Gender differences in presentation of disease and clinical outcome after vascular surgery

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Financial support for printing of this thesis was generously provided by the Departments of Radiology and Epidemiology of the Erasmus University Medical Center, the Erasmus University Rotterdam, VASCUTEK Nederland, the J.E. Jurriaanse Stichting, and the Van Beek-Donner Stichting.

Cover design: Nathalie Grootenboer and A.W. Everaers
Layout: A.W. Everaers
Printed by: Ipskamp Drukkers BV
ISBN: 978-94-6191-454-5

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Sekseverschillen in presentatie en uitkomsten na vaatchirurgische ingrepen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 7 November 2012 om 15.30 uur

door

Nathalie Grootenboer
geboren te Djeddah, Saoedie-Arabië

ERASMUS UNIVERSITEIT ROTTERDAM

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Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

To mom and dad with love

Contents

Prologue

When we started this project back in 2007 cardiovascular disease was, as it is still now, a 'hot' topic. It is a field in medicine which has received a lot of attention and funding and has therefore been extensively researched. The striking feature, which can not be found to the same degree in other fields of medicine, is that all the attention went to men. Back in 2007 only one cardiovascular conference had ever been organised for women and it focussed on how to recognise a stroke or heart attack occurring in your husband!

I feel we have come a long way since then, the American Heart Association leading the way with their campaigns followed in our own country on a national level by the "Hartstichting" with their 2010 campaign. All are striving to create awareness for cardiovascular disease in women. I feel honoured to have contributed, in however small a way, to this movement and will continue to do so as we still have a lot more to do.

Chapter 1

General Introduction and outline of this thesis

For a long time, cardiovascular disease was considered a male disease. However, for women too, cardiovascular disease is the leading cause of death, and one out of every three women dies as a result of it. At the moment in the Netherlands, more women than men die annually due to cardiovascular disease. Women are less likely to die from a myocardial infarction but more likely to die from a cerebrovascular accident (CVA) (figure 1)[1]. Seeing that women in general have a longer life expectancy this has huge implications for our health care system

about easily identifiable (female) diseases such as breast cancer, and also don't recognise their a-typical symptoms as being cardiovascularly related[4]. Whatever the reason may be, this view has contributed to the fact that most cardiovascular studies are based on populations that include a majority of male patients. Due to the underrepresentation of women, treatment guidelines are based on a predominately male population and it is debatable whether these guidelines can be applied to women. A reason for this scepticism is that for coronary artery disease, gender differences

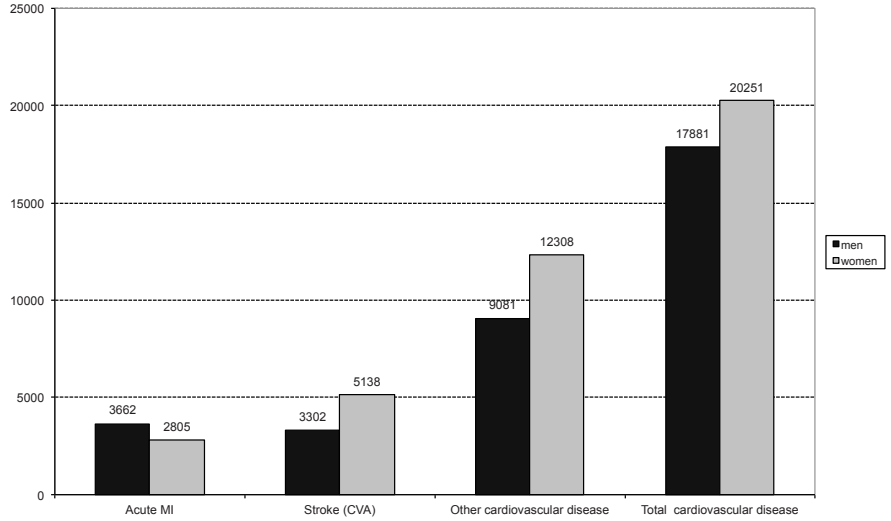


Figure 1. Cardiovascular causes of death for women and men in the Netherlands 2011 (source CBS)

The reason for the focus on men in my opinion is twofold. On the one hand doctors are less inclined to think of cardiovascular disease in women as it often presents itself in a different manner than in men[2,3]. Women do not have 'typical' male symptoms and also convey their history differently than men (emphasising emotions such as stress), which could distract the thought of cardiovascular disease being present. On the other hand women themselves worry more

have been well documented and show that women fare worse when suffering from this condition. We know for a fact that the pathophysiology differs between men and women. Until the menopause women are protected by hormones, leading to a slower progression of atherosclerosis which in its turn leads to a more diffuse condition compared to the more focal condition observed in men (figure 2). After the menopause however, women 'catch up', and have higher inci-

dence rates of cardiovascular disease compared to men[1]. The difference in pathophysiology leads to a different presentation of symptoms. Women less often report 'typical' chest pain but more often suffer from fatigue and more generalised pain in the upper half of the body[5,6].

ed in women, but unfortunately it has also been demonstrated that women are treated less aggressively and lag behind in both primary and secondary preventions[10,11].

Sometimes the kind of treatment also does not suffice for women. A good

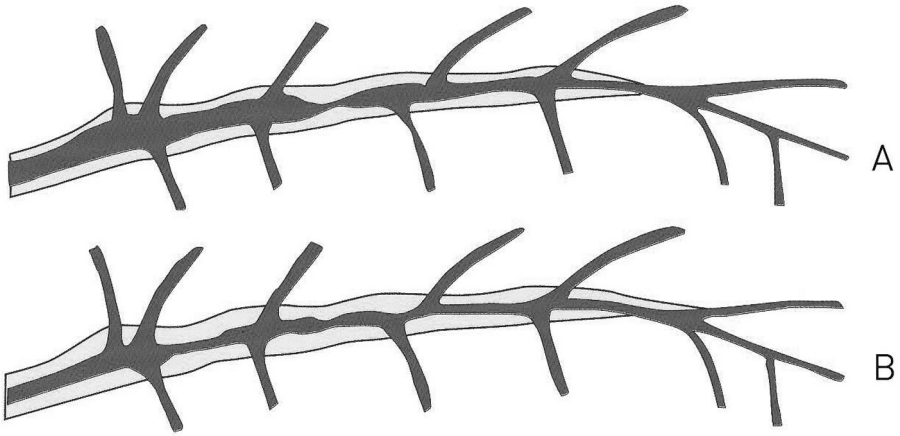


Figure 2. Atherosclerosis in an artery: A 'typical' pattern showing a focal malformation (obstruction). B image of diffuse malformations (non-obstructive)

Seeing that conventional diagnostic tests are aimed at finding focal malformations, women undergoing these tests often get a negative test. They are, therefore thought not to have a cardiovascular problem while in actual fact they have a functional problem instead of an obstructive one. This leads to a delay in diagnosis or even the entire diagnosis being missed.

There are also differences between the genders as far as risk factors for cardiovascular disease are concerned. Smoking, diabetes and hypertension have been demonstrated to be much higher relative risk factors for myocardial infarction and cardiovascular death in women than in men[7-9]. It is not fully understood which mechanisms lie at the base of this. It is therefore extra important that these comorbidities are well treated/regulat-

example is heart failure. It is understood that women mostly suffer from diastolic heart failure, compared to systolic heart failure in men. All therapies, both invasive and medicational, have focussed on systolic heart failure, which is quite a different disease, thus leading to suboptimal treatment of women with heart failure[12].

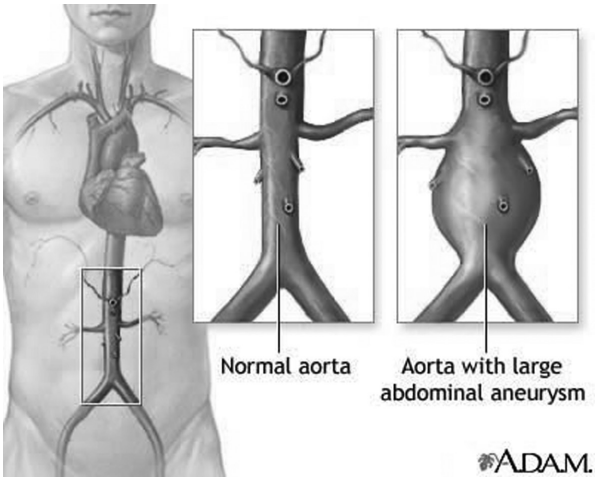
Regarding invasive coronary artery interventions, women receive fewer coronary angiographies and revascularisation procedures and have higher complication and mortality rates following these procedures[13,14].

Gender differences in non-cardiac vascular diseases have been researched to a far lesser extent. Because mechanisms in peripheral vascular disease are thought to be similar to those in coronary artery disease we

set out to study gender differences in non-cardiac vascular diseases such as abdominal aortic aneurysms (AAA) and stroke due to carotid artery stenosis.

Abdominal Aortic Aneurysm (AAA)

The current management of abdominal aortic aneurysms (AAA) arose from two randomized controlled trials (RCTs) conducted in the '90s, which indicated no benefit of operation versus surveillance for AAAs smaller than 5.5 cm. Although these two RCTs included a predominantly male population (83% in the UK Small Aneurysm trial and 99.2% in the ADAM trial) their results are applied to both sexes[15,16]. Gender specific differences in the expression of enzymes, responsible for vascular structure degradation have been documented, higher risks of rupture have been reported for women and women also seem to fare worse after both elective and ruptured AAA repair. All these factors have led to doubt about whether the current management of AAAs ensures that women receive adequate treatment.



Stroke due to carotid artery stenosis

Stroke is the leading cause of disabling disease and the third major cause of death in the Western world. More women than men die of stroke each year[17]. Approximately 20% of strokes can be attributed to atherosclerotic disease of the carotid arteries. For patients with symptomatic carotid artery disease two RCTs) clearly demonstrated the benefit of carotid endarterectomy (CEA) over medical treatment[18,19]. They also demonstrated, however, that women benefit less than men due to their higher perioperative risk and lower stroke risk with medical treatment alone. In the last decade, carotid artery stenting (CAS) has emerged as an alternative to surgical endarterectomy in an effort to minimize interventions. The published and ongoing studies focused on comparing treatment strategies and not on the possible effect of gender differences on outcomes. It remains unclear whether gender influences the outcome after carotid revascularization. Also, the impact of gender may differ depending on whether a patient is symptomatic vs. asymptomatic and which procedure is used, CEA or CAS.

Aim and outline of this thesis

The aim of the studies described in this thesis was to evaluate the effect of gender on the diseases and intervention techniques in question.

We started by reviewing the literature and addressing the epidemiology, etiology, risk of rupture and treatment of abdominal aortic aneurysms and to what extent gender plays a role, giving an extensive overview of the current state of knowledge regarding gender and abdominal aortic aneurysms. **(Chapter 2)**

The review described in Chapter 2 gave us reason to believe that the current management of abdominal aortic aneurysms was not optimal for women and led us to conduct a systematic review and meta-analysis on the topic. The aim was to assess possible differences in mortality between men and women with an abdominal aortic aneurysm (AAA) treated with elective open repair, elective endovascular repair, ruptured open repair and ruptured endovascular repair **(Chapter 3).**

In **Chapter 4** we sought to aid clinicians by performing a systematic review of current guidelines on AAA screening as recommendations on the same topic varied across the guidelines and there is still no consensus on which patient groups to screen. The role of women in screening programs also still needed to be determined.

As in other fields, minimally invasive surgery also made its entrance in vascular surgery and endovascular aneurysm repair (EVAR) was implemented widely. To see whether this technique benefitted women too we reviewed the literature and give an overview in **Chapter 5.**

After having performed the review on EVAR in women in Chapter 5 we were able to analyse one of the world's biggest EVAR registries in the world. 11,000 men and 700 women were registered in the EUROSTAR database and we analysed their 30-day and long-term outcomes leading to the results as depicted in **Chapter 6**.

The database we used for our final study was the Carotid Artery Revascularization and Endarterectomy Registry (CARE-Registry). We determined the influence of gender on short-term outcome in both symptomatic and asymptomatic patients treated either by carotid endarterectomy (CEA), or carotid angioplasty and stenting (CAS) (**Chapter 7)**.

Finally, **in Chapter 8,** the findings of this thesis and their implications are summarised and discussed and suggestions for further research are outlined.

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Chapter 2

Epidemiology, Aetiology, Risk of Rupture and Treatment of Abdominal Aortic Aneurysms: Does Sex Matter?

N. Grootenboer, J.L. Bosch, J.M. Hendriks, M.R.H.M. van Sambeek

Eur J Vasc Endovasc Surg. 2009 Sep;38(3):278-84. Epub 2009 June 21. Review.

Abstract

Objectives
To unravel the extent to which gender plays a role in the epidemiology, aetiology, risk of rupture and treatment of abdominal aortic aneurysms (AAAs) and to give an overview of these factors.

Design, Materials and Methods
A literature review was performed in the Medline database and Cochrane Library for gender-specific articles on epidemiology, aetiology, risk of rupture and treatment of AAAs.

Results
Our literature review suggests that the prevalence of AAA in women is underestimated. Regarding aetiology, an oestrogen-mediated reduction in macrophage MMP-9 production seems to be an important mechanism causing gender-related differences in AAA development. We found consensus in the literature that women run a greater risk of rupture compared to men under the current management rules for AAAs. Their treatment mortality also seems to be higher for both elective and ruptured repair.

Conclusions
Gender-specific guidelines should be put into place for the management of AAAs and awareness for this disease should be increased, both in women themselves and in their doctors.

Introduction

The current management of abdominal aortic aneurysms (AAAs) has mainly resulted from two randomised controlled trials (RCTs), which indicated no benefit of operation vs. surveillance for AAAs smaller than 5.5 cm in diameter. [1] and [2] Nevertheless, there are good indications to treat certain smaller-diameter aneurysms (e.g., rapid growth and saccular form). Although these two RCTs included a predominantly male population (the UK Small Aneurysm trial, 83% and the ADAM trial, 99.2%), their results are applied to both sexes. There is, however, increasing evidence that this may not be correct. Gender-specific differences in the expression of enzymes, responsible for vascular structure degradation, have been documented, higher risks of rupture have been reported for women and women also seem to fare worse after both elective and ruptured AAA repair.

To assess whether current management of AAAs ensures that women receive adequate treatment it is necessary to unravel the extent to which gender plays a role in the epidemiology, aetiology, risk of rupture and treatment of AAAs. The aim of this review was to give an overview of the current state of knowledge regarding these factors.

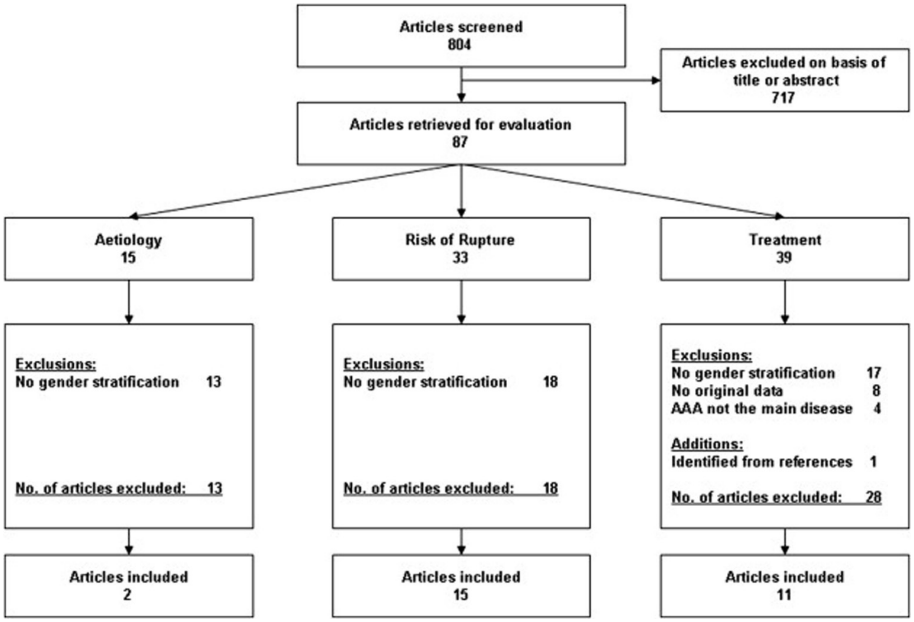

Figure 1. Literature search

Methods

Three searches of the Medline database and Cochrane Library were performed by the first author. For 'aetiology', keywords describing AAA, aetiology, MMP and genes were used. For 'risk of rupture', keywords describing AAA, rupture and outcome were used. For 'treatment', we used keywords describing AAA, treatment and outcome. Each of these searches was combined with the search term ('women', 'gender', 'female', 'sex') to identify gender-related articles. Articles retrieved were restricted to

those published in English, Dutch, French, German and Spanish. Lists of references of identified articles were checked to obtain additional references. Articles were excluded if AAA was not the main disease, and if they did not report on the relevant topic for men and women separately. Case-reports and reviews were also excluded. (See the flowchart for the description of the selection procedure) (Fig. 1). In perusing the gender-specific articles identified through the searches, references were found to further pertinent articles that did not meet the search criteria in full. These articles have also been included in this review.

Epidemiology

The prevalence of AAA varies with a number of factors, including advancing age, family history, gender and tobacco use. The prevalence of AAAs larger than 2.9 cm in diameter ranges from 1.9% to 18.5% in men and 0% to 4.2% in women, the ranges being explained by the different age groups used and the differences in case-mix. [3], [4], [5] and [6]

The prevalence of AAAs in women is currently considered too low for their inclusion in ultrasonographic screening programmes and stratified analyses in the various RCTs. Wanhainen recently demonstrated that prevalence in women is underestimated by using the standard definition for AAA of a 30 mm diameter. The prevalence for 65–75-year-old was 16.9% for men and 3.5% for women, whereas when using another definition, ≥1.5 × normal infrarenal aortic diameter (predicted from a nomogram), the prevalence was 12.9% for men and 9.8% for women.[7]

Aetiology

Histologically, AAAs are characterised by destruction of elastin and collagen in the media and adventitia, smooth muscle cell loss with thinning of the medial wall, infiltration of lymphocytes and macrophages and neovascularisation.[8] Traditional views held that most aneurysms were caused by degenerative atherosclerotic disease but, in recent years, matrix metalloproteinases (MMPs) are considered to play an important role.

Matrix metalloproteinases (MMPs)

Experimental data of human AAAs suggest that matrix metalloproteinases (MMPs) and other proteases, derived from macrophages, 'activated' endothelial cells, aortic smooth muscle cells and adventitial fibroblasts, are secreted into the extracellular matrix causing its degradation and leading to aneurysm formation. [9] and [10] While some MMPs have a particular affinity for specific components of the connective tissue matrix (e.g., MMP-3 for elastin), the breakdown of other components, such as collagen, probably requires a mixture of MMPs (e.g., MMP-1 for collagen types I and III, MMP-9 for collagen type IV). [11] and [12] The MMPs are released into the tissues as inactive MMPs, which are then converted into an active state. Several studies have reported on the gender-specific aspects of MMP-9. [13] and [14] This metalloproteinase is actively produced by aneurysm-infiltrating macrophages and its expression appears to correlate with increasing aneurysm diameter.[15] Hovsepian et al. reported that MMP-9 plasma levels appeared to directly reflect the amount of MMP-9 produced within aneurysm tissue.[16] MMP-9 plasma levels also decreased substantially after surgical AAA repair. Two experimental studies showed that MMP-9 expression was up to 10 times higher

in male vs. female rats, that oestradiol-treated male rats had smaller aneurysms and less macrophage infiltration and MMP-9 expression than non-treated male rats. Male-to-male aortic transplants uniformly developed aneurysms, female-to-female aortic transplants remained resistant to aneurysm formation, but female aortas transplanted to male recipients lost their aneurysm resistance.[13] These data suggest that an oestrogen-mediated reduction in macrophage MMP-9 production may be one mechanism causing gender-related differences in AAA development.

Genetics

A positive family history of AAA in a first-degree relative is known to increase the risk of aortic aneurysm.[17] Brothers of patients with an AAA seem to be at highest risk. [18] and [19] One explanation is that families are usually subjected to similar socio-economic and environmental factors. Blanchard et al., however, showed that after correcting for these factors, positive family history remained an independent risk factor for the development of AAA.[20] Investigations have been undertaken to identify a possible inheritability pattern or gene accounting for AAA formation. Majumder et al. and Kuivaniemi found the recessive inheritance pattern to best fit their data. [21] and [22] In contrast, Verloes et al. found that a single dominant gene gave the best explanation of their findings.[23]

In families where AAAs appear to be inherited dominantly, no significant difference in the transmission of the disease between mothers and fathers has been found. It has, however, been observed that, in these families, AAAs are transmitted from one of the parents to a son in 79% of the cases and only in 21% of the cases to a daughter.[22]

Vlijmen-van Keulen et al. studying three Dutch families with four or five affected siblings identified a candidate locus at chromosome 19q13.3.[24] When analysis was performed on affected sib-pairs, no evidence was found that this locus was common in familial AAA.

Overall, there is considerable evidence for genetic factors to play a role in AAA formation, but to date no single gene or polymorphism has been identified as a common denominator. The exact role of genders also still needs to be determined.

Risk of AAA rupture

An AAA is usually asymptomatic, but when it ruptures patients' overall mortality may be as high as 80–90%.[25] Therefore, ideally, factors contributing to rupture should be identified so that appropriate screening and treatment guidelines can be formulated to prevent AAAs from rupturing. The UK Small Aneurysm trial reported a 4 times higher risk of rupture for women than men (hazard ratio (HR) 4.0; 95% confidence interval (CI): 2.0–7.9). This higher risk was confirmed in a study with patients unfit for elective study.[26] A 3-times higher risk of rupture for women was found and occurring at a smaller diameter than men (5.0 ± 0.8 vs. 6.0 ± 1.4, p = 0.001) in patients kept under surveillance.[27]

Recently, several studies have evaluated the factors that may contribute to AAA rupture. The most commonly reported factors were aneurysm size, aneurysm growth rate and biomechanical factors.

Aneurysm size

Absolute AAA diameter

It is universally agreed that the diameter of an AAA is an important predictor of rupture. Szilagyi et al. were among the first to demonstrate this.[28] Since then, several studies have looked into this relationship. [26], [27], [29] and [30] These studies show considerable variation in the estimates of actual rupture risk for any specific AAA diameter. The Joint Council of the American Association for Vascular Surgery and Society for Vascular surgery suggest that a diameter of 5.5 cm may be the best threshold for repair in the 'average' patient.[31] They also recommend elective repair as from 4.5 cm in women, although no evidence is presented for this recommendation.

Relative AAA diameter

There are significant variations in aorta diameter. In a normal male adult for instance, the aorta diameter gradually decreases from 28 mm in the thorax to 20 mm infrarenally. It increases with age, increasing height, weight, body mass and body surface area (BSA). In women, aorta diameter is on average 2 mm smaller than in men. [32], [33] and [34] For this reason, various authors have suggested using relative AAA diameter instead of absolute AAA diameter.

Several criteria have been used to define relative AAA diameter:

- AAA size vs. predicted normal aortic diameter. The predicted diameter is calculated using nomograms that take age, body surface area (BSA) and gender into account.[33]

  Lanne et al. found that while the absolute AAA diameter did not significantly differ (46.5 mm vs. 48 mm) between men and women, BSA was lower in women than men, 1.63 m^2 (1.42–1.95) vs. 1.89 m^2 (1.47–2.37), $p < 0.0001$, so that the predicted normal aortic diameter was smaller (16.4 mm (14.3–17.8) vs. 19.7 mm (18.0–21.6); $p < 0.0001$). Thus, the relative AAA diameter increase from the predicted size was larger in women than in men (2.93 (2.25–3.53) vs. 2.46 (1.90–2.94); $p < 0.0001$).[35]

- Maximum AAA diameter vs. suprarenal aortic diameter Using computed tomography (CT), Forbes et al. demonstrated that AAAs of equal size represent a significant greater relative dilatation in women compared to men (2.83 ± 0.52 vs. 2.55 ± 0.42, $p = 0.02$).[29]

Growth rate

Most authors agree that a faster AAA growth rate is associated with increased rupture risk. [36] and [37] Three studies, encompassing 1639 patients, reported growth rates stratified for gender. The first[38] reported a faster growth rate in women compared with men (2.43 mm per year vs. 1.65 mm per year). High initial diameter ($p < 0.001$) and female sex ($p = 0.003$) were significant predictors of increased growth rate. The second[39] study found that growth rates in women were significantly higher than men (3.67 mm per year (range: 1.2–37.02) vs. 2.03 mm per year (range: 4.80–21.00), $p < 0.01$), once again showing that initial aortic diameter (AP) (odds ratio (OR) 3.83, $p < 0.001$) and female sex (OR 2.04, $p = 0.006$) were independent risk factors for expansion.

The third study reported that higher AAA growth rate (+1.82 mm per year, $p = 0.008$) and aneurysm diameter (+0.06 mm per year, $p = 0.049$) were associated with female gender.[40] In contrast, Brown et al., in a study with 895 patients, reported no significant

difference in AAA expansion rate between men and women.[36]

Biomechanical factors

Aneurysms rupture when the local stress in the wall exceeds the corresponding local wall strength. In practice, this means that larger aneurysms have a higher wall stress, and therefore have a higher rupture rate than smaller aneurysms. This is confirmed by a study that showed that peak wall stress was a significant independent predictor of rupture (OR = 25, 95% CI: 5.7–110; $p < 0.0001$).[41] In other studies, computer-based three-dimensional 'finite element analyses' were used to determine the wall stress distribution in AAA. One such study revealed that aneurysms of similar size arising from small aortas have much greater wall stress than those arising from larger aortas.[42] The only study to specifically report on gender differences in these biomechanical properties[43] suggested a trend towards a decrease in ultimate tensile strength in females compared to men (87.6 ± 6.7 N cm^{-2} vs. 67.6 ± 8.1 N cm^{-2}, $p = 0.09$). Owing to a small population size their results were only nearly significant.

Treatment

Since the first open surgical repair in the 1950s, elective operative mortality has decreased dramatically[44] but to a lesser extent for women than for men. The introduction of endovascular aneurysm repair (EVAR) marked a further decrease in operative mortality. Again this effect, is not as pronounced for women, one reason being that they receive less EVAR treatment. [45] and [46] In 2003, it was reported that EVAR was performed in 28% of women compared to 44.3% of men ($p < 0.001$).[46] The poorer anatomical suitability of women compared with men most commonly given as reason.

There has been an overall trend (for both sexes) towards a reduction in ruptured AAA repair in the last decade.[46] From 1994 to 2003, ruptured AAA repair decreased by 29.3% for men and 12.2% for women ($p < 0.001$). So while for men it decreased significantly, it did not for women.[46] Mortality associated with rupture remains high and is also significantly higher for women than for men (52.8% vs. 44.2%; $p < 0.01$).[46]

Probability of admission to hospital and operative treatment

It has been suggested that women are admitted to hospital less frequently than men when suffering from an AAA. One study, considering admissions for ruptured AAA, found that only 50% of women were admitted to hospital vs. 59% of men.[47]

Once admitted to hospital with the diagnosis of AAA, women have lower rates of surgery than men for both elective[48] and ruptured repair.[47] The probability of receiving treatment for a ruptured AAA ranges from 37% to 70% for women compared with 63% to 89% for men. [46], [47], [49], [50], [51] and [52]

Treatment mortality

Once it has been decided to perform surgery, women also have higher 30-day mortality. One of the largest studies, with more than 400 000 patients, using the 1979–1997 National Hospital Discharge Survey (NHDS) data reported significantly higher 30-day mortalities for women than men for both elective and ruptured AAA repairs.[53] A recent study by Wanhainen, of over 10 000 primary AAA repairs, reported women also to have a significantly higher 30-day mortality after elective repair, but only found a near significant increase for women after ruptured AAA repair.[54]

Discussion

Epidemiology

Wanhainen demonstrated that depending on the definition of an AAA used, the prevalence of AAA in women could be much higher than currently thought. It seems reasonable to assume that a definition of 30 mm for the average woman is inappropriate and leads to an underestimate of the prevalence of AAA. The prevalence of AAAs in men and women is probably not as far apart as first thought and a greater awareness of this disease in women is desirable and their inclusion in screening programmes warrants close consideration.

Aetiology

Only in the case of MMPs have gender-specific (experimental) studies been undertaken. The results of these provide evidence of gender-related differences in AAA development, which may reflect an oestrogen-mediated reduction in macrophage MMP-9 production. These observations explain why AAAs hardly occur pre-menopausally in women. This apparent correlation suggests that gender-based experimental studies may provide important information on the occurrence and development of AAAs in humans.

Risk of rupture

Numerous studies have reported 3–4 times higher risks of rupture for women, with ruptures also occurring at smaller diameters than for men. [26] and [27] Further, while the incidence of AAA rupture between men and women is about 3:1,[47] most studies indicate the ratio of men to women undergoing an elective operation for AAA to be approximately 5:1. Similarly, a population-based screening study found the prevalence ratio of men to women aged 65–80 years with AAA to be almost 6:1.[55] In other words, it would appear that a disproportionate number of women present with ruptured AAA. In addition, several studies also found that women had a higher proportion of ruptured vs. elective repair than men. [27], [47] and [56] Several authorities have suggested that this problem can be overcome by using relative AAA diameters, but such guidelines are not widely applied in clinical practice. If they were, the higher risk of rupture in women could be reduced.

Whether or not the higher reported AAA growth rate for women simply reflects a more advanced stage in aneurysm development (during which AAA diameter increases exponentially) rather than a specific gender-related feature is not clear.

Biomechanical studies also appear to hold promise for modelling aneurysm development, but only a single paper was found that dealt with gender differences in the tensile strength of aortas. It reported a lower tensile strength for women. Biomechanical studies may represent a fruitful area for further investigation of the effect of gender. They will most probably lead to superior indicators of rupture than AAA diameter.

Treatment

In the last decade, the rate of repair of ruptured AAAs has significantly declined for men but not for women. Mortality associated with repair also remains higher for women than for men. Mortality associated with elective repair has decreased dramatically for both sexes but again to a lesser extent for women.

