxiety	+	+	+	-	-
Angry/upset	-	-	-	+	-

Table 2. lContinued

Cognitive function	-	-	+	-	-
Depression/feeling down	+	+	+	-	-
Fear of the future/unknown	-	-	+	-	-
Social outcomes					
Impact on family members	+/-	+/-	+	-	-
The amount people worry about me	+/-	-	+	-	-
Social life	+	+/-	+	-	-
Information					
Need for information	-	-	-	-	+
Lack of information	-	-	-	-	+
Opportunity to gather information	-	-	-	-	+
Self-control					
Decision-making	-	-	-	-	-

SF-36, Short Form 36-item survey; EQ-5D, EuroQoL 5D; AneurysmDQoL, Aneurysm Dependent Quality of Life; AneurysmSRQ, Aneurysm Symptom Rating Questionnaire; AneurysmTSQ, Aneurysm Treatment Satisfaction Questionnaire; + = included; +/- = partially included; - = not included.

Quality of life assessment in quantitative and qualitative studies

The 33 studies reported a total of 54 QoL scales, the majority of which were quantitative. A detailed overview of all scales used is provided in **Figure 3**.

The most frequently used quantitative scales were the generic SF-36 (reported in 16 studies or 30% of all reported scales) and the EQ-5D (reported in eight studies or 15% of all reported scales). The aneurysm specific scales, AneurysmDQoL (Aneurysm Dependent Quality of Life), AneurysmSRQ (Aneurysm Symptom Rating Questionnaire), and AneurysmTSQ (Aneurysm Treatment Satisfaction Questionnaire), were only reported by Peach et al. (**Figure 3**).[51]

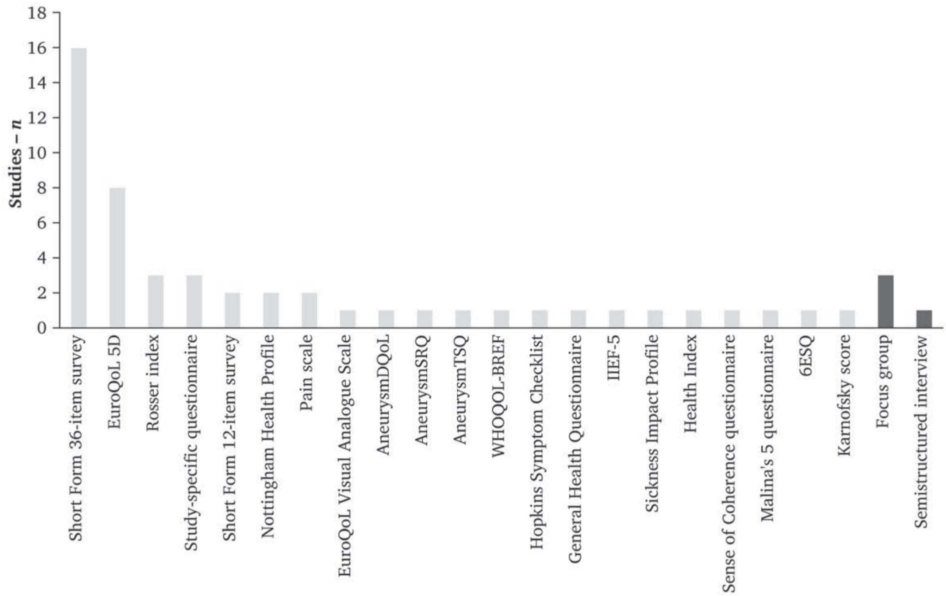


Figure 3. Quantitative and qualitative tools used to evaluate the quality of life (QoL) of patients undergoing elective abdominal aortic aneurysm repair

Light red bars represent quantitative research. Dark red bars represent qualitative research. AneurysmDQoL, Aneurysm Dependent Quality of Life; AneurysmSRQ, Aneurysm Symptom Rating Questionnaire; AneurysmTSQ, Aneurysm Treatment Satisfaction Questionnaire; WHOQOL-BREF, World Health Organisation Quality of Life Questionnaire - BREF; IIEF-5, International Index of Erectile Function - 5; ESQ, Experience of Service Questionnaire.

As the SF-36 was reported in 16 studies, it allowed for a meta-analysis of its sensitivity to changes in QoL following elective AAA. The mean SF-36 scores were pooled for predefined time points (**Figure 4**). It was concluded that SF-36 scores did not vary over time, with the exception of a transient drop in the scores of two questionnaire items (role physical and vitality) following OR. Pooling of the EQ-5D and aneurysm specific scales was not possible owing to insufficient data and study heterogeneity.

Four studies applied a qualitative approach, of which three relied on focus groups and one on semi-structured interviews (**Figure 3**).[58-61] A comprehensive overview of aspects identified in the qualitative studies is provided in **Supplementary Appendix 4**. In summary, qualitative evaluation of the patient's perspective on QoL identified six main themes: functional outcomes; (physical) symptoms; psychological symptoms; social outcomes; communication; and self control (**Table 2**).

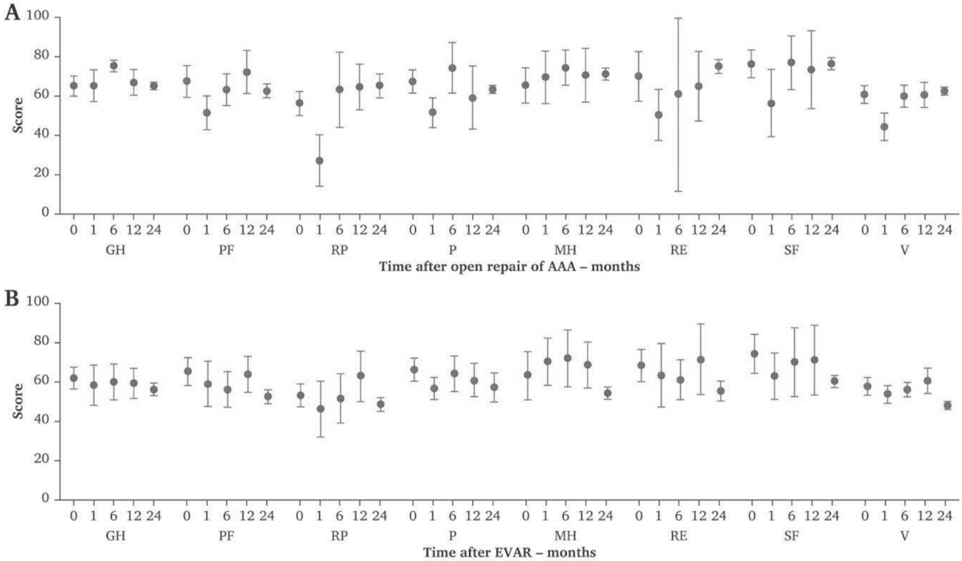


Figure 4. Pooled results of the Short Form 36 item survey (SF-36) over time with 95% confidence intervals for (A) open and (B) endovascular (EVAR) repair for abdominal aortic aneurysm (AAA) in 33 studies.

GH, general health; PF, physical functioning; RP, role physical; P, bodily pain; MH, mental health; RE, role emotional; SF, social functioning; V, vitality.

Comparison of aspects covered in quantitative scales vs. qualitative studies

Aspects emerging from qualitative research (patient's perspective) were mapped against aspects covered by the most used quantitative QoL scales (generic and aneurysm specific) to evaluate parallels and discrepancies (**Table 2**). The comparison revealed poor alignment of the generic QoL questionnaires with the patient's perspective as reported by the four qualitative studies included in this review. The SF36 and EQ-5D covered few of the aspects that patients in the qualitative studies reported as being important (i.e. functional outcomes and pain [**Table 2**]). The three aneurysm specific questionnaires were better aligned with aspects considered relevant by patients but still missed "concerns regarding symptoms" and "the impact of possible outcomes/complications". "Self control and decision making", which was brought forward by patients in all four qualitative studies, was not captured in any of the quantitative questionnaires.

The impact of follow up on quality of life

Three of 33 studies (10%) addressed the QoL with regard to follow up and/or re-interventions. One quantitative study evaluated the impact of a re-intervention in the first year after EVAR due to endoleaks.[53] It found similar mean EQ-5D scores at the one year follow up for patients both with and without endoleaks (endoleak 0.88 ± 0.18; no endoleak 0.88 ± 0.16; P=0.94). Two qualitative studies addressed the patients attitudes towards the possibility of a reintervention in elective repair.[58,59] It was concluded that the possibility of a re-intervention influenced the choice of repair (i.e. patients preferred to not have a re-intervention). No qualitative study specifically addressed the impact on QoL of an actual re-intervention. Qualitative studies found that patients have a positive attitude towards follow up visits, and generally feel reassured by follow up scans. Quotes from patients reported in qualitative research are summarised in **Table 3**, to illustrate the findings regarding re-interventions.

Table 3. Impact of re-interventions and follow up on quality of life

The possibility of re-interventions influenced the choice of repair	"I looked at both procedures and I recognized that there was a slightly higher chance of not making it through with the incision in my stomach, but I didn't think it was significant enough to go for the through the groin, and possibly having to redo it." [58]
	"For me it was the longevity of the stents. The stability of the stent as far as it dropping out of position, no follow-up in my case [was most important]." [58]
Experience lack of information about follow-up	"Recovery time. Didn't realize monitoring would be continued, thought I was cured." [59]
	"I was surprised that I needed another stent and balloon after the first trouser stent." [59]
Feeling reassured by follow-up scans	"It is a pleasure coming here and being told you're OK." [61]

DISCUSSION

This scoping review shows that there is currently no established tool that fully captures all aspects of the patient's perspective on QoL appropriate for the QoL aspect in a COS for elective AAA repair. In order to fulfil the need for a COS for the management of elective AAA disease, a more comprehensive overview of the patient's perspective is required.

The medical field is rapidly changing from hierarchically structured to shared forms of decision making. The development of a COS provides the opportunity to put patients at the centre of care, by ensuring that outcomes important to patients are included, monitored, and assessed in clinical studies and practice.[1,2] Moreover, consistent reporting of a disease specific COS enables systematic evidence synthesis, and reduces study heterogeneity and reporting bias.[3,4]

In the context of AAA, improvements in peri-operative care, patient selection, and surgical techniques (such as the introduction of EVAR) led to marked reductions in procedural complications and death.[62] As a result, traditional (surgical) outcome measures such as peri-operative mortality and/or complication rates became less discriminatory parameters, especially in the case of EVAR, to evaluate patient care, and patient derived outcomes gained in importance.[63] So far, most studies that have addressed the patient's perspective in the context of elective AAA repair have relied on generic quantitative QoL questionnaires.

A critical question is whether these questionnaires adequately capture the patient's perspective. For example, health status, a dimension included in many quantitative QoL questionnaires, is different from perceived QoL, and does not truly reflect the patient perspective.[8] The question arises to what extent the generally applied quantitative QoL questionnaires reflect the patient's perspective on QoL.

Based on this scoping review it was concluded that quantitative QoL questionnaires lack the sensitivity to detect changes in QoL associated with elective AAA repair, and do not capture several important dimensions identified in qualitative studies of what patients consider to be "quality of life". This latter aspect may reflect the fact that the SF-36 and EQ-5D (cost utility analysis) are primarily designed to evaluate the health status of patients rather than the full spectrum of QoL.[64]

In contrast to quantitative research, qualitative research strategies allow for in depth evaluation of patient thoughts, and are therefore more suitable to evaluate QoL.[12,65] Based on qualitative research, Peach et al. designed AAA specific questionnaires to assess QoL (AneurysmDQoL), symptoms (AneurysmSRQ), and treatment satisfaction (AneurysmTSQ).[51,61] While these questionnaires largely cover the aspects emerging from other qualitative studies, they do not address themes such as the "ability of self control and decision making" and "concerns about symptoms". Moreover, these AAA specific scales designed by Peach et al. are based on the data of a single study.[61] Hence, it cannot be ruled out that the aspects addressed are incomplete, and/or that cultural interferences impact the conclusions. In addition, these AAA specific questionnaires have not been widely validated in clinical practice. So, while these AAA specific questionnaires take an important first step towards the inclusion of PROs in AAA management, they require further refinement.

Perceptions of "quality of life" influence medical decision making. In the case of elective AAA repair, the impact of follow up and re-interventions on "quality of life" is a recurring point in the debate regarding EVAR vs. OR.[5,66] From a health provider's perspective, it is generally assumed that mandatory follow up and risk of late graft failure and re-interventions after EVAR negatively affect QoL.[5,66] However, there is limited evidence to support these assumptions. This review shows that only three studies specifically address the impact of follow up and potential re-interventions on a patient's perspective of QoL.[53,58,59] One emerging conclusion is that, in contrast, to general assumptions, patients experience follow up as reassuring. In fact, patients report that dissatisfaction with follow up was due to a lack of follow up after OR rather than to excessive follow up after EVAR. Similar conclusions are drawn from the qualitative PREFER study (Preferences of Patients, Their Family Caregivers and Vascular Surgeons in the Choice of Abdominal Aortic Aneurysms Treatment Options), which explored patients' motivations to decide on EVAR or OR.[67,68] In the current study, it was found that patients and caregivers were not concerned about a more intense follow up. Therefore, the general notion that intensive mandatory follow up negatively impact QoL is not correct.

A critical finding of this review is that the median follow up of all QoL assessments of elective AAA repair was one year (**Figure 2**). As the majority of re-interventions occur after one year, information on the impact of actual reinterventions on aspects of the QoL of patients with AAA is missing.[69,70] To address this knowledge gap, longer follow up times and more qualitative research is needed to more adequately explore the patient's perspective with regard to elective repair and its possible complications.[71] Addressing long term aspects is vital, as elective AAA repair is a purely prophylactic procedure and does not come with additional benefits. Hence, elective AAA repair should not harm patients over their life expectancy.

A challenge in the evaluation of the QoL of patients with AAA is the asymptomatic nature of aortic aneurysm disease.[72] In contrast to symptomatic diseases that result in discomfort or are directly life threatening and therefore likely to gain significant improvement in QoL after intervention, treatment of asymptomatic AAA will most likely not lead directly to tangible benefits and consequent clear improvements in QoL. This aspect may explain the apparent unresponsiveness of the generic quantitative QoL scales. In fact, a study of subjective outcomes following open surgical repair reported that 18% of patients indicated that they would not undergo AAA repair again knowing the recovery process, even though they fully understood the implications of AAA rupture.[73] Therefore, instead of focusing on improvement of QoL after repair, the aim should be to minimise deterioration in QoL during follow up and following elective repair.