Once admitted to hospital, women also have less chance of receiving operative treatment and their outcomes are worse than men. A striking feature of many of the articles that

report a higher mortality for women is that many use North American population-based databases and very large sample populations. Whether this outcome reflects an inherent bias in these types of databases or more accurate statistical results because of the larger populations is not clear. If the latter is the case and there is a real difference in mortality for men and women, it is possible only to speculate about the reasons for this at present. These differences would be similar to those seen in coronary heart disease where women have a worse outcome, which is only partly explained by greater age.[57] As with coronary heart disease, women with an AAA may have worse risk factor profiles (other than age), resulting in greater co-morbidity.[58] Several alternative suggestions have been put forward to explain their worse treatment mortality such as their poorer anatomical suitability compared to men for EVAR and the lack of endovascular surgical devices specifically designed for women. Furthermore women with an AAA may be more likely than men to be current smokers.[5] Women may also have different role patterns and/or attitudes than males. By the time they develop an AAA they have often survived their spouse and may choose not to be operated on. There is also evidence that, as in the case of myocardial infarction (MI), women delay seeking medical attention.[59] A reduced awareness of AAA in women, both in the women themselves and their doctors, as well as gender bias, both of which may result in diagnostic and surgical delay probably also play a role. Support for this suggestion is provided by the fact that the proportion of women in surgical series is generally less than the proportion determined from autopsy studies, ultrasound studies, hospital discharge data and national mortality information. [46] and [60]

Conclusions

All the above findings indicate that women have a greater chance of rupture compared to men under the current management regime for AAAs. While women are older than men when they experience a ruptured AAA, they are still dying from a condition that could have been detected and treated. Allowing for the greater life expectancy of women at all ages, there appears to be a need for greater attention to aneurysm disease in women. Many reasons have been but forward for this disproportionately poorer outcome for women, the most important ones being the current absolute threshold for repair and the lower awareness and therefore diagnosis of AAA in women. These findings warrant gender-specific guidelines for the management of AAAs. A greater effort should also be made to increase the awareness, of both women and their doctors for this disease.

Conflict of Interest/Funding

None.

Acknowledgements

This research was supported by an unrestricted educational grant from the Foundation 'Lijf en Leven'. We thank the members of the Assessment of Radiological Technology (ART) group for their comments and suggestions. We would also like to thank Jan Grootenboer for editing this article and his sharp eye for detail.

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Chapter 3

Systematic review and meta-analysis of sex differences in outcome after intervention for abdominal aortic aneurysm

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Br J Surg Volume 97, Issue 8, pages 1169–1179, August 2010

Abstract

Background
The aim of this study was to assess possible differences in mortality between men and women with an abdominal aortic aneurysm (AAA) treated either by elective repair or following aneurysm rupture.

Methods
A systematic literature search was performed using the MEDLINE, Cochrane and Embase databases. Data were analysed by means of bivariate random-effects meta-analysis. Data were pooled and odds ratios (ORs) calculated for women compared with men.

Results
Sixty-one studies (516 118 patients) met the predetermined inclusion criteria. Twenty-six reported on elective open AAA repair, 21 on elective endovascular repair, 25 on open repair for ruptured AAA and one study on endovascular repair for ruptured AAA. Mortality rates for women compared with men were 7·6 versus 5·1 per cent (OR 1·28, 95 per cent confidence interval (c.i.) 1·09 to 1·49) for elective open repair, 2·9 versus 1·5 per cent (OR 2·41, 95 per cent c.i. 1·14 to 5·15) for elective endovascular repair, and 61·8 versus 42·2 per cent (OR 1·16, 95 per cent c.i. 0·97 to 1·37) in the group that had open repair for rupture. The group that had endovascular repair for ruptured AAA was too small for meaningful analysis.

Conclusion
Women with an AAA had a higher mortality rate following elective open and endovascular repair.

Introduction

For both men and women, the main treatment guideline for elective repair of abdominal aortic aneurysm (AAA) is a diameter measuring at least 5·5 cm. This guideline is based on a predominantly male population in natural history studies[1, 2]. For smaller AAAs (4·0–5·5 cm) the treatment guideline is based on two randomized controlled trials (RCTs): the UK Small Aneurysm Trial (UKSAT) and the Aneurysm Detection And Management (ADAM) trial[3, 4]. Both RCTs reported that surgery for AAAs smaller than 5·5 cm had no long-term survival benefit over regular surveillance. Neither trial initially distinguished between men and women. The UKSAT included 17 per cent women, whereas the ADAM trial included only 0·8 per cent. A follow-up report to the UKSAT compared results between men and women[5]; even though no difference in mortality was reported, a threefold higher risk of rupture was found for women (hazard ratio 3·0, 95 per cent confidence interval (c.i.) 1·99 to 4·53), and at smaller aortic diameter than for men: mean(s.d.) 5·0(0·8) versus 6·0(1·4) cm. These findings were confirmed by Brown and colleagues[6], who reported a four times higher risk of rupture in women with an AAA between 5·0 and 5·9 cm[6]. As the average diameter of a healthy infrarenal aorta is 1·99 cm in men and 1·66 cm in women, doubts are raised as to how applicable the results of these studies are for the development of treatment guidelines applied to both men and women[7].

Conflicting results regarding the influence of sex on operative mortality have been reported for both elective and ruptured AAA repair[8–24]. Therefore, currently it is unclear whether mortality is different for women versus men. Before treatment guidelines for AAA are reconsidered it is essential to gain insight into whether treatment outcomes differ between men and women. The impact of sex on mortality may be different for elective versus ruptured AAA repair, and for open versus endovascular repair. As AAA anatomy is a major selection criteria for endovascular aneurysm repair (EVAR) and women have been reported to have a poorer anatomical suitability, it is important to evaluate whether mortality is different for men and women in these groups[25, 26]. In this systematic review, the mortality rates of women versus men for elective and ruptured AAA repair by either an open or endovascular procedure were analysed.

Methods

A literature search was performed in July 2009 using the databases of the Cochrane Library and MEDLINE. The search was subsequently reproduced in Embase and records unique to Embase were retrieved. Keywords describing AAA, open repair, endovascular repair and mortality were used (Appendix 1, supporting information). The PRISMA statement was adhered to in conducting this research[27]. The English language literature[28] published between January 1995 and July 2009 was searched. As current practice is based primarily on the two RCTs published since 1995, the search was started from January 1995. Additional studies were identified by reviewing the reference lists of articles. Contact with authors was sought if articles were not available for logistical reasons.

Studies were included if they fulfilled all of the following criteria: 30-day or in-hospital mortality was reported separately for women and men; mortality was stratified by manner of repair (open versus endovascular) and

by status of repair (elective versus ruptured); and at least ten women were treated in the study. Inclusion was not limited to RCTs. Studies that reported on mortality of infected, mycotic, inflammatory and (predominantly) suprarenal aneurysms were excluded, as were reviews and case reports. The most recent data were used if multiple reports from one institution were published or in the case of multiple articles covering the same study population. Two authors independently reviewed and extracted data from each article using a specially derived data extraction form. Discrepancies were resolved by consensus. The extracted study data included: study characteristics (number of centres, study interval, study design); treatment criteria (AAA diameter, growth rate); patient demographics (number of men and women, age, co-morbidities); lesion characteristics (mean maximum AAA diameter); procedure characteristics (tube graft, bifurcated graft, aortou-

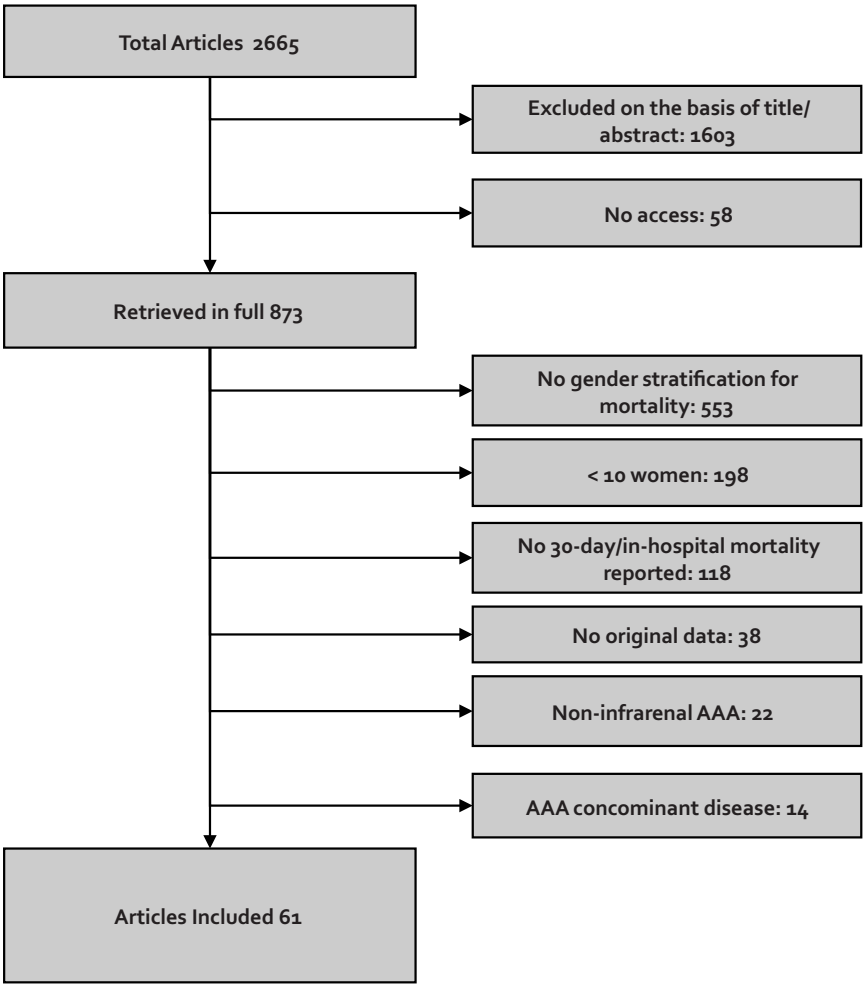

Fig 1. Study selection. AAA, abdominal aortic aneurysm

ni-iliac graft with crossover, clamp time); and outcomes including 30-day or in-hospital mortality and complications.

Data synthesis and analysis

Four groups were defined according to the manner of intervention (open versus endovascular) and status of the AAA (elective versus ruptured). Co-morbidities and complications were mostly not stratified by sex for the elective open repair and ruptured open repair groups and were therefore reported for the total group in appendices. In the elective EVAR group, co-morbidities and complications were stratified by sex in eight of the 21 studies and this information was pooled based on these studies only. Co-morbidities were grouped into 'diabetes', 'hypertension', 'cardiac', 'cerebrovascular', 'pulmonary', 'renal' and 'smoking'. Complications were grouped into 'cardiac', 'cerebrovascular', 'pulmonary', 'renal', 'bowel ischaemia', 'sepsis or multiple organ failure' and 'endoleak' (the latter for EVAR only). To avoid double counting, the highest rate within each co-morbidity or complication group was reported.

In the studies found, procedure characteristics were not stratified by sex and so it was not possible to assess possible differences between men and women.

The primary outcome of interest was mortality. To pool mortality across the studies a bivariate random-effects meta-analysis was used[29, 30]. The random-effects analysis weighed the outcome of the study according to both the within-trial variance and between-trial variance which implied that the pooled results and confidence intervals took heterogeneity across the studies into account[29]. The bivariate analysis allowed calculation of the odds of death for women and men separately together with the co-variance between them. Based on this the odds ratio (OR) of mortality among women compared with men was then calculated. The standard method of adding 0·5 to all cell counts was used to avoid 'zero' cells, resulting in a well defined OR and confidence interval for each study. Both unadjusted (crude) and adjusted ORs were calculated. The latter were adjusted for patients' age in all analyses for the four groups and additionally for AAA diameter in the elective EVAR group.

Results

Literature and study characteristics

A total of 2665 articles were identified from the literature search. On the basis of title and abstract, 1004 articles were retrieved in full and 61 of these met the inclusion criteria (Fig.1). The primary reason for exclusion was lack of sex stratification when reporting mortality. Review of the reference list of each article did not lead to any additional articles being included. Of the 61 included articles, 26 reported on elective open repair[8, 9, 11, 18, 20, 31–51, 21] on elective EVAR[20, 31, 36, 52–69, 25] on open repair of ruptured AAA[8, 13, 18, 21, 24, 31, 33, 36, 40, 49, 51, 70–83], and one study on EVAR for ruptured AAA[36] (Tables1 and 2). Eight studies reported mortality data for both elective and emergency open repair. Two studies reported on both elective open repair and elective EVAR, and one study reported mortality data for all four treatment groups. Thirty-two studies were performed in North America, 19 in Europe, four in Australia, two in Japan, one in Canada, one in China, one in New Zealand

Table 1. Characteristics and 30-day mortality of patients treated electively for abdominal aortic aneurysm

Study	No. of patients		Age (years)*		AAA diameter (mm)*		30-day mortality†	
	Women	Men	Women	Men	Women	Men	Women	Men
Open repair								
Berge *et al* [31]	81	450	-	-	-	-	1 (1)	24 (5.3)
Faizer *et al* [32]	105	453	71‡	71‡	-	-	1 (1)	25 (5.5)
Hultgren *et al* [33]	1478	7305	71.7 (7.3)	70.2 (7.3)	-	-	121 (8.2)§	574 (7.9)§
Bonamigo *et al* [34]	100	575	68.9 (9.1)	67.4 (7.2)	5.94 (1.5)	6.57 (2.25)	4 (4.0)¶	15 (2.6)¶
Haug *et al* [35]	23	82	80.8	82.2	68	65	2 (9)	9 (11)
Leon *et al* [36]	2746	7974	73.2 (7.95)#	71.4 (7.98)#	-	-	225 (8.2)**	415 (5.2)**
Lifeline[20]	69	265	70 (7.8)‡	70 (7.8)‡	57.1 (11.7)‡	57.1 (11.7)‡	1 (1)¶	3 (1.1)¶
Mackenzie *et al* [37]	42	177	69.9‡	69.9‡	-	-	5 (12)**	3 (1.7)**
Urbonavicius *et al* [38]	17	52	-	-	-	-	3 (18)	5 (10)
Rigberg *et al* [9]	18	71	-	-	-	-	0 (0)**	0 (0)**
Sasaki *et al* [39]	11	89	71‡	71‡	57.9 (10.2)‡	57.9 (10.2)‡	0 (0)**	1 (1)**
Stenbaek *et al* [40]	109	488	71 (6.4)	70 (7)	-	-	12 (11.0)§	42 (8.6)§
Biancari *et al* [41]	239	1672	68 (8)‡	68 (8)‡	-	-	15 (6.3)	85 (5.1)
Upchurch *et al* [42]	68	90	70.3‡	70.3‡	58‡	58‡	1 (1)	4 (4)
Rayan *et al* [43]	100	321	74.4 (7.1)‡	74.4 (7.1)	-	-	2 (2.0)**	5 (1.6)**
Alonso-Perez *et al* [44]	13	170	77‡	77 (2)‡	-	-	3 (23.1)**	19 (11.2)**
El-Sabrout *et al* [45]	95	412	-	-	-	-	3 (3)	3 (0.7)
Huber *et al* [11]	3340	13114	73.1 (7.2)	71.2 (7.4)	-	-	204 (6.1)**	485 (3.7)**
Brady *et al* [46]	136	684	70‡	70‡	49.5‡	49.5‡	9 (6.6)	37 (5.4)
Heller *et al* [19]	81384	277137	73	70	-	-	6267 (7.7)	14134 (5.1)
Dardik *et al* [47]	510	1825	71.8 (0.3)	70.1(0.2)	-	-	23 (4.5)**	58 (3.2)**
Akkersdijk *et al* [48]	30	261	69‡	69‡	58‡	58‡	1 (3)**	11 (4.2)**
Semmens *et al* [49]	139	797	72.4 (6.9)	70.4 (6.7)	-	-	5 (3.6)	35 (4.4)
Katz *et al* [8]	1469	6716	72.1 (7.8)	69.1 (7.6)	-	-	156 (10.6)**	457 (6.8)**
Starr *et al* [50]	92	490	68	68	-	-	4 (4)**	25 (5.1)**
Henderson and Effeney[51]	68	185	70‡	70‡	-	-	0 (0)	23 (12.4)
Pooled outcome††	**92482**	**321855**	**72.9 (0.5)**	**70.1 (0.5)**	**56.1 (5.0)**	**57.5 (6.5)**	**7068 (7.6)**	**16094 (5.1)**

Endovascular repair								
Berge *et al* [31]	17	119	-	-	-	-	1 (6)	3 (2.5)
Ting *et al* [52]	15	85	75 (7)‡	75 (7)‡	62 (8)‡	62 (8)‡	0 (0)**	2 (2)**
Azizzadeh *et al* [53]	58	340	73‡	73‡	-	-	1 (2)	4 (1.2)
Biebl *et al* [54]	40	326	74 (7)	73 (8)	-	-	0 (0)	4 (1.2)
Leon *et al* [36]	295	1384	73.2 (8.0)#	71.4 (8.0)#	-	-	15 (5.1)**	24 (1.7)**
Lifeline[20]	235	1828	76.4 (7.7)	72.8 (7.8)	55.8 (10.2)‡	55.8 (10.2)‡	5 (2.1)¶	27 (1.5)¶
Zarins *et al* [55]	23	289	70 (7)‡	70 (7)‡	50 (3)‡	50 (3)‡	0 (0)	6 (2.1)
Sampaio *et al* [56]	29	212	79.9 (1.11)	74.9 (0.48)	54.1 (1.1)	55.5 (0.8)	2 (7)	2 (0.9)
Criado *et al* [57]	24	216	75.5‡	75.5‡	-	-	0 (0)	0 (0)
Elkouri *et al* [58]	11	89	76 (7)‡	76 (7)‡	58 (11)‡	58 (11)‡	0 (0)	0 (0)
Nordness *et al* [59]	17	101	75.1 (9.4)	73 (7)	61.9 (11.6)	57.5 (9.7)	2 (12)	0 (0)
Parlani *et al* [60]	25	377	75.3	71.3	52.2	50.8	0 (0)	5 (1.3)
Shames *et al* [61]	42	203	76 (6)	72 (7)	-	-	1 (2)	3 (1.5)
Slovut *et al* [62]	27	143	73.6 (7.2)‡	73.6 (7.2)‡	55 (8)‡	55 (8)‡	0 (0)	4.52 (1.4)
Wyers *et al* [63]	34	168	74 (7)‡	74 (7)‡	-	-	0 (0)	1 (0.6)
Sanchez *et al* [64]	22	133	76.3 (6.4)	72 (7.2)	54.1	56.7	1 (5)	4 (3.0)
Wolf *et al* [65]	26	163	77.9 (6.3)	73.1 (8.1)	57.2 (10.9)	57.8 (9.4)	0 (0)	2 (1.2)
Howell *et al* [66]	23	192	72 (8.2)‡	72 (8.2)‡	55.5 (11)‡	55.5 (11)‡	0 (0)	0 (0)
Mathison *et al* [67]	24	281	75.9 (6.7)	74.4 (7.9)	52.1 (6.8)	57 (11.8)	0 (0)‡‡	8 (2.8)‡‡
Romero *et al* [68]	17	156	73‡	73‡	58‡	58‡	1 (6)¶	5 (3.2)¶
Cao *et al* [69]	10	105	69.8 (7)‡	69.8 (7)‡	-	-	0 (0)	0 (0)
Pooled outcome††	**1014**	**6910**	**74.6 (2.0)**	**72.6 (1.3)**	**55.5 (2.4)**	**55.4 (2.5)**	**29 (2.9)**	**102 (1.5)**

*Values are mean(s.d). †Values in parentheses are percentages. ‡Mean value for total group (men and women). §Sixty-day mortality. ¶Thirty-day or in-hospital mortality. #Mean age for total study population (elective abdominal aortic aneurysm (AAA), ruptured AAA, open and endovascular repair). **In-hospital mortality. ††Data reported as total (s.d). ‡‡All deaths that occurred within 30 days after procedure and those beyond 30 days that were directly related to the procedure.

Table 2 Characteristics and 30-day mortality of patients treated for ruptured abdominal aortic aneurysm

Reference	No. of patients		Age (years)*		AAA diameter (mm)*		30-day mortality†	
	Women	Men	Women	Men	Women	Men	Women	Men
Grant *et al* [70]	115	493	75.5(10.7)	71.9(8)			55(47.8)‡	175(35.5)‡
Berge *et al* [31]	63	236	-	-	-	-	38(60)	88(37.3)
Sharif *et al* [71]	28	150	79.9 (7.4)	72.7 (7)	-	-	12(43)	90(60.0)
Hultgren *et al* [33]	598	3536	75.2 (7.3)	72.1 (7.8)	-	-	270(45.2) §	1447(40.9) §
Filipovic *et al* [72]	976	5059	79.8	74.9	-	-	512(52.5)	2430(48.0)
Visser *et al* [19]	663	4930	75.5	71.2	-	-	325(49.0)‡	1972(40.0)‡
Stone *et al* [24]	17	67	71.9 (7.4)¶	71.9 (7.4)¶	-	-	6(35)	31(46)
Leon *et al* [36]	476	1587	73.2 (8.0)#	71.4 (8.0)#	-	-	245(51.5)‡	628(39.6)‡
Stenbaek *et al* [40]	42	207	77 (6.6)	71 (8.4)	-	-	28(67) §	115(55.6) §
Korhonen *et al* [73]	105	728	70.5 (8.4)¶	70.5 (8.4)¶	-	-	54(51.4)	340(46.7)
Janczyk *et al* [74]	29	71	74 (8.6)	74 (8.6)	-	-	13(45)‡	34(48)‡
Roddy *et al* [75] *(1)*	40	209	69¶	69¶	-	-	8(20)	54(25.8)
Roddy *et al* [75] *(2)*	26	48	85¶	85¶	-	-	12(46)	18(38)
Hans and Huang [76]	16	85	-	-	-	-	11(69)	37(44)
Turton *et al* [21]	32	70	78.8¶	78.8¶	-	-	16(50)	38(54.3)
Heller *et al* [19]	15176	52575	78	72	-	-	9834(64.8)	21871(41.6)
Evans *et al* [77]	105	481	74**	72**	-	-	40(38.1)‡	159(33.1)‡
Sasaki *et al* [78]	30	153	69.8 (0.7)	69.8 (0.7)	-	-	12(40)	52(34.0)
Alonso-Perez *et al* [79]	13	99	80 (3)¶	80 (3)¶	-	-	7(54)‡	66(67)‡
Semmens *et al* [49]	41	242	74.8 (6.7)	71.9 (7.3)	-	-	19(46)	84(34.7)
Dardik *et al* [80]	108	419	75 (0.7)	71.2 (0.4)	-	-	56(51.9)‡	194(46.3)‡
Katz *et al* [8]	307	1522	76 (9.3)	71 (8.2)	-	-	189(61.6)‡	724(47.4)‡
Barry *et al* [81]	17	77	77.2 (6)	71.6 (6)	-	-	13(76)	36(47)
Rutledge *et al* [82]	307	1173	72.2 (9.8)¶	72.2 (9.8)¶	-	-	192(62.5)‡	621(52.9)‡
Hardman *et al* [83]	24	130	75.5	70.5	-	-	12(52)††	48(38)††
Henderson *and Effeney* [51]	19	82	70¶	70¶	-	-	3(16)‡	26(32)‡
Pooled outcome‡‡	**19373**	**74429**	**77.5(1.6)**	**72.1(1.0)**			**11982(61.8)**	**31376(42.2)**
Endovascular repair								
Leon *et al* [36]	14	41	73.2(8.0)#	71.4(8.0)#			2(14)	18(44)

*Values are mean(s.d). †Values in parentheses are percentages. ‡In-hospital mortality. §Sixty-day mortality. ¶Mean value for total group (men and women). #Mean age for total study population (elective abdominal aortic aneurysm (AAA), ruptured AAA, open and endovascular repair). **Based on all admitted patients(operated and non-operated). ††Thirty-day or in-hospital mortality. ‡‡Data reported as total(s.d.).

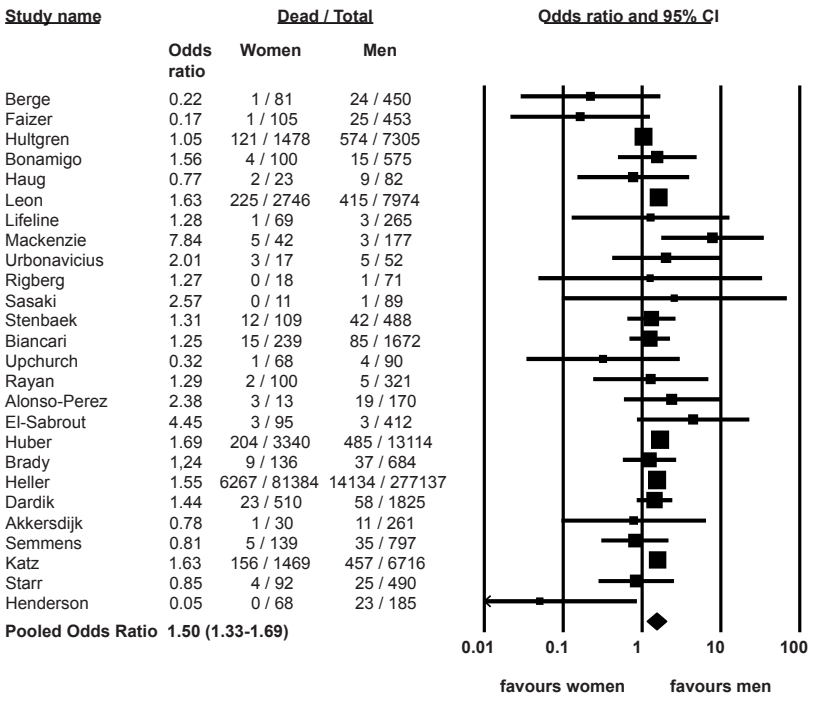

Figure 2. Forest plot of mortality for women versus men after elective open abdominal aortic aneurysm (AAA) repair. Odds ratios are shown with 95 per cent confidence intervals

and one in Brazil. The articles were published between 1995 and 2008, and patients were enrolled from February 1979 to November 2007. All but five studies were retrospective. Seventeen of the 61 studies were analyses of registries or databases (Appendix 2, supporting information).

For the elective open repair group, treatment criteria such as AAA diameter or rapid AAA growth were reported in two of 26 articles[32, 46]. For the elective EVAR group this was six of 21[55, 57, 58, 60, 62, 66]. In these studies the indication to intervene was an AAA diameter of 4·0 to above 5·5 cm. For the group with ruptured AAA treated by open repair, rupture was assumed to be the reason for treatment as this was reported explicitly in ten of the 25 articles[8, 18, 70, 71, 77–81, 83]. Only one study was retrieved that described EVAR for ruptured AAA[36], precluding meaningful analysis.

Patient characteristics

Tables1 and 2 show the patient demographics for all four treatment groups. The total number of patients in the included articles was 516 118: 112 883 women and 403 235 men. The proportion of women varied from 12·8 per cent in the elective EVAR group to 22·3 per cent in the elective open repair group. On average, women were older than men in all groups. The largest difference in age was found in the group that had open repair of ruptured AAA where women were on average 5 years older than men (mean 77·5 versus 72·1 years) (Table2). Details of co-morbidities are shown in Appendices 3a and 3b (supporting information).

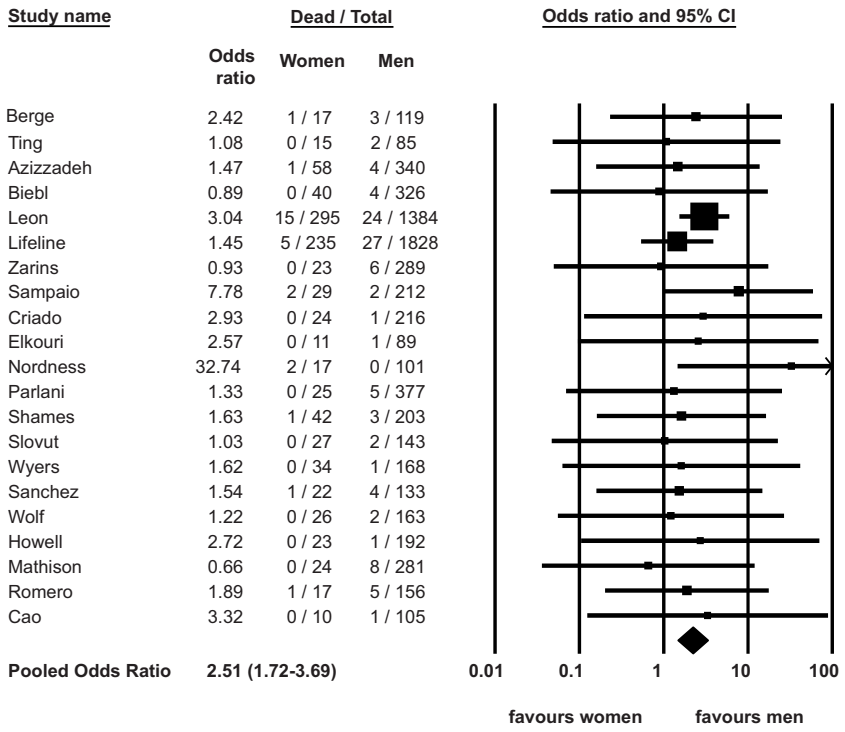

Figure 3. Forest plot of mortality for women versus men after elective endovascular repair. Odds ratios are shown with 95 per cent confidence intervals

For the elective open surgery group, seven of 26 studies reported mean AAA diameter; only two, however, reported mean AAA diameter stratified by sex (Table1)[34, 35]. For the elective EVAR group, the majority of the studies reported mean AAA diameter (13 of 21) and six of these stratified by sex; mean AAA diameter was 55·5 mm for women and 55·4 mm for men. Papers on ruptured AAA did not report aneurysm diameter.

Thirty-day or in-hospital mortality

For the elective open repair group, the mortality rate was 7·6 per cent for women and 5·1 per cent for men. The unadjusted OR for mortality among women versus men was 1·50 (95 per cent c.i. 1·33 to 1·69) (Fig.2). After adjustment for age the OR was 1·28 (95 per cent c.i. 1·09 to 1·49).

For the elective EVAR group, the mortality rate was 2·9 per cent for women and 1·5 per cent for men (unadjusted OR 2·51, 95 per cent c.i. 1·72 to 3·69) (Fig.3). After adjustment for age the OR was 2·41 (95 per cent c.i. 1·49 to 3·88). It remained the same after additional adjustment for AAA diameter (OR 2·41, 95 per cent c.i. 1·14 to 5·15).

For the group with open repair of a ruptured AAA, the mortality rate was 61·8 per cent for women and 42·2 per cent for men (unadjusted OR 1·41, 95 per cent c.i. 1·22 to 1·63) (Fig.4); the adjusted OR was 1·16 (95 per cent c.i. 0·97 to 1·37).

Complications

Where complications were reported by sex after elective EVAR, there were higher rates of conversion and/or aborted procedures for women com-

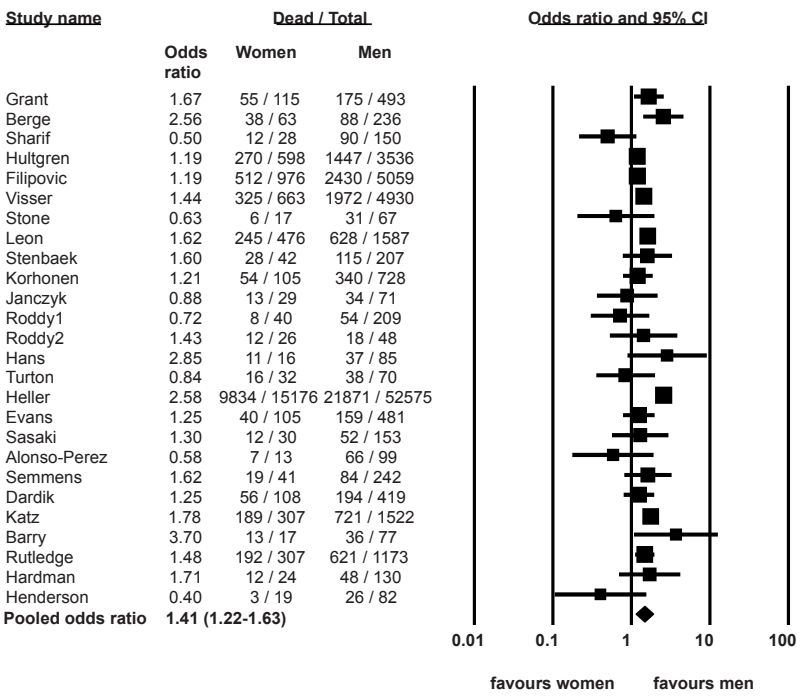

Figure 4. Forest plot representation for women versus men after open repair of ruptured abdominal aortic aneurysm (AAA). Odds ratios are shown with 95 per cent confidence intervals

Table 3. Complications after elective endovascular aneurysm repair

	Conversion/Aborted		Hospital stay (days)		Endoleak	
Reference	Women	Men	Women	Men	Women	Men
Sanchez *et al* [64]	5 (23)*	1 (0.8)*	3.3	1.9	1 (5)¶	4 (3.0)¶
Nordness *et al* [59]	2 (12) †	2 (2.0) †	-	-	2 (12)#	3 (3.0)#
Sampaio *et al* [56]	-	-	3.9	3.3	-	-
Parlani *et al* [60]	1 (4)	5 (1.3)	-	-	-	-
Shames *et al* [61]	6 (14)	1 (0.5)	2.9	2.6	-	-
Howell *et al* [66]	0 (0)	0 (0)	-	-	-	-
Mathison *et al* [67]	4 (17) ‡	10 (3.6) §	4.5	3.8	7 (35)	60 (22.1`)
Lifeline[20]	20 (8.5)	71 (3.9)	-	-	-	-
Pooled outcome	**38 (9.8)**	**90 (2.9)**	**3.6**	**3.1**	**10 (16)**	**67 (13.0)**

Values is parentheses are percebtages. *Conversion or aborted procedure; †one conversion and one aborted procedure; ‡four aborted procedures; §six conversions and four aborted procedures. ¶Types 1 and 3 endoleak; #types 1 and 2 endoleak.

pared with men (9·8 versus 2·9 per cent respectively) and endoleaks (16 versus 13·0 per cent) (Table3). Details of other complications in each group are shown in Appendices 4a and 4b (supporting information).

Discussion

The debate on whether sex itself influences mortality following AAA repair or whether women have worse risk profiles than men is still ongoing. Before this question can be answered an actual difference in mortality between women and men needs to be demonstrated. Many studies have examined sex differences in mortality, sometimes with conflicting results[8, 11, 16, 17]. The present study reviewed the literature published between 1995 and 2009.

The mortality rate was significantly higher for women after both elective open repair and EVAR. Women were on average older than men, but the difference persisted after adjustment for age. The difference in mortality was most pronounced after EVAR. The mortality rate was also higher for women after open repair of a ruptured AAA, but the difference was not statistically significant after adjustment for age.

Previous studies have suggested several possible mechanisms to explain the higher consequent mortality among women compared with men[84, 85]. The most important factors include the absolute criteria for repair, the use of endovascular devices that are not specifically designed for women, and the reduced awareness of AAA in women compared with men.

It has been suggested that women with an AAA should have treatment at a smaller diameter than men. However, it is still common practice to treat both sexes at an AAA diameter of 5·5 cm. As the normal aortic diameter of a woman is smaller than that of a man, by the time it has reached 5·5 cm the aorta has undergone a bigger relative increase in diameter. By using this absolute size threshold, women could be in a later stage of atherosclerotic disease when they undergo surgery, leading to inferior outcomes.

Women are thought to have poorer anatomical suitability than men for EVAR[86]. This was reflected in the present study by the higher conversion rate in women. Endovascular devices have, as yet, not been designed specifically for women, which could play a role in the worse outcome. The aorta and access arteries are often smaller in women, making EVAR more difficult to perform than in men.

The most likely explanation for the higher mortality rate in women, however, is that cardiovascular disease as a whole, including AAA, is underrecognized in women. This leads to an array of problems such as delayed diagnosis and intervention, but also to fewer primary and secondary preventive measures including cardiovascular medication and lifestyle adjustment.

Every systematic review is limited by the level of detail and quality of the original reports. Owing to the lack of standardization in the studies for many of the variables considered, it was possible to adjust only for age and AAA diameter. Co-morbidities were reported poorly and only a few studies stratified for men and women. The studies that did report stratified co-morbidity data did not show very different results for men and women. Another limitation of this study is the inclusion of predominantly non-ran-

domized trials. Observational studies are known to be subject to selection bias but, as there was only one randomized trial reporting sex-specific results, a meta-analysis of RCTs was not possible. Another limitation is that many of the articles reporting a higher mortality rate for women studied population-based databases with very large sample populations. The reason for this remains unclear.

Although an apparent difference in mortality rates following open repair of ruptured AAA was found, it did not remain statistically significant after adjustment. Either there could be a lack of power in the setting of a small difference, taken that the crude OR was statistically significant and after adjustment it approached significance. Alternatively, factors related to acute rupture, such as shock, may play a more substantial role than sex itself.

The present study demonstrated that women have a higher consequent mortality rate than men after elective AAA treatment. This suggests that current treatment criteria are not optimal for women. Women may be in a worse medical state than men at which they undergo surgery. The AAA diameter when repair becomes indicated in women remains to be determined. Meanwhile, women with an AAA smaller than 5·5 cm in diameter should be treated only after every effort has been made to ensure that they are in the same cardiovascular condition as men. Women may have a worse risk profile than men; the difference in consequent mortality could possibly be explained by less effective perioperative investigation and secondary prevention. EVAR in women also needs to be considered thoroughly as outcomes were worst in the elective EVAR group. Current practice does not seem to be optimal for women, and this is further reflected by the higher procedure abortion and conversion rates.

Acknowledgements

This research was supported by an unrestricted educational grant from the Foundation 'Lijf en Leven'. The authors thank the members of the Assessment of Radiological Technology group for their comments and suggestions. The authors declare no conflict of interest.

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Appendices

Appendix 1 Search

((((((abdominal aort*[text word])) AND ((aneurysm*[text word]))))) OR ((Aortic Aneurysm, Abdominal[Mesh])))))

AND (((((((Blood vessel Prosthesis Implantation [Mesh])) OR ((Blood Vessel Prosthesis[Mesh]))) OR ((repair[text word]))) OR ((endovascular surgery[text word]))) OR ((open surgery[text word]))) OR ((Aortic Aneurysm, Abdominal/surgery[Mesh])))))

AND ((((((((((((((Aortic Aneurysm, Abdominal/mortality[Mesh])) OR ((Aortic Aneurysm, Abdominal/complications[Mesh]))) OR ((Hospital mortality[Mesh]))) OR ((Surgical Procedures, Minimally Invasive/mortality[Mesh]))) OR ((Treatment Outcome[Mesh]))) OR ((Vascular Surgical Procedures/mortality[Mesh]))) OR ((Vascular Surgical Procedures/adverse effects[Mesh]))) OR ((mortality[text word])))))

NOT ((((((((((Animals[Mesh])) NOT ((Humans[Mesh])))) OR ((Editorial[Publication Type]))) OR ((Comment[Publication Type]))) OR ((Letter[Publication Type]))) OR ((Meta-Analysis[Publication Type]))) OR ((Review[Publication Type]))) OR ((Case Reports[Publication Type]))))))) AND ((English[lang]))

Limit: start 1995

Appendix 2 Characteristics of studies reporting mortality of abdominal aortic aneurysm repair for women and men separately

Study	Year of publication	Study location	Study period	Type of study	No. of centres	Database name
Elective open AAA repair						
Berge[31]	2008	Norway	1983–2002	OR	1	
Faizer[32]	2007	Canada	1999–2004	OR	2	
Hultgren[33]	2007	Sweden	1987–2002	OR	Database	National Board of Health and Welfare
Bonamigo[34]	2006	Brazil	1983–2003	OR	1	
Haug[35]	2005	Norway	1983–2002	OR	3	
Leon[36]	2005	USA	1995–2003	OR	Database	Illinois Hospital Association COMPdata
Lifeline[20]	2005	USA	–	OP	Multi	Lifeline Registry
Mackenzie[37]	2005	Australia	1991–1998	OR	1	
Urbonavicius[38]	2005	Lithuania	1999–2003	OR	1	
Rigberg[9]	2004	USA	2001–2002	OR	1	
Sasaki[39]	2004	Japan	1991–2002	OR	1	

Stenbaek[40]	2004	Sweden	1981–2000	OR	1	
Biancari[41]	2003	Finland	1991–1999	OR	Database	Finnvacs registry
Upchurch[42]	2003	USA	1988–2000	OR	1	
Rayan[43]	2002	USA	1990–1999	OR	1	
Alonso-Perez[44]	2001	Spain	1995–1996	OR	Database	21 hospitals
El-Sabrout[45]	2001	USA	1993–1998	OR	1	
Huber[11]	2001	USA	1994–1996	OR	Database	NIS
Brady[46]	2000	UK	1991–1998	RP	Multi	UKSAT
Heller[18]	2000	USA	1979–1997	OR	Database	National Hospital Discharge Survey (NHDS)
Dardik[47]	1999	USA	1990–1995	OR	Database	Maryland Health Services Cost Review Commission (HSCRC)
Akkersdijk[48]	1998	NL	1993–1995	OP	5	
Semmens[49]	1998	Australia	1985–1994	OR	Database	WA Linked Database
Katz[8]	1997	USA	1980–1990	OR	Database	The Michigan Inpatient Data Base
Starr[50]	1996	USA	1983–1988	OR	1	
Henderson[51]	1995	Australia	1986–1991	OR	1	

Elective endovascular AAA repair

Berge[31]	2008	Norway	1983–2002	OR	1	
Ting[52]	2008	China	1999–2007	OR	1	
Azizzadeh[53]	2006	USA	1999–2004	OR	1	
Biebl[54]	2005	USA	–	OR	Multi	
Leon[36]	2005	USA	1995–2003	OR	Database	Illinois Hospital Association COMPdata
Lifeline[20]	2005	USA	–	OR	Multi	Lifeline Registry
Zarins[55]	2005	USA	1997–1999	OR	Multi	
Sampaio[56]	2004	USA	1996–2003	OR	1	
Criado[57]	2003	USA	1999–2000	OP	Multi	
Elkouri[58]	2003	USA	1996–2001	OR	1	
Nordness[59]	2003	USA	1997–2001	OR	1	
Parlani[60]	2003	Italy	1997–2002	OR	1	
Shames[61]	2003	USA	1999–2001	OR	2	
Slovut[62]	2003	USA	1999–2002	OR	3	
Wyers[63]	2003	USA	1996–2001	OR	2	
Sanchez[64]	2002	USA	1999–2000	OR	1	
Wolf[65]	2002	USA	1996–2001	OR	1	
Howell[66]	2001	USA	1998–l2001	OP	1	
Mathison[67]	2001	USA	1994–2000	OR	1	
Romero[68]	2001	USA	1995–1999	OR	1	
Cao[69]	1999	Italy	1997–1998	OR	1	

Ruptured AAA: open repair

Grant[70]	2008	New Zealand	1993–2005	OR	Database	NZVASC (national audit Database)
Berge[31]	2008	Norways	1983–2002	OR	1	
Filipovic[72]	2007	UK	1998–2002	OR	Database	English National Hospital Episode Statistics

Hultgren[33]	2007	Sweden	1987–2002	OR	Database	Registry of the National Board of Health and Welfare
Sharif[71]	2007	Ireland	1999–2004	OR	2	
Leon[36]	2005	USA	1995–2003	OR	Database	Illinois Hospital Association COMPdata
Stone[24]	2005	USA	1998–2003	OR	1	
Visser[13]	2005	NL	1991–2000	OR	Database	Prismant
Janczyk[74]	2004	USA	1990–1999	OR	1	
Korhonen[73]	2004	Finland	1991–1999	OR	Database	Finnvasc registry
Stenbaek[40]	2004	Sweden	1981–2000	OR	1	
Hans[76]	2003	USA	1980–2001	OR	2	
Roddy[75]	2003	USA	1980–2000	OR	1	
Evans[77]	2000	UK	1983–1995	OR	Multi	
Heller[18]	2000	USA	1979–1997	OR	Database	National Hospital Discharge Survey (NHDS)
Turton[21]	2000	UK	1990–1997	OR	1	
Alonso-Perez[79]	1999	Spain	1995–1996	OR	Multi	
Sasaki[78]	1999	Japan	1968–1997	OR	Multi	
Dardik[80]	1998	USA	1990–1995	OR	Database	Maryland Health Services Cost Review Commission (HSCRC)
Semmens[49]	1998	Australia	1985–1994	OR	Database	WA Linked Database
Barry[81]	1997	Ireland	1987–1993	OR	1	
Katz[8]	1997	USA	1980–1990	OR	Database	The Michigan Inpatient Data Base
Hardman[83]	1996	Australia	1985–1993	OR	1	
Rutledge[82]	1996	USA	1988–1993	OR	Database	North Carolina Medical Database Commission
Henderson[51]	1995	Australia	1986–1991	OR	1	
Ruptured AAA: endovascular repair						
Leon[36]	2005	USA	1995–2003	OR	Database	Illinois Hospital Association COMPdata

OR, observational retrospective; OP, observational prospective; RP, randomized prospective.

Appendix 3a Elective endovascular repair: risk factors and co-morbidities

Study	Diabetes†				Hypertenstion‡				Cardiac§				Cerebrovascular‖				Pulmonary#				Renal**				Smoking††			
	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%
Elective: Endovascular																												
Berge[31]	12*	8.8	12*	8.8	76*	55.9	76*	55.9	60*	44.1	60*	44.1	21*	15.4	21*	15.4	17	12.5	17	12.5	17*	12.5	17*	12.5	NR	–	NR	–
Ting[52]	13*	–	13*	–	72*	–	72*	–	55*	–	55*	–	10*	–	10*	–	31*	–	31*	–	42*	–	42*	–	49*	–	49*	–
Azizzadeh[53]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Biebl[54]	5	13	43	13	30	75	204	89	9	24	157	49	4	10	39	12	14	35	74	23	0	0	6	1.9	NR	–	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Lifeline[20]	255*	12.4	255*	12.4	1321*	64	1321*	64	1705*	82.7	1705*	82.7	NR	–	NR	–	602*	29.2	602*	29.2	70*	3.4	70*	3.4	NR	–	NR	–
Zarins[55]	–	13*	–	13*	–	63*	–	63*	NR	–	NR	–	NR	–	NR	–	–	28*	–	28*	NR	–	NR	–	–	87*	–	87*
Sampaio[56]	1	3.5	39	18.6	26	89.7	154	72.6	6	20.7	73	34.4	NR	–	NR	–	NR	–	NR	–	5	17.2	27	12.9	14	48.2	177	83.9
Criado[57]	–	12*	–	12*	70*	–	70*	–	–	38*	–	38*		14*		14*	–	21*	–	21*	–	14*	–	14*		74*		74*
Elkouri[58]	12*	–	12*	–	79*	–	79*	–	59*	–	59*	–	NR	–	NR	–	30*	–	30*	–	NR	–	NR	–	75*	–	75*	–
Nordness[59]	NR	–	NR	–	9	5.3	55	5.4	7	4.1	61	6.0	NR	–	NR	–	NR	–	NR		2	1.2	4	4.0	13	7.6	83	8.2
Parlani[60]	2	8	33	9	22	88	238	63	13	52	182	48	NR	–	NR	–	12	48	203	54	2	8	41	11	10	40	230	61
Shames[61]	5	11	16	7.7	32	76	104	51	16	38	120	59	7	17	30	15	9	21	53	26	5	11	26	13	23	54	136	67
Slovut[62]	–	12.9*	–	12.9*	–	67.1*	–	67.1*	–	64.7*	–	64.7*	NR	–	NR	–	39*	22.9*	39*	22.9*	–	14.1*		14.1*	NR	–	NR	–
Wyers[63]	–	14*	–	14*	–	61*	–	61*	–	57*	–	57*	–	20*	–	20*		29*		29*	–	12*	–	12*		80*		80*
Sanchez[64]	3	13.6	11	8.3	17	77.3	76	57.1	11	50	90	67.7	9	40.9	25	18.8	8	36.4	44	33.1	3	13.6	15	11.3	10	45.5	102	76.7
Wolf[65]	NR	–	NR	–	NR	–	NR	–	13	50	99	63	NR	–	NR	–	13	50	45	28	NR	–	NR	–	NR	–	NR	–
Howell[66]	NR	–	NR	–	NR	–	NR	–	121*	56.2	121*	56.2	NR	–	NR	–	92*	42.7	92*	42.7	NR	–	NR	–	NR	–	NR	–
Mathison[67]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Romero[68]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Cao[69]	13*	–	13*	–	67*	–	67*	–	52*	–	52*	–	11*	–	11*	–	53*	–	53*	–	11*	–	11*	–	33*	–	33*	–

*Mean value for total group (men and women). †Diabetes was unspecified. ‡Hypertension was unspecified. §Defined as 'coronary heart disease', 'cardiac disease', 'angina', 'myocardial infarction or coronary artery disease', 'coronary artery bypass graft/percutaneous transluminal angioplasty', 'coronary artery disease', 'heart disease', 'coronary revascularization'. ‖Defined as 'cerebrovascular insufficiency', 'stroke', 'cerbrovascular accident'. #Defined as 'respiratory disease', 'chronic obstructive pulmonary disease, a forced expiratory volume less than 1.0 litre or use of home oxygen'. **Defined as 'serum creatinine over 140 mmol/l', 'serum creatinine over 120 mmol/l', 'serum creatinine over 3.0 mg/dl', 'creatinine over 1.5 mg/dl', 'renal dysfunction', 'renal insufficiency', 'chronic renal insufficiency'. ††Defined as 'ever smoked', 'ex-smoker', 'smoker', 'smoking'. NR, not reported.

Appendix 3b Open elective and ruptured aneurysm repair, and endovascular ruptured aneurysm repair: risk factors

Study	Diabetes*		Hypertension†		Cardiac‡		Cerebrovascular§		Pulmonary‖		Renal#		Smoking**	
	Total group	%	Total group	%	Total group	%	Total group	%	Total group	%	Total group	%	Total group	%
Elective: open repair														
Berge[31]	33	6.2	255	48	247	46.5	88	16.6	16	13	51	9.6	275	51.8
Faizer[32]	NR	–	480	86	220	39.4	12	2.2	65	11.6	11	2	NR	–
Hultgren[33]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Bonamigo[34]	42	6.2	432	64	145	21.5	19	2.8	NR	–	35	5.2	457	67.8
Haug[35]	5	4.8	38	36.2	31	29.5	7	6.7	7	6.7	17	15.2	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Lifeline[20]	42	12.6	224	67.1	198	59.3	NR	–	96	28.7	10	3	NR	–
Mackenzie[37]	11	5.0	149	69.6	71	32.4	29	13	NR	–	12	5.5	60	27.4
Urbonavicius[38]	NR	–	NR	–	34	49.3	NR	–	18	26.1	11	15.9	NR	–
Rigberg[9]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Sasaki[39]	NR	–	NR	–	47	47	NR	–	NR	–	NR	–	NR	–
Stenbaek[40]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Biancari[41]	135	7	782	41	915	48	216	11	266	14	84	4	646	34
Upchurch[42]	NR	–	106	69	90	57	NR	–	NR	–	NR	–	154	97.5
Rayan[43]	52	12	258	61.1	194	46	NR	–	NR	–	22	5.2	384	91
Alonso-Perez[44]	20	11.2	93	51.7	75	41	20	11.4	75	44.1	41	28.3	141	83
El-Sabrout[45]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Huber[11]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Brady[46]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	510	62.2
Heller[18]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Dardik[47]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Akkersdijk[48]	20	7	77	26	124	42.6	26	9	44	15	7	2	126	43
Semmens[49]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Katz[8]	NR	–	2509	30.7	2431	29.7	NR	–	NR	–	326	4	NR	–
Starr[50]	79	13.6	373	64.1	NR	–	NR	–	NR	–	117	20.1	NR	–
Henderson[51]	NR	–	108	43	103	40.7	NR	–	NR	–	NR	–	189	74
No. of studies		10		14		15		8		8		13		10
Weighted mean		8.6		54.1		42.0		9.1		19.9		9.2		63.2
Ruptured: open repair														
Berge[31]	21	7	126	42.1	133	44.5	38	12.7	16	15.4	63	21.1	94	31.4
Grant[70]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Filipovic[72]	285	4.7	1720	28.5	1092	18.1	246	4.1	925	15.3	528	8.7	NR	–
Hultgren[33]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Sharif[71]	NR	–	NR	–	38	27.1	NR	–	NR	–	15	10.3	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Stone[24]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Visser[13]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Janczyk[74]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Korhonen[73]	56	6.7	311	37.2	NR	–	122	13.4	122	13.4	28	3.3	151	18.1
Stenbaek[40]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–

Hans[76]	NR	–	NR	–	74	73.3	NR	–	NR	–	NR	–	NR	–
Roddy[75]	24	7.4	NR	–	NR	–	NR	–	NR	–	NR	–	77	23.8
Evans[77]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Heller[28]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Turton[21]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Alonso-Perez[79]	13	12.9	62	60	43	41.3	16	16.2	33	38.8	56	61.5	68	77.3
Sasaki[78]	12	6.6	58	31.7	33	18	18	9.8	7	3.8	21	11.5	NR	–
Dardik[80]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Semmens[49]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Barry[81]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Katz[8]	NR	–	330	18	369	20.2	NR	–	NR	–	342	18.7	NR	–
Hardman[83]	5	3.7	71	52.2	48	35.3	23	16.9	32	23.5	7	5.1	94	79.7
Rutledge[82]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Henderson[51]	NR	–	39	39	23	22.8	NR	–	NR	–	NR	–	61	60
No. of studies		7		8		9		6		6		8		6
Weighted mean		7.0		38.6		33.4		12.2		18.4		17.5		48.4
Ruptured: endovascular repair														
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–

and co-morbidities

*Defined as 'diabetes mellitus', 'insulin dependence/use of oral antidiabetic medication', 'hyperglycaemia requiring diet, oral medication or insulin treatment'. †Defined as 'hypertension', 'diastolic blood pressure over 105 mmHg measured on admission or use of antihypertensive medication', 'at least 180/90 mmHg or antihypertensive medication', 'medication or blood pressure > 160/95 mmHg', 'over140 mmHg'. ‡Defined as 'cardiopathy (angina or previous myocardial infarction (MI) or cardiac failure or dilated cardiopathy or ventricular arrhythmia or symptomatic valvular disease)', 'MI (electrocardiogram (ECG) indicating MI less than 6 months ago)', 'previous MI', 'angina pectoris (current or treated angina pectoris)', 'angina pectoris, MI or treatment with aortocoronary bypass/percutaneous coronary intervention', 'ischaemic heart disease', 'angina (history of MI, angina, ischaemic changes on ECG, previous coronary artery bypass graft)', 'coronary artery disease (CAD)', 'myocardial disease', 'CAD chronic not further defined', 'ECG ischaemia: defined as more than 1 mm ST depression or T wave changes'. §Defined as 'symptomatic', 'history of transient ischaemic attack (TIA) or cerebral infarction/bleeding (CVA)', 'cerebrovascular disease', 'history of stroke/TIA', 'all grades of previous stroke and includes TIA', 'previous CVA/TIA'. ‖Defined as 'pulmonary obstructive disease', 'symptomatic or abnormal chest X-ray or abnormal respiratory function assessment', 'pulmonary disease associated with chronic outflow obstruction, with exclusion of specific lung diseases (e.g. sarcoidosis) recorded on the patient's history and the use of bronchodilators', 'chronic obstructive pulmonary disease', 'lung disease', 'asthma or chronic obstructive disease'. #Defined as 'creatinine over >1.4 mg/dl', 'serum creatinine over 110 mmol/l', 'requiring haemodialysis', 'serum creatinine over 140 mmol/l', 'serum creatinine over 1.5 mg/dl', 'renal failure, according to Glasgow Aneurysm Score', 'renal failure: creatinine over 150 mmol/l', creatinine over 0.18 mmol/l', 'renal disease, failure: history of chronic or acute renal failure with a serum urea level greater than 20 mmol/l and/or creatinine level above 150 mmol/l at presentation', 'renal failure chronic', 'serum creatinine over 0.19 mmol/l', 'creatinine at least 2.0mg/dl'. **Defined as 'smoker', 'current smoker', 'positive smoking history', 'current + ex-smoker combined', 'tobacco use: yes'. NR, not reported.

Appendix 4a Elective endovascular repair: in-hospital/30-day complications

Study	Cardiac*				Cerebrovascular†				Pulmonary‡				Renal§				Bowel ischaemia‖				Sepsis or MOF#				Endoleak**			
	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂	%	♀	%	♂		♀	%	♂	%	♀	%	♂	%
Elective: endovascular																												
Berge[31]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Ting[52]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Azizzadeh[53]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Biebl[54]	1	2.4	20	6.1	1	2.4	0	0	1	2.4	4	1.2	1	2.4	13	4	0	0	4	1.2	NR	–	NR	–	NR	–	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Lifeline[20]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Zarins[55]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Sampaio[56]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Criado[57]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Elkouri[58]	15††	–	15††	–	NR	–	NR	–	5††	–	5††	–	3††	–	3††	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Nordness[59]	NR	–	NR	–	0	0	1	1	2	11.8	1	1	2	11.8	2	2	0	0	1	1	NR	–	NR	–	2	11.8	3	3
Parlani[60]	1	4	3	0.8	1	4	0	0	NR	–	NR	–	1	4	2	0.5	0	0	1	0.3	NR	–	NR	–	NR	–	NR	–
Shames[61]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Slovut[62]	NR	–	NR	–	0	0	0	0	1††	–	1††	–	2††	–	2††	–	1††	–	1††	–	NR	–	NR	–	NR	–	NR	–
Wyers[63]	6††	3	6††	3	NR	–	NR	–	3††	1.5	3††	1.5	12††	6	12††	6	NR	–	NR	–	NR	–	NR	–	30	15††	30	15††
Sanchez[64]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	1	4.5	4	3
Wolf[65]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Howell[66]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	82††	42	82††	42
Mathison[67]	1	4.2	8	2.8	0	0	1	0.36	NR	–	NR	–	0	0	10	3.6	NR	–	NR	–	1	4.2	0	0	7	35	60	22.1
Romero[68]	5	29	17	11	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Cao[69]	NR	–	NR	–	1††	–	1††	–	NR	–	NR	–	1††	–	1††	–	NR	–	NR	–	NR	–	NR	–	18††	16	18††	16

††Mean value for total group (men and women). *Defined as 'cardiac', 'early cardiovascular event', 'myocardial infarction', 'troponin change without electrocardiographic change for 2 of 3', 'adverse cardiac event'. †Defined as 'stroke', 'non-disabling'. ‡Defined as 'pulmonary complications', 'respiratory failure', "respiratory failure: intubation for more than 2 days', 'acute respiratory distress syndrome'. §Defined as 'renal (more than 30 per cent increase in serum creatinine, no haemodialysis)', 'renal failure', 'acute renal failure', 'renal infarction', 'transient renal deterioration defined as more than 30 per cent rise in serum creatinine', 'renal infarction and nephrectomy'. ‖Defined as 'bowel (bowel ischaemia or prolonged ileus for more than 4 days)', 'bowel ischaemia', 'ischaemic colitis'. #Sepsis or multiple organ failure (MOF) defined as 'sepsis'. ** 'Endoleaks type 1 and 2', 'endoleaks', 'endoleaks type 1 and 3','endoleaks type 1, 2 and 4'. NR, not reported

Appendix 4b Open elective and ruptured aneurysm repair, and endovascular ruptured aneurysm repair: in-hospital/30-day complications

Study	Cardiac*		Cerebrovascular†		Pulmonary‡		Renal§		Bowel ischaemia‖		Sepsis or MOF#	
	Total group	%	Total group	%	Total group	%	Total group	%	Total group	%	Total group	%
Elective: open repair												
Berge[31]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Faizer[32]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Hultgren[33]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Bonamigo[34]	39	5.8	NR	–	37	5.5	8	1.2	32	4.7	NR	–
Haug[35]	11	10.5	NR	–	14	13.3	10	11.4	NR	–	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Lifeline[20]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Mackenzie[37]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Urbonavicius[38]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Rigberg[9]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Sasaki[39]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Stenbaek[40]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Biancari[41]	139	7	NR		NR		NR		NR		NR	
Upchurch[42]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Alonso–Perez[44]	22	12.2	NR	–	36	19.9	29	16.1	6	3.3	12	6.6
El–Sabrout[45]	10	1.9	9	1.8	NR	–	25	4.9	3	0.6	NR	–
Huber[11]	1297	7.9	NR	–	NR	–	NR	–	NR	–	NR	–
Brady[46]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Heller[18]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Dardik[47]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Akkersdijk[48]	29	10	NR	–	29	10	NR	–	NR	–	NR	–
Semmens[49]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Katz[8]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Starr[50]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Henderson[51]	15	5.9	NR	–	NR	–	NR	–	1	0.7	2	1.3
Ruptured: open repair												
Berge[31]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Grant[70]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Filipovic[72]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Hultgren[33]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Sharif[71]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Stone[24]	8	10	1	1	NR	–	10	12	12	14	NR	–
Visser[13]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–

Janczyk[74]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Korhonen[73]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Stenbaek[40]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Hans[76]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Roddy[75]	15	4.6	6	1.9	22	6.8	5	1.5	8	2.5	NR	–
Evans[77]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Heller[18]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Turton[21]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Alonso–Perez[79]	41	45.1	NR	–	36	39.6	47	51.6	9	10	11	12.2
Sasaki[78]	21	1.1	NR	–	23	1.3	45	2.5	16	0.9	–	–
Dardik[80]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Semmens[49]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Katz[8]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Hardman[83]	14	12.1	NR	–	23	19.8	63	54.3	14	12.1	30	25.9
Rutledge[82]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–
Henderson[51]	13	13	2	2	16	16	NR	–	5	5	16	16
Ruptured: endovascular repair												
Leon[36]	NR	–	NR	–	NR	–	NR	–	NR	–	NR	–

*Defined as 'coronary', 'myocardial infarction (MI)', 'cardiac complications', 'cardiac complications: increase in cardiac enzymes accompanied by electrocardiographic changes or development of arrhythmia', 'ischaemia or infarction', 'heart failure', 'acute MI or heart failure'. †Defined as 'neurological deficit lasting more than 24 h or any new infarct on brain imaging','stroke'. ‡Defined as 'pulmonary', 'respiratory complications', 'pulmonary complications', 'respiratory failure'. §Defined as 'renal', 'renal failure', 'renal dysfunction', 'renal insufficiency in a patient without preoperative renal failure', 'renal failure with dialysis', 'temporary or permanent dialysis', 'acute respiratory failure'. ‖Defined as 'gastrointestinal', 'intestinal ischaemia', 'gut infarction', "colon ischaemia', 'ischaemic colitis', 'gut ischaemia'. #Defined as 'sepsis, 'multiple organ failure (MOF)'. NR, not reported.