In summary, there are currently no scales that cover all aspects of QoL in the context of elective AAA repair. In order to meet the need for a AAA specific COS, existing scales should be optimised to include more aspects that patients consider to be important regarding their QoL than is currently the case.[7] **Table 2** provides a list of items that should be included in future studies. This is a comprehensive list and a more condensed set of outcomes would be useful in the light of AAA surgery trials. In fact, information on critical outcome aspects that emerged from the qualitative studies, such as "recovery time" and "the ability to go home". Outcomes related to self control are generally missing from most study protocols. In line with the concept of a COS, definition of outcome sets should be performed in consultation with patients (i.e. representative focus groups should be conducted in order to define a COS for future studies). In addition, preexisting (validated and non-validated) tools, such as the Hospital Anxiety and Depression Scale, can be used to provide further input. Owing to the lack of qualitative data, the question remains whether all aspects that patients report as important are captured. The aneurysm specific scales defined by Peach et al. provide a promising first step but must be further validated and expanded.[51,61] Moving forward, a more comprehensive tool that enables the detection of changes in QoL following AAA repair must be developed. Such a tool should also include the individual patient motives and priorities, which are often influenced by age and context in time.[74,75] In other words, patients should not only be asked to report on specific items, but also on how they feel about and prioritise different items. Sanderson et al. provides a methodological strategy to develop a prioritised patient derived COS.[76]

Although QoL is mostly subjective in nature, its measurement should meet scientific criteria, such as validity and reliability. Therefore, during the development of a QoL COS, extensive validation of both qualitative and quantitative research is needed.[77]

Limitations

The focus of this study was on QoL aspects of a COS, as QoL is most widely used to evaluate the patient's perspective. Yet, COSs are not exclusively about QoL and other aspects need to be considered when designing a COS. The evaluation of possible outcome differences between EVAR and OR, and aspects beyond elective AAA repair (e.g. AAA surveillance) were beyond the scope of this review. Inclusion of studies with different methodologies and sample sizes resulted in considerable heterogeneity between the studies pooled in the meta-analysis. Consequently, only the SF-36 scores could be pooled. Finally, women were under represented. To design a COS that represents the entire patient population, efforts must be made to adequately address sex specific aspects.

Conclusion

Exclusive reliance on generic QoL questionnaires cannot be recommended in the development of a COS to evaluate the QoL of patients undergoing elective AAA repair. They are poorly aligned with the patient's perspective and are insufficiently sensitive to change. Aneurysm specific questionnaires provide an important first step in the understanding and incorporation of the patient's perspective but require extension and further validation. Despite efforts to evaluate care from a patient's perspective, there is a paucity of data in this field. Therefore, more qualitative research should be conducted, and stronger patient involvement is required to allow for the development of a disease specific COS that adequately incorporates the patient's perspective on treatment outcomes. This way, a COS can provide clinicians with a tool to evaluate and target issues important to patients, and ultimately to strive for higher quality of care.

REFERENCES

1. Jones JE, Jones LL, Keeley TJ, Calvert MJ, Mathers J. A review of patient and carer participation and the use of qualitative research in the development of core outcome sets. PLoS One 2017;12: e0172937.
2. Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). Trials 2014;5:15e49.
3. COMET initiative. Core outcome measurements in effectiveness trials. Available at: https://www.comet-initiative.org/ [Accessed 14 February 2021].
4. Clarke M, Williamson PR. Core outcome sets and systematic reviews. Syst Rev 2016;5:11.
5. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's Choice e European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2019;57:8e93.
6. IMPROVE Trial Investigators. Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. Eur Heart J 2015;36:2061e9.
7. Powell JT, Ambler GK, Svensjö S, Wanhainen A, Bown MJ. Beyond the AAA guidelines: core outcome sets to make life better for patients. Eur J Vasc Endovasc Surg 2019;57:6e7. 8 Hamming JF, De Vries J. Measuring quality of life. Br J Surg 2007;94:923e4.
9. Beattie DK, Golledge J, Greenhalgh RM, Davies AH. Quality of life assessment in vascular disease: towards a consensus. Eur J Vasc Endovasc Surg 1997;13:9e13.
10. Devlin N, Appleby J. Getting the most out of PROMS: putting health outcomes at the heart of NHS decision-making. King's fund. Available at: https://www.kingsfund.org.uk/sites/default/files/Getting-the-most-out-of-PROMs-Nancy-Devlin-John-ApplebyKings-Fund-March-2010.pdf [Accessed 14 February 2021].
11. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? Br J Cancer 1988;57:109e12.
12. Green J, Thorogood N. Qualitative Methods for Health Research. Thousand Oaks, CA: SAGE; 2018.
13. Higginson IJ, Carr AJ. How can quality of life measures be used in the clinical setting? BMJ 2001;322:1297e300.
14. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473e83.
15. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337e43.
16. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18:143e9.
17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169:467e73.
18. PRISMA Statement. PRISMA for scoping reviews. Available at: http://www.prisma-statement.org/Extensions/ScopingReviews [Accessed 14 February 2021].
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8:19e32.
20. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69.
21. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13:141e6.

22. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L, et al. Scoping reviews: time for clarity in definition, methods, and reporting. J Clin Epidemiol 2014;67:1291e4.
23. Critical Appraisal Skills Programme. CASP qualitative checklist. Available at: https://casp-uk.b-cdn.net/wp-content/uploads/ 2018/03/CASP-Qualitative-Checklist-2018_fillable_form.pdf [Accessed 2 May 2021].
24. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman G, Burgess A, editors. Analysing Qualitative Data. London: Routledge; 1994. p. 173e94.
25. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. Qual Health Res 2006;16:377e94.
26. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ 2010;341:c4587.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139e45.
28. Higgins JP, Thompson SG. Quantifying heterogeneity in a metaanalysis. Stat Med 2002;21:1539e58.
29. Magee TR, Scott DJ, Dunkley A, St Johnston J, Campbell WB, Baird RN, et al. Quality of life following surgery for abdominal aortic aneurysm. Br J Surg 1992;79:1014e6.
30. Sandström V, Björvell H, Olofsson P. Functional status and wellbeing in a group of patients with abdominal aortic aneurysm. Scand J Caring Sci 1996;10:186e91.
31. Mangione CM, Goldman L, Orav EJ, Marcantonio ER, Pedan A, Ludwig LE, et al. Health-related quality of life after elective surgery: measurement of longitudinal changes. J Gen Intern Med 1997;12:686e97.
32. Hennessy A, Barry MC, McGee H, O'Boyle C, Hayes DB, Grace PA. Quality of life following repair of ruptured and elective abdominal aortic aneurysms. Eur J Surg 1998;164:673e7.
33. Perkins JM, Magee TR, Hands LJ, Collin J, Galland RB, Morris PJ. Prospective evaluation of quality of life after conventional abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 1998;16:203e7.
34. Lloyd AJ, Boyle J, Bell PR, Thompson MM. Comparison of cognitive function and quality of life after endovascular or conventional aortic aneurysm repair. Br J Surg 2000;87:443e7.
35. Malina M, Nilsson M, Brunkwall J, Ivancev K, Resch T, Lindblad B. Quality of life before and after endovascular and open repair of asymptomatic AAAs: a prospective study. J Endovasc Ther 2000;7: 372e9.
36. Aquino RV, Jones MA, Zullo TG, Missig-Carroll N, Makaroun MS. Quality of life assessment in patients undergoing endovascular or conventional AAA repair. J Endovasc Ther 2001;8:521e8.
37. Ballard JL, Abou-Zamzam AM, Teruya TH, Bianchi C, Petersen FF. Quality of life before and after endovascular and retroperitoneal abdominal aortic aneurysm repair. J Vasc Surg 2004;39:797e803.
38. Lottman PE, Laheij RJ, Cuypers PW, Bender M, Buth J. Healthrelated quality of life outcomes following elective open or endovascular AAA repair: a randomized controlled trial. J Endovasc Ther 2004;11:323e9.
39. Soulez G, Thérasse E, Monfared AA, Blair JF, Choiniére M, Elkouri S, et al. Pain and quality of life assessment after endovascular versus open repair of abdominal aortic aneurysms in patients at low risk. J Vasc Interv Radiol 2005;16:1093e100.
40. Vogel TR, Nackman GB, Crowley JG, Bueno MM, Banavage A, Odroniec K, et al. Factors impacting functional health and resource utilization following abdominal aortic aneurysm repair by open and endovascular techniques. Ann Vasc Surg 2005;19:641e7.

41. Aljabri B, Al Wahaibi K, Abner D, Mackenzie KS, Corriveau MM, Obrand DI, et al. Patient-reported quality of life after abdominal aortic aneurysm surgery: a prospective comparison of endovascular and open repair. J Vasc Surg 2006;44:1182e7.
42. Kurz M, Meier T, Pfammatter T, Amann-Vesti BR. Quality of life survey after endovascular abdominal aortic aneurysm repair in octogenarians. Int Angiol 2010;29:249e54.
43. Ehlers L, Laursen KB, Jensen MB. Health-related quality-of-life in patients after elective surgery for abdominal aortic aneurysm. J Med Econ 2011;14:787e91.
44. Khan JA, Mazari FA, Abdul Rahman MN, Mockford K, Chetter IC, McCollum PT. Patients' perspective of functional outcome after elective abdominal aortic aneurysm repair: a questionnaire survey. Ann Vasc Surg 2011;25:878e86.
45. K¸!ısis K, Krievin¸"s D, Na"skovi"ca K, Gedin¸"s M, Savlovskis J, E" z!ıte N, et al. Quality of life after endovascular abdominal aortic aneurysm repair: nellix sac-anchoring endoprosthesis versus open surgery. Medicina (Kaunas) 2012;48:286e91.
46. Hinterseher I, Kuffner H, Berth H, Gäbel G, Bötticher G, Saeger HD, et al. Long-term quality of life of abdominal aortic aneurysm patients under surveillance or after operative treatment. Ann Vasc Surg 2013;27:553e61.
47. Mouawad NJ, Leichtle SW, Manchio JV, Lampman RM, Halloran BG, Whitehouse Jr WM. Construct domain analysis of patient health-related quality of life: physical and mental trajectory profiles following open versus endovascular repair of abdominal aortic aneurysm. Patient Relat Outcome Meas 2013;4:1e6.
48. Pol RA, Zeebregts CJ, van Sterkenburg SM, Ferreira LM, Goktay Y, Reijnen MM. Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) Investigators. Outcome and quality of life after endovascular abdominal aortic aneurysm repair in octogenarians. J Vasc Surg 2014;60:308e17.
49. Tocher JM. Expectations and experiences of open abdominal aortic aneurysm repair patients: a mixed methods study. J Clin Nurs 2014;23:421e8.
50. de Bruin JL, Groenwold RH, Baas AF, Brownrigg JR, Prinssen M, Grobbee DE, et al. Quality of life from a randomized trial of open and endovascular repair for abdominal aortic aneurysm. Br J Surg 2016;103:995e1002.
51. Peach G, Romaine J, Holt PJ, Thompson MM, Bradley C, Hinchliffe RJ. Quality of life, symptoms and treatment satisfaction in patients with aortic aneurysm using new abdominal aortic aneurysm-specific patient-reported outcome measures. Br J Surg 2016;103:1012e9.
52. Kato T, Tamaki M, Tsunekawa T, Motoji Y, Hirakawa A, Okawa Y, et al. Health-related quality of life prospectively evaluated by the 8-item short form after endovascular repair versus open surgery for abdominal aortic aneurysms. Heart Vessels 2017;32:960e8.
53. Dijkstra ML, Zeebregts CJ, Verhagen HJM, Teijink JAW, Power AH, Bockler D, et al. Incidence, natural course, and outcome of type II endoleaks in infrarenal endovascular aneurysm repair based on the ENGAGE registry data. J Vasc Surg 2020;71:780e9.
54. Pettersson ME, Bergbom I. Life is about so much more: patients' experiences of health, well-being, and recovery after operation of abdominal aortic aneurysm with open and endovascular treatment e a prospective study. J Vasc Nurs 2019;37:160e8.
55. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005;365:2187e92.

56. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg Jr FT, Kohler TR, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012;367:1988e97.
57. EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005;365:2179e86.
58. Dubois L, Novick TV, Power AH, DeRose G, Forbes TL. Identification of patient-derived outcomes after aortic aneurysm repair. J Vasc Surg 2014;59:1528e34.
59. Lee R, Jones A, Woodgate F, Bellamkonda K, Killough N, FulfordSmith L, et al. The experience of patients during the clinical management pathway of abdominal aortic aneurysms at a NHS trust. J Patient Exp 2017;4:202e9.
60. Letterstål A, Eldh AC, Olofsson P, Forsberg C. Patients' experience of open repair of abdominal aortic aneurysm•preoperative information, hospital care and recovery. J Clin Nurs 2010;19:3112e22.
61. Peach G, Romaine J, Wilson A, Holt PJ, Thompson MM, Hinchliffe RJ, et al. Design of new patient-reported outcome measures to assess quality of life, symptoms and treatment satisfaction in patients with abdominal aortic aneurysm. Br J Surg 2016;103:1003e11.
62. Bulder RMA, Talvitie M, Bastiaannet E, Hamming JF, Hultgren R, Lindeman JHN. Long-term prognosis after elective abdominal aortic aneurysm repair is poor in women and men: the challenges remain. Ann Surg 2020;272:773e8.
63. Dawson J, Doll H, Fitzpatrick R, Jenkinson C, Carr AJ. The routine use of patient reported outcome measures in healthcare settings. BMJ 2010;340:c186.
64. Payakachat N, Ali MM, Tilford JM. Can The EQ-5D detect meaningful change? A systematic review. Pharmacoeconomics 2015;33:1137e54.
65. Lyttkens L, Wanhainen A, Svensjö S, Hultgren R, Björck M, Jangland E. Systematic review and meta-analysis of health related quality of life and reported experiences in patients with abdominal aortic aneurysm under ultrasound surveillance. Eur J Vasc Endovasc Surg 2020;59:420e7.
66. National Institute of Health and Care Excellence (NICE). Abdominal aortic aneurysm: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng156/resources/ abdominal-aortic-aneurysm-diagnosis-and-management-pdf66141843642565 [Accessed 14 February 2021].
67. Reise JA, Sheldon H, Earnshaw J, Naylor AR, Dick F, Powell JT, et al. Patient preference for surgical method of abdominal aortic aneurysm repair: postal survey. Eur J Vasc Endovasc Surg 2010;39:55e61.
68. Faggioli G, Scalone L, Mantovani LG, Borghetti F, Stella A, PREFERstudy group. Preferences of patients, their family caregivers and vascular surgeons in the choice of abdominal aortic aneurysms treatment options: the PREFER study. Eur J Vasc Endovasc Surg 2011;42:26e34.
69. Hiramoto JS, Reilly LM, Schneider DB, Sivamurthy N, Rapp JH, Chuter TA. Long-term outcome and reintervention after endovascular abdominal aortic aneurysm repair using the Zenith stent graft. J Vasc Surg 2007;45:461e5.
70. Al-Jubouri M, Comerota AJ, Thakur S, Aziz F, Wanjiku S, Paolini D, et al. Reintervention after EVAR and open surgical repair of AAA: a 15-year experience. Ann Surg 2013;258:652e
71. Machin M, Ulug P, Pandirajan K, Bown MJ, Powell JT. Towards a core outcome set for abdominal aortic aneurysm: systematic review of outcomes reported following intact and ruptured abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2021;16:909e18.
72. Cronenwett JL, Johnston W, Rutherford RB. Rutherford's Vascular Surgery. Philadelphia, PA: W.B. Saunders; 2010.

73. Williamson WK, Nicoloff AD, Taylor Jr LM, Moneta GL, Landry GJ, Porter JM. Functional outcome after open repair of abdominal aortic aneurysm. J Vasc Surg 2001;33:913e20.
74. Lennings CJ. Optimism, satisfaction and time perspective in the elderly. Int J Aging Hum Dev 2000;51:167e81.
75. Carr AJ, Higginson IJ. Are quality of life measures patient centred? BMJ 2001;322:1357e60.
76. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. Arthritis Care Res 2010;62:647e56.
77. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patientbased outcome measures for use in clinical trials. Health Technol Assess 1998;2:1e74.

SUPPLEMENTAL MATERIAL

Supplementary Appendix 1. PRISMA-ScR guidelines checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/ objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3-4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5-6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	5-6 +7

7

Supplementary Appendix 1. Continued

Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	5-6 +7
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7-8
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	7-8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	9
Limitations	20	Discuss the limitations of the scoping review process.	11-12
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	9-12
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	1

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Supplementary Appendix 2. Literature search strategy

Component 1: Abdominal aortic aneurysm (AAA)

("Aortic Aneurysm, Abdominal"[Mesh] OR "AAA"[tiab] OR (("Aneurysm"[Mesh] OR "Aneurysm"[tw] OR "Aneurysms"[tw]) AND ("Abdomen"[Mesh] OR "Abdominal Cavity"[Mesh] OR "Abdomen"[tw] OR "Abdominal"[tw] OR "Aorta, Abdominal"[Mesh] OR (("Aorta"[tw] OR "Aortic"[tw]) AND ("abdominal"[tw] OR "abdomen"[tw])))))

Component 2: Quality of Life

("Quality of Life"[Mesh] OR "Patient Reported Outcome Measures"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR "Health Status"[Mesh] OR "Health Status Indicators"[Mesh] OR "Patient Preference"[Mesh] OR "Interviews as Topic"[Mesh] OR "Focus Groups"[Mesh] OR "Qualitative Research"[Mesh] OR "QoL measurement"[tw] OR "Quality of life"[tw] OR "QoL"[tw] OR "Patient reported outcome measure"[tw] OR "Patient reported outcome measures"[tw] OR "PROM"[tw] OR "PROMs"[tw] OR "SF-36"[tw] OR "Short Form 36"[tw] OR "SF-12"[tw] OR "Short Form 12"[tw] OR "Questionnaire"[tw] OR "Questionnaires"[tw] OR "EQ-5D"[tw] OR "EQ5D"[tw] OR "HR-QoL"[tw] OR "HRQoL"[tw] OR "HRQL"[tw] OR "Functional status"[tw] OR "Health status"[tw] OR "Patient experience"[tw] OR "Patient perception"[tw] OR "Patient attitude"[tw] OR "Patient preference"[tw] OR "Patient experiences"[tw] OR "Patient perceptions"[tw] OR "Patient attitudes"[tw] OR "Patient preferences"[tw] OR "Patients experience"[tw] OR "Patients perception"[tw] OR "Patients attitude"[tw] OR "Patients preference"[tw] OR "Patients experiences"[tw] OR "Patients perceptions"[tw] OR "Patients attitudes"[tw] OR "Patients preferences"[tw] OR "Patient's experience"[tw] OR "Patient's perception"[tw] OR "Patient's attitude"[tw] OR "Patient's preference"[tw] OR "Patient's experiences"[tw] OR "Patient's perceptions"[tw] OR "Patient's attitudes"[tw] OR "Patient's preferences"[tw] OR "Patients' experience"[tw] OR "Patients' perception"[tw] OR "Patients' attitude"[tw] OR "Patients' preference"[tw] OR "Patients' experiences"[tw] OR "Patients' perceptions"[tw] OR "Patients' attitudes"[tw] OR "Patients' preferences"[tw] OR "Semi-structured interview"[tw] OR "Semi-structured interviews"[tw] OR "Interview"[tw] OR "Interviews"[tw] OR "Focus group"[tw] OR "Focus groups"[tw] OR "Qualitative research"[tw])

Supplementary Appendix 3. Data extraction qualitative research

1. Dubois[5]8

Aim: to identify novel concepts that could be developed into patient-based outcomes to be evaluated in future prospective data.

Focus group: patients who had undergone open repair or EVAR.

Key Findings

The most important outcome among both open and EVAR groups was recovery time. Concerns about recovery time were among the most important factors that motivated patient decisions. Another emerging theme was the importance that patients placed on functional outcomes after surgery. In contrast, they placed little importance on traditional outcomes, such as the chance of dying or serious complications.

Other frequently mentioned outcomes included postoperative pain, time to walking normally, loss of appetite, extent and location of incisions, difficulty with urination, constipation, discomfort or numbness in the legs, weight loss, and impact on cognition.

Patients differed in how much information they wanted about the procedure and their level of involvement in decision-making.

Patients held unrealistic or unfulfilled expectations about the procedure ad its intended risk and necessary recovery, particularly in regard to the endovascular repair.

Clarifying how much a patient and the family wish to know about surgery may emerge as an important step in the consent process, as each discussion must be individualized.

Clarifying patient expectations surrounding not only expected risks and benefits but also the functional impact of surgery and its recovery should be of prime importance to surgeons.

Theme	Quotes
Recovery time	"Because my mind was on recovery, and if the open surgery was less recovery, I would have had that." "It wasn't the small difference in chance of dying after the surgery, it was the recovery time"
Energy level	"I'd say energy level is the most important to me."
Postoperatieve pain	"The things I wasn't expecting was the pains I've had in my legs and the problems I've had with my legs."
Time to walking normally	"Even now I have trouble with walking. It feels like I'm walking on a sponge, it never improved."
Loss of appetite	"I love to eat. You know you lose your appetite, it's no good. If you don't eat you can't get your strength back."
Extent and location of incision	"My first one [consideration] would be location of the incision; the longer it is, the longer it will take to heal."
Difficulty with urination	"To me it was going home with the catheter, I still can't pee right like I say when you took your diapers off at 2 years old, you didn't expect to wear them again."
Constipation	"I had a really hard time with constipation, ever since my surgery I have an awful time. It's very, very slow."
Discomfort or numbness in the legs	"I had significant numbness in my legs, sitting or walking became very uncomfortable."
Durability of repair	"I looked at both procedures and I recognized that there was a slightly higher chance of not making it through with the incision in my stomach, but I didn't think it was significant enough to go for the through the groin, and possibly having to redo it."

Supplementary Appendix 3. Continued

Weight loss	"For me it was the weight loss, I lost a lot of weight after my operation, and I haven't gained it back."
Impact on cognition	"I would have opted for the other way [stent], because I was diagnosed with pre-dementia and I was concerned about the long surgery and being lost after. I'd be worried about the effects on the brain."
Length of hospital stay	"I think my biggest thing, I didn't want to be in the hospital for any length of time."
Being able to go home after surgery	"Knowing that you are going to be able to go home is most important."
Impact on caregivers	"Mine was the biggest impact on family members of the procedure."
Chance of dialysis	"I would have liked to have known what my chances were that I would be on dialysis."
Risk of infection	"I would say risk of infection is important."
Night sweats	"I'll be soaking wet from sweat ever since the operation, and I never had that before. I just wake up and the bed is soaked."
Chance of impotence	"I would have liked to have known side effects or ramifications like chances of impotence, I didn't realize that these things could happen."
Depression	"If you have depression, I think it is pretty darn serious."
Need for lifelong surveillance	"For me it was the longevity of the stents. The stability of the stent as far as it dropping out of position, no follow-up in my case [was most important]."
Time to return to work	"Returning to work, that was most important."
Time to resume driving	"I drive for a living there.I was given a choice and took the one that got me driving again soonest."
Chance of dying	"I'd say the chances of survival of the operation would be important to me. Probably if there was a big difference in mortality, I would pick the one with the least opportunity to die."
Chance of serious complication	Risk of complications was my biggest consideration between
Chance of stroke	"The only thing else that I was concerned about was the chance of stroke."
Undervaluing or underappreciating the risk of death	"It didn't make a difference to me, the dying bit." "I'm not frightened of that. We're all going to die. And at my age what the heck." "But that [risk of death] didn't bother me. Like it happens when it happens."
Differing informational needs about the risks of the procedure and decision-making preferences	"I think I'm a little bit different, the less I know the better it is, because I don't have to wait, lay and think about it." "I was given a choice but I didn't take it, I said to him, you're the professional guy at this, what do you think?" "I did feel that there could have been more dialogue between the team and the patient." "One recommendation would be for someone, people like me, a learning presentation." "Quite frankly, I didn't have enough information to make a learned decision."

Supplementary Appendix 3. Continued

Unrealistic or unfulfilled expectations about the procedure and the risks	"I had angioplasty and it was nothing. I thought it was going to be like that." "I hardly call a stent an operation." "Would have been easier to accept it [complication], if I had known about it." "I was told 3-4 weeks [recovery], it took me about 4 months." "I said it was nothing, it was just a stent, and I couldn't understand why I felt so rotten."
2. Lee [59]	
Aim: to ascertain patients' experience during the clinical care pathway, which encompasses surveillance and intervention.	
Focus group: patients under surveillance or who had undergone open repair or EVAR.*	
Key Findings	
The most important themes regarding AAA management were provision of information and explanation, and regular monitoring (screening) of AAA. Only a small proportion of patients was anxious about having the aneurysm. The majority of patients do not view AAA as a disease. Although the provision of information/explanation is important to many patients, we also need to respect patients' wishes regarding the amount of explanation each individual would prefer. It is clear that for some patients, having more explanation may not be to their benefit, as was the case for the patient who did not want to know much about their condition. The ability to tailor the amount of information to suit the individual patient is perhaps the one overlooked pillar of "personalised" medicine."	
Theme	**Quotes**
EVAR (suprised regarding surgery)	"I was somewhat surprised that the whole procedure was so comfortable." "How wonderful it all turned out." "How painless it was." "A few things went wrong. This was very worrying." "Yes, the insistence of open surgery when requested keyhole. Had to fight for 2 years with…eventually granted." "Only that I was aware (ie, no general anaesthetic)." "Recovery time. Didn't realise monitoring would be continued, thought I was cured." "As the time approached for surgery, I became more anxious and realised that it is one thing to talk about AAA surgery but quite another thing to be there having it done." "No warning of the effect that morphine could have after surgery." "I was surprised that I needed another stent and balloon after the first trouser stent." "I was surprised at the amount of bruising that was present after the surgery." "Speed of recovery . . . explained." "Yes—the superb skill and technology involved." "It was explained to me before op surgery." "How simple keyhole."

Supplementary Appendix 3. Continued

OR (suprised regarding surgery)	"The after effects of it. Never did and never will get rid of the pain, nearly 3 years ago." "Adhesions occurred which lead to urgent 2nd operation—complicated and lead to hallucinations. Hernia and blockage involved." "The risk factor was not initially expected by acceptable." "That there were 2 options." "The extent of problem when diagnosed as being two separate items." "Loss of sexual ability. (No sperm or semen production)." "The speed at which I recovered but I didn't put in a lot of effort to get fit." "Speed of admission to surgical pre-op assessment once AAA measured at >5.5 cm." "The humanity of the surgeons and nurses and the rapidity of my recovery." "My surprise was I woke up in recovery and was being watched over by an RAF flight Lt and I thought I was back in the RAF!." "My rate of recovery and the efficiency and skill of ward staff." "In retrospect it was only after surgery that I fully realised how major the surgery was considered." "Only the time I was ill afterwards." "Surprised it was possible."

Supplementary Appendix 3. Continued

What was important during the clinical care pathway	"Saw a Dr after the procedure whose comment was 'it took a long time and wasn't straight forward'—I didn't understand and still don't." "Important to be given detailed information on condition of AAA to date following 6 month appointments." "To have an update from time to time of the situation regarding the AAA." "Being kept informed." "That I could ask question and get answers." "Good explanation of surgery. Faith in the medical team." "Being given good information as to what had happened and what could happen." "The constant information I received and the encouragement. The care was never absent and of a standard that is worthy of special mention." "That the surgeon explain the procedure fully." "Excellent communication by surgeon and all other medical contacts backed by superb technology in expert hands." "Everything was fully explained so that I understood what was going on and what the eventual surgery would entail." "Good information at all stages." "Being kept informed at every stage of the procedure." "The information, knowing everything in advance." "The continuous monitoring and de-briefing process and the honest no-frills approach of the teams involved." "The information and follow up." "The doctors explaining everything to us in detail which was most important." "I was seen promptly and hand the condition explained to me clearly and sympathetically." "Information on condition." (continued) "Information, Information, Information. That is why the AAA Seminar which I attended with my wife, was such a breath of fresh air." "Fully being kept informed of my situation." "Nothing was rushed and full explanations of the conditions were given." "Information about the aneurysm good and clear explanation on diagnosis and instructions upon future actions to be taken." "Was informed from start my aneurysm was not overtly large and has increased only marginally over the last several years." "Being kept informed." "Needed reassurance that it wasn't life threatening if dealt with at 5.5." "The clear explanation of future monitoring and the implications of the size of the size of the AAA." "Clear understanding of AAA, treatment and recovery plan."

Supplementary Appendix 3. Continued

Regularity of AAA monitoring	"That the condition was monitored and action taken as necessary." "Regular monitoring and talking to staff." "That I was being monitored on a regular basis." "That it is monitored and can be treated if required." "Monitoring." "Assurance that scanning annually would keep an eye on it, and that until I get the next scan I won't know whether it is growing." "Knowing that the conditions is being correctly (adequately) monitored." "Consistent monitoring." "That someone is keeping an eye on the size of the AAA." "Regularity of scans." "Scan frequency." "That I have annual monitoring which so far has not indicated any changes in my condition." "Pleased that I am monitored." "The regular visits to the JRH for checking. I'm relatively new to the monitoring but appreciative of it." "Regular monitoring." "Monitoring." "To be checked regularly." "Not to be forgotten." "Good to know the medics are looking out for me. Think there was a long gap of no monitoring (in Kent) before moving to Oxfordshire in 2007 which in retrospect is worrying. All OK in recent years though." "Regular monitoring." "The understanding that I will receive annual monitoring."
Immediacy of management if and when required	"To be kept informed/ have procedures explained. The surgical procedure was quick, relatively painless and recovery faster than expected. The nursing care, both ICU and ward, was extremely good." "I was seen promptly and hand the condition explained to me clearly and sympathetically." "That I was kept in hospital immediately as it was discovered and operated on as soon as possible." "The speed from diagnosis to surgery the detailed pre-surgery assessment." "Speed of action." "After my doctor confirmed my self-diagnosis the speed at which I was referred to wexham park hospital then on to John Radcliffe." "The competence and care of the of the medical team and the speed of surgery being undertaken from diagnosis."
Confidence in expertis of the surgical/medical team	"The competence and care of the of the medical team and the speed of surgery being undertaken from diagnosis." "Good explanation of surgery. Faith in the medical team." "Excellent communication by surgeon and all other medical contacts backed by superb technology in expert hands." "The fact that the RIGHT people were aware of my problem and consequently the problems were being resolved." "The quality of care delivered by the whole team." "The obvious expertise of the unit." "Very good medical care which I received." "Confidence in all medical AAA treatment etc."

Supplementary Appendix 3. Continued

3. Letterstål [60]

Aim: to elucidate patients' lived experience of the care pathway of going through open surgery for AAA (before surgery, during hospital stay, being at home).

Interview: patients who had undergone open repair.

Key Findings

Patients' experience of the AAA care pathway revealed a lack of information about alternatives to conservative management and the risks associated with the surgical treatment as well as the impact on HRQL. The unexpectedly long rehabilitation period caused strong emotions (irritation and anger) and was difficult to talk about with significant others. Patients had an increasing need for a dialogue with the hospital staff; this was not met during either hospital stay or follow-up, leaving patients with questions and concern about coming home as well as about the future. Patients wished to partake in their care and to get a chance to talk about the emotional effect of the surgery, but found the dialogue to be focussed on the physical recovery. The lack of dialogue included not receiving information and explanations about actions and decisions of the healthcare staff i.e. an overall sense of not knowing what to expect. Patients worry on becoming dependent on significant others. Patients reported physical impairments, most difficult major fatigue, altered taste sensation and loss of appetite.