Chapter 4

Systematic review of guidelines on abdominal aortic aneurysm screening

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J Vasc Surg. 2012 May;55(5):1296-1304. Epub 2011 Feb 16. Review.

Abstract

Objectives

Usually, physicians base their practice on guidelines, but recommendations on the same topic may vary across guidelines. Given the uncertainties regarding abdominal aortic aneurysm (AAA) screening, physicians should be able to identify systematically and transparently developed recommendations. We performed a systematic review of AAA screening guidelines to assist physicians in their choice of recommendations.

Methods

Guidelines in English published between January 1, 2003 and February 26, 2010 were retrieved using MEDLINE, CINAHL, the National Guideline Clearinghouse, the National Library for Health, the Canadian Medication Association Infobase, and the G-I-N International Guideline Library. Guidelines developed by national and international medical societies from Western countries, containing recommendations on AAA screening were included. Three reviewers independently assessed rigor of guideline development using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. Two independent reviewers performed extraction of recommendations.

Results

Of 2415 titles identified, seven guidelines were included in this review. Three guidelines were less rigorously developed based on AGREE scores below 40%. All seven guidelines contained a recommendation for one-time screening of elderly men by ultrasonography to select AAAs ≥5.5 cm for elective surgical repair. Four guidelines, of which three were less rigorously developed, contained disparate recommendations on screening of women and middle-aged men at elevated risk. There was no agreement on the management of smaller AAAs.

Conclusion

Consensus exists across guidelines on one-time screening of elderly men to detect and treat AAAs ≥5.5 cm. For other target groups and management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance.

Clinical Relevance

Usually, physicians base their practice on guidelines, but recommendations on the same topic may vary across guidelines. Given the uncertainties regarding AAA screening, physicians should be able to identify systematically and transparently developed recommendations. To assist physicians, a systematic review of national and international guidelines on AAA screening was performed. Consensus was found across the included guidelines on one-time screening of elderly men to detect and treat AAAs ≥5.5 cm. For other target groups and management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance.

Abdominal aortic aneurysms (AAAs) contribute significantly to disease burden in developed countries, accounting for approximately 0.5% of total mortality in the United States.[1] Because rupture of an AAA is preceded by a preclinical detectable phase and because accurate tests and effective treatment are available, screening is likely to be beneficial. A recent Cochrane systematic review, including four screening trials, showed a significant decrease in AAA-related mortality in asymptomatic men aged 65 to 79 years who underwent ultrasound screening.[2] A beneficial effect on total mortality was not demonstrated and uncertainties remain regarding other target groups, the optimal screening strategy, policy toward small AAAs, cost-effectiveness, and psychological effects of screening.

In the United Kingdom, the National Health Service Abdominal Aortic Aneurysm Screening Program is being introduced gradually with a full coverage across England expected by March 2013. In this program, men aged 65 are invited for a one-time ultrasound scan examination. In the United States, an abdominal ultrasound scan study for AAA detection is offered as part of the one-time "Welcome to Medicare" preventive health examination. Medicare covers AAA screening for all men who turned 65 years of age and smoked at least 100 cigarettes and individuals with a family history of AAA.[3] In many Western countries, however, systematic, nationwide screening programs are not implemented, and decisions on screening are made on the individual level by primary care physicians. For example, in The Netherlands, systematic screening programs are only allowed in a research setting.[4] Instead, opportunistic screening of siblings of patients with an AAA is recommended.

The purpose of guidelines is to close the gap between the best available evidence and what physicians do in their practice. The usual method of disseminating and implementing guidelines is rather passive, by publication in medical journals or mailing to targeted professionals. This method does not seem to achieve the guidelines' aim: changing physicians' behavior.[5] Variations in recommendations across guidelines on the same topic may cause physicians to lose confidence in the construction process and validity of guidelines and lead to a further derivation from this aim. In addition, relationships with the industry can potentially influence choices made within guideline development, making the validity of recommendations even more questionable.[6] Given the potential uncertainties regarding AAA screening, physicians require recommendations that have been developed systematically and transparently.[7]

Our purpose was to assist physicians in their choice of recommendations

on AAA screening by a systematic review and critical appraisal of current guidelines.

Methods

Data sources and searches.

The literature search, used for a previous article on cardiovascular risk assessment,[8] was updated to identify guidelines of interest. Briefly, MEDLINE, CINAHL, and four guideline-specific databases: the National Guideline Clearinghouse (United States), the National Library for Health on Guideline Finder (United Kingdom), Canadian Medical Association Infobase (Canada), and the G-I-N International Guideline Library (http://www.g-i-n.net) were searched. Guidelines published from January 1, 2003, to February 26, 2010, and in the English language were considered. Additional guidelines were sought by searching websites of guideline development organizations. See Appendix, online only, for the exact search.

Study selection.

A guideline was only considered if it met the Institute of Medicine definition for clinical practice guidelines. In order to meet this definition, a guideline has to contain "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." In order to meet inclusion criteria, guidelines had to: (1) be developed on behalf of a national or international medical specialty society; (2) contain recommendations for an asymptomatic population with no previous diagnosis of AAA; and (3) originate from or apply to Western countries (eg, the United States, Canada, Australia, New Zealand, or the United Kingdom).

Titles and abstracts were reviewed independently by two reviewers (B.S.F. and E.B.C.). Articles were only excluded if both reviewers agreed on the decision. Discrepancies were resolved by consensus. The first author made the final selection of articles based on full text.

Data extraction and quality assessment.

Relevant recommendations from the included guidelines were independently extracted by two reviewers (B.S.F. and N.G). Discrepancies were resolved by consensus. Each guideline provided one or more relevant recommendations. Data extracted included the reported methodology for evidence synthesis, formulating of recommendations, consideration of cost-effectiveness, the target population, the strategy for delivery of the test, recommended tests, and test thresholds for intervention and follow-up. In addition, the recommendation was classified as "for," "consider," "not for not against," "insufficient evidence," or "against."

The quality of development of each included guideline was determined using the "Rigor of Development" domain of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, a seven item score.[9] This score looks at: (1) methods to search for evidence; (2) criteria for selecting the evidence; (3) methods for formulating the recommendations; (4) consideration of health benefits, side effects, and risks; (5) supporting evidence; (6) procedures for external peer review; and (7) the update process. Each item is rated on a 4-point Likert scale. Three reviewers (B.S.F., N.G., and J.J.V.) independently scored each guideline. Additional information on development was also examined by these three reviewers by perusing websites of guideline develop-

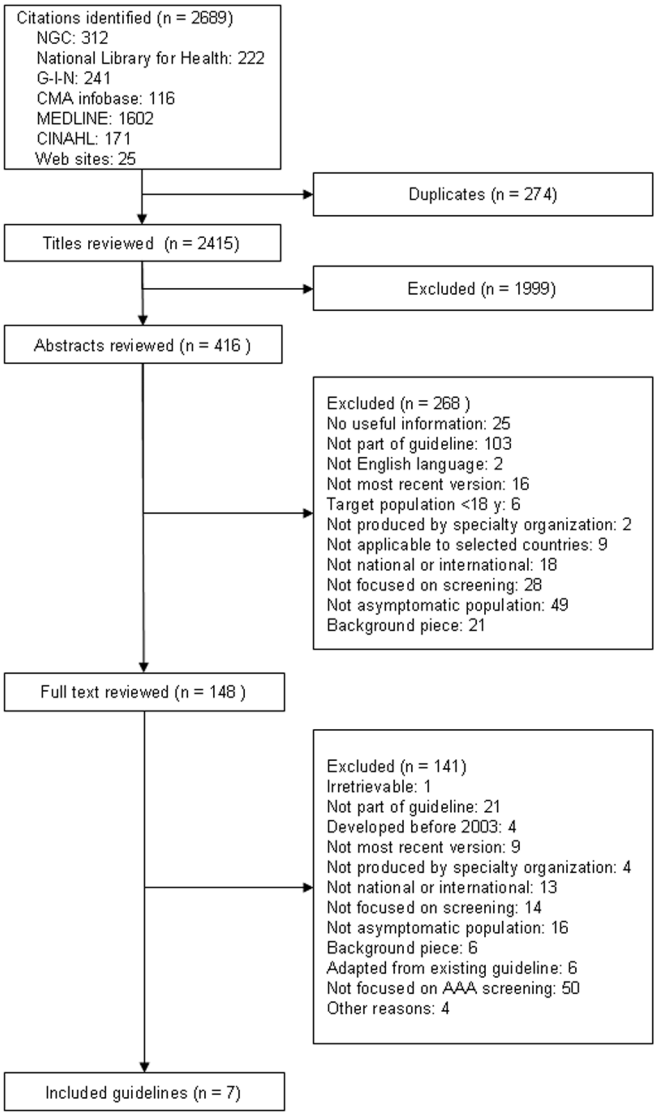

Fig 1. Literature search and selection. Numbers of guidelines of each step of the process are indicated. Group totals may exceed the reported numbers for the excluded articles at abstract and full text level because several reasons for exclusion were allowed. *AAA,* Abdominal aortic aneurysm; *CMA,* Canadian Medical Association; *NGC,* National Guideline Clearinghouse.

ers. For each reviewer, AGREE scores were calculated as a percentage using the sum of the seven items and the maximum possible score. Final rigor scores were calculated by averaging the AGREE scores from all reviewers (see Table I, online only, for AGREE item scores per guideline). Reproducibility of the three reviewers' average rigor scores was measured with an intraclass correlation coefficient. We ranked included guidelines according to their average score. Editorial independence from funding body,

external funding, and disclosure of relationships with industry by individual guideline group members were assessed (B.S.F.) and checked (N.G.). Discrepancies were resolved by consensus. SRS version 4.0 (Mobius, Ottawa, Ontario, Canada), a web-based software package developed for systematic review data management, was used to remove duplicates, store citations and track results at title, abstract, quality assessment, and data extraction levels.

Data synthesis and analysis.

We constructed a table to compare the recommendations from the included guidelines. The table was divided into the following sections: (1) methodology of guideline development; (2) consideration of cost-effectiveness regarding the recommendation; (3) target group and delivery of AAA screening; (4) tests considered; and (5) thresholds for intervention and follow-up.

Results

Selection and assessment of guidelines.

We screened 2415 guidelines for eligibility at title level, of which 416 were included for review at abstract level (Fig 1). Of these, seven guidelines relevant to AAA screening were eligible for full data extraction. Table II summarizes the selected guidelines, together with rigor scores and conflict of interest results. Most guidelines (six of seven) were developed in North America. AGREE scores varied from 17% to 79% with three guidelines (Canadian Cardiovascular Society [CCS], Society for Vascular Surgery [SVS]1, and SVS2) having an AGREE score below the median, 40%. Reproducibility of the AGREE scores by the three reviewers was good, with an intraclass correlation coefficient of 0.86. In two of the seven guidelines (American College of Cardiology [ACC], SVS2), at least one panel member declared having a relevant financial relationship with the industry. None of these guidelines reported exclusion of group members from voting or discussions. Only one guideline (United States Preventive Services Task Force [USPSTF]) contained a statement of being developed independently from the funding organization. Two guidelines (National Screening Committee [NSC] and CCS) neither reported that they were developed independently from funding organization(s), nor did they report a statement about conflicts of interest of group members. The seven included guidelines contained 12 recommendations on AAA screening (Table III). Two (USPSTF and ACC) of the seven guidelines were developed on the basis of a systematic review of the medical literature. The remaining five guidelines were developed using a non-systematic selection of previously developed systematic reviews or primary research. Evaluation of cost-effectiveness of AAA screening strategies was done in six of seven guidelines by reviewing existing decision modeling studies.

Table 1 Characteristics of 7 Guidelines on AAA Screening

Guideline, Year[Reference]	Organization(s) Responsible for Guideline Development	Country that guideline applies to	AGREE Rigor Score, %	Conflicts of Interest
USPSTF, 2005[22]	U.S. Preventive Services Task Force	United States of America	79%	EI
ACC, 2005[23]	American College of Cardiology, and American Heart Association	United States of America	63%	SCI[a]
NSC, 2007[24]	National Screening Committee	United Kingdom	41%	-
CSVS, 2007[25]	Canadian Society for Vascular Surgery	Canada	40%	SCI
CCS, 2005[26]	Canadian Cardiovascular Society	Canada	38%	-
SVS1, 2009[27]	Society for Vascular Surgery	United States of America	25%	SCI[a]
SVS2, 2004[28]	Society for Vascular Surgery, American Association of Vascular Surgery, and Society for Vascular Medicine and Biology	United States of America	17%	SCI

Abbreviations: EI, editorial independence declared; FIP, funding by industrial partner reported; FPO, funding by external public organization reported; SCI, statement about conflicts of interest of group members present.
[a]Relationship with industry reported by any group member.

Table 2 Recommendations (n=12) in Guidelines (n=7) on Screening for Abdominal Aortic Aneurysm

	USPSTF	USPSTF	USPSTF	ACC	NSC
AGREE rigor score, %	79%	79%	79%	63%	41%
Method to evaluate evidence	Meta-analysis; systematic review	Meta-analysis; systematic review	Meta-analysis; systematic review	Systematic review	Review of published systematic reviews, meta-analyses or guidelines; review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Systematic review of cost-effectiveness studies	Systematic review of cost-effectiveness studies	Systematic review of cost-effectiveness studies	Review of cost-effectiveness studies	Review of cost-effectiveness studies
Target group	Men aged 65 - 75 y who have ever smoked[c]	Men aged 65 - 75 y who have never smoked	Women	Men aged ≥ 60 y who are siblings or offspring of patients with AAAs; men aged 65 - 75 y who ever smoked[c]	Men aged 65 y
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Not reported	Population-based / mass screening
Recommendation	For	Not for not against	Against	For	For
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography; physical examination	Abdominal ultrasonography
Intervention(s)	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Surgical repair if infrarenal or juxtarenal AAAs ≥ 5.5 cm (repair is probably indicated in patients with suprarenal or type IV thoracoabdominal aortic aneurysms 5.5 - 6.0 cm); no intervention if infrarenal or juxtarenal AAAs 4.0 - 5.4 cm, but repair can be beneficial in patients with infrarenal or juxtarenal AAAs 5.0 - 5.4 cm	Referral to a vascular surgeon if AAA ≥ 5.5 cm

Surveillance	Not reported	Not reported	Not reported	Monitoring by ultrasound or computed tomographic scans every 6 to 12 months to detect expansion if infrarenal or juxtarenal AAAs 4.0 - 5.4 cm; monitoring by ultrasound examination every 2 to 3 years is reasonable if AAAs smaller than 4.0 cm in diameter	A follow-up will be arranged in 3 months if AAA 4.5 - 5.4 cm; a follow-up will be arranged in one year if AAA measures 3.0 - 4.4 cm
Screening Intervals	One-time screening	One-time screening	One-time screening	One-time screening if not in above categories	One-time screening if not in above categories

Table 2 – Continued

	CSVS	CSVS	CSVS	CSVS
AGREE rigor score, %	40%	40%	40%	40%
Method to evaluate evidence	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data
Target group	Men aged 65 - 75 y who are candidates for surgery and are willing to participate	Women aged > 65 y and multiple RFs[a]	Women aged > 65 y, adult populaton aged < 65 y	Deducted from text: Men aged > 75 y and multiple RFs[a]

Strategy	Population-based / mass screening	Individualized investigation	Population-based / mass screening	Individualized investigation
Recommendation	For	Consider	Against	Consider
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography
Intervention(s)	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm
Surveillance	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms
Screening Intervals	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm

Table 2 – Continued

	CCS	SVS1	SVS2
AGREE rigor score, %	38%	25%	17%
Method to evaluate evidence	Review	Review	Review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Review of cost-effectiveness studies	Review of cost-effectiveness studies, but not for AAA screening	Review of cost-effectiveness studies

Target group	Men aged 65-74 y; women aged 65 y with cardiovascular disease and positive family history of AAA men aged ≥ 50 y and positive family history of AAA;	Men aged ≥ 65 y; men aged ≥ 55 y and family history of AAA; women aged ≥ 65 y and family history of AAA or who have smoked	Men aged 60 - 85 y; women aged 60 - 85 y and cardiovascular risk factors (not specified); men and women aged > 50 y and family history of AAA
Strategy	Population-based / mass screening	Population-based / mass screening	Population-based / mass screening
Recommendation	For	For	For
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography
Intervention(s)	Referral to vascular surgeon if AAA ≥ 4.5 cm; surgical repair if men AAA > 5.5 cm and if women AAA > 5.0 cm; consider surgical repair if > 1 cm growth in 1 year	Surgical repair if fusiform AAA ≥ 5.5 cm, saccular AAA[b] , young healthy patients, and especially women, with AAA 5.0 - 5.4 cm[b]; statins[b], smoking cessation, ACE inhibitors/angiotensin receptor blockers[b] if surveillance (AAA 3.5 - 5.4 cm: not clearly described)	Referral to a vascular specialist if AAA > 4.5 cm; surgical repair if > 5,5 cm: policy not clearly described
Surveillance	Repeat ultrasound every 6 months if AAA ≥ 4.5 cm; repeat ultrasound in 1 year if AAA 4.0 - 4.5 cm; repeat ultrasound in 2 year if AAA 3.5 - 3.9 cm; repeat ultrasound in 3 years if AAA 3.1 - 3.4 cm	Repeat ultrasound every 6 months if AAA 4.5 - 5.4 cm; repeat ultrasound in 1 year if AAA 3.5 - 4.4 cm; repeat ultrasound in 3 years if AAA 3.0 - 3.4 cm; repeat ultrasound in 5 years if AAA 2.6 - 2.9 cm	Repeat ultrasound every 6 months if AAA 4.0 - 4.5 cm; annual ultrasound examination if AAA 3.0 - 4.0 cm
Screening Intervals	Repeat ultrasound follow-up in 3-5 years if aortic diameter < 3.0 cm	One time screening if aortic diameter < 2.6 cm and 65 years of age or older; not reported if aortic diameter < 2.6 cm and age 55 - 65 years of age	One time screening if aortic diameter < 3.0 cm

eTable. AGREE Instrument Rigor of Development Domain Results

Guidelines	Reviewer	Methods to search for evidence	Criteria for selecting the evidence	Methods for formulating the recommendations	Health benefits, side effects and risks	Supporting evidence	Procedures for external expert review	Update process	Domain score, %*
USPSTF	A	4	4	3	4	4	3	4	90.5
	B	4	3	4	3	4	3	2	76.2
	C	4	3	2	2	3	4	4	71.4
ACC	A	3	1	2	4	4	3	4	66.7
	B	3	3	3	3	3	3	3	66.7
	C	1	1	3	3	3	4	4	57.1
NSC	A	4	1	1	1	4	1	3	38.1
	B	2	2	2	3	1	2	2	33.3
	C	4	4	1	1	4	3	1	52.4
CSVS	A	1	1	1	4	4	1	3	38.1
	B	2	1	2	2	3	2	2	33.3
	C	1	1	2	4	3	3	3	47.6
CCS	A	1	1	1	4	4	2	1	33.3
	B	1	1	2	2	3	2	2	28.6
	C	2	2	3	3	4	2	2	52.4
SVS1	A	1	1	1	3	3	1	1	19.0
	B	1	1	2	2	2	1	1	23.8
	C	1	1	2	2	2	2	2	33.3
SVS2	A	1	1	1	3	3	1	1	19.0
	B	1	1	1	2	3	1	1	14.3
	C	1	1	1	3	3	1	1	19.0

AGREE, Appraisal of Guidelines Research and Evaluation; USPSTF, United States Preventative Services Task Force; ACC, American College of Cardiology; NSC, National Screening Committee; CSVS, Canadian Society for Vascular Surgery; CCS, Canadian Cardiovascular Society; SVS, Society for Vascular Surgery. 4 = strongly agree; 3 = agree; 2 = disagree; 1 = strongly disagree.

*Domain scores are calculated as (Σ item scores – 7)/(28-7).

Areas of agreement and disagreement among recommendations.

All guidelines contained at least one recommendation that supported AAA screening in elderly men. Although guideline groups (six of seven) generally agreed on the age at which screening should be started in elderly men (that is 65 years of age), they disagreed on whether a smoking history should be present or not. In recommendations from two (USPSTF and ACC) of the seven guidelines, ever smoking (current or past smoking) was required. In the other five guidelines, screening was recommended for elderly men regardless of smoking habits.

Three guidelines (USPSTF, ACC, and NSC) only contained recommendations for AAA screening in elderly men

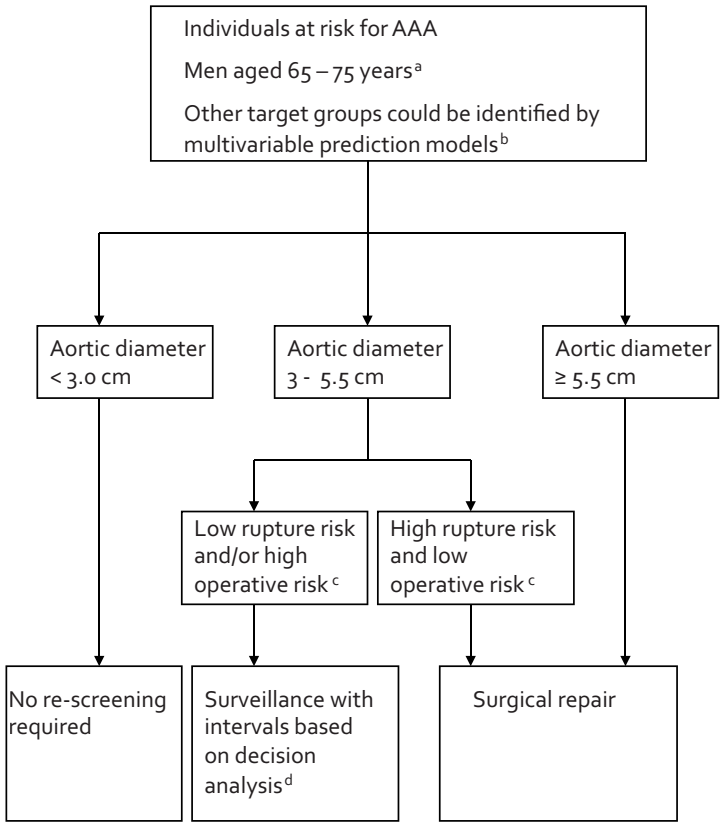

Fig 2. Summarizing screening algorithm and suggestions for future research. [a] Restricting this target group by adding a history of smoking requires the reduced life expectancy caused by smoking to be taken into consideration in decision analysis. [b] Multivariable modeling to predict abdominal aortic aneurysm (*AAA*) risk can be used to identify groups at high risk within men 50 to 65 years, men _75 years, and women _60 years. Variables to consider are age, gender, family history of AAA, history of smoking, history of cardiovascular disease, other cardiovascular risk factors.[14,18] The expected benefit of screening these groups can be calculated by decision analysis. [c] Prediction models considering variables such as age, gender, aortic diameter size, smoking status, blood pressure, history of cardiovascular disease, pulmonary and renal impairment can estimate these risks.[23-25] [d] The optimal intervals for periodic ultrasound scan surveillance can be calculated with cost-effectiveness analysis

or recommended explicitly against screening women. These three guidelines had the highest AGREE scores. Guidelines with lower AGREE scores also contained recommendations for other target groups. Four guideline groups (Canadian Society for Vascular Surgery [CSVS], CCS, SVS1, and SVS2) recommended screening in women if risk factors for development of AAA were present. Although in two of these guidelines (CSVS and CCS) multiple risk factors were required, in two guidelines (SVS1 and SVS2) the presence of one risk factor was considered sufficient reason to screen. Three guidelines (CCS, SVS1, and SVS2) recommended screening of middle-aged men (that is 50 or 55 years) if a family history of AAA is present. Although not all guideline groups reported an age criterion when screening should no longer be offered, in most guidelines (four of seven) 75 years of age was considered as the upper age limit.

Abdominal ultrasonography was unanimously advocated as the primary screening test and only one guideline group (ACC) recommended physical examination as a useful screening tool in addition to ultrasonography. All guideline groups recommended elective surgical repair at an abdominal aortic diameter of 5.5 cm in elderly men. Some guideline groups advocated using a lower threshold (ie, 5.0 cm) for women (CCS and SVS2) or young healthy patients (SVS2) as an indication for surgical repair.

Except for the USPSTF guideline, all guidelines contained recommendations for surveillance of those with aneurysms smaller than 5.5 cm in diameter. These recommendations, however, varied across the guidelines with respect to the intensity of follow-up and aorta diameter cutoff values for the monitoring intervals. The two Canadian guideline groups (CSVS and CCS) were unique in recommending periodic rescreening for individuals with abdominal aortic diameters below 3 cm; the remaining guideline groups recommended one-time screening.

Discussion

In summary, we identified seven guidelines on AAA screening. A majority of guidelines lacked a systematic method for the evaluation of the evidence or achieved a low AGREE score for rigor of development. Most guidelines contained recommendations that were in favor of one-time AAA screening for men 65 years and older using ultrasonography scans. Four guidelines, of which three had low AGREE scores, also contained disparate recommendations on screening women and middle-aged men at elevated risk, whereas guidelines with higher AGREE scores did not. Although an abdominal aortic diameter of 5.5 cm was unanimously used as criterion for elective surgical repair in elderly men, no consensus existed on management of smaller AAAs.

A previously published review already summarized and discussed a selection of three guidelines on AAA screening, but the review was neither systematic nor were the selected guidelines appraised on quality.[10] We used a sensitive search strategy to identify guidelines and we assessed the included guidelines by a validated tool, the AGREE instrument. Our article can also have additive value to guideline summaries provided by the National Guideline Clearinghouse, as this database has only summarized some of the guidelines that we reviewed, and does not appraise guidelines on quality of development.[11] We tried to create awareness of differences across

guidelines from Western countries, which generally have a comparable population health status and access to medical resources.[12] The differences, which we identified, can have major implications for clinical practice. Because most guidelines were produced by North American organizations, this report is most valuable to guide physicians from this region in choosing which recommendations to follow. Physicians may decide based on AGREE scores and their specific clinical context which recommendations to adopt or to avert.

Despite these strengths, we have to face certain limitations of our review. First, we neither evaluated the source nor the quality of the underlying evidence that supported the recommendations, but instead assessed the guidelines' construction processes. For example, disparate evidence cited by guideline developers could provide possible causes for variation in recommendations. Transparent development methods and complete information on how judgments were made increase the reliability of recommendations and allow physicians to make more informed decisions on adopting them. Which recommendations would result in better outcomes can be determined in comparative effectiveness research,[13] but this was beyond the scope of our review. Second, the AGREE instrument only considers the details of reporting information related to the development of the guideline. The true quality of the guideline can, therefore, not be fully captured. For example, a guideline group which performs a systematic search for evidence and which does not report detailed information on the search strategy followed, will receive a low AGREE score for this item. In reality, the search followed may be adequate for identifying solid evidence. Although we did search the organization's website for additional background information, we did not contact guideline developers for additional information that was lacking in the guideline document or on the website. Third, the AGREE instrument provides a quality score on a linear scale. This means that each item is weighed equally. We believe that all items of the AGREE Rigor of Development domain are relevant, supporting equal weighting across items. The contribution of each individual item to the total quality of a guideline is, however, difficult to assess. Fourth, it was difficult to quantify the true degree of influence by industry relationships. We had to rely on the disclosures that were believed to be relevant for decision-making by group members themselves. We also could not assess the size of entanglements with industry, because guidelines did not report the payment amounts received.