Theme	Quotes
Living with a deadly threat awaiting surgery	"The surgeon told me that it could be dangerous if the aneurysm was untreated. I had a brother-in-law who died of a ruptured aneurysm; I kind of knew what it was all about." "I worked the whole time to distract my thoughts on what could happen before the surgery had been performed." "One should not have to wait as long as I did. It was a time of distress. We haven't been away for a vacation for three years because I was afraid of not being near a hospital."
Knowing the general but not specific risks with AAA surgery	"The only thing I heard was that every surgical procedure is risky." "I understood that the operation was going to be difficult and now that it's over I can agree." "The only information I thought was satisfactory was the booklet they sent to me. But I didn't think I was open for this information anyway."
Confiding in treatment decision but having no option to decline	"I had no option to decline treatment. I had to take a chance because I wanted to go on living for the sake of my children." "The surgeon recommended the treatment and I completely left the decision in his hands".
Experiencing dependency and embarrassment because of unexpected complications and lack of control	"I felt a little bit embarrassed getting help with my personal hygiene." "Later, how should I say, I wasn't able to control my diarrhoea. I couldn't manage to get to the toilet in time, this made me feel embarrassed, but they helped to wash me afterwards."
Experiencing changes in taste sensations and loss of weight	"The food didn't taste of anything, so that's why I didn't want to eat. I was overweight before the surgery, but when I came home I had lost16 kg."
Sleeping patterns being affected by the surgical experience	"I had terrible nightmares (...) I slept very badly and I got sleeping pills (...) You know, there were more psychological issues afterwards (...) things that made one feel a bit anxious. What will happen later? Is everything going to heal as planned."
Lacking dialogue according to one's needs	"If I should summarise my impression of the information before and after the surgery I would say that nothing came spontaneously." "It was not much of a dialogue with the nurses. The only thing they talked about was the physical effects following surgery but not the emotional influence."
Being worried about going home	"I didn't have an individual appointment with the physician, instead the usual questions were asked during his rounds. I told him that the only thing I was afraid of was how to manage everything at home." "I hope the thing in my belly is staying put."

Supplementary Appendix 3. Continued

Adapting to health care staff and structure instead of personal needs at follow-up	"Afterwards I thought to myself that I should have asked more questions, but I don't know why I didn't." "The health care sector is lacking a lot of money so I don't want to bother and I didn't have that many questions anyway".
Gradually understanding the magnitude and risks associated with treatment causes strong emotions	"When I realised the magnitude of the surgery I became speechless. I couldn't understand that I had survived all this. I must have a guardian angel". "The worst thing is that I couldn't have imagined that it would take such a long time to recover. The thing that really irritates me the most is the fact that I haven't got the strength to do anything. (…) If my husband doesn't do as I say, I get really angry and my reaction surprises me.."
Experiencing remaining physical complications	"I was extremely tired, so the first thing I did when I came home was to go to bed. The fatigue felt almost physical and it has taken so long to disappear. When I forced myself to be awake I got really unbearable." "I no longer have an appetite. I have to force myself to eat. It doesn't taste as it used to, it doesn't taste well". Other unexpected remaining physical problems were numbness in the leg/s, swollen vocal cords, diarrhoea, nausea and sleeping disturbances.
Feeling unprepared coping with everyday life and concerns from significant others	"I was thinking a lot of how everything was going to turn out. I had to keep it up because my husband wasn't able to manage household duties so well." "It is very difficult to talk about the operation and my husband doesn't say anything, but I imagine he thinks about it a lot."
Being alone with difficult experiences	"I understand there was a crisis at one point during the operation. It felt like I was disappearing, as if I was going to die. Yes, it felt just like that, but one tries to get these thoughts out of one's head."
4. Peach [70]	
Aim: to design three new condition-specific questionnaires based on the experiences of patients with AAA to provide robust, separate assessments of QoL, symptoms and treatment satisfaction for use in clinical practice, audit and research.	
Focusgroup: patients were enrolled in preoperative surveillance or had undergone open repair or EVAR.	
Key Findings	
Preoperative anxiety was particularly prevalent (referred to as a "ticking time bomb"). Another theme was the impact of lifestyle restrictions on QoL. Patients had the feeling to limit their physical activity. Other notable themes included failure of well-being to return to preoperative levels, impact on relationships with family members and the fact that some felt unprepared for the severity of the operation, or complications. The most mentioned symptom was pain and feelings of lethargy. The most frequently concern was that patients did not feel it had been made clear how serious their condition was. Patients also frequently mentioned that they had not been given any choice about the type of intervention.	
Theme	**Quotes**
Preoperative anxiety	"What QoL could I have with a time-bomb inside of me"' "I waited 18 months and it was getting bigger and bigger and I was on edge waiting for the results." "I didn't worry at first, but when it was said that action was needed I got worried".
Postoperative anxiety	"Once you have one thing that was completely symptomless you wonder what else you might have wrong with you".
Restrictions of activity	"I was terrified to do anything."
Impact on work	"I got through all the tests to be a truck driver and they sent me for all these tests and then doc said you won't get the job, you've got an aneurysm."
Relief of anxiety after operation	"When I had the operation it felt like someone had defused the bomb".

Supplementary Appendix 3. Continued

Impact on social life	"I find it overwhelming in a crowded room since the operation. Prior to that you couldn't keep me out of a crowded pub." "I don't feel sociable."
Financial implications	"Commercial driver: 'I'm now restricted to a 1 year [driving] licence."
Loss of independence	"I don't go out so much since the operation."
Not returned to 'normal'	"Nothing was the same [after the operation] and nothing still is."
Not prepared for severity	"It didn't feel like a serious operation."
Increased awareness of own mortality	"[I had a] sense of mortality…You're going to die one day."
Positive impact on relationships	"Quality of life, in some respects, has improved. I spend more time interacting with family and value each day more than before."
Lethargy	"Had no get up and go."
Leg pain	"Aches in legs all the time now."
Back pain	"I get lower back pain."
Abdominal pain	"Had a routine examination (scan) for stomach pains and found AAA."
Buttock pain	"I had some pain in my left buttock for some time."
Calf pain	"I get aching in the legs sometimes – claves below the knees."
Low mood	"I got so depressed I had to have antidepressants afterwards."
Weight loss	"I lost a lot of weight…I've lost a stone."
Bruising	"I had a lot of bruising after – black and blue to the knees."
Leg swelling	'Had a small amount of swelling and the nurse said it would go down."
Leg numbness	"I had this strange numbness."
Decreased activity	"Physical activity is down – perhaps because I'm thinking I shouldn't overdo it."
General weakness	"I feel a lot weaker to what I used to."
Profuse sweating	"Boiling hot, then sweating, then chills".
Poor appetite	"I would fantasize about food but if it was put in front of me I thought oh no."
Poor balance	"The legs worked but felt different – wobbly like I was drunk."
Leg weakness	"The right leg is not as strong as the left. That's new since the operation."
Leg heaviness	"My right leg was really heavy, like a lump of lead."
Poor cognitive function	"I put Christmas cards there and list there and couldn't put the two together."
Panic attacks	"I had panic attacks for a couple of weeks – and that's not something I've ever had before."
Hallucinations	"I had hallucinations I had been taken by a group and they were going to kill me."
Changes in bowel function	"I went to my doctor because I had a lot of flatulence that was causing discomfort."
Changes in urinary function	"The next day I had waterwork problems and still have."
Wound problems	"Wound from second operation bled and bled and oozed congealed blood."
Unclear about risks (e.g. air travel)	"No one said what you can do and what you can't."
No choice in type of operation	"The stent option wasn't mentioned."

Supplementary Appendix 3. Continued

Not clear how serious AAA was	"No mention of taking it easy until after the opereation…that was the first I knew how serious it was."
Scans reassuring NOT a burden	"It's a pleasure coming here and being told you're OK."
Complications sometimes confusing	"Was told I had a bent limb. I didn't understand."
Insufficient time to discuss diagnosis	"There wasn't a lot of time to ask questions."
Familial risks unclear	"[The information leaflet] didn't deal with the risks of having an aneurysm – risk factors, genetics, smoking."
Felt unready to go home	"I didn't feel ready to go home….I was more knackered than I expected to be."
Little contact with surgeon	"Although you get the scan you don't automatically get [to see] the consultant."
No warning about side-effects	"There was a lack of information about any likely adverse outcomes of the operation." "I had no appreciation of what I would feel like after this operation."
Poor understanding of AAA	"If the AAA bursts the chances of surviving are pretty slim – but that is something I found out from the web, not from here." "How do they do it? Where does the blood go? I didn't really get an answer I understood."
Little time for consent	"It would have been better to have had the consent form sooner."
Insufficient feedback about scans	"When they scan you they don't tell you [the results] – the operator of the scanner. You have to make an appointment."
Hospital stay too long	"They kept me in for a day longer than I felt was needed."
Postoperative wound management unclear	"I wasn't sure when to take the dressings off." "Some hospitals don't tell you what to do but say they will write to the GP and patients can talk to them."
Insufficient follow-up/ support	"I objected to being cut out of the physiotherapists list without seeing me."
Local follow-up would be preferable	"The only thing was can we have scans at [local hospital] because it's so much closer to home."
Worried about radiation in theatre	"Worried…how much radiation I was going to get."

Supplementary Appendix 4. Summary of themes emerging form qualitative research

Theme	Subtheme	
Functional outcomes		
Recovery (general)	Recovery time	"my mind was on recovery" [58] "the longer [the incision] the longer it take to heel" [58] "I didn't want to be in the hospital for any length of time" [58] "speed of recovery" [59] 'I couldn't have imagined that it took so long to recover" [60] "nothing was the same [after the operation] and nothing still is" [61]
	Time to walking normally	"even now I have trouble walking" [58]
Being able to go home		"knowing that you are able to go home is the most important" [58]
Work	Return to work	"returning to work, that was most important" [58] "I drive for living…driving again soonest" [58]
Financial implications		"commercial driver: I'm now restricted to a 1 year licence"[61]
Energy level		"energy level is most important to me" [58]
Restrictions of activity		"I was terrified to do anything" [61] "physical activity is down – perhaps because I'm thinking I shouldn't overdo it" [61]
(Physical) symptoms		
Pain		"was the pain in my legs" [58] "never did and never will get rid of the pain" [59] "how painless it was" [59] "aches in the legs at all time now" [61] "I get lower back pain" [61] "I had some pain in my left buttock for some time" [61]
Numbness legs		"I had significant numbness in my legs" [58]
Problems walking		"it feels like I'm walking on a sponge, it never improved" [58] "the legs worked but felt different – wobbly like I was drunk" [61]
Loss of appetite		"you known you lose your appetite, it's no good" [58] "didn't taste of anything" [60] "I no longer have an appetite"[60]
Weight loss		"I lost 16 kg" [60] "I lost a lot of weight" [61]
Urination		"…catheter, I still can't pee right" [58] "the next day I had waterwork problems and I still have" [61]
Bowel problems		"I had a really hard time with constipation" [58] "I had a lot of flatulence" [61]
Nausea		"other unexpected remaining physical problems were … nausea" [60]
Lethargy		"had no get up and go" [61]
Weakness		"I feel a lot weaker than I used to" [61]
Tiredness		"I was extremely tired" [60]
Sleep/sleeping disturbances		"I slept very badly" [60]

Supplementary Appendix 4. Continued

(Night) sweats		"I'll be soaking wet from sweat" [58] "boiling hot, then sweating, then chills" [61]
Bruising		"the amount of bruising" [59] "I had a lot of bruising" [61]
Swelling		"had a small amount of swelling" [61]
Physiological outcomes		
General		"you know there were more psychological issues afterwards" [60]
Concerns	Outcomes	"the only thing I was concerned about was the chance of stroke" [58] "a few things went wrong that was very worrying" [59]
Embarrassment / concerns about bodily symptoms		"I felt a little bit embarrassed getting help with my personal hygiene" [60]
Anxiety		"things that made one feel a bit anxious" [60]
Relief		"when I had the operation it felt like someone had defused a bomb" [61]
Cognitive function		"worried about the effects on the brain" [58] "I put Christmas cards there and the list there and couldn't put the two together" [61]
Depression		"If you have depression, I think that is pretty darn serious" [58] "I got so depressed that I Had to have antidepressant afterwards" [61]
Fear of the future/ unknown		"what will happen later" [60] "I hope the thing in my belly is staying put" [60] "I was thinking a lot how everything was going to turn out" [60] "once you have a thing that was completely symptomless you wonder what else might have been wrong with you" [61]
Social outcomes	Impact on family members	"mine was the biggest impact on family members of the procedure" [58] "I spend more time interacting with family and value each day more than before" [61]
	Social life	"I find it overwhelming in a crowded room since the operation" [61] "I don't feel sociable" [61] "I don't go out so much since the operation" [61]
Information		
Importance	General	"I didn't understand and I still don't" [59] "[important to] being kept informed" [59] "[important] that I could ask questions and get answers" [59] "[important] clear understanding of AAA, treatment, and recovery plan" [59] "the less I know the better it is" [58]
	AAA	"needed reassurance that it wasn't life threatening if dealt with at 5.5" [59]

Supplementary Appendix 4. Continued

Lack of information	General	"it was not much of a dialogue"[60] "I did feel that there could be more dialogue between the team and the patient"[58] "quite frankly, I didn't have enough information to make a learned decision"[58] "I didn't realise that monitoring would be continued. I thought I was cured"[59]
	Complications	'there was a lack of information about any likely adverse outcomes of the operation"[61] "I would like to have known what my chances were that I would be on dialysis"[58] "I would have liked to known side effects or ramifications like chances of impotence"[58] "would have been easier to accept it [complication] if I had known about it"[58] "was told I had a bent limb. I didn't understand"[61]
	Activity	"no one said what you can do and what you can't"[61]
Opportunity to gather information/dare to ask		"I don't want to bother and I didn't have that many questions anyway"[60] "afterwards I thought to myself that I should have asked more questions, but I don't know why I didn't"[60] "there wasn't a lot of time to ask questions"[61]
Self-control	Decision-making	"I was given a choice but I didn't take it, I said to him, you're the professional guy"[58] "yes the insistence of open surgery when requested keyhole. Had to fight for 2 years…eventually granted"[59] "the surgeon recommended…I completely left the decision in his hands"[60] "the stent option wasn't mentioned"[61] "they kept me In for a day longer than I felt was needed"[61] "I objected to being cut out the physiotherapist list without seeing me"[61]

Supplementary Table 1. Quality assessment of qualitative studies according to CASP tool.