Although all guidelines agreed upon screening elderly men, some guidelines advocated a more selective screening regime based on smoking history. Selective screening instead of whole population screening could result in too many missed AAAs.[14] Nevertheless, a modeling study showed that selective screening of men aged 65 to 75 years who have ever smoked, as recommended by the USPSTF and ACC, did not severely affect the detection rate.[15] Using ever-smoking as a preselection tool, however, potentially has the disadvantage that ever-smoking not only acts on prevalence of AAA, but also on comorbidities.[16] The expected gain in life years by AAA screening could then be nullified by the raised competing risk due to other death causes. This was not taken into account for calculation of the effectiveness of screening in the previously mentioned modeling study.[15] Other guideline groups recommend-

ed screening also in populations other than men aged 65 to 75 years if risk factors are present (eg, men aged 50 to 65 years, men older than 75 years, and women). For these populations, no clear evidence exists from experimental research for such a recommendation.[2] The reasoning is that the risk of having an AAA is markedly increased if risk factors are present. The odds ratio, however, generally needs to be high before a risk factor can be used for risk classification.[17] The odds ratios of single risk factors other than smoking are low for clinically relevant large AAAs. [14] and [18] Therefore, combining risk factors may be warranted to avoid unnecessary ultrasonographies and over-diagnosis of small AAAs for which the optimal treatment strategy is unclear. [19] and [20] On the other hand, when screening is recommended both at a younger age if risk factors are present and at an older age regardless of risk factors, such as in ACC, CCS, SVS1, and SVS2 guidelines, then a bias similar to lead time bias could occur. Only the AAAs that are vulnerable to rupture in the short term contribute to benefit of screening at an earlier age. Slowly growing AAAs would most likely be identified at the older screening age. The additional benefit of screening in middle-aged men and women at elevated risk can be explored by comparing the different screening strategies in a decision analysis.

The variation in recommendations for policy toward small asymptomatic AAAs is relevant because with screening approximately 90% of the detected AAAs will be smaller than 5.5 cm in diameter. [18] and [21] Two guideline groups (CCS and SVS2) suggested using smaller diameters for women and healthy young patients as the threshold for elective surgical repair. Two meta-analyses did not show an improvement of overall survival in the immediate surgical repair group as compared to those allocated to surveillance. [19] and [20] There was insufficient power to identify subgroups that might benefit from immediate repair. A recent published trial not included in the two meta-analyses also did not demonstrate a benefit on overall mortality after immediate endovascular repair, although this trial was stopped earlier because the event rate of the primary outcome measure of rupture or aneurysm-related death was too low to achieve sufficient statistical power.[22] According to the Cochrane review,[20] an individual patient-level data meta-analysis is under way to conduct subgroup analyses, which are expected to elucidate risks and benefits of each treatment option for aneurysm size subgroups, and age subgroups (for example ≤69 years, and >69 years). Multivariable prediction models of rupture and operative risk could also be used to identify those expected to benefit from immediate surgical repair. Multiple predictors determine rupture [23] and [24] and operative risk[25] and, therefore, variation in treatment effect is difficult to be captured by single patient characteristics. The use of prediction models for rupture risk and operative risks has the advantage that predictors that influence both, for example, female gender,[26] can be taken into account. A combination of a high-predicted rupture risk and a low-predicted operative risk is then likely to result in a survival benefit from immediate surgical repair. In the absence of experimental evidence for a survival benefit, the trade-off between immediate surgical repair and surveillance can be based on costs and quality of life by using decision modeling and cost-effectiveness analyses. In addition, the optimal screening and monitoring intervals can then be evaluated.

Although methods are available for integrating various recommendations into a single guideline, our purpose was not to create a new "universal" AAA screening guideline. However, a summarizing screening algorithm comprising the recommendations that the guidelines had in common and our suggestions for future research is depicted in Fig 2. The actual implementation of these recommendations in primary care is critical in optimizing patient outcomes. Methods to measure and improve the delivery and adherence of AAA screening interventions are, for example, performance measures and decision support systems, but these are still topics for further research. [27] and [28]

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Chapter 5

Endovascular abdominal aortic aneurysm repair in women

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Acta Chir Belg 2011 Jan-Feb;111(1): 2-6

Abstract

The objective of this review was to establish the role of endovascular aortic aneurysm repair (EVAR) in women. A step by step approach was taken looking at sex and gender differences in epidemiology, pathogenesis and natural history. We then proceed to discuss the results from the three randomized controlled trials comparing EVAR to open repair. Finally, sex-specific secondary prevention, risk factor management and medication, is discussed. Women seem to have higher mortality and more complications after EVAR. Risk factors such as diabetes and hypertension are associated with worse outcome in women compared to men. The role of EVAR in women is poorly investigated and its definite role remains to be determined. Aggressive treatment of risk factors and the optimisation of medication in women are indicated and deserve more attention in clinical practice and future research.

Introduction

In the last 50 years a lot of research has been done on cardiovascular disease. This research has taught us a lot about the causes, the symptoms and how we can best treat cardiovascular disease. Unfortunately most of this research was done in men and we have learnt that these results can not just simply be generalized and implemented in women.

A lot of research has focused on coronary artery disease where apparent sex and gender differences are already well established. Women receive a later diagnosis than men, receive less aggressive treatment and have higher complication and mortality rates following revascularization procedures.[1-2]

For non-cardiac vascular disease such as abdominal aortic aneurysm, studies are fewer, but the mechanisms are thought to be the same. Here too, it is thought that women are diagnosed later, are admitted to hospital less frequently and have worse outcome after repair.[3]

Endovascular repair has emerged as an alternative to surgery in an attempt to minimize surgery. Although initially introduced as an alternative to no repair for the very frail and unfit-for-open surgery patients, it is being implemented widely in current practice.

As a result of this wide implementation more knowledge is being generated and advancements are being made to the devices. Most patients receiving EVAR, however, are men and therefore it remains uncertain whether women are benefitting to the same extent as men are.

In this review we will take a step-by-step approach starting with the sex and gender differences in the basics such as the epidemiology and pathogenesis of abdominal aortic aneurysms and proceeding to an overview of results from the major trials looking at (endovascular) abdominal aortic aneurysm repair. The foregoing will enable us to arrive at a better understanding of the role of endovascular aneurysm repair in women.

Epidemiology (and risk factors)

The prevalence of abdominal aortic aneurysms is subject to a number of variables including, age, gender, family history and smoking status. Most studies looking at risk factors have been done in men and one can not assume that the magnitudes of these risk factors are the same in men and women. Physiological differences exist between men and women. Also there are risk factors unique to women such as endogenous and exogenous oestrogen, many believing to account for the serious increase in the progression of atherosclerosis after menopause.

AAAs of 3.0cm or larger are thought to occur in between 1.9%-18.5% in men and 0%-4.2% in women, depending on age and composition of casemix.[4] It was recently demonstrated, however, that by using the standard definition of AAA (30mm) the prevalence in women is underestimated. By using the more precise, but clinically "more difficult" to use, definition of ≥1.5 x normal infrarenal aortic aneurysm, the prevalence was quite similar, 12.9% for men vs. 9.8% for women respectively.[5]

Pathogenesis

The underlying cause of abdominal aortic aneurysm is mostly unknown in the majority of patients. Traditional views are that atherosclerosis causes the dilatation but a genetic component has also been suggested. The fact that a positive family history in a first-degree relative increases the risk of AAA points in this direction, but another explanation could be that families are generally subjected to the same environmental and social factors. The actual cause most likely is multifactorial, in which proteases (matrix metalloproteinases (MMPs) in particular) play an important role in the degradation of the vascular wall and thus to dilatation and eventually rupture of the aorta. Sex differences have been reported for these MMPs suggesting oestrogen-mediated reductions in the production of MMP-9 (an MMP with particular affinity for the breakdown of collagen).[6] This could explain the difference in prevalence between men and women at younger age (oestrogen protection in women) and the increased rate of abdominal aortic aneurysms in women after middle-age.

Natural history

Abdominal aortic aneurysms are usually asymptomatic and found whilst performing diagnostic strategies for other purposes. Once diagnosed, surveillance is indicated to prevent rupture.

Understanding which factors contribute to rupture is therefore vitally important.

Several studies have looked into factors contributing to AAA rupture and apart from aneurysm size and aneurysm growth rate, women have been reported to have a 3 to 4 fold higher risk of rupture.[7-8]

This fact is easily understandable if one takes into account that the normal size of the aorta differs substantially between men and women. The normal diameter of a female is on average smaller than that of a man. So using a definition of 3.0cm for an aneurysm and 5.5cm as a threshold for repair leads to a higher relative increase in AAA diameter for the average women compared to the average man. To overcome this problem it has been suggested to use relative AAA diameters instead of absolute diameters. A way of doing this is by comparing the AAA diameter to the predicted normal diameter, which is calculated using nomograms developed by Sonesson et al., which take age, gender and body surface area into account[9].

Example

For a 75-year-old male with a BSA of 2.3 m², the predicted aortic diameter (nomogram) is 21.9 mm. If this person then has an AAA of 40 mm, dividing 40 mm by 21.9 indicates that the aneurysm of this patient has increased 1.83 times. But if an AAA of 40 mm is encountered in a 50-year-old female with a BSA of 1.4 m², the normal aortic diameter of this patient has enlarged by 2.88 times. It seems quite reasonable to assume that a 40 mm diameter aneurysm that has expanded 2.9 times from the original size has a weaker arterial wall than a 40 mm diameter aneurysm that has expanded only 1.9 times

This approach has been deemed clinically unfriendly and is therefore not implemented widely.

Treatment

Open surgical repair

The main treatment guideline for the elective repair of abdominal aortic aneurysms is a diameter of 5.5cm. At this diameter the operative risk is thought to be smaller than the risk of rupture. For aneurysms smaller than 5.5cm two randomized controlled trials (RCTs) demonstrated no benefit of open surgery over surveillance of the aneurysm[10-11]. Unfortunately few women were included in these trials (17% in the UK Small aneurysm trial and 0.8% in the ADAM trial), raising doubts as to whether these results and recommendations, when generalized, lead to the appropriate management in women. A recently published systematic review and meta-analysis looking at 30-day outcome after aneurysm repair reported women to have significantly higher mortality rates following elective open repair.[12] Ruptured open repair was not significantly different between women and men but the absolute mortality rates were 61.8% for women and 42.2% for men.

Endovascular repair

Endovascular abdominal aortic aneurysm repair (EVAR) was developed in an attempt to reduce mortality and morbidity and to provide an alternative to patients at (too) high risk for open surgical repair. The thought was that due to its less invasive nature, it might lead to better results and less costs. The choice between open en endovascular repair should be made on an individual basis taking patient factors and the surgeon's experience into account. In short it is thought that young patients with a low to average operative risk may benefit from open surgical repair and average to high risk patients with favorable anatomy from endovascular repair.

EVAR has lead to a decrease in short-term mortality, but women have not benefitted from this decrease as much as men, which has been suggested to be a result of their poorer anatomical suitability[13-14]. Access arteries and the aorta itself are on average smaller in women and endovascular stents and deployment devices have not been specifically designed for women. This all could be the explanation of their statistically significant worse outcome in mortality, 2.9% versus 1.5% and higher complication rates such as conversion.[12]

The three RCTs comparing EVAR to open repair started off with very promising results for EVAR.[15-17] 30-day survival of endovascular patients was up to 3-fold better than open surgically repaired patients. Then 2-4 years later the mid-term results were published, already showing the difference receding. Finally, the recently published long-term survival results of the DREAM and EVAR 1 trial show no difference in long-term survival.[18] Outcomes other than mortality, such as systemic complications, graft related complications, reinterventions and not to be forgotten, costs are therefore very important.

Interesting, the percentage of women in these three trials was around 9% in the DREAM trial and the EVAR-1 trial and 0.6% in the OVER trial. No gender-specific analyses were done in the DREAM and OVER trial. In the EVAR-1 trial sub-analyses were performed. Variables found to predict serious graft complications after EVAR were older age, large initial AAA diameter and large common iliac artery diameters. Gender was not a predictor, but

there were probably too few women (n=79) in this study to show a significant result. The hazard rate ratio for women was 1.46 (0.91-2.36)[19]. For re-interventions after EVAR again older age, large initial AAA diameter, and large common iliac artery diameters were significant predictors. The HRR for women was 1.60 (0.89-2.88)[19]. Both HRRs show a trend in much higher complications and reinterventions in women, and indicate that the reason for them not being statistically significant most likely is due to the small sample size of women.

Another issue with EVAR is the need of diligent follow-up. In general EVAR patients require, 1, 6, 12 month, and yearly thereafter (for life) imaging studies to evaluate the status of the stent. These assessments are necessary because as opposed to open surgical repair late complications, necessitating reinterventions are quite common after endovascular repair.

The EVAR 2 trial, comparing endovascular repair of the unfit-for-open surgery patients to no repair, showed a benefit of EVAR over no repair for aneurysm-related death but not for all-cause mortality.[20] Also, graft-related complications, reinterventions and costs were high.

Currently gender-specific analyses are being conducted in the EUROSTAR database, a European multicenter registry encompassing around 10.000 patients who received elective endovascular repair. This database will have enough power to demonstrate possible sex and gender differences in mortality and complications following EVAR and the results are expected in the first half of 2011.

Secondary prevention

The same risk factors have been reported to have different effects in women compared to men. The INTERHEART study, with a study population of over 27,000 patients reported a much stronger effect of certain risk factors associated with myocardial infraction (MI) in women than men. Most pronounced were diabetes [4.26 (3.68-4.94) vs. 2.67(2.43-2.94) and hypertension [2.95(2.66 -3.28) vs. 2.32(2.16-2.48)][21], for women and men respectively. Levy et al.[22] in 1996 already reported these two risk factors to have much worse outcomes in women compared to men. Furthermore the INTERHEART group just recently published these risk factors and some other risk factors comprising the metabolic syndrome to be much higher in women compared to men[23]. While MI is the main outcome in this study, Huxley et al.[24] reported the relative risk for fatal coronary heart disease associated with diabetes also to be 50% higher in women compared to men. Seeing that the prevalence and outcome/mortality associated with these risk factors is higher in women, aggressive treatment is indicated in women when these risk factors are detected.

Medication is another field in which great sex difference are known to exist but not implemented widely in clinical practice. Women have been underrepresented in clinical drug studies and female animals have been studied less in preclinical studies. Seeing the physiological differences between women and men, these differences will also affect drug efficacy and safety. Pharmacokinetics in women is affected by lower weight, body composition, slower gastrointestinal motility, less gastric secretion, different enzymatic activity and slower glomerular filtration rate. All the above factors should be taken into account when prescribing medicine to women and in general lower dosages should be administered to women. Another

example are β-blockers. Metoprolol and Propanolol are metabolized in the liver by CYP2D6, this substrate is much more active in men than women. This leads to an increase in plasma levels of around 100% in women. Adverse drug reactions are therefore 50-75% more likely in women. Thus, for the example of β-blockers, it would be safer to use a β-blocker which is metabolized less or not at all by CYP2D6, such as Atenolol. Pharmacodynamic differences in women include greater sensitivity to opoids, leading to a stronger analgesic response, so here too lower dosages should be given to women[25].

But apart from the difference in pharmacokinetics and dynamics, medical undertreatment of vascular surgery patients as a whole is big problem. Although this affects both sexes, women receive significantly less medication compared to men. Furhermore, the sole information whether or not a patients receives medications is inadequate. Important to know is whether the treatment target of medication is achieved. Only once this target is reached do patients have good secondary prevention. So a patient receiving a statin should be tested to see whether the appropriate level of LDL is achieved, because only knowing whether he or she receives medication is therefore not sufficient.

Considerations

EVAR is a widely available alternative to open repair of an abdominal aortic aneurysm. In light of the recent published long-term results of EVAR, the precise role of EVAR is not completely defined. Modeling and cost-effectiveness studies will need to shed light on in which situations one treatment is preferred to the other.

We can also conclude that the role of EVAR in women is poorly investigated. Just as after open repair, women also seem to have higher mortality rates and more complications than man after EVAR. Whether this is mainly due to different effects of the same risk factors or whether this specific treatment is prone to worse outcome due to the fact that anatomy plays such an important role remains to be determined.

Therefore at this moment it is difficult to state what the role of EVAR in women should be. What is apparent though is that aggressive treatment of risk factors and the optimisation of medication in women is indicated and deserves more attention in clinical practice and further research.

Acknowledgements

This research was supported by an unrestricted educational grant from the Foundation "Lijf en Leven".

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Chapter 6

Gender differences in 30-day and long-term outcomes after endovascular repair of abdominal aortic aneurysms: Results from the EUROSTAR study

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Submitted

Abstract

Objective

The purpose of this study was to determine the effect of gender on 30-day and long-term outcomes after elective endovascular aortic repair (EVAR)

Methods: Patients entered into the EUROSTAR study (European collaborators on stent-graft techniques for abdominal aortic aneurysm repair) formed the basis of our study. Data were analyzed by means of multivariable logistic regression for 30-day mortality and composite outcome of mortality, systemic complication or conversion. Kaplan-Meier survival analyses were used to compare long-term survival and long-term event-free survival times between women and men over a median follow-up period of 12.6 months. The log rank test was used to test for differences. Cox proportional hazards regression was used to analyze survival and event-free survival (with endpoint mortality or re-intervention). Multivariable analyses were adjusted for age, comorbidities, aneurysm characteristics and treatment characteristics.

Results

There were 9227 patients available for analysis (623 women and 8604 men). No difference in 30-day mortality was demonstrated for women compared to men (OR 0.89, 95%CI 0.48 -1.67), but women did have a statistically significant higher cumulative incidence of the composite end-point mortality, systemic complication or conversion (OR 1.32, 95%CI 1.05-1.66). The Kaplan-Meier curves demonstrated worse outcomes for both long-term survival (p=0.05) and long-term event-free survival (p=0.004). Survival analyses adjusting for covariates demonstrated a higher albeit statistically non-significant difference in long-term mortality for women compared to men (HRR 1.21, 95%CI 0.96-1.53) and a statistically significant higher rate of the composite endpoint mortality or re-intervention (HRR 1.28, 95%CI 1.07-1.54).

Conclusions

Our results suggest that women undergoing endovascular aortic repair have higher complication and re-intervention rates compared to men implying that the role of elective EVAR in women needs to be reconsidered.

Introduction

The three large randomized controlled trials comparing endovascular aneurysm repair (EVAR) to open repair have shown that 30-day mortality can significantly be reduced by endovascular repair 1-3. EVAR has been associated with similar long-term mortality and higher delayed complication and re-intervention rates compared to open repair in the EVAR 1 trial and DREAM trial, but not in the OVER trail. In the OVER trial women comprised 0.6% of the study population; in the other two trials women comprised 9% of the study population.

Determining the role of EVAR for AAA repair depends on being able to identify variables that influence outcomes after EVAR. A recent study demonstrated that age and the American Society of Anesthesiology Physical Status Classification Score (ASA) are independent predictors of mortality. Gender was not an independent predictor for mortality but was an independent predictor for procedure related complications, women having a 4 times higher rate of complications compared to men4. It has been suggested, as is the case for many other vascular procedures, that women have more complications as a result of the smaller diameter of their arteries. Various studies have put forward possible mechanisms for the worse outcome and have demonstrated significantly higher mortality in women following (endovascular) AAA repair5-7. Such studies are few and the role of female sex has been poorly investigated mainly due to the low proportion of females in clinical trials evaluating EVAR.

The aim of this study therefore was to determine the effect of gender on mortality and morbidity after endovascular aneurysm repair using one of the largest endovascular aneurysm repair registries.

Methods

Study Design

This study was part of the European collaborators on stent-graft techniques for abdominal aortic aneurysm repair (EUROSTAR) study, a voluntary registry, which was established in June 1996. Objective of the EUROSTAR study was to collect and analyze information from a prospective longitudinal cohort of patients who underwent endovascular treatment of AAAs.8 Patients with an asymptomatic intact and infrarenal aneurysm were prospectively enrolled into the registry. The last patient was included in November 2006. The median follow-up of the whole cohort was 12.6 months.

Data collection

Patient characteristics, comorbidities, aneurysm characteristics, treatment characteristics, postoperative outcomes and information at follow-up visits (1, 3, 6, 12, 18, and 24 months and yearly thereafter) were recorded on a standardized case record form 8. All cardiovascular comorbidities were scored using the Society for Vascular Surgery (SVS) – International Society for Cardiovascular surgery risk score and recoded into a yes/ no variable where a score of 0 represented no comorbidity present and a score of 1,2, or 3 indicated the comorbidities present. American Society of Anesthesiology (ASA) score9-10 (Appendix 1). The following commercially available and CE-approved stent-grafts were used: Zenith (Cook Inc, Bloomington, Indiana; 3705 patients), Talent (Medtronic Vascular; 2589 patients), Excluder (W.L.Gore & Associates, Inc, Flagstaff, Ariz; 1290 patients), AneuRx (Medtronic Vascular, Santa Rosa,

Table 1. Patient demographics.

	Women (623)			Men (8604)			
	Available	**Value**		**Available**	**Value**		**P-value**
Age, mean (+-sd)	623 (100%)	75.49	7.72*	8604 (100%)	72.35	7.72*	**<0.001**
ASA, n with class 3 or 4 (%)	614 (98.6%)	316	51.47%	8501(98.8%)	4299	50.57%	0.668
Comorbidities (SVS) n (%)							
Diabetes	597 (95.8%)	62	10.39%	8346 (97%)	1097	13.14%	0.053
Smoking	596 (95.7%)	182	30.54%	8316 (96.7%)	4312	51.85%	**<0.001**
Hypertension	598 (96%)	429	71.74%	8356 (97.1%)	5452	65.25%	**0.001**
Hyperlipidemia	585 (93.9%)	282	48.21%	8186 (95.1%)	3818	45.64%	0.464
Cardiac	595 (95.5%)	323	54.29%	8354 (97.1%)	5084	60.86%	**0.002**
Carotid	588 (94.4%)	95	16.16%	8254 (95.9%)	1455	17.63%	0.365
Renal	594 (95.3%)	94	15.82%	8282 (96.3%)	1605	19.38%	**0.033**
Pulmonary	593 (95.2%)	215	36.26%	8289 (96.3%)	3505	42.28%	**0.004**
Previous laparotomy	610 (97.9%)	217	35.57%	8472 (98.5%)	2148	25.35%	**<0.001**
Obesity	609 (97.8%)	170	27.91%	8461 (98.3%)	2233	26.39%	0.411
AAA characteristics (mean +-sd)							
AAA diameter	607 (97.4%)	57.34	11.04*	8401 (97.6%)	58.16	12.29*	0.109
Neck diameter	600 (96.3%)	22.57	3.47*	8234 (95.7%)	24.04	3.26*	**<0.001**
Neck length	589 (94.5%)	26.72	12.48*	8046 (93.5%)	27.74	12.67*	0.059
Distance renal artery – iliac bifurcation	552 (88.6%)	116.17	20.18*	7514 (87.3%)	119.06	20.63*	**0.001**
Significant angulation	618 (99.2%)	366	59.22%	8559 (99.5%)	4312	50.38%	**<0.001**
Classification of AAA (DE vs. ABC)	623 (100%)	73	11.71%	8604 (100%)	1600	18.59%	**0.000**
Treatment characteristics							
Time since start	623 (100%)	5.99	2.39	8604 (100%)	5.74	2.31	**0.007**
Type of anaesthesia							
General	623 (100%)	444	71.27%	8604 (100%	5807	67.49%	0.052
Regional	623 (100%)	139	22.31%	8604 (100%)	2262	26.29%	**0.029**
Local	623 (100%)	40	6.42%	8604 (100%)	535	6.22%	0.840

ASA: American Society of Anesthesiology, SVS: Society of Vascular Surgery, AAA: Abdominal Aortic Aneurysm, sd: standard deviation Classification of AAA see appendix 2:

Calif; 1022 patients), Powerlink (Endologix, Irvine, Calif; 166 patients), Lifepath (Edwards Lifesciences, Irvine Calif, 136 patients), Fortron (Cordis, a Johnson & Johnson company, Miami lakes, Fla; 97 patients) Anaconda (Sulzer Vascutek Ltd, Inchinnan, Scotland; 87 patients), EVT (Guidant inc Menlo Park, Calif; 77 patients). In the remaining 58 patients the type of stent graft used was not documented. Patients treated with first generation devices (Vanguard or Stentor stent-graft) were excluded from the analysis as these devices have long been withdrawn from the market.

Table 2. 30-day and long-term outcomes

	Women (623)			Men (8604)			
	Available	**n / mean**	**% / SD**	**Available**	**n / mean**	**% / SD**	**p-value**
30-day outcomes							
Intraoperative							
Duration of procedure, minutes	601	137.72	64.62	8303	128.99	58.42	**<0.001**
Replaced bloodvolume, ml	136	693.84	714.14	1289	583.18	737.79	0.095
Endoleak	623	114	18.3	8604	1382	16.1	0.144
Blocking of side branches	623	100	16.1	8604	1668	19.4	**0.041**
Device-related complications	607	42	6.9	8502	351	4.1	**0.001**
Failure to complete procedure	607	20	3.3	8502	122	1.4	**<0.001**
Arterial complications	607	34	5.6	8502	279	3.3	**0.002**
From operation to discharge							
Systemic complications	623	90	14.4	8604	927	10.8	**0.005**
Procedure and device related	607	25	4.1	8502	216	2.5	**0.019**
Access site and lower limb complications	607	56	9.2	8502	508	6.0	**0.001**
Conversion to bifurcation graft	623	21	3.4	8604	179	2.1	**0.033**
AAA rupture	623	2	0.3	8604	49	0.6	0.581
Hospital stay	603	11.06	17.02	8412	7.62	10.15	**<0.001**
30-day Death:							
All cause	623	12	1.9	8604	164	1.9	0.972
Long-term outcomes							
Abnormal findings or systemic complications	623	45	7.2	8604	649	7.5	0.770
Procedure or device related complications	623	144	23.1	8604	1868	21.7	0.413
Graft migration	495	8	1.6	7272	133	1.8	0.732
Graft stenosis	495	2	0.4	7272	51	0.7	0.774
Graft thrombosis	495	7	1.4	7272	136	1.9	0.465
Endoleak	495	55	11 .1	7272	521	7.2	**0.001**
Bleeding perianeurysmal (rupture)	495	1	0.2	7272	35	0.5	0.727
Intervention transfemoral (PTA)	495	25	5.1	7272	387	5.3	0.794
Intervention transabdominal (conversion)	495	9	1.8	7272	88	1.2	0.238
Intervention extra anatomic (crossover)	495	7	1.4	7272	96	1.3	0.860
Late Death:							
All cause	623	72	11.6	8604	857	10	0.201

PTA: percutaneous transluminal angioplasty

Table 3a Odds ratios (OR) from logistic regression analysis for 30-day mortality and for the combined endpoint of 30-day mortality, systemic complications and conversion. Univariable is unadjusted, multivariable is adjusted for covariates.

	30-day Mortality				30-day Mortality, Systemic Complications and Conversion			
	Univariable		Multivariable		Univariable		Multivariable	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Gender	1.01	0.56-1.83	0.89	0.48-1.67	**1.39**	**1.12-1.72**	**1.32**	**1.05-1.66**
Age			**1.07**	**1.05-1.10**			**1.02**	**1.01-1.03**
ASA (3or4)			**2.45**	**1.67- 3.59**			**1.7**	**1.49-1.95**
CV Comorbidities:								
Diabetes			1.05	0.68-1.64			0.94	0.77-1.13
Smoking			**1.42**	**1.02-1.97**			0.93	0.81-1.06
Hypertension			0.86	0.61-1.23			0.98	0.85-1.13
Hyperlipidemia			0.77	0.55-1.07			1.03	0.90-1.18
Cardiac			1.34	0.93-1.95			1.05	0.91-1.21
Carotid			1.22	0.83-1.77			1.03	0.87-1.21
Renal			**2.02**	**1.43-2.82**			**1.41**	**1.21-1.65**
Pulmonary			1.18	0.85-1.64			1	0.88-1.15
Previous laparotomy			1.04	0.74-1.47			0.98	0.85-1.13
Obesity			**0.58**	**0.39-0.87**			0.91	0.79-1.05
AAA characteristics:								
AAA diameter			**1.03**	**1.02-1.04**			**1.01**	**1.01-1.02**
Neck diameter			0.98	0.93-1.02			1.01	0.99-1.02
Neck length			0.99	0.97-1.00			0.99	0.99-1.00
Distance a.renalis – iliac bifurcation			0.99	0.99-1.00			0.99	0.99-1.00
Significant angulation			1.1	0.80-1.52			**1.15**	**1.01-1.31**
Classification AAA (DE vs. ABC)			1.09	0.75-1.59			1.03	0.88 -1.21
Treatment characteristics:								
Time since start			1.01	0.95-1.09			**0.88**	**0.86-0.91**
Type anaesthesia			**1.66**	**1.16-2.36**			**1.53**	**1.32-1.76**

ASA: American Society of Anesthesiology physical status classification score, CV: Cardiovascular, AAA: Abdominal Aortic Aneurysm.