	Dubois (2014) [58]	**Lee (2017)** [59]	**Letterstal (2010)** [60]	**Peach (2016)** [61]
1. Aims	Yes	Yes	Yes	Yes
2. Qualitative methodology	Yes	Yes	Yes	Yes
3. Design - question	Yes	Can't tell	Yes	Yes
4. Recruitment – aims	Yes	Yes	Yes	Yes
5. Data collection	Yes	Can't tell	Yes	Yes
6. Researcher – participants	No	Can't tell	Can't tell	Can't tell
7. Ethical issues	Yes	Can't tell	Yes	Yes
8. Data analysis (rigorous)	Yes	Can't tell	Yes	Yes
9. Statement findings	Yes	Yes	Yes	Yes
10. Valuable	Yes	Yes	Yes	Yes

PART III

Summary and future perspectives

Chapter 8

General discussion and future perspectives

Ruth M.A. Bulder

GENERAL DISCUSSION

Elective abdominal aortic aneurysm (AAA) repair is a prophylactic procedure with the goal to prolong patients' life-expectancy by preventing aneurysm rupture.[1,2] Over the past 25 years, the management of AAA disease has undergone profound developments. The gradual adaptation of endovascular aneurysm repair (EVAR) over traditional open repair resulted in a significant reduction of procedural mortality.[1,2] This, along with surgical ameliorations in general, resulted in an altered AAA patient population, including a broader spectrum of patients eligible for repair.[3] Patients of higher age, with more comorbidities and more women are now offered repair in the current era. Simultaneously, the recognition of AAA patients as high cardiovascular risk patients, has led to a progressive implementation of cardiovascular risk management (CVRM).[4] Although, AAA care has developed significantly over the past 25 years, several controversies and challenges remain.

The first part of this thesis focused on key questions regarding the 'EVAR-first strategy'. Taking into consideration the emerging concerns regarding its long-term durability that challenge EVAR as primary option for repair. It evaluated the presumed long-term survival differences of EVAR versus open repair. Thereby, it evaluated the impact of the developments in AAA management on the long-term life-expectancy. The second part of this thesis focused on other outcomes important in the evaluation of AAA care. It evaluated the presumed long-term cost difference of EVAR and open repair. In addition, it investigated how the patient perspective is currently embedded in AAA research. Hopefully, the data presented in this thesis can be used to further optimize (surgical) care for abdominal aortic aneurysm patients.

The five main conclusions of this thesis are that I) long-term (relative) survival between open versus endovascular aneurysm repair is equal; II) AAA patients remain a persistently high long-term (10-year) excess mortality after elective repair, with no change in mortality rates over the past 25 years; III) women have a notably higher short-and long-term mortality; IV) endovascular and open repair are considered cost equivalent; V) and the evaluation of the patient perspective/quality of life of AAA patients needs improvement.

PART I: AAA TREATMENT AND SURVIVAL

<u>I: Long-term survival is similar for open and endovascular aneurysm repair</u>

Although EVAR is now widely considered as primary option for repair, concerns exist regarding an impaired long-term survival in patients who underwent EVAR versus open repair.[5] In this context, it is important to note that these concerns are based on a small group of patients at risk and low generalizability of randomized controlled trials, as well as potential confounding by indication due to differences in patient characteristics between EVAR and open repair in retrospective cohorts.

In **Chapter 2** we therefore performed a systematic review and meta-analysis evaluating the survival of elective EVAR versus open repair, aiming to summarize the survival data and to minimize these impending factors. The analysis included 53 studies, which enrolled patients between 1980 – 2006.

Asymmetrical medical decision making, causing confounding by indication, was reflected in the age-difference between patients undergoing EVAR and open repair in the retrospective cohort studies, with the preference for EVAR in older patients. Although it is not possible to correct for all aspects of confounding by indication, any impact of age- and sex-dependent differences can be minimized by a relative survival analysis.[6,7] Furthermore a relative survival analysis allows to evaluate disease-specific excess mortality compared to the general population. Pooled results showed superior 30-day mortality of EVAR and demonstrated equivalent 3, 5, and 10 years relative survival rates of EVAR and open repair. Notably, the relative survival showed a steady decline from 3 to 10 years follow-up for both EVAR and open repair. This observation implicates that AAA patients have a high disease-specific excess mortality which persists after (successful) AAA repair.

II: Persistent high disease-specific excess mortality after elective AAA repair

To further evaluate the high disease-specific excess mortality after elective AAA repair observed in **Chapter 2**, we performed two time-trend analyses in **Chapter 3** and **Chapter 4**.

Over the past decades, the introduction of EVAR, ameliorations in surgical care, and the progressive implementation of CVRM lowered the procedural mortality, widened the spectrum of patients eligible for repair, and recognized AAA patients as (extremely) high cardiovascular risk patients. The question is to what extent these changes impacted the long-term survival of AAA patients, especially since results of **Chapter 2** showed a high excess mortality after repair. In **Chapter 3** we performed a time-trend analysis of the Swedish National Patient registry data. A time trend analysis was facilitated as both EVAR and the implementation of CVRM occurred in well-defined time frames. Three periods were compared, a period of predominantly open repair (2001 – 2004), a transition period (2005 – 2011), and a period with preferred EVAR (2012 – 2015). Over time, the proportion of patients with pharmaceutical CVRM gradually increased. Relative survival analyses were used 1) to address sex- age- and year- dependent differences in patient characteristics and life-expectancy over time, and 2) to evaluate possible changes in disease-specific excess mortality over time. This analysis showed that the changes in AAA management clearly improved short-term survival, but failed to improve long-term survival of AAA patients. In fact, AAA patients show an alarmingly high long-term excess mortality after AAA repair compared with the matched general population. Notably, women showed a profound survival deficit, with a doubled excess mortality rate of women compared to men.

This persistent high long-term excess mortality is an alarming result as it may imply that AAA patients are still sub-optimally treated for their long-term mortality risk. However, it could possibly be explained by an increased patient frailty over time, because EVAR has lowered the threshold for repair resulting in older and more comorbid patients being treated in the most recent period (chronological bias).[3,8,9,10] Thereby, the Swedish data was only available from 2001 onwards, a time when awareness for CVRM was already increasing, hence a potential benefit of CVRM could have been masked. At last, the results of the Swedish study could have reflected a national phenomenon. Therefore, in **Chapter 4** we validated and further elaborated the results of **Chapter 3** using another patient cohort with a more extensive period of follow up including the period before CVRM had been implemented. **Chapter 4** described a time-trend analysis of Dutch National data, including all patients who underwent elective AAA repair between 1995 – 2017. Consequently, three periods were compared, a period dominated by open repair and rudimentary CVRM (1995 – 2000), a transition period (2001 – 2011) and a period with an EVAR-first strategy and full implementation of CVRM (2012 – 2017). All analyses were stratified by age and sex. Relative survival and corresponding excess mortality rates were used to adjust for changes in patient characteristics and life-expectancy over time and to evaluate disease-specific mortality. The study confirmed the persistent high long-term excess mortality of AAA patients, highlighting a clear sex- but no age-disparity, with a clear survival deficit in women. The potential interfering effect of chronological bias by an increase of patient age and comorbidity profile was addressed in sensitivity analyses. These showed that the persistent high excess mortality is largely independent of changes in patient selection.

In an attempt to gain insight in the cause for the persistent high excess mortality we evaluated the causes of death distribution. **Chapter 3** and **Chapter 4** showed a higher proportion of cardiovascular death in the AAA population compared to the general population. Consequently, in **Chapter 4** we performed a competing risk of death analysis to evaluate the risk of patients dying from cardiovascular versus non-cardiovascular causes over time. [11] Hypothetically, the implementation of CVRM could lead to a decrease of the cardiovascular mortality, thereby exposing the patient to other competing mortality risks and thus masking a potential beneficial effect of CVRM on overall mortality. The competing risk of death analysis showed that the risk of cardiovascular versus non-cardiovascular death did not change over time. This suggests that CVRM has a marginal effect on cardiovascular mortality in AAA patients. In this, women showed a higher risk for cardiovascular mortality, which persisted for a longer time after repair. No differences were found between age-groups.

The competing risk of death analysis indicates that the lack a of a survival benefit of CVRM could not be explained by the phenomenon of competitive deaths.[11] An alternative explanation for the limited impact of CVRM on cardiovascular mortality could be that AAA patients are relatively undertreated for their cardiovascular risk factors. Despite consensus endorsing maximal CVRM in AAA patients, studies show that approximately half of AAA patients do not receive optimal CVRM or fail to meet their target levels.[12] Thereby, it cannot be excluded that low therapy adherence biased the results leading to an underestimation of the possible beneficial effect of CVRM. Another hypothesis includes that CVRM has no effect on the long-term survival.[4] This could be due to the potential resistance of AAA patients to classical CVRM, as risk factors for AAA disease differ from traditional atherosclerotic risk factors.

At last, the finding of this thesis that there were no differences in excess mortality rates between age categories, implies that the existence of an AAA reflects overall vulnerability, resulting in an inevitable high mortality risk, regardless of whether a patient is 65 or 85 years old (**Chapter 4**). Therefore, future studies should focus on exploring the high sex-dependent excess mortality, and strategies to reduce accompanied comorbidity risks.

III: Women with an AAA have a profoundly impaired prognosis

AAA disease associates with a well-known sex-disparity, with higher short- and long-term mortality rates in women after elective repair.[13] The short-term mortality deficit of women is most pronounced after open repair, as mortality rates with EVAR are lower and more comparable to men. Given that women are at higher risk to undergo open repair, the high mortality rates have far-reaching consequences for medical decision-making. **Chapter 5** consisted of an in-dept exploration for the reason of this high procedural mortality of women after open repair. Results identified intestinal ischemia as the main contributor (44%) for procedural mortality after elective open repair in women. This observation aligns with other reports identifying female sex as independent risk factor for the development of intestinal ischemia after aneurysm repair. [14] The reason for this association, however, remains unclear. Possible hypotheses include selection bias (selection of more complex patients considered unsuitable for EVAR undergo open repair), anatomical differences (women have smaller vessel diameters, more angulation, less resilient mesenteric vascularization), and procedural aspects (women undergo more suprarenal clamping).[15,16,17]

In **Chapter 3** and **Chapter 4**, we aimed to evaluate the long-term excess mortality, with a specific emphasis on the outcomes of women. The data demonstrated an alarmingly poor long-term prognosis for women, with a doubled disease-specific excess mortality compared to men (Relative Excess Risk: 1.87 (95%CI 1.73–2.02). Direct explanations for this profound survival disadvantage of women are missing. A potential explanation includes a higher frailty profile of women. As women seem relatively protected against AAA development, eventual development of the disease may reflect a higher allostatic load.[15] However, **Chapter 4** indicated that the sex-disparity is not likely to be explained by a higher age in women at time of repair as there were no significant survival differences between age categories. Moreover, the comorbidity profile for men and women was equal, with an even lower effect size of comorbidity scores on survival in women. Therefore, the higher excess mortality of women probably does not solely relate to a higher comorbidity profile. These results are supported by a recent meta-analysis reporting fewer baseline comorbidities of women.[18] Note that this could also reflect an unawareness of (cardiovascular) comorbidities in the female population.[19] In **Chapter 4** the competing risk of death analysis of cardiovascular versus non-cardiovascular death showed that women have a higher cardiovascular risk of death, which persists for a longer time after repair compared to men. This finding suggests that women are sub-optimally treated for their cardiovascular risk, or that classical CVRM is not evenly effective in men and women.[12]

PART II: ASPECTS OF MEDICAL DECISION-MAKING

IV: Similar costs of open and endovascular aneurysm repair

Amid the concerns about the long-term durability of EVAR, the presumed higher costs after EVAR remain a matter of debate, challenging EVAR as primary option of repair.[20] However, these conclusions are interfered by time-related effects as confounding by indication, time-dependent effect modification, and asymmetrical evaluation of outcomes. The aim of **Chapter 6** was to settle the discussion with respect to excessive long-term costs for EVAR. To account for the interfering effects, we performed a time-comparative analysis, which evaluated a period of exclusive open repair (1998-2000) with a period of established EVAR (2010-2012) while still allowing for a significant follow-up. Considering the broad spectrum of available endovascular devices and the fact that the device-costs are highly negotiable, a break-even approach was used. This point reflects the costs of an endovascular device at which EVAR and open repair reach cost equivalence. Asymmetrical evaluation of reinterventions was accounted by a systematic evaluation of all reinterventions related to the primary procedure. Although this evaluation showed clear differences in the type of reintervention, it was concluded that the number of procedure related reinterventions was similar for EVAR and open repair. Cost-equivalence for EVAR and open repair was reached at an endovascular device price of approximately 13.000, which reflects the current mean reported prices for an endovascular device.[21,22,23] Hence, for most routine repairs EVAR is not costlier than open repair until at least 5 years of follow-up.

V: Need for improved patient involvement in AAA

The developments in AAA management led to a considerable reduction in procedural morbidity and mortality.[24] As result, traditional outcome parameters as mortality- and complication rates become less discriminatory to evaluate care, and patient-derived outcomes gain importance. Thereby, as an AAA is mostly asymptomatic any intervention is likely to highly impact patients' quality of life. Considering this, to further improve care for AAA patients, it is essential to thoroughly understand the patient perspective in order to be able to adequately involve patient priorities in the evaluation of care. In an effort to systematically include the patient perspective in AAA research, there is a call for the development of Core Outcome Sets (COS).[25] COS are collections of key-outcomes, including the patient perspective, that are recommended to be reported in future research.[26] Today, studies addressing the patient perspective generally rely on quality of life (QoL) as its quantitative equivalent. **Chapter 7** consisted of a scoping review, which aimed to provide an overview the currently used quality of life (QoL) tools in AAA repair and to evaluate whether these tools adequately reflect the patient perspective and could therefore be incorporated in COS.[27,28] It is concluded that the patient perspective of AAA patients is mainly evaluated by general quantitative QoL scales (88%), such as the SF-36 (48%) and EQ-5D (24%). It was shown that these scales poorly align with the patient perspective. Efforts are made for disease-specific QoL tools (AneurysmDQol, AneurysmSRQ, AneurysmTSQ), which better align with the patient perspective, but still lack some important aspects. Hence, it was concluded that there is currently no established tool that fully captures all aspects of the patient perspective on QoL. To fulfill the need for COS a more comprehensive understanding and overview of the patient perspective is warranted.

FUTURE PERSPECTIVES

This thesis showed that over the past 25 years the management of AAA care has clearly improved from a surgical perspective. This is evident through lower procedural mortality rates and a broader spectrum of patients eligible for elective repair. However, despite these advancements, challenges remain concerning the severely impaired long-term mortality of AAA patients after elective repair, the profound survival disadvantage of female AAA patients, and inclusion of the patient perspective in the evaluation of care.

How to answer future research questions. The role for alternative study designs.

This thesis revealed that, despite several developments in AAA management, long-term survival of AAA patients has not changed over the past 25-years. In fact, the long-term life-expectancy of AAA patients remains severely impaired after elective repair. Since the main goal of elective AAA repair is to prolong life-expectancy by preventing aneurysm rupture, the persistent high long-term excess mortality questions the overall benefit of elective repair when weighted against the possible risk of rupture. Furthermore, the reason for the persistently low long-term excess survival remains unknown, particularly regarding the role of cardiovascular risk management (CVRM).