Outcomes

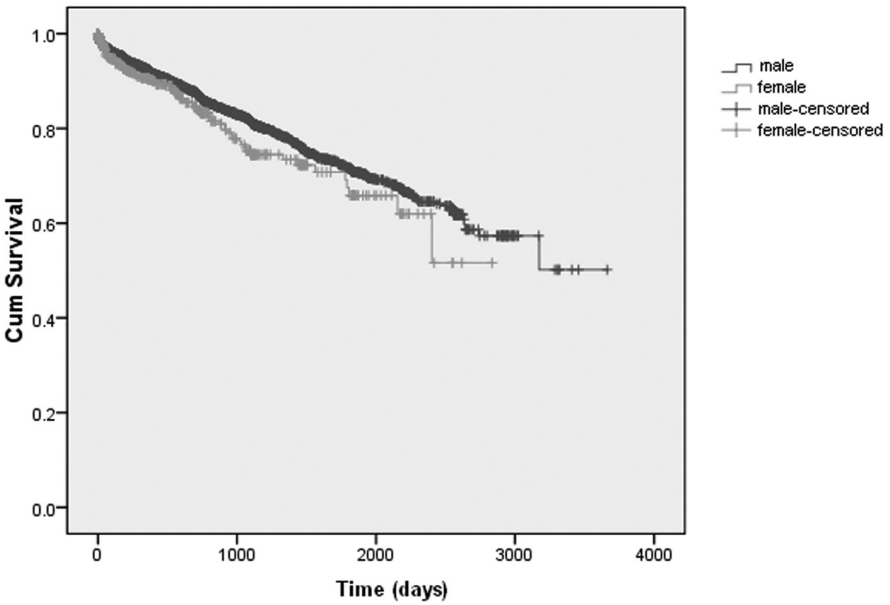
The primary outcome was 30-day mortality. Secondary outcomes were a 30-day composite endpoint (consisting of mortality, systemic complications and conversion), long-term survival and long-term event-free survival. 30-day outcomes were in-

Table 3b Hazard rate ratio (HRR) from Cox proportional hazards regression analysis for survival and for event-free survival (death or apercutaneous transluminal angioplasty (PTA), a transabdominal surgical intervention (conversion) or an extra-anatomic surgical bypass procedure (femoral-femoral or axillo-femoral cross-over). Univariable is unadjusted, multivariable is adjusted for covariates.

	Survival				Event-free survival (death or re-intervention)			
	Univariable		Multivariable		Univariable		Multivariable	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Gender	1.25	1.00-1.56	1.21	0.96-1.53	**1.30**	**1.09-1.56**	**1.28**	**1.07-1.54**
Age			**1.05**	**1.04-1.06**			**1.03**	**1.02-1.03**
ASA (3or4)			**1.63**	**1.42-1.87**			**1.28**	**1.15-1.43**
CV Comorbidities:								
Diabetes			1.10	0.92-1.32			1.10	0.95-1.27
Smoking			**1.14**	**1.01-1.30**			1.02	0.92-1.13
Hypertension			**0.84**	**0.74-0.96**			0.97	0.87-1.08
Hyperlipidemia			**0.71**	**0.62-0.82**			**0.79**	**0.70-0.88**
Cardiac			**1.23**	**1.07-1.42**			**1.15**	**1.03-1.29**
Carotid			1.11	0.95-1.30			1.01	0.88-1.16
Renal			**1.53**	**1.33-1.77**			**1.32**	**1.17-1.49**
Pulmonary			**1.32**	**1.16-1.50**			**1.23**	**1.11-1.36**
Previous laparotomy			1.11	0.97-1.27			1.11	0.97-1.24
Obesity			0.88	0.76-1.02			0.92	0.82-1.03
AAA characteristics:								
AAA diameter			**1.02**	**1.01-1.02**			**1.02**	**1.01-1.02**
Neck diameter			1.02	1.00-1.04			1.02	1.00-1.04
Neck length			0.99	0.99-1.00			1.00	0.99-1.00
Distance a.renalis – iliac bifurcation			1.00	1.00-1.01			1.00	1.00-1.00
Significant angulation			0.95	0.84-1.08			1.00	0.91-1.11
Classification AAA (DE vs. ABC)			1.12	0.97-1.30			**1.19**	**1.05-1.35**
Treatment characteristics:								
Time since start			0.98	0.95-1.01			0.97	0.94-0.99
Type anaesthesia			1.13	0.98-1.29			**1.15**	**1.03-1.29**

ASA: American Society of Anesthesiology physical status classification score, CV: Cardiovascular, AAA: Abdominal Aortic Aneurysm.

Figure 1 Kaplan-Meier survival curves for women and men



Numbers at risk at each time point

Women	459.5	88.5	13.5	-	-
Men	6518	1399	242	7	0.5

cluded in the analysis of long-term outcomes. Systemic complications included cardiac, cerebral, pulmonary, renal, hepatobililiary, or bowel complications and sepsis. An event was defined as either death or a re-intervention which could be a percutaneous transluminal angioplasty (PTA), a transabdominal surgical intervention (conversion) or an extra-anatomic surgical bypass procedure (femoral-femoral or axillo-femoral cross-over).

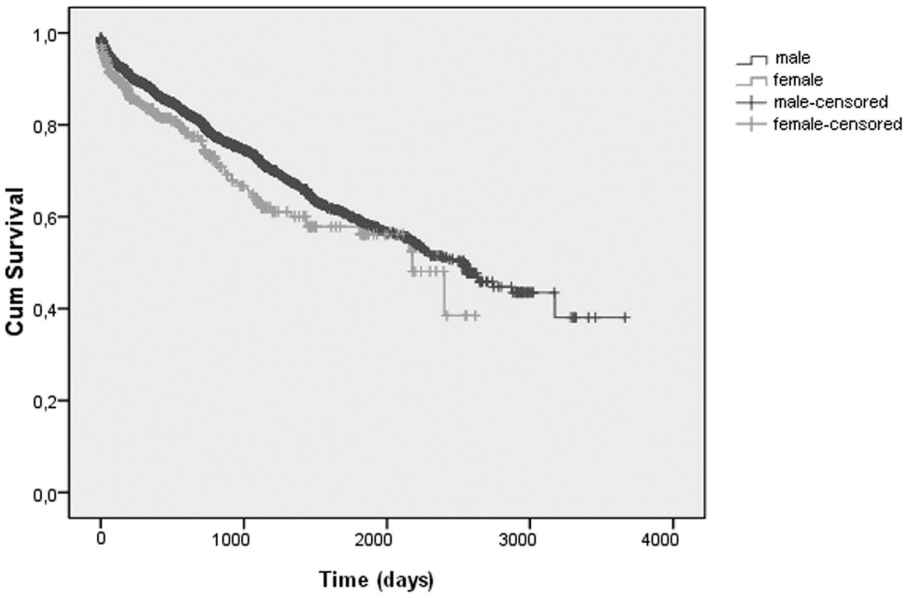
Statistical methods

For each of the 9227 patients, 27 variables were considered in the analyses and of the total 249.129 (that is, 9227 x 27) data points, 6286 (2.5%) were missing values. We used multiple imputations following fully conditional specification to account for the missing values and to avoid biased estimates of our parameters 11.

Data were presented for women and men separately. Continuous variables were expressed as mean ± sd, and categorical variables were presented as frequencies. Differences in patient characteristics and outcomes were compared with t tests, Wilcoxon tests, or the $\chi 2$ statistic, as appropriate.

Multivariable logistic regression analysis was used to compare 30-day outcomes between women and men ad-

Figure 2 Kaplan-Meier event-free survival curves for women and men (death or reintervention)



Numbers at risk at each time point

Women	**469.5**	**79.5**	**12**	**-**	**-**
Men	**6616.5**	**1329.5**	**218.5**	**7**	**-**

justing for covariates. Kaplan-Meier survival analysis was used to compare long-term survival and long-term event-free survival times between women and men without adjustment. To test for differences, the log rank test was used. Cox proportional hazards regression analysis was used to compare long-term outcomes between women and men adjusting for covariates.

Odds ratios for women compared to men were calculated for the 30-day outcomes. Hazard rate ratios for women compared to men were calculated for long-term outcomes.

As the effect of gender was our main interest we constructed various models, starting with a univariable model for gender and then gradually adding groups of covariates to result in multivariable models to see whether and how the outcome for gender was affected. The groups of covariates we added were: 1) age and ASA, 2) cardiovascular risk factors or a history of cardiovascular disease or other relevant disease (diabetes, smoking, hypertension, hyperlipidemia, cardiac disease, carotid disease, pulmonary disease, renal disease, previous laparotomy, and obesity), 3) AAA characteristics (AAA diameter, neck diameter, neck length, distance from the

renal artery to iliac bifurcation, significant angulation, classification of AAA (according to EUROSTAR protocol8) and finally 4) treatment characteristics (time since start of study indicating the degree of advancement of the stent graft, and type of anesthesia).

All tests were performed 2-sided, and a probability value of <0.05 was considered statistically significant. All analyses were performed with SPSS software version 17.0. The first author (NG) had full access to the data and the senior author (JB) takes full responsibility for its integrity.

Results

There were 9227 patients for analysis (623 women and 8604 men). Mean age was 75 years for women and 72 years for men (p<0.001) (Table 1). Regarding cardiovascular comorbidities women more often than men had hypertension and a previous laparotomy, while men more often had diabetes, were current or ex-smokers, and had a history of cardiac, renal or pulmonary disease. For AAA characteristics women more often had significant angulation of their AAA and smaller AAA neck diameters while men had higher classed AAAs. Women more often received general anesthesia whereas men received more regional anesthesia (Table 1).

Thirty-day mortality was 1.9% for both women and men, whilst intra-operative and post-operative (device related and systemic) complications were significantly higher for women compared to men. Hospital stay was also significantly longer, on average four days, for women than for men. Late outcomes did not differ significantly between women and men, except for the rate of endoleaks, 11.1% for women compared to 7.2% for men (p=0.001). Long-term mortality was 11.6% for women and 10% for men (p=0.201) (Table 2).

Multivariable logistic regression adjusting for age, ASA, comorbidities, AAA characteristics and treatment characteristics demonstrated no difference in 30-day mortality for women compared to men (OR 0.89, 95%CI 0.48 -1.67). Variables that did independently influence 30-day outcome were age, ASA, smoking, renal comorbidity, AAA diameter and type of anesthesia. General anaesthesia was associated with higher mortality rate then regional or local anaesthesiea.

For the composite endpoint of 30-day mortality, systemic complication and conversion to a surgical procedure, female sex did have an independent influence (OR 1.32, 95%CI 1.05-1.66). Other independent variables were age, ASA, renal comorbidity, AAA diameter, significant angulation, time since start of the study and type of anesthesia. (Table 3a).

The Kaplan Meier survival curve and the log rank test (p=.05) showed worse survival for women compared to men (Figure 1). The Kaplan Meier event-free survival curve and the log rank test (p=0.004) again showed worse outcome for women compared to men (Figure 2). In the Cox proportional hazards model adjusting for age, ASA, cardiovascular comorbidities, AAA characteristics and treatment characteristics no difference was demonstrated in survival for women compared to men (HRR 1.21, 95%CI 0.96-1.53). Variables that did influence survival were age, ASA, smoking, hypertension, hyperlipidemia, cardiac disease, renal disease, pulmonary disease and AAA diameter. For the composite endpoint of event-free survival (death or re-intervention), female sex did have a statistically significant independent effect

(HRR 1.28 95%CI 1.07-1.54). Other independent variables were age, ASA, hyperlipidemia, cardiac disease, renal disease, pulmonary disease, AAA diameter and type of anesthesia. (Table 3b)

Discussion

The current study based on the EUROSTAR registry represents one of the first big scale investigations into the role of female sex on mortality and morbidity after endovascular aneurysm repair (EVAR). No difference in 30-day mortality was demonstrated for women compared to men, but women did have a higher incidence of the composite end-point (mortality, systemic complication or conversion). Hospital stay was also longer for women than for men. The Kaplan-Meier curves demonstrated worse outcomes in women for both long-term survival and long-term event-free survival. Adjusting for covariates demonstrated a higher albeit statistically non-significant difference in long-term mortality and a statistically significant higher rate of the composite endpoint (mortality or re-intervention) in women compared to men.

Differences existed between women and men in the registry which need to be taken into account when comparing outcomes between the two groups. Factors that were less favorable in women included their more advanced age, more frequent hypertension or previous laparotomy, less favorable AAA morphology, and more frequent use of general anethesia. To analyze whether these factors can explain the poorer outcomes we performed a multivariable adjustment and found that the OR and HRR for the composite endpoints hardly decreased suggesting that gender is an independent predictor for the composite endpoint.

Anatomy is frequently indicated as an explanation for the higher rate of complications (mostly periprocedural) for women compared to men. This was confirmed in the present study where anatomical differences between men and women were observed. Due to women's smaller artery diameters, problems obtaining access and completing the procedure can be expected more frequently, as was demonstrated in this study (Table 2). Due to these difficulties procedural time was longer in women than in men. Also, in women significantly more frequently angulation of the aneurysm was observed compared to men, which is another variable known to negatively influence outcome.

Our 30-day mortality outcomes are consistent with the results from three RCTs of endovascular AAA repair demonstrating no difference between women and men 1-3. An inferior 30-day composite endpoint for women compared to men, however, has not previously been demonstrated to such an extent.

The EVAR-1 trial depicted a trend of worse outcomes for serious graft complications after EVAR (HRR 1.46, 95%CI 0.91-2.36) and reinterventions after EVAR (HRR 1.60, 95%CI 0.98-2.88) for women, but was unable to demonstrate a significant difference probably due to the small sample size of women (n=79). In contrast, our study included a far larger number of women and clearly demonstrated a significant difference in the composite 30-day (death, systemic complications or conversion) and composite long-term endpoint (death or re-intervention).

Wisniowski et al. recently also demonstrated female sex to be an independ-

ent predictor of higher re-intervention rates compared to men with only 15 women in his study.4. With respect to the other variables which were independently associated with worse outcome, our study demonstrated that high ASA class, renal comorbidity, type of anesthesia and age are the major variables that have a negative impact on outcome, which is in line with most other large studies 12.

This study has several limitations. First of all, this study was based on registry data collected in daily clinical practice. As with all registries, inclusion of all consecutive patients at all sites cannot be ensured, leading to possible generalizability issues. Nevertheless, everything was done to make the registry as complete as possible and this same limitation also applies to (randomized) trials. Second, although data was collected prospectively, it is possible that events were not recorded due to loss of follow-up. Third, no comprehensive information regarding medication was documented in the database, making it impossible to adjust for its effect. Finally, although we demonstrated a correlation between gender and outcome, a true causal relationship is difficult if not impossible to establish. All-in-all the demonstrated associations do suggest that gender independently affects outcome.

Our findings have implications for both clinical decision making and for the device industry. Anatomical features once again arise as a major component influencing the success of EVAR. Tailored devices for women taking their anatomical situation into consideration could narrow the gap between men and women. Device manufacturing companies have not been aware of the typical differences of aortoiliac dimensions in females, i.e. smaller infrarenal neck diamtere, greater angulation and a different aorto-iliac configuration as refelected by the AAA classification. Devices tailord according to these anatomic characterstics should be made available by the industry. Modeling and cost-effectiveness studies (taking into account the higher complication and re-intervention rates and longer hospital stays) will be needed to shed light on the role that EVAR may play in elective aneurysm repair in women given the poorer results compared to that of men. Until then endovascular treatment of AAAs should be performed with caution in women.

Collaborative centres

The EUROSTAR Collaborative Centers are:

Austria: Vienna, University Hospital.

Belgium: Aalst, City Hospital; Aalst, Onze Lieve Vrouwe Hospital; Antwerpen, Hospital Middelheim; Antwerpen, St Vincentius Hospital; Antwerpen, University Hospital; Antwerpen, Monica Hospital/OLV/ Eeuwfeestkliniek; Antwerpen, St Augustinus Hospital; Arlon, Clinique St Joseph; Assebroek, Hospital St Lucas/St Jozef; Aye, Hospital Princesse Paola; Baudour, Reseau Hospital de Medecine Sociale; Bonheiden, Imelda Hospital; Brasschaat, Hospital Klina; Brugge, Hospital St Jan; Brussels, Hospital Erasme; Brussels, Free University Hospital; Brussels, Clinique de l'Europe St Michel; Brussels, Hospital Brugmann; Brussels, Central Hospital Edith Cavell; Brussels, Hospital d'Iris Sud; Brussels, University Hospital St Luc; Brussels, Clinique Saint Jean; Charleroi, University Hospital; Dendermonde,

Hospital St Blasius; Duffel, Hospital St Maarten; Eeklo, Hospital Heilig

Hart; Geel, Hospital St Dimpna; Genk, St Jan Hospital; Gent, Volkskliniek; Gent, Hospital St Lucas; Gent, St Jan Palfijn Hospital; Gent, University Hospital; Gent, Hospital Maria Middelares - St Jozef; Gilly, St Joseph Hospital; Haint Saint Paul, Hospital de Jolimont; Halle, Hospital St Maria; Hasselt, Virga Jesse Hospital; Herenthals, St Elisabeth Hospital; Heusden-Zolder, St Franciskus Hospital; Ieper, Hospital Jan Yperman; Knokke, Gezondheidszorg Oostkust; Kortrijk, Hospital Groenige; La Louvie` re, Central Hospital de Tivoli; Leuven, University Hospital; Leuven, Heilig Hart; Lie` ge, University Hospital; Lie` ge, Hospital St Joseph; Lie`ge-Chenee, NotreDame des Bruyeres; Lier, Heilig Hart Hospital; Lommel, Maria Hospital; Malmedy, Hospital Reine Astrid; Mechelen, Onze Lieve Vrouwe Hospital; Mont Godinne, Hospital de Mont Godinne; Mouscron, Central Hospital; Namur, Central Hospital Regional; Namur, Hospital St Elisabeth; Ottignies, Clinique Saint-Pierre; Reet, Hospital Heilige Familie; Roeselare, City Hospital; Roeselare, Heilig Hart Hospital; Sambreville, Hospital Val de Sambre; St Niklaas, Hospital Maria Middelares; St Truiden, St Trudo Hospital; Tielt, St Andries Hospital; Tongeren, Hospital Vesalius; Tournai, Hospital Notre Dame et St Georges; Tournai, Central Hospital; Turnhout, St Josef Hospital; Turnhout, St Elisabeth Hospital; Veurne, St Augustinus Hospital; Vilvoorde, St Josef Hospital; Zottegem, St Elisabeth Hospital.

Denmark: Copenhagen, Rigshospitalet; Odense, University Hospital.

France: Draguignan, Hospital Notre Dame; Lyon, Hospital E Herriot; Paris, Hospital Henri Mondor.

Germany: Bonn, Surgical University Hospital; Dusseldorf, Augusta Hospital; Frankfurt, City Hospital; Frankfurt, Bethanien Hospital; Frankfurt, St Katharinen Hospital; Hamburg, Altona General Hospital; Karlsruhe, Hospital Karlsruhe; Kempten, Hospital Kempten; Koblenz, Bundeswehrzentral; Leipzig, Park-Hospital; Marburg, Philipps-University; Munchen, Hospital Rechts der Isar; Munchen, City Hospital; Mu¨ nchen, Ludwig-Maximilian University

Hospital; Oldenburg, Pius Hospital; Ulm, University Hospital.

Greece: Athens, University Medical School.

Ireland: Dublin, St James Hospital.

Israel: Tel Aviv, Sheba Medical Centre.

Italy: Perugia, Hospital Monteluce; Roma, Hospital San Giovanni; Varese, Hospital diCircolo.

Luxembourg: Luxembourg, Central Hospital.

Monaco: Monaco, Cardiothoracic Centre.

The Netherlands: Alkmaar, Medical Centre; Amsterdam, Academic Medical Centre; Amsterdam, Free University Hospital; Amsterdam, Onze Lieve Vrouwe Hospital; Apeldoorn, Gelre Hospital; Arnhem, Rijnstate; Breda, Amphia Hospital; Delft, Reinier de Graaf Group; Doetinchem, Slingerland Hospital; Dordrecht, Albert Schweitzer Hospital;

Drachten, Ny Smellinghe Hospital; Eindhoven, Catharina Hospital; Enschede, Medisch Spectrum Twente; Geldrop, St Anna Hospital; Groningen; University Hospital; Groningen, Martini Hospital; Leeuwarden, Medical Centre; Maastricht, University Hospital; Nieuwegein, St Antonius Hospital; Nijmegen, Canisius Wilhelmina

Hospital; Nijmegen, University Hospital St Radboud; Rotterdam, St Clara Hospital; Rotterdam, Dijkzicht Hospital; Rotterdam,

Franciscus Hospital; The Hague, Medical Centre Haaglanden Westeinde; The Hague, Leijenburg Hospital; Tilburg, Elisabeth Hospital; Tilburg, Tweesteden Hospital; Utrecht, University Hospital; Veldhoven, St Josef Hospital; Zwolle, Isala Hospital

Norway: Oslo, Aker University Hospital; Oslo, Ulleval Hospital; Trondheim, University Hospital.

Poland: Lublin, L'Academie de medicine; Warsaw, Medical University; Warsaw, MSWiA Hospital; Warsaw, Central Military Hospital.

Spain: Barcelona, University Hospital; Barcelona, Ciutat Sanitaria I Universitaria de Bellvitge; Barcelona, Hospital Santa Creu I S Pau; Donostia San Sebastian, Hospital de Gipuzkoa; La Corun˜ a, Hospital Juan Canalejo; La Corun˜ a, Hospital Santa Teresa; Leon, Hospital de Leon; Lugo, Hospital Xeral Lugo; Madrid, University Hospital de la Princesa;

Madrid, Virgen de la Salud; Madrid, Hospital Ramon y Cajal; Madrid, Fundacion Jimenez Diaz; Madrid, University Hospital of Getafe; Madrid, Hospital de la Zarzuele; Madrid, Hospital Ruber International; Malaga, HR Carlos Haya; Pamplona, University Hospital of Navarra; Valladolid, Hospital Valladolid.

Sweden: Lund, University Hospital; Orebro, Medical Centre; Stockholm, Karolinska Hospital.

Switzerland: Bern, Clinic for Cardiovascular Surgery; Zurich, Gefasszentrum.

Turkey: Ankara, Hacettepe University Hospital; Istanbul, Memorial Hospital; Istanbul, University Hospital.

United Kingdom: Bournemouth, Royal Hospital; Bristol, Royal Infirmary; Chester, Countess of Chester Hospital; Glasgow, Gartnavel Hospital; Hull, Royal Infirmary; Liverpool, Royal University Hospital; Manchester, Withington

Hospital; New Castle-Upon-Tyne, Freeman Hospital.

Appendices

Appendix 1

SVS-ISCVS risk score

Diabetes: 0 = none; 1 = adult onset; diet controlled; 2 = adult onset, insuline-controlled: 3 = juvenile onset

Smoking: 0 = none or none for last ten years; 1 = none current , but smoked in last 10 years; 2 = current , less than 1 pack/day; 3 = current, greater than 1 pack/day

Hypertension: 0 none; 1 = easily controlled with single drug; 2 = controlled with 2 drugs; 3 =requires more than 2 drugs or uncontrolled

Hyperlipemia: 0 = cholesterol/triglycerides within normal limits for age; 1 = mild elevation, controllable by diet; 2 = types II, III or IV, requiring strict dietary control; 3 = requiring dietary and drug control

Cardiac status: 0 = asymptomatic, normal ECG; 1 = asymptomatic, remote myocardial infarction (MI) by history (> 6 months) or occult MI by ECG; 2 = stable angina, controlled ectopy or symptomatic arrythmia, drug compensated congestive heart failure (CHF); 3 = unstable angina, symptomatic or poorly controlled ectopy or arrhythmia, poorly compensated CHF, MI within 6 months

Carotid disease: 0 = no symptoms , no bruit, no evidence of disease; 1= asymptomatic but with evidence of disease; 2 = transient or temporary stroke; 3 = completed stroke with permanent neurologic deficit

Renal status: 0 = no know renal disease, serum creatinine < 1.5 mg/dl, creatinine clearance greater than 50 ml/min;

1 = creatinine 1.5- 3.0 mg/dl, clearance 30-50 ml/min; 2 = creatinine 3.0-6.0 mg/dl, clearance 15-30 ml/min; 3 = creatinine > 6.0 mg/dl, clearance < 15 ml/min or on dialysis or with transplant

Pulmonary status: 0 = asymptomatic, normal chest X-ray, pulmonary function tests (PFT) 20% of predicted; 1 = asymptomatic or mild dyspnea on exertion, mild X-ray parenchymal changes, PFT 65 tot 80% of predicted; 2 = between 1 and 3; 3 = vital capacity less than 1.85 L, FEV1 less than 1.2 L or less than35% of predicted, maximal voluntary ventilation less than 28 L/min or less than 50 % of predicted, PCO_2 greater than 45 mmHg, supplemental oxygen use necessary or pulmonary hypertension.

ASA Physical Status Classification
ASA I: healthy patient for elective operation
ASA II: patient with mild systemic disease, limits activity but is not incapaciting
ASA III: patient with severe systemic disease that is constant threat of life, limits activity but is not incapaciting
ASA IV: patient with incapaciting systemic disease that is a constant threat of life
ASA V: moribund patient not expected to live 24 hours without operation

Measurements (see figure 1 on page 3)	
D1: Suprarenal aorta diameter	H1: Lenght lower renal a. & neck aneur.
D2: (a/b/c): Infrarenal aorta diameter (if length of healthy aorta < 15 mm, use a 3 mm scale)	H2: Lenght lower renal a. & dist. aneur.
D3: Aneurysm diameter (outer wall to outer wall)	H3: Lenght lower renal & ao. bifurcat
D3a: Free lumen: inner diameter of thrombus lined lumen.	H4a: Lenght lower renal a. & R. comm il bifurcat.
D4: Terminal aortic transverse diameter	H4b: Lenght lower renal a. & L. comm il bifurcat.
D5a: Right common iliac art. diameter	
D5b: Left common iliac art.diameter	

SUGGESTED TIME SCHEDULE	preop.	1 month or predischarge	3 months	6 months	12 months	18 months	24 months	yearly upto 10 years
Clinical data	x	x	x	x	x	x	x	x
CTA	x	x	x**	x	x	x	x	x
Angiography	x							
Plain abdominal X-ray*		x			x		x	x
Duplex**	x	x	x	x	x			

*in 4 projections: AP, lateral, right and left obligue **optional examination

Interpretation-dates: d d m m y y

Patient study number: Center no. Patient no. for Center

Appendix 2

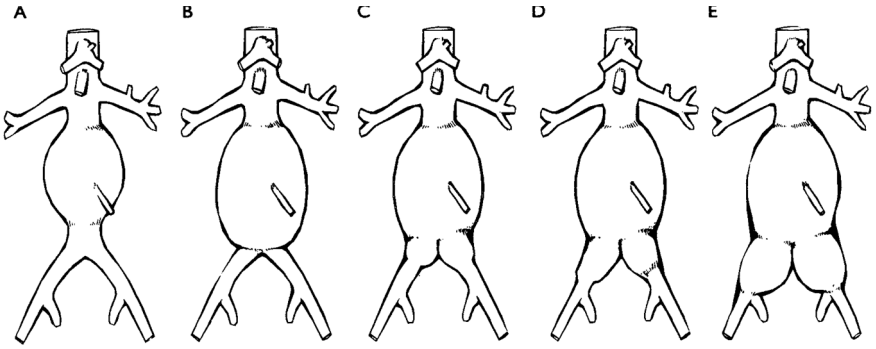


Figure 1 ◆ AAA classification according to the EUROSTAR protocol. Category A is characterized by a normally sized aortic segment of 1.5 to 2 cm in length above the bifurcation (distal cuff); this type of AAA is suitable for a tube graft. In category B, the aneurysm extends to the common iliac arteries (CIAs), which are of normal size; for this AAA, a bifurcated device is required. In class C, the CIAs are aneurysmal in the proximal third; however, there is an adequate sealing zone that does not jeopardize the internal iliac arteries. The CIAs in category D have a normal diameter only in their distal third, and device implantation may compromise the internal branches if the stent-graft extends down to the external iliac artery. In class E aneurysms, the iliac bifurcation is involved, and endografting invariably leads to occlusion of the ipsilateral internal iliac artery.

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Chapter 7

Sex differences in short-term outcome after carotid endarterectomy or carotid angioplasty and stenting: The CARE-Registry

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Submitted

Abstract

The impact of sex on short-term outcome after carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS) remains unclear and may differ between symptomatic and asymptomatic patients. Prior studies focused on different treatment options for carotid artery stenosis but few original studies analyzed the effect of sex on outcome.

Patients entered into the Carotid Artery Revascularization and Endarterectomy registry (CARE-registry) from 2005 until September 2009 were analyzed. Our outcome of interest was 30-day stroke or death. Propensity score matching followed by stratified Cox-proportional hazards regression was performed to evaluate the influence of sex.

There were 12701 patients in total. The event rate for the symptomatic CEA group was 4.4% for women and 2.9% for men. In the symptomatic CAS group it was 5.1% for women and 4.4% for men. The asymptomatic CEA group showed event rates of 2.8% vs. 2.1% and for the asymptomatic CAS group of 2.6% vs. 2.4%, for women vs. men respectively. These differences remained non-significant after propensity score matching and multivariable regression. Sex-differences were most pronounced in the symptomatic CEA group (HRR 1.62, 95%CI 0.81-3.23).

In conclusion our data does not provide strong evidence for sex-differences in short-term outcome following CEA or CAS. Event rates were higher for women in all groups but not statistically significant. A trend of a higher event rate for women was seen in the symptomatic CEA group.

Indexing words: Carotid Stenosis, Carotid Endarterectomy, Stents, Female

Introduction

Stroke is the leading cause of disabling disease and the third major cause of death in the Western world. More women than men die of stroke each year1.

For patients with symptomatic carotid artery disease two randomized controlled trials (RCT) clearly demonstrated the benefit of carotid endarterectomy (CEA) over medical treatment2-3. The ECST also demonstrated that women benefit less than men due to their higher perioperative risk and lower stroke risk with medical treatment alone while the NASCET showed the same trend however not statistically significant2-3. In patients with asymptomatic carotid artery disease studies again demonstrated a significant benefit of surgery over medical treatment for men but not for women4.

As a result of these studies it is advocated to treat symptomatic stenoses (50-99% for men and 70-99% for women) when a stroke or death rate <6% following CEA can be ensured and for asymptomatic stenosis (60-99%) when a stroke or death rate <3% can be ensured. Timing of CEA is also an important factor; best results are obtained if CEA is performed within 2 weeks of the onset of symptoms and is no longer beneficial after 12 weeks. With regards to timing, gender differences were also demonstrated, showing a shorter beneficial time window for women compared to men5.

In the last decade, carotid angioplasty and stenting (CAS) has emerged as an alternative to CEA in an effort to minimize the need for surgery. Compared to CEA it is less invasive and traumatic and patients with contraindications for surgical repair can still be treated. The clinical trials comparing CAS to CEA demonstrate equal or inferior results for CAS. The two most recent RCTs, the European International Carotid Stenting Study (ICSS), reported significantly fewer events after CEA compared to CAS6 and the American Carotid Revascularization Endarterctomy vs. Stenting Trial (CREST) trial showed equal results7. (The latter trial however encompassed nearly 50% asymptomatic patients). The ICSS further demonstrated that women had equal results in the CEA and CAS group (event rate 8%) while men did better in the CEA group compared to the CAS group (4% vs. 9%). The CREST investigators reported no significant interaction (p=0.34) between treatment effect and sex. A recent meta-analysis showed CEA to be superior to CAS for short-term outcomes but no longer significant for intermediate term outcomes, the difference driven mainly by non-disabling stroke8. No sex-specific analyses were reported.

Published and ongoing studies focused on comparing treatment strategies and not on sex differences in outcomes. In general, women are underrepresented in cardiovascular studies and sub-analyses often lack statistical power. It remains unclear whether sex influences the outcome after CEA or CAS. Also, the impact of sex may differ between symptomatic and asymptomatic patients and between type of procedure, CEA or CAS.

The aim of the study was to determine the influence of sex on short-term outcome in both symptomatic and asymptomatic patients treated either by CEA or CAS. We used the Carotid Artery Revascularization and Endarterectomy Registry (CARE-Registry), currently the largest registry on CEA and CAS.

Methods

Study design and patient selection

Patients entered into the CARE-Registry from 2005 until September 2009 formed the basis of our analysis. The objectives and design of the CARE-Registry have previously been reported9. In short, the CARE-Registry is an American web-based data collection tool developed by The American College of Cardiology's National Cardiovascular Data Registry. It collects and analyzes clinical data to measure clinical practice, patient outcomes, and enable quality improvement for patients undergoing CEA or CAS. It also satisfies the Center for Medicare and Medicaid Services criteria for reimbursement. Outcome events and follow-up were defined prospectively and preprocedure, postprocedure and follow-up assessments are performed by independent neurologists. The NCDR performs annual onsite audits on a random sample of participating hospitals, evaluating consistency and accuracy in data reporting compared with source documentation.

The majority of patients had significant carotid artery stenosis (≥50% NASCET measurement) and underwent CEA or CAS and were categorized into: 1) symptomatic CEA, 2) symptomatic CAS, 3) asymptomatic CEA, and 4) asymptomatic CAS.

Patient and lesion characteristics

For all patients, we recorded demographics, cardiovascular risk factors, cardiac history, neurological history, hostile neck, and anatomical configuration. Demographics included, age, sex and race. Cardiovascular risk factors included, tobacco history (defined as 'current', 'former' or 'never'), renal dysfunction (GFR<60), renal failure (serum creatinine >1.5mg/dL (within 3 months prior to the current procedure), currently on dialysis, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on at least 2 occasions, or use of antihypertensive medication), dyslipidemia (total cholesterol >200 mg/dL, or LDL ≥ 130 mg/dL, or HDL < 40 mg/dL), diabetes mellitus (fasting blood glucose of > 126 mg/dL or a history of diabetes, regardless of duration or need for antidiabetic agents), peripheral artery disease (PAD), chronic lung disease (history of chronic lung disease, e.g., chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or currently chronically treated with inhaled or oral pharmacological therapy), body mass index (obesity defined as BMI >30) and major surgery planned within 8 weeks. Cardiac history included, ischemic heart disease (prior myocardial infarction (MI), prior coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) and >=50% stenosis in at least one major coronary artery demonstrated by conventional coronary angiography), two or more major coronary arteries with stenosis ≥70% (LAD, LCX, RCA), MI within 6 weeks, Angina Canadian Cardiovascular Society (CCS) Class III or IV within 6 weeks, New York Heart Association (NYHA) classification III or IV within 6 weeks, chronic heart failure, pacemaker or implantable cardioverter defibrillator (ICD), atrial fibrillation or flutter, moderate to severe aortic stenosis, moderate to severe mitral stenosis, and mechanical aortic or mitral valve. Neurological history included, dementia, history of seizure, previous carotid intervention, previous neurological events, acute evolving stroke, and whether the lesion was symptomatic or asymptomatic (symptomatic defined as target lesion symptomatic within past 6 months). Prior neck involvement included, previous neck radiation (x-ray therapy of the neck

prior to current procedure), prior neck surgery (extensive (i.e., radical) neck dissection (other than CEA) prior to current procedure), tracheostomy present, and previous laryngeal nerve palsy. Anatomical features included restenosis after prior CEA, restenosis after prior CAS, contralateral carotid artery occlusion, fibromuscular dysplasia carotid artery, spontaneous carotid artery dissection, and stenosis grade. Stenosis grade was obtained directly from CTA and/or MRA and or indirectly from Duplex Ultrasound. The peak systolic volume (PSV) was then transformed to stenosis grade using the Heijenbrok et al10 formula.

Device characteristics

Stents used included the ACCULINK Carotid Stent System (Abbott), the Xact carotid stent system (Abbott), the Precise nitinol stent system (Cordis), the Carotid Wallstent Monorail Endoprothesis (Boston Scientific), the NexStent Carotid Stent and Delivery System (EndoTex), the Protégé Self-Expanding Nitinol Stent (ev3 Inc.), and non-carotid stents (off label use).

Embolic protection devices were attempted in 94% and successful in 92% of the cases. Embolic protection devices included the Emboshield (Abbot), Angioguard (Cordis), the Accunet (Cordis), The SpiderFX (ev3 Inc.), the Filterwire (Boston Scientific), the Proxis (St Jude), the TriActiv (Kensey Nash), the Guardwire (Medtronic), Neuro protection system (Gore), Mo.Ma Ultra Proximal Cerebral Protection (Invatec), and the FiberNet (Lumen Biomedical Inc.)

Clinical follow-up and end points

Post-operative information was obtained at discharge and follow-up.

Our outcome of interest was the composite endpoint of 30-day stroke or death (stroke or death occurring during in-hospital stay or stroke or death occurring after hospital discharge but within the first 30-days after CEA or CAS). 30-day follow-up was complete for 65% of patients (8316/12701). 77% (312/405) of the events occurred pre-discharge. Median time to discharge was 1 day (IQR = 1,2).

Due to the fact that 30-day follow-up was complete for 65% of the patients we did an additional in-hospital events analysis (stroke or death occurring during in-hospital stay) of which we had 100% follow-up

Statistical analysis

Continuous variables were described as means and standard deviations (SD) and compared using unpaired t-tests. Categorical variables were described as counts and percentages and compared using the chi-square test or Fisher exact test.

Missing data were dealt with by multiple imputations with the Markov chain Monte Carlo algorithm. Overall, 6.9% (880/12701) patients required imputation. Most (508/880) required imputation for pre-procedural creatinine; the remaining was spread out among the other variables.

To isolate the effect of sex on 30-day stroke or death, propensity score matching was used to perform adjusted analyses. Propensity score methodology has been shown to adequately balance two groups on observed characteristics and has advantages over traditional multivariable adjustments11. A nonparsimonious logistic regression model was developed to estimate the propensity score using an extensive list of demographics, cardiovascular risk factors, disease history, and anatomical variables. A 1:1 match on the logit of the propensity score was used where a caliper

of 0.2 times the pooled standard deviation of the logits was enforced11 along with exact matching on procedure type (CEA/CAS) and status (symptomatic/asymptomatic). Standardized differences demonstrate balance before and after matching. This is the preferred metric, as it is unaffected by a smaller sample in the matched cohort12. A value of '10' was used as cut-point to determine balance of variables13. Finally, stratified Cox-proportional hazard regression analysis was performed to determine the effect of sex on the 30-day outcome and a logistic regression analysis was performed for the in-hospital outcome.

SAS, version 9.2 (SAS Institute, Cary, North Carolina), was used to conduct our analyses. All analyses were pre-specified, and a 2-sided P-value less than 0.05 was considered statistically significant. All analyses were performed at the Mid America Heart Institute in Kansas City, MO.

Results

Patient characteristics

There were 12701 patients, including 7661 men (4910 CAS and 2751 CEA) and 5040 women (3159 CAS and 1881 CEA).

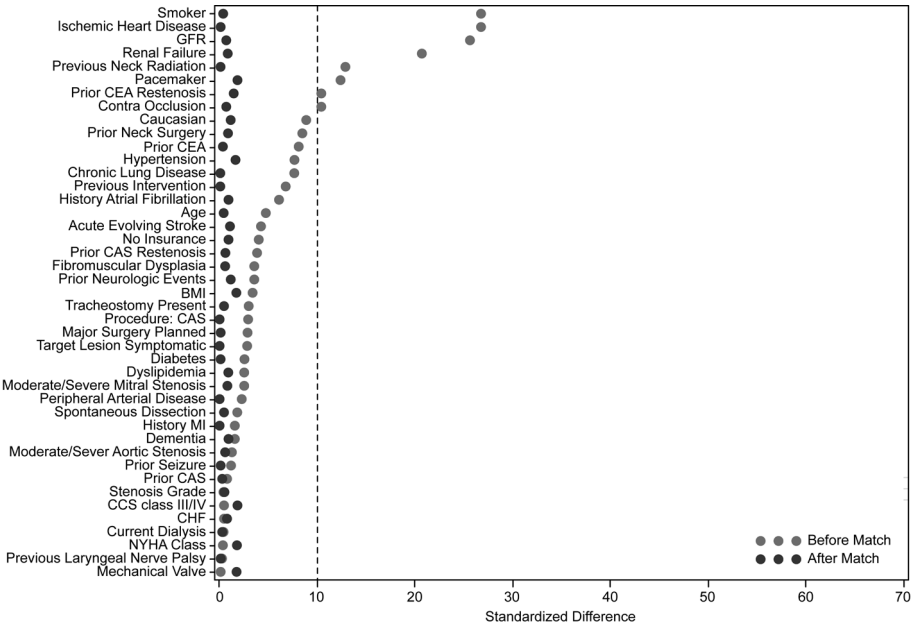

Figure a

Y-axis shows the variables considered.

X-axis shows the standardized difference of these variables between women and men, before (red) and after (blue) matching. The standardized difference represents how many standard deviations two groups differ by, and is described as a percentage. A value of "10" means that two groups differ by 0.1 standard deviation. The hatched line represents the cut-point to determine balance of variables. This figure demonstrates that after matching all variables are well balanced.

BMI = body mass index, CAS = carotid angioplasty and stenting, CCS = Canadian cardiovascular society, CEA = carotid endarterectomy, CHF = congestive heart failure, GFR = glomerular filtration rate, MI = myocardial infarction, NYHA = New York Heart association

Table 1. Descriptives stratified by sex

Patient Characteristics

	Women		Men		
	n=5040	**%**	**n= 7661**	**%**	**p-value**
Mean age (±SD)	71.2 (±10.1)		70.7 (±9.7)		0.008
Caucasian race	4603	91.4	7176	93.8	<0.001
Procedure type					
Symptomatic CEA	601	11.9	1009	13.2	
Symptomatic CAS	1359	27.0	2077	27.1	
Asymptomatic CEA	1280	25.4	1742	22.7	
Asymptomatic CAS	1800	35.7	2833	37.0	
Cardiovascular risk factor					
Ever smoked	3337	66.2	5985	78.1	<0.001
Renal failure	580	11.5	1449	18.9	<0.001
Renal dysfunction	2213	46.0	2420	33.2	<0.001
Currently on dialysis	108	2.1	169	2.2	0.795
Hypertension	4522	90.0	6681	87.6	<0.001
Dyslipidemia	4130	82.2	6344	83.1	0.168
Diabetes Mellitus	1838	36.6	2700	35.4	0.176
Peripheral arterial disease	1930	38.4	3019	39.6	0.171
COPD	1396	27.8	1862	24.4	<0.001
BMI	30.3 (±28.1)		29.4 (±18.9)		0.050
Major surgery	185	3.7	324	4.3	0.112
Cardiac history					
Ischemic heart disease	2340	46.6	4564	59.8	<0.001
>=2 Major coronary artery>70%	962	21.4	2160	31.5	<0.001
MI within 6 weeks	117	2.3	160	2.1	0.381
Angina CCS III or IV within 6 weeks	349	7.0	540	7.1	0.783
NYHA III or IV within 6 weeks	365	7.3	563	7.4	0.826
Chronic heart failure	768	15.3	1180	15.5	0.782
Pacemaker/ICD	263	5.2	638	8.4	<0.001
Atrial fibrillation	526	10.5	949	12.5	<0.001
Aortic stenosis	174	3.5	283	3.7	0.463
Mitral stenosis	64	1.3	77	1.0	0.168
Mechanical aortic or mitral valve	108	2.2	166	2.2	0.910

Neurological history					
Dementia	148	2.9	205	2.7	0.389
Seizure	129	2.6	182	2.4	0.519
Previous carotid intervention	1272	25.3	1711	22.4	<0.001
Previous neurological events	2292	45.6	3620	47.5	0.038
Acute evolving stroke	77	1.5	160	2.1	0.021
Target lesion symptomatic	1960	39.0	3086	40.5	0.099
Prior neck involvement					
Prior neck radiation	117	2.3	359	4.7	<0.001
Prior neck surgery	172	3.4	393	5.2	<0.001
Tracheostomy present	41	0.8	85	1.1	0.098
Previous laryngeal nerve palsy	38	0.7	55	0.7	0.523
Anatomical features					
Restenosis after prior CEA	660	13.1	748	9.8	<0.001
Restenosis after prior CAS	117	2.3	136	1.8	0.032
Contralateral occlusion	365	7.3	779	10.2	<0.001
Fibromuscular dysplasia	41	0.8	40	0.5	0.044
Spontaneous dissection	46	0.9	57	0.8	0.304
Stenosis grade	72.6 (±18.7)		72.5(±19.1)		0.787
Medication - preprocedural					
ASA (Aspirin)	3920	78.4	6068	79.8	0.023
Clopidogrel	2953	59.0	4606	60.6	0.145
Medication - discharge					
ASA (Aspirin)	4379	88.3	6841	90.5	<0.001
Clopidogrel	3497	70.6	5504	72.9	0.022
Statin	3482	70.2	5494	72.7	0.004
Other lipid lowering agent (non-statin)	813	16.4	1289	17.1	0.485

BMI = body mass index, CAS = carotid angioplasty and stenting, CCS = Canadian cardiovascular society, CEA = carotid endarterectomy, CHF = congestive heart failure, GFR = glomerular filtration rate, MI = myocardial infarction, NYHA = New York Heart association

Descriptives of the sexes differed significantly for the following variables (Table 1). Women were older than men and more often African American. Women more often had renal dysfunction, hypertension, chronic obstructive pulmonary disease and higher BMI. Men were more likely to have a history of or be current smokers, and more often had renal failure. Men had higher rates of ischemic heart disease, more often had >= 2 major coronary arteries >70% stenosis, more likely had a pacemaker or ICD and more likely had a history of atrial fibrillation. Women more often had a previous carotid intervention while men more often had acute

Table 2. 30-day stroke or death rates and hazard rate ratios (HRR) with accompanying confidence intervals (c.i.) for women and men.

	Women (%)	95%c.i.	Men (%)	95%c.i.	HRR unadj	95%c.i.	HRR adj	95%c.i.
Symptomatic CEA	4.4	2.8-6.0	2.9	1.9-3.9	1.50	0.90-2.53	1.62	0.81-3.23
Symptomatic CAS	5.1	3.9-6.3	4.4	3.5-5.3	1.15	0.85-1.57	1.11	0.74-1.65
Asymptomatic CEA	2.8	1.9-3.7	2.1	1.4-2.8	1.35	0.74-1.54	0.96	0.53-1.72
Asymptomatic CAS	2.6	1.9-3.3	2.4	1.8-3.0	1.06	0.80-1.42	0.89	0.56-1.43

CEA = carotid endarterectomy, CAS = carotis angioplasty and stenting, c.i. = confidence interval

evolving strokes. Men more often had prior neck radiation and prior neck surgery. Women had higher rates of restenosis after both CEA and CAS, but men had higher rates of contralateral occlusion. Pre-procedural, men received more aspirin, and at discharge they received more aspirin, clopidogrel and statins.

After matching, 8414 patients were available for analysis, 4207 men and 4207 women (2629 CAS and 1578 CEA for each sex). Matching led to two well balanced groups. (Figure a)

picted in Table 2. Table 3 depicts the in-hopital stroke or death rates.

For the symptomatic CEA patients event rates were 4.4% for women and 2.9% for men. The unadjusted HRR for women vs. men was 1.50 (95%CI 0.90-2.53). After matching, the adjusted HRR was 1.62 (95%CI 0.81-3.23) p=0.17. For the symptomatic CAS patients, event rates were 5.1% for women and 4.4% for men (unadjusted HRR 1.15 95%CI 0.85-1.57). After matching the adjusted HRR was 1.11 (95%CI 0.74-1.65) p=0.61. For the asymptomatic CEA patients, event

Table 3 In-hospital stroke or death rates and odds ratios (OR) with accompanying confidence intervals (c.i.) for women and men.

	Women (%)	95%c.i.	Men (%)	95%c.i.	OR unadj	95%c.i.	OR adj	95%c.i.
Symptomatic CEA	3.3	1.9-4.8	2.3	1.4-3.2	1.48	0.90-2.71	1.55	0.72-.30
Symptomatic CAS	3.8	2.7-4.8	3.7	2.9-4.5	1.01	0.71-1.45	1.12	0.72-1.72
Asymptomatic CEA	2.0	1.2-2.7	1.7	1.1-2.3	1.18	0.69-2.02	0.95	0.51-1.78
Asymptomatic CAS	2.0	1.4-2.7	1.8	1.3-2.3	1.11	0.72-1.71	0.84	0.51-1.41

CEA = carotid endarterectomy, CAS = carotis angioplasty and stenting, c.i. = confidence interval

Primary end point

The 30-day stroke or death rates and unadjusted and adjusted hazard rate ratios (HRR) with accompanying 95% confidence intervals (95% c.i.) are depicted in Table 2. Table 3 depicts the in-hopital stroke or death rates.

For the symptomatic CEA patients event rates were 4.4% for women and 2.9% for men. The unadjusted HRR for women vs. men was 1.50 (95%CI 0.90-2.53). After matching, the adjusted HRR was 1.62 (95%CI 0.81-3.23) p=0.17. For the symptomatic CAS patients, event rates were 5.1% for women and 4.4% for men (unadjusted HRR 1.15 95%CI 0.85-1.57). After matching the adjusted HRR was 1.11 (95%CI 0.74-1.65) p=0.61. For the asymptomatic CEA patients, event rates were 2.8% for women and 2.1% for men (unadjusted HRR 1.35 95%CI 0.74-1.54; adjusted HRR 0.96 95%CI 0.53-1.72) p=0.88.

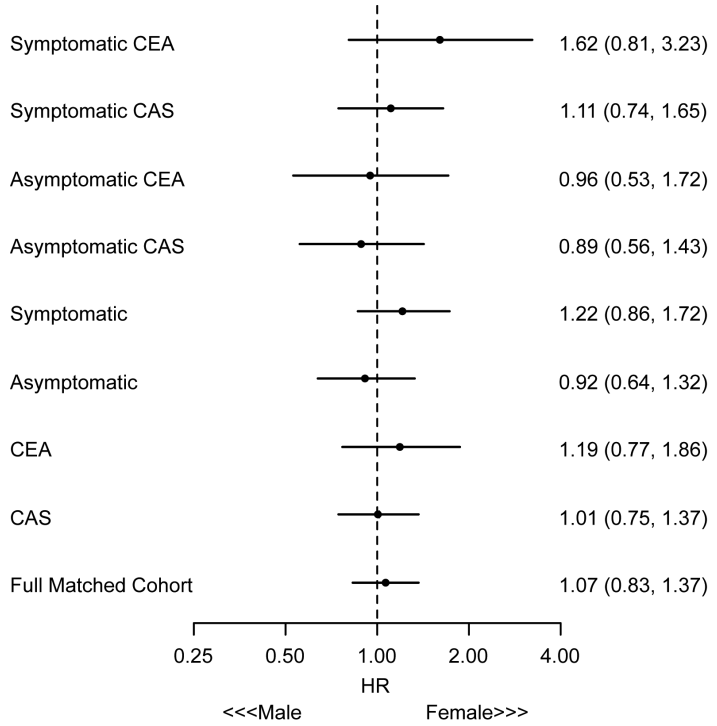

Figure b

Forest plot representation of 30-day stroke or death of women compared to men. For each group the hazard rate ratio (HRR) with accompanying 95% confidence interval is given.
The vertical line represents a HRR of 1 (no difference). The dots represent the HRRs, the horizontal lines the 95% confidence intervals. The higher the HRR, the worse the outcome for women.
CEA = carotid endarterectomy, CAS = carotid angioplasty and stenting, OR = odds ratio

For asymptomatic CAS patients, event rates were 2.6% for women and 2.4% for men (unadjusted HRR 1.06; 95%CI 0.80-1.42; adjusted HRR 0.89 95%CI 0.56-1.43) p=0.63

Figure b, apart from the above-mentioned results, also depicts the HRR for all symptomatic patients, all asymptomatic patients, all CEA combined, all CAS combined and all patients combined. Women did slightly worse in the combined CEA and combined symptomatic groups and slightly better in the combined asymptomatic group. Figure c depicts the odds ratios of gender for the in-hospital event rates matched cohort.

Sex differences in 30-day stroke or death were most pronounced in the symptomatic CEA group. The power to detect a clinically relevant difference of 2% was 37%, 60%, 80% and 89%, for the symptomatic CEA, symptomatic CAS, asymptomatic CEA and asymptomatic CAS group, respectively.

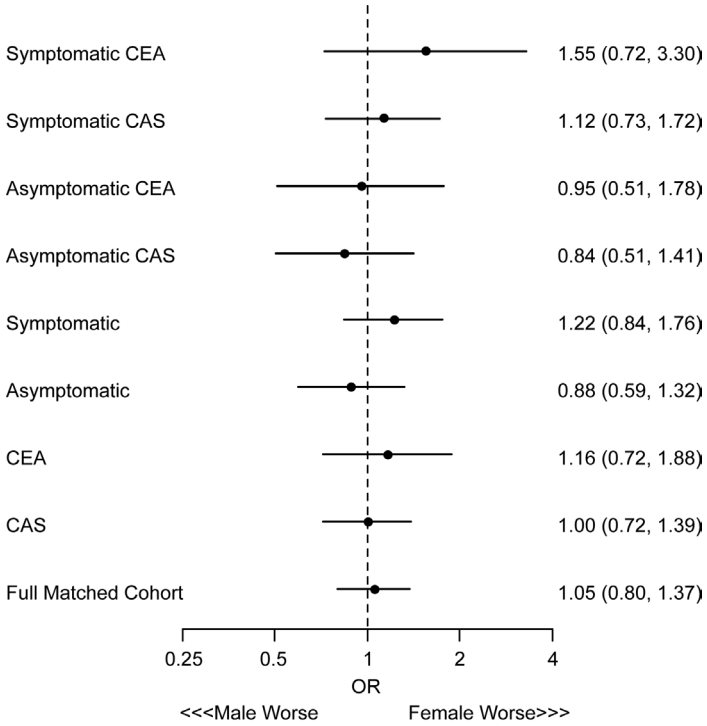

Figure c
Forest plot representation of in-hospital stroke or death of women compared to men. For each group the odds ratio (OR) with accompanying 95% confidence interval is given.
The vertical line represents a OR of 1 (no difference). The dots represent the ORs, the horizontal lines the 95% confidence intervals. The higher the OR, the worse the outcome for women.
CEA = carotid endarterectomy, CAS = carotid angioplasty and stenting, OR = odds ratio

Discussion

In this study from a large national registry, 30-day and in-hospital stroke or death rates associated with CEA or CAS were not significantly different between women and men. The event rates were slightly higher for women for all four groups but not statistically significantly so. The difference was most pronounced in the symptomatic CEA group were women had a 30-day event rate of 4.4% vs. 2.9% for men. It is possible that a difference does exist but that the CARE registry as yet has insufficient numbers of events to detect this as demonstrated by the power calculations. For both women and men and for both CEA and CAS, event rates were higher for symptomatic than for asymptomatic patients. For symptomatic patients, CEA had lower event rates than CAS for both women and men. For all four groups, event rates were below the recommended standard threshold of perioperative risk for CEA or CAS. Our results suggest a higher event rate for women with a symptomatic lesion treated with CEA. The reason why women may be at higher operative risk remains speculative. Both symptomatic and asymptomatic randomized CEA trials were not powered to determine the influence of sex on perioperative outcome but all did demonstrate less

benefit of surgery for women compared to men.

For CAS the ICSS demonstrated no differences for women in perioperative outcome compared to CEA6. (Combined outcome of stroke or death or MI, both had an event rate of 8%) This trial received some comments because less strict criteria (experience) was needed for stenters compared to surgeons. The results from the CREST, the American trial comparing CEA to CAS and with equally strict criteria for surgeons as stenters, reported equal results between the two treatment groups for their combined outcome of stroke or death or MI. The CREST, however, in comparison to the ICSS, included silent MIs in their outcome. When looking at the outcome stroke or death, the CREST, just as the ICSS, reported significantly higher event rates after CAS than CEA. The outcome of stroke or death has not been stratified on sex in ICSS and CREST yet, complicating comparability. De Rango et al. recently demonstrated no statistically significant difference between CAS and CEA for women in 30-day stroke or death. Long term outcomes, although not statistically significant, did favour CAS (4.1% vs. 8.1%) and the authors conclude that CAS may be the treatment of choice for asymptomatic women seeing that their risk of surgery seems to be higher14. A recently published meta-analysis of individual patient data from three randomized controlled trials (EVA-3S, SPACE, and ICSS) showed a clear benefit of CEA over CAS for men for the outcome stroke or death (event rate of 5.4% vs. 9.0%, risk ratio (RR) 1.68 (95%CI 1.25-2.25)) but not for women (event rate 6.9% vs. 8.5%, RR 1.22 (95%CI 0.79-1.89))15. The CREST Lead-in Phase study (CAS) n=1564) reported stroke or death rates for symptomatic women of 5.6% and for symptomatic men of 5.9%. Asymptomatic women had event rates of 4.1% and asymptomatic men of 3.5%16. Our event rates are lower but in line with the abovementioned studies.

The present study has some limitations. First of all, our study was not a RCT and was based on retrospective analysis of data. As with all registries, inclusion of all consecutive patients at all sites can not be ensured, leading to possible generalizability issues. Although there is standardization and uniformity in processes related to data collection, with quality controls and participant feedback, any voluntary national database effort is inherently limited.

Secondly, evident differences between the female and male population were adjusted for by propensity score matching, but inevitably, we could not account for everything.

Thirdly, 30-day follow-up was available for 65% of patients. But seeing 77% of events occurred pre-discharge, up to which point data was available for all participants, a potential bias in effect estimates due to informative censoring will be limited. We also did an additional analysis with in-hospital events as our outcome of which we had 100% follow up. For all four groups this lead to unchanged direction of the effect estimates, enforcing our belief that bias in effect estimates of the 30-day outcome will be limited.

Concluding, the results from this study do not provide strong evidence that women have higher 30-day stroke or death rate following CEA or CAS. Women do, however, seem to have higher 30-day stroke or death rate following CEA for a symptomatic lesion. Further studies and pre-specified subgroup analyses by sex are needed to confirm this.

Acknowledgements

This research was supported by an unrestricted educational grant from the Foundation 'Lijf en Leven'.

Conflicts of Interest/ Disclosures

None

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Chapter 8

Summary and general discussion
Samenvatting

Summary and general discussion

In this thesis we described studies which evaluated the effect of gender on the presentation of cardiovascular disease and clinical outcome after vascular surgery. The main conditions studied were abdominal aortic aneurysms and carotid artery stenoses. In **Chapter 1**, the rationale for this research is presented. Since cardiovascular disease has for a long time been thought to occur mainly in men, women have been underrepresented in cardiovascular studies. Guidelines are therefore based on a predominately male population and it is debatable whether these guidelines can be applied to women. Cardiovascular disease is the main cause of death for women too and one out of every three women dies as a result of it.

Main results and interpretation

In order to evaluate the effect of gender on abdominal aortic aneurysm outcome we started by conducting a review (**Chapter 2**). We focussed on the epidemiology, aetiology, risk of rupture and outcome after treatment and demonstrated that the prevalence of abdominal aortic aneurysms (AAAs) is underestimated in women. On the one hand we believe this to be due to the fact that the diagnosis is usually made based on an absolute measurement (30 mm) instead of a relative one (1.5 times the normal size of the aorta). On the other hand the awareness of this disease in women is low. We also found that as far as aetiology is concerned, an oestrogen-mediated reduction in macrophage MMP-9 production seems to be an important mechanism causing gender-related differences in AAA development. This would explain why AAAs hardly occur pre-menopausal. Furthermore, we found consensus in the literature that women run a 3 to 4 times greater risk of rupture compared to men under the current management of AAAs, and that their peri-procedural mortality is higher for both elective and ruptured repair. We conclude that although many reasons have been put forward for this disproportionately poorer outcome for women, the most important ones are the current absolute threshold for repair and the lower awareness, and therefore diagnosis, of AAA in women.

In **Chapter 3** we present the results of the systematic review and meta-analysis we performed, analysing the mortality rates of women versus men for elective and ruptured AAA repair by either an open or endovascular procedure. Sixty-one studies, encompassing over half a million patients met the inclusion criteria. We demonstrated that the mortality rate was significantly higher for women after both elective open repair and elective endovascular aneurysm repair (EVAR). Women were on average older than men, but the difference persisted after adjustment for age. The difference in mortality was most pronounced after elective EVAR. The mortality rate was also higher for women after open repair of a ruptured AAA, but this difference was not statistically significant after adjustment for age.