To address these issues new research strategies are required. Currently, randomized controlled trials (RCTs) are considered to provide the highest quality of evidence.[29] However, RCTs are limited, as they do not represent the real-world patient population due to strict inclusion criteria, are timely with a limited follow-up, are costly, and are considered unethical for a variety of research questions. For example, it is considered unethical to randomize between elective repair and no repair, making it impossible to evaluate the true survival benefit of elective repair. On the same note, current CVRM practice does not allow to randomize between optimal CVRM and no CVRM. Moreover, due to the low number of events, sufficient patient enrollment is impractical. Due to limited patients at risk, RCTs are underpowered to identify optimal treatment strategies for specific subgroups, such as women. Hence, new research strategies are eagerly anticipated.[30]

In the recent years, several alternative RCT designs have been introduced, such as stepped-wedged randomized controlled trials, registry based randomized controlled trials and trials-within-cohorts.[31] The use of these innovative trials designs shows promising results in overcoming the limitations of RCTs in surgical research.[32,33,34,35] Consequently, large (population-based) datasets will play an important role in the future when correctly handled and interpretated. Thereby, these datasets can also contribute to reflect towards one's own clinical abilities. Currently, quality audits serve as the basis for clinical reflection. By linking quality audits with large databases, not only the registration burden can be reduced, but also insight can be gained into variables not captured in current quality registries or variables with a low event rate. For example, in the Netherlands, the Dutch Surgical Aneurysm Audit provides valuable (pre) operative information, but lacks long-term survival data and detailed patient characteristics.[36] Linking multiple registries with a correct handling of them will provide meaningful information for evaluating care in the future.

Patient frailty: daily practice vs. research. The need for an unified frailty measurement.

One aspect highlighted in this thesis is the importance of adequately characterizing and evaluating the impact of patient frailty on outcome measures in AAA research (**Chapter 3** + **Chapter 4**). This is particularly important in AAA disease, given that the patient population consists of primarily older adults with multiple (chronic) comorbidities. Additionally, with the introduction of EVAR more patients whom were previously deemed at too high risk for open repair are now being considered for repair. From a clinical perspective, the assessment of patient frailty will enhance pre-operative risk stratification and empower clinicians to make informed decisions regarding the appropriate type of procedure or to determine when a procedure is likely to be futile.

Although the importance of patient frailty is widely acknowledged; the challenge lies in the fact that there is currently no consensus on how to best assess it. Interestingly, while decisions on patient frailty are made on a daily basis in the clinic, frailty assessment in research is heterogenous and inconsistent with clinical results.[37,38,39] The absence of a standardized definition and measurement tool for frailty poses a significant challenge to ongoing research and clinical practice. To establish a unified frailty assessment further research is needed. Firstly, a scoping review should be conducted to provide an overview of the currently employed frailty tools in AAA research, examine their correlation to clinical outcomes, and asses their predictive value. Secondly, it would be particularly interesting to investigate how vascular surgeons determine patient frailty (eyeball test) and identify differences between the surgeon's eye and currently employed research tools.[40] This could be accomplished by a Delphi study. With the information obtained, a prospective study can evaluate which variables are suitable for frailty assessment in AAA research. By addressing these challenges, we can take significant steps to establish new, unified frailty measurements that are universally applicable, clinically relevant, and associate with clinical outcomes.

Female patients: disadvantaged every step of the way.

The severely impaired long-term life-expectancy of women after elective AAA repair is perhaps the most alarming finding of this thesis. In AAA disease, a clear sex-disparity exists at all stages of disease. While women have a lower prevalence of disease, they develop an AAA at older age, experience higher rupture rates at lower diameters, and exhibit profoundly higher short- and long-term mortality compared to men.[41,42] Furthermore, women are banned from screening programs, which probably lead to an accumulation of risk factors before AAA presentation. Giving the higher prevalence of AAA in men, it is not surprising that most evidence is derived from studies that underrepresent women. In fact, less than 5% of trial population is female.[43] As result, current guidelines and care strategies clearly leave women at a disadvantage. To optimize AAA care for women, a better understanding of the sex-disparity in AAA disease is warranted. This necessitates the establishment of sufficiently powered cohorts of women, which can be achieved through international collaboration among clinical centers, databases, and vascular registries along with standardized monitoring and outcome reporting.

These efforts will enable us to address several ongoing challenges related to female AAA patients. One primary challenge is to evaluate the reason behind the sex-dependent long-term mortality deficit in women. While this is generally attributed to women's pre-operative condition, this thesis demonstrates that the sex disparity cannot be solely explained by women's higher age or comorbidity profile at time of repair (**Chapter 4**). However, based on the (cardiovascular) literature, the recognition of comorbidities in women may be less straight forward and currently overlooked.[44] This is supported by the observation that women tend to have a more extensive vascular disease with a higher prevalence of concomitant thoracic aortic aneurysms.[45] This may call for a different approach of pre-operative screening for women. Moreover, it would be of interest to assess women with AAA in conjunction with other cardiovascular

diseases to determine whether the significant sex-disparity is specific to AAA or extends to the broader female cardiovascular population in general.
Another challenge is the ongoing scientific uncertainty regarding the surgical threshold for women. It is hypothesized that a lower surgical threshold for women would prevent accumulation of risk factors, broaden the eligibility for EVAR, and reduce the risk of rupture.[46,47] However, the finding that women face a high procedural mortality risk, particularly after open repair (30-day mortality of 12%) (**Chapter 5**) challenges a lower surgical threshold, which potentially put women at risk of death by performing a prophylactic procedure. Furthermore, the result that women have a severely impaired life-expectancy after repair (**Chapter 3** + **Chapter 4**) questions the overall survival benefit of a lower threshold. Consequently, a randomized trial seems inevitable at this point.[46]

Cardiovascular death and events. Consider it a dynamic process.
This thesis showed that the progressive implementation of CVRM did not alter the cardiovascular mortality risk, nor impacted overall long-term life-expectancy of AAA patients over the past 25 years (**Chapter 3** + **Chapter 4**). A clear univocal explanation for this apparent limited impact of CVRM on long-term mortality is missing.[48,49] Not surprisingly, future studies are needed to evaluate the prevalence, therapeutic effect, and therapy adherence of CVRM in the AAA population.

As mentioned before, adaptive trials designs can be employed to evaluate the therapeutic effect of CVRM. One important aspect to consider is that studies conducted in the general cardiovascular population indicate that while CVRM clearly reduces or postpones cardiovascular events, its impact on overall (cardiovascular) survival is marginal.[50] In this thesis, the primary focus was on long-term survival. Thus, although an effect of CVRM on cardiovascular survival could not be demonstrated, there may still be an effect on cardiovascular events. Therefore, future studies should include both the effect of CVRM on cardiovascular mortality and events. In this, it is crucial to acknowledge that cardiovascular mortality and events are competitive and thereby a dynamic process. To be more specific, a patient might experience numerous events before dying (e.g. non-fatal myocardial infarction), whereas a patient who primarily dies is no longer at risk for events. As a result, a statistical model that simultaneously considers events and mortality is required. Multistate models represent stochastic processes in which patients can occupy different intermediate states (disease conditions) before reaching the final outcome. Thereby correcting for competing risks (e.g. malignant death over cardiovascular death).[51,52] Therefore, the application of multistate models is essential to simultaneously evaluate the effect of CVRM on cardiovascular events and mortality.

Patient perspective. The need for qualitative research.
A critical component in improving care for AAA patients is to involve the patient itself. **Chapter 7** shows that the patient's perspective is not yet adequately captured in the research of AAA care and that to adequately involve the patient in AAA research, a more thorough understanding of the patient perspective is needed. Qualitative research provides the opportunity to explore the patient perspective in-depth.[53] This will allow clinicians to appraise patient preconceptions, treatment experience, quality of

life, illness understanding, and subsequent need or desire for information.[54] Therefore, moving forward qualitative research must be the cornerstone in AAA research.

To illustrate: a noteworthy aspect that has emerged from this thesis is that a most important facet for patients in their care is their perceived need for information (**Chapter 7**). While this may appear obvious, studies show a clear discrepancy between the information that clinicians consider important and subsequently provide, and what patients truly find important.[55] By employing qualitative research to explore the information needs of patients, we can better align the perspectives of patient and clinician and deliver information that is both clinically relevant and relevant for patients.[56]

Figure 1. Future perspectives in AAA research

- We must critically appraise the reason for the high sex-specific long-term excess mortality.
- There is a need for alternative study designs to answer future research questions.
- Large population-based datasets are essential not only to evaluate real-world patient practice but also to reflect towards one own's clinical performance.
- We need a unified patient frailty tool which is clinically relevant but also practical for (retrospective) research.
- To improve outcomes for female AAA patients, a more women centered approach is necessary.
- The prevalence, adherence and therapeutic effect of CVRM on cardiovascular mortality and events must be evaluated for the AAA population.
- Cardiovascular mortality and events should (statistically) be considered a dynamic process.
- The patient perspective must be better understood and incorporated in AAA care.
- Qualitative research must be a cornerstone in AAA research.

REFERENCES

1. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kölbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines Committee, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholt JS, de Vega M, Vermassen F, Document Reviewers, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019;57:8-93.
2. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, Mastracci TM, Mell M, Murad MH, Nguyen LL, Oderich GS, Patel MS, Schermerhorn ML, Starnes BW. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018;67:2-77.
3. Pleumeekers HJ, Hoes AW, van der Does E, van Urk H, Hofman A, de Jong PT, Grobbee DE. Aneurysms of the abdominal aorta in older adults. The Rotterdam Study. Am J Epidemiol. 199515;142:1291-1299.
4. Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022;146:e334-e482.
5. Powell JT. Prophylactic Abdominal Aortic Aneurysm Repair? Open Repair Brings Early Pain but Later Gain. Eur J Vasc Endovasc Surg. 2016;52:719-720.
6. Perme MP, Henderson R, Stare J. An approach to estimation in relative survival regression. Biostatistics. 2009;10:136-146.
7. Nelson CP, Lambert PC, Squire IB, Jones DR. Relative survival: what can cardiovascular disease learn from cancer? Eur Heart J. 2008;29:941-947.
8. Greenland S, Morgenstern H. Confounding in health research. Annu Rev Public Health. 2001;22:189-212.
9. Groenwold RH. Verstoring in observationeel onderzoek: 'confounding'. Methodologie van onderzoek 2 [Bias in observational research: 'confounding']. Ned Tijdschr Geneeskd. 2012;156:A4221. In Dutch.
10. Platt RW, Schisterman EF, Cole SR. Time-modified confounding. Am J Epidemiol. 2009;170:687-694.
11. de Glas NA, Kiderlen M, Vandenbroucke JP, de Craen AJ, Portielje JE, van de Velde CJ, Liefers GJ, Bastiaannet E, Le Cessie S. Performing Survival Analyses in the Presence of Competing Risks: A Clinical Example in Older Breast Cancer Patients. J Natl Cancer Inst. 2015;108:djv366.
12. Tomee SM, Bulder RMA, Meijer CA, van Berkum I, Hinnen JW, Schoones J, Golledge J, Bastiaannet E, Matsumura JS, Hamming JF, Hultgren R, Lindeman JH. Excess mortality for abdominal aortic aneurysms and the potential of strict implementation of cardiovascular risk management. A multi-facetted study integrating meta-analysis-, national registry-, and PHAST and TEDY trial data. Eur J Vasc Endovasc Surg. 2022;S1078-5884:00805-X.
13. Talvitie M, Stenman M, Roy J, Leander K, Hultgren R. Sex Differences in Rupture Risk and Mortality in Untreated Patients With Intact Abdominal Aortic Aneurysms. J Am Heart Assoc. 2021;10:e019592.

14. Ultee KH, Zettervall SL, Soden PA, Darling J, Bertges DJ, Verhagen HJ, Schermerhorn ML; Vascular Study Group of New England. Incidence of and risk factors for bowel ischemia after abdominal aortic aneurysm repair. J Vasc Surg. 2016;64:1384-1391.
15. Pouncey AL, Powell JT. Womens lives at stake: Women Suffer Disproportionately After Abdominal Aortic Aneurysm Repair, So What Can We Do About It? Eur J Vasc Endovasc Surg. 2021;62:1-3.
16. Pouncey AL, David M, Morris RI, Ulug P, Martin G, Bicknell C, Powell JT. Editor's Choice - Systematic Review and Meta-Analysis of Sex Specific Differences in Adverse Events After Open and Endovascular Intact Abdominal Aortic Aneurysm Repair: Consistently Worse Outcomes for Women. Eur J Vasc Endovasc Surg. 2021;62:367-378.
17. Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT; SWAN collaborators. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet. 2017;389:2482-2491.
18. Tedjawirja VN, de Wit MCJ, Balm R, Koelemay MJW. Differences in Comorbidities Between Women and Men Treated with Elective Repair for Abdominal Aortic Aneurysms: A Systematic Review and Meta-Analysis. Ann Vasc Surg. 2021;76:330-341.
19. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T, Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation. 2005;111:499-510.
20. National Institute of Health and Care Excellence. Abdominal aortic aneurysm: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng156/chapter/Recommendations#monitoring- and-reducing-the-risk-of-rupture. [Accessed 24 June 2020].
21. Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, Michaels J, Thomas S, Sculpher M, Woolacott N. Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model. Health Technol Assess. 2009;13:1-189, 215-318, iii.
22. Jacoba Berghmans CH, Lübke T, Brunkwall JS. A Cost Calculation of EVAR and FEVAR Procedures at an European Academic Hospital. Ann Vasc Surg. 2019;54:205-214.
23. Lemmon GW, Neal D, DeMartino RR, Schneider JR, Singh T, Kraiss L, Scali S, Tassiopoulos A, Hoel A, Cronenwett JL. Variation in hospital costs and reimbursement for endovascular aneurysm repair: A Vascular Quality Initiative pilot project. J Vasc Surg. 2017;66:1073-1082.
24. Bulder RMA, Talvitie M, Bastiaannet E, Hamming JF, Hultgren R, Lindeman JHN. Long-term Prognosis After Elective Abdominal Aortic Aneurysm Repair is Poor in Women and Men: The Challenges Remain. Ann Surg. 2020;272:773-778.
25. Powell JT, Ambler GK, Svensjö S, Wanhainen A, Bown MJ. Beyond the AAA Guidelines: Core Outcome Sets to Make Life Better for Patients. Eur J Vasc Endovasc Surg. 2019;57:6-7.
26. COMET initiative. Core outcome measurements in effectiveness trials. Available at: https://www.comet-initiative.org/ [Accessed 21 June 2023].
27. Hamming JF, De Vries J. Measuring quality of life. Br J Surg. 2007;94:923-924.
28. Powell JT, Ambler GK, Svensjö S, Wanhainen A, Bown MJ. Beyond the AAA Guidelines: Core Outcome Sets to Make Life Better for Patients. Eur J Vasc Endovasc Surg. 2019;57:6-7.
29. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016;374:2175-2181.

30. Wallis CJD, Detsky AS, Fan E. Establishing the Effectiveness of Procedural Interventions: The Limited Role of Randomized Trials. JAMA. 2018;320:2421-2422.
31. Augustinus S, van Goor IWJM, Berkhof J, Daamen LA, Groot Koerkamp B, Mackay TM, Molenaar IQ, van Santvoort HC, Verkooijen HM, van de Ven PM, Besselink MG. Alternative Randomized Trial Designs in Surgery: A Systematic Review. Ann Surg. 2022;276:753-760.
32. Höfler M. Causal inference based on counterfactuals. BMC Med Res Methodol. 2005;5:28.
33. Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328:2446-2447.
34. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183:758-764.
35. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008;19:766-779.
36. Dutch Surgical Aneurysm Audit (DSAA). DICA. Available at: https://dica.nl/dsaa/home. [Accessed 30 December 2022].
37. Drudi LM, Ades M, Landry T, Gill HL, Grenon SM, Steinmetz OK, Afilalo J. Scoping review of frailty in vascular surgery. J Vasc Surg. 2019;69:1989-1998.
38. Wang J, Zou Y, Zhao J, Schneider DB, Yang Y, Ma Y, Huang B, Yuan D. The Impact of Frailty on Outcomes of Elderly Patients After Major Vascular Surgery: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2018;56:591-602.
39. Barbey SM, Scali ST, Kubilis P, Beck AW, Goodney P, Giles KA, Berceli SA, Huber TS, Upchurch GR, Yaghjyan L. Interaction between frailty and sex on mortality after elective abdominal aortic aneurysm repair. J Vasc Surg. 2019;70:1831-1843.
40. George EL, Kashikar A, Rothenberg KA, Barreto NB, Chen R, Trickey AW, Arya S. Comparison of Surgeon Assessment to Frailty Measurement in Abdominal Aortic Aneurysm Repair. J Surg Res. 2020;248:38-44.
41. Grootenboer N, van Sambeek MR, Arends LR, Hendriks JM, Hunink MG, Bosch JL. Systematic review and meta-analysis of sex differences in outcome after intervention for abdominal aortic aneurysm. Br J Surg 2010;97:1169–1179.
42. Johansson M, Harris RP. Thresholds in women with abdominal aortic aneurysm. Lancet. 2017;389:2446-2448..
43. Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM; EVAR-1, DREAM, OVER and ACE Trialists. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017;104:166-178.
44. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, Guerrero M, Kunadian V, Lam CSP, Maas AHEM, Mihailidou AS, Olszanecka A, Poole JE, Saldarriaga C, Saw J, Zühlke L, Mehran R. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet. 2021;397:2385-2438.
45. Hultgren R, Larsson E, Wahlgren CM, Swedenborg J. Female and elderly abdominal aortic aneurysm patients more commonly have concurrent thoracic aortic aneurysm. Ann Vasc Surg. 2012;26:918-923.

46. Vascular News. WARRIORS randomized trial aims to examine early EVAR in women. Available at: https://vascularnews.com/warriors-randomised-trial-aims-to-examine-early-evar-in-women/. [Accessed 21 December 2022].
47. Pouncey AL, Powell JT. Womens lives at stake: Women Suffer Disproportionately After Abdominal Aortic Aneurysm Repair, So What Can We Do About It? Eur J Vasc Endovasc Surg. 2021;62:1-3.
48. Saratzis A, Dattani N, Brown A, Shalhoub J, Bosanquet D, Sidloff D, Stather P; Vascular and Endovascular Research Network (VERN). Multi-Centre Study on Cardiovascular Risk Management on Patients Undergoing AAA Surveillance. Eur J Vasc Endovasc Surg. 2017;54:116-122
49. Bath MF, Gokani VJ, Sidloff DA, Jones LR, Choke E, Sayers RD, Bown MJ. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. Br J Surg. 2015;102:866-872.
50. Nicolajsen CW, Søgaard M, Eldrup N, Jensen M, Larsen TB, Goldhaber SZ, Nielsen PB. Temporal trends in abdominal aortic aneurysmal disease: a nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy. Eur J Prev Cardiol. 2022;29:1957-1964.
51. Schmoor C, Schumacher M, Finke J, Beyersmann J. Competing risks and multistate models. Clin Cancer Res. 2013;19:12-21.
52. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389-2430.
53. Phoenix M, Nguyen T, Gentles SJ, VanderKaay S, Cross A, Nguyen L. Using qualitative research perspectives to inform patient engagement in research. Res Involv Engagem. 2018;4:20.
54. Chenail RJ. How to Conduct Qualitative Research on the Patient's Experience. The Qualitative Report. 2011;16:1172-1189
55. de Mik SML, Rietveld B, Auwerda A, Balm R, Ubbink DT. Best-Worst Scaling Study to Identify Complications Patients Want to Be Informed About Prior to Abdominal Aortic Aneurysm Surgery. Patient. 2020;13:699-707.
56. Letterstål A, Eldh AC, Olofsson P, Forsberg C. Patients' experience of open repair of abdominal aortic aneurysm--preoperative information, hospital care and recovery. J Clin Nurs. 2010;19:3112-3122.

Chapter 9

Summary

Ruth M.A. Bulder

SUMMARY

The goal of elective abdominal aortic aneurysm (AAA) repair is to prevent AAA rupture and, thereby, prolong patients' life-expectancy. While AAA management has significantly developed over the past decades, with the introduction of endovascular aneurysm repair (EVAR) and the gradual adaptation of cardiovascular risk management (CVRM), several controversies and challenges remain. The primary aim of this thesis was to evaluate presumed survival differences between EVAR and open repair, as well as to evaluate the impact of changes in AAA management on the long-term life-expectancy of patients undergoing elective repair. A specific emphasis was placed on sex-dependent differences, in particular impaired outcomes for women. The second aim of this thesis was to evaluate other crucial outcomes in the assessment of AAA care, including the costs and the patient perspective.

PART I: SURVIVAL OUTCOMES

Chapter 2 provides an overview of the current literature regarding survival differences between EVAR and open repair. While EVAR has emerged as preferred option for repair due its lower short-term mortality compared to open repair, concerns exist regarding its long-term durability. These concerns challenge EVAR as preferred option for repair. The comparison between EVAR and open repair is complicated due to the preference of EVAR in frailer patients and open repair in fitter patients, leading to confounding by indication. In this review, relative survival analyses were used to account for sex and age-specific patient differences. This demonstrated comparable long-term mortality rates for EVAR and open repair. Notably, the study showed a steady decline of relative survival during follow-up for both EVAR and open repair. This implies that that AAA patients experience a high disease-specific mortality even after repair.

Over the past 25 years, the introduction of EVAR and the gradual adaptation of CVRM have changed the management of AAA disease. The question is to what extent these changes impacted the long-term life-expectancy of AAA patients, especially considering the observed high long-term excess mortality in **Chapter 2**. **Chapter 3** and **Chapter 4** describe a time-trend analysis of survival outcomes following elective AAA repair. Relative survival analyses were used to 1) address differences in patient characteristics and life-expectancy over time, and to 2) evaluate disease-specific excess mortality. **Chapter 3** includes 12 907 patients undergoing elective AAA repair between 2001 and 2015 in Sweden. This study showed an unchanged and persistently impaired relative survival over time, with a severe survival deficit for women. The question arises as to whether this result reflects sub-optimal treatment of AAA patients, a changing patient population over time, a missed effect of CVRM, or a national phenomenon. Therefore, **Chapter 4** validated and further elaborated on the results in another patient cohort with a more extensive period of follow-up, including a period before the implementation of CVRM. The study included 40 730 patient undergoing elective AAA repair between 1995 and 2017 in the Netherlands. This study confirmed the persistently high long-term excess mortality, highlighting a clear sex- but no age-disparity, with a doubled excess mortality rate for women compared to men. Changes in patient population marginally impacted excess-mortality rates. Furthermore, competing risk of death analysis showed that despite the gradual increase of CVRM, the risk of cardiovascular versus non-cardiovascular death remained similar over time, with a higher risk of cardiovascular death for women. The persistent

9

high excess mortality rates suggest that long-term mortality of AAA patients is not affected by the type of procedure or aneurysm rupture, but rather by existing comorbidities. This calls for a critical appraisal of the basis for the sex-dependent excess mortality.

The profound sex-difference in AAA repair is further emphasized in **Chapter 5**. The excess mortality of women after elective AAA repair in part relates to the high short-term mortality of women after open repair, as mortality rates with EVAR are lower and more comparable to those in men. The high short-term mortality after open repair has far reaching consequences, because women are at greater risk to undergo open repair due to a higher rate of unsuitability for EVAR. The study describes and in-depth evaluation of patient records, evaluating the cause of the female-sex associated mortality after open repair. This identifies intestinal ischemia as the main contributor (44%) to the high mortality. The reason for this association remains unclear. Possible hypotheses include selection bias (selection of more complex patients considered unsuitable for EVAR undergo open repair), anatomical differences (women have smaller vessel diameters, more angulation, less resilient mesenteric vascularization), and procedural aspects (women undergo more suprarenal clamping).

PART II: OTHER OUTCOMES IMPORTANT IN AAA MANAGEMENT

The second part of this thesis focused on other outcomes important in the evaluation of AAA care. **Chapter 6** evaluates the presumed cost-differences between EVAR and open repair, taking into account effect modification, confounding by indication, and asymmetric evaluation of outcomes. This time-comparative study design used a break-even point approach, which reflects the costs of an endovascular device at which EVAR and open repair reach cost equivalence. This was considered relevant as device-costs are highly negotiable. Cost equivalence for OR and EVAR was reached at a break-even price of approximately €13 000, corresponding to the market price of an endovascular device. Hence, EVAR and open repair can be considered cost-equivalent. Furthermore, systematic evaluation of re-interventions showed that while the type of re-intervention differs substantially between EVAR and open repair, the proportion of re-interventions is equal until 5-years follow-up.

Chapter 7 describes a scoping review of quality of life (QoL) assessment in elective AAA repair research. In order to better incorporate the patient perspective in research, Core Outcome Sets (COS) are being defined for a variety of diseases. In the field of abdominal aortic aneurysm, efforts to capture the patient's perspective focus on generic quantitative QoL scales. The question arises whether these quantitative QoL scales adequately reflect the patient perspective and whether they can be included in the QoL aspect of COS. The scoping review included 33 studies, of which were 29 quantitative and 4 qualitative. Quantitative studies (i.e. traditional QoL scales) were aligned with qualitative studies (i.e. patient perspective) to identify parallels and discrepancies. This showed that there is currently no tool that fully captures all aspects of the patient perspective. In order to fulfil the need for a COS for the management of AAA disease, a more comprehensive overview of the patient's perspective is required.

The general discussion in **Chapter 8** provides an overview of the conclusions found and the issues that remained to be studied. Furthermore, it discusses the future perspectives in elective AAA research. Although from a surgical perspective, the management of AAA disease substantially improved, several challenges remain. This thesis settles the discussion regarding the presumed long-term survival difference of EVAR and open repair. While it showed similar long-term survival rates for EVAR and open repair, it revealed a persistently high sex-dependent excess mortality after elective repair. This persistent high (cardiovascular) excess mortality calls for a critical appraisal of the effect of CVRM and the basis for the excess mortality in AAA patients. The severe survival deficit for women calls for a more women-focused research approach. Furthermore, future challenges lie in a better incorporation of the patient perspective in the evaluation of AAA care.

Chapter 10

Nederlandse samenvatting

Ruth M.A. Bulder

ELECTIEVE ABDOMINALE ANEURYSMA CHIRURGIE: UITDAGINGEN BLIJVEN BESTAAN

Een aneurysma van de aorta abdominalis (AAA) is een lokale verwijding van de buikslagader. De buikslagader of abdominale aorta is de grote lichaamsslagader die door de buik van het hart richting de benen loopt. Een AAA geeft meestal geen klachten en wordt vaak per toeval ontdekt. Hoe groter het aneurysma of hoe sneller het groeit, des te groter de kans op een scheur (ruptuur) in de bloedvatwand. Als een aneurysma ruptureert, is de kans op overlijden groot (80%) omdat er een massale levensbedreigende bloeding ontstaat.

Het doel van planbare (electieve) aneurysma chirurgie is om het aneurysma vroegtijdig uit te schakelen, daarmee een ruptuur te voorkomen, en daarmee de levensverwachting van patiënten te verlengen. De afgelopen decennia heeft de electieve AAA zorg verschillende ontwikkelingen ondergaan. Tegenwoordig is het mogelijk om via een kleine operatie in de lies een kunststof vaatprothese (endoprothese) in opgevouwen toestand via de liesslagader tot in de buikslagader op te schuiven. De endoprothese verstevigt de vaatwand van binnenuit en schakelt hiermee de bloedtoevoer naar het aneurysma uit. Dit wordt ook wel endovasculaire aneurysma repair (EVAR) genoemd. De andere optie is open repair. Bij open repair wordt door middel van een grote buikoperatie het aneurysma vervangen door een kunststof prothese. De introductie van EVAR heeft de procedurele sterfte aanzienlijk doen dalen ten opzichte van open repair. Hierdoor is electieve AAA chirurgie tegenwoordig beschikbaar voor een bredere patiëntenpopulatie, inclusief patiënten die voorheen als niet geschikt voor operatie werden beschouwd. Naast chirurgische verbeteringen worden aneurysma patiënten tegenwoordig erkend als patiënten met een hoog risico op bijkomende hart- en vaatziekten. Hierdoor ontvangen steeds meer patiënten cardiovasculair risicomanagement (CVRM) in de vorm van bloeddruk- en cholesterolverlagende medicatie en verschillende leeftstijladviezen. Ondanks de ontwikkelingen in AAA management op chirurgisch en CVRM gebied, blijven er verschillende controverses en uitdagingen bestaan.

Het eerste deel van dit proefschrift focust zich op de vermeende verschillen in lange termijn overleving tussen EVAR en open repair. Daarbij werd er gekeken wat de impact was van de veranderingen in abdominaal aneurysma management op de levensverwachting. Hierbij lag specifieke nadruk op geslachtsafhankelijke verschillen, vooral met betrekking tot inferieure resultaten voor vrouwen. In het tweede deel van dit proefschrift is er gekeken naar andere uitkomsten die relevant zijn in de medische besluitvorming rondom electieve AAA zorg, namelijk de kosten en het perspectief van de patiënt.

DEEL I: OVERLEVINGSUITKOMSTEN

Hoofdstuk 2 vormt een overzicht van de huidige literatuur met betrekking tot korte- en lange termijn overleving na electieve EVAR en open repair. Hoewel EVAR tegenwoordig wordt beschouwd als de 'eerste keus behandeling' vanwege een lagere procedurele sterfte in vergelijking met open repair, bestaan er zorgen over de duurzaamheid van EVAR op de lange termijn. Het is van belang je te realiseren dat de vergelijking tussen EVAR en open repair wordt bemoeilijkt door een onevenredige patiënten selectie, wat direct invloed heeft op de uitkomsten. EVAR wordt vaker toegepast bij oudere en kwetsbare patiënten, terwijl open repair vaker wordt toegepast bij jongere en fitte patiënten. Dit leidt in vergelijkend onderzoek tot 'confounding by indication'. Want oudere/kwetsbaardere patiënten hebben bij voorbaat een hoger risico op vroegtijdig overlijden ten opzichte van jongere fittere patiënten. Om het effect van confounding by indication te minimaliseren is er in **Hoofstuk 2** gebruik gemaakt van 'relatieve survival analyses'. Relatieve survival vergelijkt de overleving van patiënten met een bepaalde ziekte (d.w.z. een AAA) met de verwachte overleving van mensen zonder ziekte in dezelfde leeftijdsgroep en geslacht. Dit biedt een meer contextuele beoordeling van de impact van een ziekte op de levensverwachting en houdt tegelijk rekening met andere factoren die de overleving beïnvloeden (d.w.z. leeftijd en geslacht). De resultaten laten zien dat de lange termijn overleving voor EVAR en open repair verglijkbaar is. Opmerkelijk is dat de relatieve overleving voor zowel EVAR als open repair gestaag afneemt in de jaren na de operatie. Dit suggereert dat AAA patiënten, zelfs na een succesvolle operatie, een hoog sterfterisico hebben wat geassocieerd lijkt met een AAA.

De afgelopen 25 jaar hebben de introductie van EVAR en de geleidelijke implementatie van CVRM de electieve AAA zorg aanzienlijk ontwikkeld. De vraag is in hoeverre deze ontwikkelingen de levensverwachting van AAA patiënten hebben verbeterd. Met name omdat we in **Hoofdstuk 2** een hoge ziekte-specifieke sterfte observeerden na de operatie. **Hoofdstuk 3** en **Hoofdstuk 4** beschrijven een tijdstrend analyses waarin werd gekeken naar de veranderingen in de lange termijn overleving van patiënten na electieve AAA chirurgie over de afgelopen 25 jaar. Relatieve survival analysen zijn gebruikt om 1) rekening te houden met verschillen in patiënt karakteristieken en levensverwachting over de tijd en 2) ziekte-specifieke sterfte te evalueren. **Hoofstuk 3** beschrijft 12 907 patiënten die tussen 2001 en 2015 in Zweden electieve aneurysma chirurgie ondergingen. Deze studie toonde een persisterend lage relatieve overleving, die niet is veranderd tussen 2001 en 2015. Om dit in perspectief te zetten: AAA patiënten hebben ondanks een succesvolle aneurysma reparatie een slechtere 10-jaars overleving dan die wordt gezien bij veel vormen van kanker. De vraag is of dit wijst op een suboptimale behandeling van AAA patiënten, het een gevolg is van de veranderde patiëntenpopulatie in de loop der tijd, een gemist effect van CVRM is, of het dat een nationaal fenomeen betreft.

In **Hoofdstuk 4** zijn daarom de resultaten gevalideerd in een ander patiëntencohort met een langere tijdsperiode. Hierbij werd ook een periode vóór de implementatie van CVRM meegenomen, waardoor het mogelijke effect van CVRM op de lange termijn overleving beter bestudeerd kon worden. De studie includeerde 40 730 patiënten die tussen 1995 en 2017 in Nederland electieve AAA chirurgie ondergingen. Deze studie bevestigde de aanhoudende lage relatieve overleving, ofwel een aanhoudend hoge ziekte-specifieke sterfte, waarbij er geen verandering in overleving over de tijd werd waargenomen. Hierin werd een duidelijk geslacht-specifiek, maar geen leeftijd-specifiek verschil in overleving gevonden. Vrouwen toonden een tweemaal hoger sterfterisico in vergelijking met mannen. Verdere analyse toonde dat veranderingen in de patiëntenpopulatie over tijd slechts een marginaal effect hadden op de overleving en dus geen duidelijke verklaring zijn voor de aanhoudende hoge ziekte-specifieke sterfte. Het effect van CVRM op de overleving werd onderzocht aan de hand van een 'competetive death analyse'. Hypothetisch gezien zou de implementatie van CVRM kunnen leiden tot een afname van hart- en vaatziekte gerelateerde sterfte, waardoor de patiënt de kans heeft om te wordt blootgesteld aan andere concurrerende doodsoorzaken zoals bijvoorbeeld kanker. Door alleen het totaal aantal doodsoorzaken in ogenschouw te nemen wordt het mogelijk gunstige effect van CVRM gemist. Gesimplificeerd; bestuderen competetive death analyses het risico op sterfte door hart- en vaatziekten versus sterfte door anderen (competitieve) doodsoorzaken. De analyse toonde aan dat het risico op sterfte door hart- en vaarziekten versus andere doodsoorzaken niet is veranderd na de implementatie van CVRM. Dit suggereert dat voor de AAA populatie CVRM weinig effect heeft op de lange termijn overleving. Terugkomend op de vraag aan het eind van **Hoofdstuk 3** lijkt de persisterend lage relatieve overleving te suggereren dat de lange termijn overleving van AAA patiënten niet zozeer wordt beïnvloed door het type operatie of aneurysma ruptuur, maar eerder door de aanwezige comorbiditeit (andere aandoeningen naast een AAA) van patiënten.

Hoofstuk 5 gaat verder in op het overlevingsnadeel van vrouwen. De hoge lange termijn sterfte van vrouwen kan deels worden verklaard door de hoge korte termijn sterfte van vrouwen na open repair (12%) en omdat de sterfte na EVAR aanzienlijk lager is (3%) en meer vergelijkbaar met mannen. De hoge sterftecijfers na open repair hebben vergaande gevolgen, omdat vrouwen vaker anatomisch niet geschikt worden gevonden voor EVAR. Om iets te kunnen doen aan de hoge sterftecijfers is beter inzicht in de onderliggende oorzaken noodzakelijk. Daarom werden in **Hoofdstuk 5** alle patiëntendossiers onderzocht van vrouwen (n = 36) die de afgelopen jaren zijn overleden na open repair in 25 verschillende Nederlandse ziekenhuizen. Hieruit blijkt dat darmischemie (ten gevolge van een probleem met de bloedtoevoer van de drie belangrijkste bloedvaten in het maag-darm kanaal) de belangrijkste doodsoorzaak was (44%) bij vrouwen na open repair. De reden dat darmischemie vaker voorkomt bij vrouwen is nog onduidelijk. Mogelijke hypothesen zijn dat vrouwen die ongeschikt worden geacht voor EVAR per definitie complexere patiënten zijn met een vooraf hoger risico op overlijden en darmischemie (selectie bias), dat de vrouwelijke anatomie kwetsbaarder is voor darmischemie door kleine vaatdiameters en een minder veerkrachtige darmcirculatie (anatomische verschillen), en als laatste dat bij vrouwen de aorta tijdens de operatie vaker boven die nierslagaders wordt geklemd wat een hoger risico geeft op darmischemie (procedurele aspecten).

DEEL II: ASPECTEN VAN MEDISCHE BESLUITVORMING

Het tweede deel van dit proefschrift gaat over andere uitkomsten die belangrijk zijn in de besluitvorming in de electieve zorg van abdominale aneurysma patiënten.

In **Hoofdstuk 6** werden de veronderstelde kostenverschillen tussen EVAR en open repair geëvalueerd. Vanwege de vermeende hogere lange termijn sterfte en mogelijk meer heroperaties, wordt de kosteneffectiviteit van EVAR in twijfel getrokken. Zoals eerder besproken wordt de vergelijking tussen EVAR en open repair bemoeilijk door 'confounding by indication' (een onevenredige selectie van patiënten). In **Hoofdstuk 6** worden de kosten tussen EVAR en open repair vergeleken over twee tijdsperiodes. Eén periode waarin voornamelijk open repair werd uitgevoerd (1998 – 2000, n= 186) en een periode waarin EVAR de meest gangbare behandeling was (2010 – 2012, n = 195). Door twee tijdsperiodes te vergelijken waarin er per periode weinig keuze was in het type operatie, hoopten we de verschillen in patiënten selectie te minimaliseren. Specifiek werd er gekeken bij welke prijs van een EVAR-device de kosten tussen EVAR en open repair gelijk waren. Deze benadering werd gekozen omdat de kosten van een EVAR-device sterk afhankelijk zijn van onderhandelingen met de industrie. Deze retrospectieve studie liet zien dat de kosten van EVAR en open repair gelijk zijn bij een device prijs van €13.000, wat grofweg overeenkomt met de huidige marktprijs van de meeste gangbare devices. Daarnaast toonde een systematische evaluatie van alle patiëntendossiers aan dat het aantal heroperaties tussen beide benaderingen gelijk is, maar dat het soort heroperatie sterk afhankelijk is van de initiële operatie (EVAR versus open repair).

Om de zorg voor abdominale aneurysma patiënten verder te verbeteren is het van belang te begrijpen hoe patiënten hun zorg ervaren. **Hoofdstuk 7** beschrijft een scoping review (inventariserende review) waarin het patiënten perspectief op de kwaliteit van leven na electieve AAA chirurgie werd onderzocht. Bij verschillende ziektebeelden worden inspanningen verricht om het perspectief van de patiënt mee te nemen in medisch wetenschappelijk onderzoek. Een van deze inspanningen heeft zich geuit in de ontwikkeling van 'Core Outcome Sets'. Dit zijn uitkomstmaten die samen met patiënten worden opgesteld en aanbevolen voor gebruik in (toekomstige) studies, met als doel het perspectief van de patiënt te waarborgen. In aneurysma onderzoek wordt het perspectief van de patiënt tot op heden met name geëvalueerd aan de hand van kwaliteit-van-leven schalen. Deze kwaliteit-van-leven schalen zijn gebaseerd op algemene (generieke) kwantitatieve (uitgedrukt in cijfers) vragenlijsten. Het is echter de vraag of deze generieke schalen het perspectief van de patiënt adequaat reflecteren. Kwalitatief (beschrijvend) onderzoek, bijvoorbeeld interviews studies, geeft daarentegen een beter diepte inzicht in het perspectief van de patiënt. In **Hoofstuk 7** werden in totaal 33 studies (29 kwantitatieve, 4 kwalitatieve) geïncludeerd. De kwantitatieve schalen werden uitgezet tegen de kwalitatieve schalen. Hieruit blijkt dat er op dit moment geen kwantitatieve schaal is die het perspectief van de patiënten voldoende weerspiegelt. Om het perspectief van de patiënt in toekomstig aneurysma onderzoek beter te waarborgen is het van belang een beter begrip te hebben van het perspectief van de patiënt. Op basis daarvan kunnen we vervolgens adequate uitkomstmaten vaststellen voor wetenschappelijk onderzoek.

De algemene discussie in **Hoofdstuk 8** biedt een overzicht van de gevonden conclusies en bespreekt de onderwerpen waar in de toekomst aandacht aan moet worden besteed. Hoewel de behandeling van abdominale aneurysma patiënten aanzienlijk is verbeterd vanuit een chirurgisch perspectief, blijven er verschillende uitdagingen bestaan. Uit dit proefschrift blijkt dat de lange termijn overleving tussen EVAR en open repair vergelijkbaar is. Echter na de operatie hebben patiënten een aanhoudend hoog risico op overlijden, wat niet direct samen lijkt te hangen met het type operatie of een late aneurysma ruptuur. Deze aanhoudende oversterfte benadrukt de noodzaak van een kritische evaluatie van de (cardiovasculaire) oversterfte van AAA patiënten na chirurgische behandeling. Het ernstige overlevingsnadeel van vrouwen vraagt om een meer vrouw gerichte onderzoek benadering. Tot slot liggen er toekomstige uitdagingen in een betere integratie van het perspectief van de patiënt in de AAA zorg.

Appendices

Curriculum Vitae

Dankwoord

CURRICULUM VITAE

Ruth M.A. Bulder was born on the 8th of November in 1995 in Groningen, The Netherlands. Ruth graduated from the secondary school in Amersfoort (Gymnasium, Johan van Oldebarnevelt) and started Medical School at the Leiden University Medical Center in 2014.

During her studies, she joined the student society of Minerva where she participated in several committees. Starting in 2018, Ruth worked as an assistant of bariatric surgery at the Nederlandse Obesitas Kliniek (NOK). In this function, she assisted during laparoscopic surgery and was responsible the team of assistants and clinical audit registration (Dutch Audit for Treatment of Obesity (DATO)). This drove her enthusiasm for surgery.

After receiving her bachelor degree in 2018, Ruth worked as a PhD researcher at the Department of Vascular Surgery. Under supervision of Prof. dr. J.F. Hamming and dr. J.H.N. Lindeman, she investigated the effectiveness of elective abdominal aortic aneurysm repair. During her time as a researcher, she was offered to opportunity to perform a part of her research in Stockholm. And to participate in several scientific courses, to present her research on multiple (inter)national meetings, and to published scientific papers that have led to this thesis. Meanwhile she continued working at the NOK.

Ruth obtained her medical degree in June 2023 and started working as a surgical resident not in training (ANIOS) at the Department of Surgery at the Haaglanden Medisch Centrum (HMC) in The Hague.

DANKWOORD

Het wad is een wereld waar de kortste weg tussen twee punten vaak geen rechte lijn is. Dat geldt ook voor een promotietraject (veelal op het wad geschreven). Dit proefschrift is tot stand gekomen dankzij de hulp en steun van velen. Een aantal personen wil ik graag in het bijzonder bedanken.

Prof. dr. Hamming, promotor, beste Jaap. Dank dat je mij als bachelor student de kans gaf om een promotietraject te starten en mij de vrijheid gaf om hieraan zelf invulling te geven. Dank voor je altijd kritisch en optimistische begeleiding. Ik bewonder jou gave om het moeilijke, makkelijk te maken.

Dr. Lindeman, copromotor, beste Jan. Ik waardeer jouw onuitputtelijke en onconventionele toewijding aan het onderzoek. Dank voor het zijn van een waardevolle sparringpartner, ook al waren we het niet altijd met elkaar eens. Jij hebt mij gestimuleerd om kritisch te blijven. Ik begin steeds meer waarde te zien in de vraag 'wat nou als je het omdraait'.

Professor Recbecka Hultgren. Dear Rebecka, thank you for the opportunity to work together in Stockholm. I admire your endless enthusiasm and clinical research perspective. Dear Mareia, thank you for being the best sparring candidate. I hope for many joint projects in the future.

Dr. Bastiaannet, beste Esther. Bedankt voor het wegwijs maken in de epidemiologie en statistiek. Altijd had jij tijd om te brainstormen over analysen en mijn vragen te beantwoorden. Zonder jou was de statistiek lang niet zo leuk geweest.

Beste chirurgen van de NOK. Dank voor de introductie op de operatiekamer het werken in een geweldig TEAM. Beste Dingeman, dank dat jij mij ooit de vraag stelde wat ik eigenlijk kwam doen. Ik had niet durven dromen dat het zo geweldig zou zijn. Dank voor het vertrouwen en de wijze lessen. Beste Knook, jarenlang een rechte horizon heeft geleid tot een waardevolle vriendschap. Hiervoor ben ik nog altijd zeer dankbaar.

Lieve Actieve Mensen. Jullie hebben het promoveren gepromoveerd tot promotietijd. Door jullie heb ik deze tijd voor geen goud willen missen en zou ik het zo opnieuw doen. Op naar nog vele borrels, zet de nacho's maar klaar!

Lieve vriendinnetjes, in het bijzonder Maud en Ilse. Het begon allemaal met rode kaarten op het JVO. Wie had dat gedacht dat we hier nu zouden staan. Het voelt als gister als we elkaar zien. Ik ben trots op wat jullie hebben bereikt en hoe jullie in het leven staan.

Lieve Kippen en huisgenootjes in Den Haag (Kim, Jacq, Caath) dank voor jullie interesse en het nodige ontnuchterende perspectief. Lieve Caroline, als twee bachelor studenten begonnen wij aan het avontuur PhD. Ik heb veel bewondering voor hoe 'you go your own way'.

Lieve Suzan, Michèle, Fenna, Merel en Karin. Jullie waren mijn onvoorwaardelijke steun in dit onderzoek. Ik ben een heel blij mens om jullie als vriendinnen te hebben. Op naar nog vele jaren samen in en vooral buiten het ziekenhuis! Ook al mochten er fysiek maar twee naast mij staan, jullie zijn de beste paranimfen die ik mij kan wensen.

Mijn broertje, Max. Er is geen betere 'little one' in deze wereld. Ik ben enorm trots op je.

Lieve pap en mam. Bedankt voor jullie onbegrensde steun en liefde. Door jullie heb ik altijd alle mogelijkheden gekregen om te doen wat ik het liefste doe en waar ik energie uit haal. Ik hou van jullie