These findings demonstrate that the current treatment criteria are not optimal for women. Possible explanations for the higher mortality in women are the absolute criteria for repair, their poorer anatomical suitability for the present EVAR devices and the under recognition of cardiovascular disease, including AAA, as a whole. This leads to delayed diagnosis and inter-

vention, but also to fewer primary and secondary preventive measures including cardiovascular medication and lifestyle adjustment.

We concluded that the threshold (AAA diameter) above which repair is indicated in women remains to be determined. Especially the indication for elective EVAR in women needs to be reconsidered thoroughly as outcomes were worst in this group (Apart from higher mortality women also have higher conversion rates and higher rates of aborted procedures). Current practice does not seem to be optimal for women.

We subsequently performed a systematic review of AAA screening guidelines **(Chapter 4)** to obtain an overview of screening recommendations, in particular with respect to women. We found seven guidelines on AAA screening. The majority lacked a systematic method for evaluating the evidence and achieved a low AGREE score for rigour of development. Most guidelines contained recommendations that were in favour of one-time AAA screening for men 65 years and older using ultrasonography scans. Four guidelines, of which three had low AGREE scores, also contained disparate recommendations on screening women and middle-aged men at elevated risk, whereas guidelines with higher AGREE scores did not. One guideline explicitly recommended that women should not be screened. Although an abdominal aortic diameter of 5.5 cm was unanimously used as the criterion for elective surgical repair in elderly men, no consensus existed on the management of smaller AAAs or the management of AAAs in women. We concluded that consensus exists across guidelines on the one-time screening of elderly men to detect and treat AAAs ≥5.5 cm. For other target groups such as for women, or for the management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance. Also, the use of the same absolute diameter for the diagnosis (30 mm) for both men and women could explain why women have been demonstrated not to benefit from screening.

In **Chapter 3** we demonstrated that women undergoing elective EVAR have far worse outcomes compared to men. We felt that further investigation was warranted and this lead to the review as portrayed in **Chapter 5**. Taking a step-by-step approach we set out to establish the role of this relatively new technique in women. The three randomized controlled trials in which EVAR is compared with open repair are discussed as are gender-specific secondary prevention, risk factor management and medication. Although we found that the role of EVAR in women has been poorly investigated, women seem to have higher mortality and more complications after EVAR. Risk factors such as diabetes and hypertension are associated with worse outcome in women compared to men. Aggressive treatment of risk factors and the optimization of medication in women are indicated and deserve more attention in clinical practice and future research. Until the definite role of EVAR in women is determined such treatment should be implemented with caution.

In **Chapter 6** we aimed to determine the effect of gender on 30-day and long-term outcomes after EVAR. We had at our disposal the EUROSTAR database, a registry containing information on more than 10,000 patients who underwent elective EVAR. We found no difference in 30-day mortality for women compared to men, but women did have a higher cumulative incidence of the composite end-point. Kaplan-Meier curves demonstrated

worse outcomes for both long-term survival and long-term event-free survival. Survival analyses adjusted for covariates and comorbidities also demonstrated no difference in mortality for women compared to men, but again women did have higher rates of the composite end-point. So although women undergoing endovascular aortic repair have the same 30-day mortality, they have significantly higher complication and re-intervention rates than men. Long-term survival and event-free survival in women is also lower than in men. In this study we again conclude, similar to the conclusions we drew in **Chapters 3 and 5**, that the role of elective EVAR in women needs to be reconsidered.

In the final chapter (**Chapter 7**) we focussed on the 30-day mortality or stroke rate after carotid artery stenosis treated by either open repair (carotid endarterectomy, CEA) or endovascular repair (carotid angioplasty and stenting, CAS). We collaborated with the National Cardiovascular Data Registry (NCDR) and were able to analyse the CARE-Registry encompassing more than 12,000 patients. The event rate for the symptomatic CEA group was 4.4% for women and 2.9% for men. In the symptomatic CAS group it was 5.1% for women and 4.4% for men. The asymptomatic CEA group showed event rates of 2.8% vs. 2.1% and for the asymptomatic CAS group of 2.6% vs. 2.4%, for women vs. men respectively. These differences remained non-significant after propensity score matching and multivariable regression. Our data did not provide strong evidence for sex-differences in short-term outcome following CEA or CAS. Event rates were higher for women in all groups but not statistically significantly so. A trend of a higher event rate for women was seen in the symptomatic CEA group.

Methodological considerations

Systematic reviews and guidelines

The health care literature contains hundreds of thousands of studies of health care interventions, and it expands vastly each year. In nearly all areas of health care, there are too many studies for people involved in providing care to identify and consider when making decisions. Researchers have recognised this problem and have come up with a solution to it by preparing systematic reviews of individual studies in order to appraise, summarise and bring together existing studies in a single document.

There are now several organisations dedicated to the preparation of systematic reviews, including the National Institute of Health and Clinical Excellence (NICE) in the UK and the Cochrane Collaborations in the USA, the latter being the largest single producer of systematic reviews in health care.

Recently a new problem has, however, arisen. Decision-makers who were once overwhelmed by the number of individual studies are now faced by a multitude of reviews. These reviews are of variable quality and scope, with more than one systematic review on important topics.

The quality and strength of evidence presented in the individual reviews should influence the conclusions drawn in any systematic review of them. The strength of the conclusions and the ability to provide decision-makers with reliable information depends on the inclusion of reviews that meet a minimum standard of quality. When assessing the quality of the reviews, one should try to avoid being influenced by extraneous variables, such as authors, institutional affilia-

tions and journal names, and should focus on the quality of the conduct of the review.

Tools have been developed which provide standards of reporting, thus making it easier to compare the various studies. The PRISMA (formerly, QUOROM) being the best known tool.

The AMSTAR tool, which became available after we started work on our systematic review, is the only tool that has been validated to assess the methodological quality of systematic reviews and can be used to determine whether the potentially eligible reviews meet minimum requirements based on quality. Important domains identified within the tool are:

- establishing the research question and inclusion criteria before the conduct of the review,
- data extraction by at least two independent data extractors,
- comprehensive literature review with search of at least two databases, key word identification, expert consultation and limits applied,
- detailed list of included/excluded studies and study characteristics,
- quality assessment of included studies and consideration of quality assessments in analysis and conclusions,
- appropriate assessment of homogeneity,
- assessment of publication bias and a statement of any conflict of interest.

Although our systematic review began before the publication of the AMSTAR tool, we used similar domains to construct our systematic review.

Guidelines

Guidelines often arise from reviews and systematic reviews but evidence for many clinical decisions is lacking or of limited quality and therefore expert panels are called upon to assess the available evidence and provide consensus recommendations. Biases and differences in values are inherent in any set of recommendations, particularly in efforts directed at saving lives, weighing the risks and benefits of intervention, and optimizing cost-effective care. Limiting bias, improving the quality of decisions, and enhancing forecasts in a world where information is incomplete is an area of active investigation and great interest.

In an attempt to aid decision makers in assessing guideline quality the Appraisal of Guidelines, REsearch and Evaluation (AGREE) instrument was developed. This tool assesses the process of guideline development and how well this process is reported, as its primary means of appraising the quality of a guideline.

As an example, in **Chapter 5**, we used this tool to determine the quality of development of each included guideline by using the "Rigor of Development" domain of the AGREE instrument. This score looked at: (1) methods used to search for evidence; (2) criteria for selecting the evidence; (3) methods for formulating the recommendations; (4) consideration of health benefits, side effects, and risks; (5) supporting evidence; (6) procedures for external peer review; and (7) the update process.

The problem with every systematic review, every guideline and every tool that assesses these, is that information is incomplete and thus every systematic review, every guideline and every assessment tool is flawed to some degree. Optimizing the available information by creating reporting standards for one, but assessment tools too, play a major role in minimizing these flaws. Clinical judgement will always remain necessary as recommendations are by default general and their application to one's unique practice remains the clinician's decision.

Registry data

Registry data is nowadays an important data source. Particularly when evaluating differences in prognosis depending on risk factors, large prospectively collected cohorts with longitudinal data collection are appropriate in establishing differences as we demonstrated in **Chapters 6 and 7**. We were very fortunate to collaborate with various groups and institutions which gave us the opportunity to analyze large cohorts of patients. We collaborated with the Catharina Hospital Eindhoven and thus were able to analyze the EUROSTAR database, comprising approximately 10,000 patients (**Chapter 6**), and with the NCDR we were able to analyze the CARE-Registry database, comprising over 12,000 patients (**Chapter 7**).

Furthermore, registry data reflects results as obtained in daily clinical practice as opposed to the highly controlled setting of an RCT. Many clinicians are thus in favour of well executed large prospectively collected cohort trials, or at least like to see 'proof' of a systematic review, by means of such a trial.

Registry data has several limitations though. First of all, registry data is collected in daily clinical practice and inclusion of all consecutive patients at all sites cannot be ensured, leading to possible generalizability issues. Nevertheless, everything was done to make the registries as complete as possible and this same limitation also applies to (randomized) trials. Secondly, although data is collected prospectively, it is possible that events are not recorded due to loss of follow-up. Thirdly, true causal relationships are difficult if not impossible to demonstrate.

Clinical relevance and future directions of research

Gender medicine is a novel and rapidly expanding field of research. Over the last few decades, but particularly since the 1990s, publications including sex- and gender-specific differences have increased. One feature common to all disciplines, except maybe cardiology, is the dramatic under-representation of investigations of sex and gender differences in clinical management. Research on clinical management, i.e. diagnostic approaches, referral practices, invasive and non-invasive therapy choices, is essential in understanding and improving clinical practice. Lack of knowledge about gender differences and inadequacies in health care provision have led to significant and potentially fatal imbalances in outcomes.

This has been demonstrated in the field of cardiology, where the numbers of women dying of heart infarction at a young age significantly dropped after two decades of research and the dissemination of essential information about gender differences in clinical presentation,

symptoms, diagnostic and therapeutic approaches. Examples from other disciplines are also starting to appear, but the information is still scarce.

The incorporation of sex- and gender-specific analyses in medical research is increasing due to pressure from public agencies, funding bodies, and the clinical and research community. Pre-specified subgroup analysis by sex is commonly a prerequisite stipulated by funding agencies for obtaining grants (NIH, ZonMW, NHS, Hartstichting). This means that the time is now ripe for sex-specific research. The 3 major areas which we believe need further work are considered below.

Improving diagnosis

It all starts with a better recognition of symptoms and improved diagnostic accuracy of tests. This requires a better understanding of the pathofysiology. As we now know for coronary artery disease gender differences do exist, necessitating functional diagnostic tests instead of solely significant stenosis (focal) assessment tests for women. We need to gain insight into the exact differences in AAA formation and carotid artery plaque formation and consistency so that we can improve the recognition of symptoms and the diagnostic accuracy of tests. What is certain is that we have to move away from absolute thresholds for diagnosis (such as 30 mm for an AAA) and instead use relative measures, so that we have no delay in diagnosis and can start treating the condition (invasively or with medication) at once.

Therapy

As far as therapy is concerned, we again need to move away from absolute thresholds for repair (at present 5.5 cm for AAAs) and to a much more tailored advice for the individual patient.

Decision tools (web based) which a clinician can easily and quickly use in the outpatient clinic and which can aid in deciding on how to treat a specific patient (invasively or with medication or both) represent the future. Before they can be developed though, more information is needed.

We need to study the differences in comorbidities (e.g. smoking, diabetes and hypertension are much higher risk factors in women than in men) and how we can best treat these (either by life-style adjustment or medication). The best strategies still need to be determined in women.

Certain therapies such as EVAR really need further investigation in women. Modelling and cost-effectiveness studies (taking their higher complication and re-intervention rates and longer hospital stay into account) are needed to shed light on the role that EVAR should have in elective aneurysm repair in women. Furthermore, because anatomical features play such an important role in endovascular repair (both in AAA and carotid artery stenosis) it would be interesting to develop more tailored devices for women and then study whether by using tailored devices the differences in outcomes disappear.

Increasing awareness

In our opinion this is the single most important aspect. As long as people are unaware of their risk of cardiovascular disease no progress can be made. By increasing awareness in both medical personnel and in the patients themselves progress can be made. Many women are still unaware that cardiovascular disease is their main cause of death and even when they do, have no idea what effect certain risk factors have on the disease. This in turn leads to less aggressive adjustments in lifestyle and adher-

ence to secondary prevention. Campaigns such as the 'Dress Red Campaign' (American Heart Association) have proven to increase awareness and better recognition of symptoms. In the Netherlands too, the 2010 campaign of the 'Hartstichting' increased the awareness from 25% to 50% in one month! Although this is a wonderful result it has been proven that repetition of the message is the only way to keep up awareness.

Incorporating gender differences in the medical curriculum is another excellent way of increasing awareness and a greater focus should be put on enhancing/facilitating this in the Netherlands too, in line with leading universities such as Harvard and the Karolinska Institute which have recently opened Gender Medicine departments.

Once the aforementioned points have been addressed, gender specific (or rather patient specific) guidelines/ decision tools can be put into place which will lead to better health care on the whole, not only for women but for men too.

Samenvatting

In dit proefschrift beschrijven wij studies waarin het effect van geslacht op de presentatie van hart-en vaatziekten en de klinische uitkomst na vaatchirurgie is onderzocht. De voornaamste onderzochte aandoeningen waren het aneurysma van de abdominale aorta (AAA) en halsslagader (carotis) stenose. In **Hoofdstuk 1** wordt de achtergrond van dit onderzoek gepresenteerd. Aangezien er lange tijd gedacht werd dat cardiovasculaire aandoeningen vooral bij mannen voorkwamen, zijn vrouwen ondervertegenwoordigd in cardiovasculaire studies. De daaruit volgende richtlijnen zijn daarom gebaseerd op een overwegend mannelijke bevolking en het is de vraag of deze richtlijnen zomaar kunnen worden toegepast op vrouwen. Hart- en vaatziekten zijn ook voor vrouwen de belangrijkste doodsoorzaak en een op de drie vrouwen overlijdt als gevolg hiervan.

Belangrijkste bevindingen

Om het effect van geslacht op de uitkomsten van een AAA te evalueren, hebben we als eerste een literatuuronderzoek verricht **(Hoofdstuk 2)**. We richtten ons op de epidemiologie, etiologie, het risico op een ruptuur en het resultaat na de behandeling, en toonden aan dat de prevalentie van het AAA wordt onderschat bij vrouwen. Enerzijds denken wij dat dit te wijten is aan het feit dat de diagnose gewoonlijk wordt gedaan op basis van een absolute maat (30 mm) in plaats van een relatieve (1.5 maal de normale grootte van de aorta). Anderzijds is het bewustzijn van deze aandoeningen bij vrouwen laag. Ten aanzien van de etiologie, lijkt de bij vrouwen oestrogeen-gemedieerde vermindering van macrofagen MMP-9 productie, een belangrijk mechanisme te zijn voor het verschil in AAA vorming tussen mannen en vrouwen. Dit zou verklaren waarom AAAs nauwelijks pre-menopauzaal voorkomen. Verder vonden we consensus in de literatuur dat vrouwen een 3 tot 4 keer groter risico op ruptuur lopen in vergelijking met mannen onder de huidige behandelingsstrategie van AAAs, en dat hun peri-procedurele sterfte kans hoger is voor zowel electieve en geruptureerde behandeling. We concluderen dat, hoewel vele redenen naar voren gebracht zijn voor deze onevenredig slechtere uitkomst voor vrouwen, de belangrijkste de huidige absolute drempelwaarde voor behandeling en het lagere bewustzijn, en dus ook diagnose, van AAAs bij vrouwen zijn.

In **Hoofdstuk 3** presenteren we de resultaten van onze systematische literatuuronderzoek en meta-analyse. We analyseerden de sterftekans van vrouwen ten opzichte van mannen na electieve en geruptureerde AAA behandeling door ofwel een open of endovasculaire procedure. Eenenzestig studies, die bij elkaar meer dan een half miljoen patiënten omvatten, voldeden aan de inclusiecriteria. We hebben aangetoond dat de sterftekans significant hoger was voor vrouwen na zowel electieve open chirurgie als electieve endovasculaire behandeling (EVAR). Vrouwen waren gemiddeld ouder dan mannen, maar het verschil bleef na correctie voor leeftijd bestaan. Het verschil in mortaliteit was het meest uitgesproken na electieve EVAR. De sterftekans was ook hoger voor vrouwen na open herstel van een geruptureerd AAA, maar dit verschil verdween na correctie voor leeftijd.

Deze bevindingen tonen aan dat de huidige behandelings criteria niet optimaal zijn voor vrouwen. Mo-

gelijke verklaringen voor de hogere sterftekans bij vrouwen zijn het absolute criterium voor behandeling, de slechtere anatomische geschiktheid voor de huidige EVAR apparaten en onder erkenning van cardiovasculaire ziekte, waaronder AAA, als geheel. Dit leidt tot vertraagde diagnose en behandeling, maar ook tot minder primaire en secundaire preventieve maatregelen, waaronder cardiovasculaire medicatie en leefstijl aanpassingen.

Wij concludeerden dat de drempelwaarde (AAA diameter) waarboven herstel moet plaatsvinden in vrouwen nog vastgesteld moet worden. Vooral de indicatie voor electieve EVAR bij vrouwen moet grondig worden herzien, omdat de uitkomsten in deze groep het slechtste waren. (naast mortaliteit ook hogere kans op conversies en afgebroken procedures). Het huidige beleid rondom AAAs lijkt niet optimaal te zijn voor vrouwen.

Vervolgens hebben we een systematisch literatuuronderzoek uitgevoerd van AAA screening richtlijnen **(Hoofdstuk 4)** om een overzicht van screening aanbevelingen te verkrijgen, met name met betrekking tot vrouwen. We vonden zeven richtlijnen voor AAA screening. Bij de meerderheid ontbrak een systematische methode voor het evalueren van het bewijs en behaalden de richtlijnen een lage AGREE score voor rigorositeit van ontwikkeling. De meeste richtlijnen deden aanbevelingen tot de eenmalige screening van mannen 65 jaar of ouder door middel van echografie. Vier richtlijnen, waarvan drie met lage AGREE scores, bevatte uiteenlopende aanbevelingen ten opzichte van vrouwen en mannen van middelbare leeftijd met enkele risicofactoren, terwijl richtlijnen met hogere AGREE scores geheel geen aanbevelingen deden voor deze groepen. Eén richtlijn meldde uitdrukkelijk dat vrouwen niet gescreend dienden te worden. Hoewel een diameter van de abdominal aorta van 5.5 cm unaniem gehanteerd werd als criterium voor electieve behandeling in oudere mannen, bestond er geen consensus over de behandelingsstrategie voor AAAs met een kleinere diameter of de behandelingsstrategie voor AAAs bij vrouwen. Wij concludeerden dat er consensus bestaat dat mannen van 65 jaar en ouder eenmalig gescreened dienen te worden en behandeld bij een diameter van het AAA van ≥5.5 cm. Voor de andere groepen, zoals patiënten met kleinere AAAs of voor vrouwen is aanvullend onderzoek nodig in de vorm van predictiemodellen en kosteneffectiviteits analyses om richting te geven. Ook zou het gebruik van dezelfde absolute diameter van de diagnose (30 mm) voor zowel mannen als vrouwen kunnen verklaren waarom vrouwen niet lijken te profiteren van screening.

In **Hoofdstuk 3** hebben we aangetoond dat vrouwen na electieve EVAR veel slechtere resultaten hadden in vergelijking met mannen. We vonden dat nader onderzoek gerechtvaardigd was en dit leidde tot het literatuuronderzoek zoals beschreven in **Hoofdstuk 5**. Door middel van een stap voor stap benadering bekeken we de rol van deze relatieve nieuwe techniek in vrouwen. De drie gerandomiseerde studies waarin EVAR wordt vergeleken met open chirurgische behandelingen worden besproken evenals seksespecifieke secundaire preventie, risicofactoren en medicatie. Hoewel de rol van EVAR bij vrouwen slecht onderzocht bleek, lijken vrouwen een hogere sterfte kans en meer complicaties te hebben na EVAR. Risicofactoren zoals diabetes en hypertensie blijken bij vrouwen geassocieerd te zijn met slechtere uitkomsten dan bij mannen. Agressieve

behandeling van risicofactoren en het optimaliseren van de medicatie bij vrouwen zijn nodig en verdienen meer aandacht in de praktijk en in toekomstig onderzoek. Tot de definitieve rol van EVAR bij vrouwen is bepaald moet dergelijke behandeling worden uitgevoerd met de nodige voorzichtigheid.

In **Hoofdstuk 6** hadden we als doel de invloed van het geslacht op 30-dagen en lange termijn resultaten na EVAR te bepalen. We hadden de EUROSTAR-database tot onze beschikking, een register met informatie over meer dan 10.000 patiënten die electieve EVAR ondergingen. We vonden geen verschil in 30-dagen mortaliteit voor vrouwen in vergelijking met mannen, maar vrouwen hadden wel een hogere cumulatieve incidentie van het samengestelde eindpunt. Kaplan-Meier curves toonden ook slechtere resultaten voor vrouwen voor zowel de overleving op lange termijn als de gebeurtenis-vrije overleving. Survival analyses gecorrigeerd voor covariaten toonden geen verschil in sterftekans voor vrouwen in vergelijking met mannen, maar vrouwen hadden wederom een hoger kans op het samengestelde eindpunt. Vrouwen die een EVAR ondergingen hadden dezelfde sterfte kans als mannen, maar hadden een aanzienlijk hogere kans op complicaties en re-interventies. De lange-termijn overleving en gebeurtenis-vrije overleving waren bij vrouwen lager dan bij mannen. In deze studie concludeerden we, zoals eerder in **Hoofstuk 3 en 5**, dat de rol van electieve EVAR bij vrouwen herzien moet worden.

In het laatste hoofdstuk **(Hoofdstuk 7)** hebben we ons gericht op de 30-dagen mortaliteit of beroerte kans na een halsslagader stenose behandeld door open reparatie (carotis endarteriëctomie, CEA) of endovasculaire behandeling (carotis angioplastiek en stenting, CAS). We werkten samen met de National Cardiovascular Data Registry (NCDR) en waren zo in staat om het CARE-register met meer dan 12,000 patiënten te analyseren. De kans op sterfte of een beroerte voor de symptomatische CEA-groep was 4.4% voor vrouwen en 2.9% voor mannen. In de symptomatische CAS groep was het 5.1% voor vrouwen en 4.4% voor mannen. De asymptomatische CEA groep vertoonde 2.8% ten opzichte van 2.1% en voor de asymptomatische CAS groep 2.6% vs 2.4%, voor vrouwen ten opzichte van mannen respectievelijk. Deze verschillen bleven niet-significant na propensity score matching en multivariabele regressie. Deze resultaten geven geen sterke aanwijzingen voor sekseverschillen op het korte termijn resultaat na CEA of CAS. De kansen op sterfte en een beroerte waren hoger voor vrouwen in alle groepen, maar niet statistisch significant. De sterkste trend voor een slechtere uitkomst voor vrouwen werd gevonden in de symptomatische CEA-groep.

Klinische relevantie en toekomstige ontwikkelingen van het onderzoek

'Gender Medicine' is een nieuw en snel groeiende gebied van onderzoek. In de afgelopen decennia, maar vooral sinds de jaren 1990, zijn de publicaties over sekseverschillen toegenomen. Een gemeenschappelijk kenmerk van alle disciplines, behalve misschien de cardiologie, is de enorme ondervertegenwoordiging van onderzoek naar sekse en sekseverschillen in klinische behandelingsstrategieën. Onderzoek naar klinische behandelingsstrategieën, dat wil zeggen diagnostische benaderingen, doorverwijzingsprakti-

jken, invasieve en niet-invasieve therapie keuzes, is van essentieel belang bij het begrijpen en verbeteren van de praktijk. Gebrek aan kennis over sekseverschillen en onvolkomenheden in de gezondheidszorg hebben geleid tot belangrijke en potentieel fatale onevenwichtigheden in uitkomsten.

Dit is aangetoond in de cardiologie, waar het aantal vrouwen dat op jonge leeftijd stierf aan een hartinfarct sterk daalde na twee decennia van onderzoek en de verspreiding van belangrijke informatie over de verschillen tussen de geslachten in klinische presentatie, symptomen, diagnostische en therapeutische benaderingen. Voorbeelden uit andere disciplines beginnen ook te verschijnen, maar de informatie is nog steeds schaars.

De integratie van seksespecifieke analyses in medisch onderzoek neemt toe als gevolg van druk van de publieke instanties, financieringsinstanties en klinische en wetenschappelijke onderzoekers. Vooraf gespecificeerde subgroepanalyses naar sekse zijn vaak een voorwaarde bepaald door financieringsinstanties voor het verkrijgen van subsidies (NIH, ZonMW, NHS, Hartstichting). Dit betekent dat de tijd nu rijp is voor seksespecifieke onderzoek. De drie belangrijkste gebieden waarvan wij denken dat verder onderzoek nodig is worden hieronder beschouwd

Verbetering van de diagnose

Het begint allemaal met een betere herkenning van de symptomen en een betere diagnostische nauwkeurigheid van testen.

Dit vereist een beter begrip van de pathofysiologie. Zoals we nu weten voor coronaire hartziekten bestaan er sekseverschillen, waardoor er functionele diagnostische tests in plaats van uitsluitend significante stenose (focale) tests noodzakelijk zijn voor vrouwen. We moeten inzicht krijgen in de precieze verschillen in AAA vorming en halsslagader plaquevorming en consistentie, zodat we de herkenning van de symptomen en de diagnostische nauwkeurigheid van testen kunnen verbeteren. Wat zeker is, is dat we moeten afstappen van absolute drempels voor de diagnose (zoals 30 mm voor een AAA) en in plaats daarvan gebruik maken van relatieve maten, zodat we geen vertraging in het stellen van de diagnose oplopen en gelijk kunnen beginnen met het behandelen van de aandoening (invasief of met medicatie).

Therapie

Wat therapie betreft, moeten we ook hier afstappen van absolute maten voor behandeling (momenteel 5.5 cm voor AAAs) en ons richten op een veel meer op maat gesneden advies voor de individuele patiënt.

Besluitvormingsinstrumenten (web-based), die een arts eenvoudig en snel kan gebruiken op de polikliniek en die kunnen helpen bij de beslissing over de wijze waarop een specifieke patiënt (invasief of met medicijnen of beide) behandeld moet worden, vertegenwoordigen de toekomst. Voordat deze echter ontwikkeld kunnen worden, is meer informatie nodig over het volgende.

- We moeten de verschillen in comorbiditeit bestuderen (bijvoorbeeld roken, diabetes en hypertensie zijn veel hoger risicofactoren bij vrouwen dan bij mannen) en hoe we deze het beste kunnen behandelen (hetzij door life-style aanpassing of medicatie). De beste strategieën moeten nog worden vastgesteld bij vrouwen.

- Bepaalde behandelingen zoals EVAR dienen nodig onderzocht

te worden bij vrouwen. Modellering- en kosteneffectiviteitstudies (hun hogere complicatie en re-interventie kans en langer verblijf in het ziekenhuis in acht nemend) zijn nodig om licht te werpen op de rol die EVAR zou moeten hebben in electieve behandeling van het AAA bij vrouwen. Bovendien, omdat anatomische kenmerken zo'n belangrijke rol spelen bij endovasculaire behandeling (zowel bij het AAA als de halsslagader stenose) zou het interessant zijn om meer op maat gemaakte apparaten voor vrouwen te ontwikkelen en dan te kijken of hierdoor de verschillen in uitkomsten verdwijnen.

Vergroting van het bewustzijn

Naar onze mening is dit het belangrijkste aspect. Zolang mensen zich niet bewust zijn van hun risico op hart-en vaatziekten kunnen we geen vooruitgang boeken. Door zowel medisch personeel als de patiënt zelf meer bewust te maken van deze risico's is vooruitgang mogelijk. Veel vrouwen zijn nog steeds niet bewust dat hart-en vaatziekten de belangrijkste oorzaak van overlijden is en zelfs als ze dat wel zijn, dan hebben ze geen idee wat het effect van bepaalde risicofactoren is op de ziekte. Dit op zijn beurt leidt tot minder agressieve aanpassingen in de levensstijl en de naleving van secundaire preventie. Campagnes zoals de 'Dress Red Campaign' (American Heart Association) hebben bewezen het bewustzijn te vergroten en de herkenning van symptomen te verbeteren. Ook in Nederland nam na de 2010-campagne van de Hartstichting het bewustzijn toe van 25% tot 50% in een maand! Hoewel dit een prachtig resultaat is, is bewezen dat herhaling van het bericht de enige manier is om dit bewustzijn te behouden.

Het opnemen van sekseverschillen in het medisch curriculum is een uitstekende manier om het bewustzijn te vergroten en een grotere nadruk zou moeten worden gelegd op het implementeren hiervan in Nederland. Dit zou in overeenstemming zijn met toonaangevende universiteiten zoals Harvard en het Karolinska Instituut die onlangs 'Gender Medicine" afdelingen geopend hebben .

Zodra de bovengenoemde punten zijn aangepakt, kunnen sekse-specifieke (of liever patiënt-specifieke) richtlijnen danwel besluitvormingsinstrumenten worden opgezet die zullen leiden tot een betere gezondheidszorg in het algemeen, niet alleen voor vrouwen maar ook voor mannen.

Chapter 9

Acknowledgements / Dankwoord
List of publications
PhD-portfolio
About the author

Acknowledgements / Dankwoord

And finally for the most fun part of this thesis, the Acknowledgements. This is the part of the thesis which will probably be read the most, but which was definitely the most difficult part to write. It will be a mix ('mengelmoes') of English, Dutch and even some Spanish ;)

Because many people have contributed to the realization of this thesis, I know I will not be able to thank everybody. I would though at least like to thank the following people who either supported me directly with the projects described in this thesis or indirectly by keeping me going.

My promotor, Professor Hunink. Dear **Myriam**, I think we conquered a more than normal amount of trials and tribulations over the last 5 years, which makes me even more proud to stand before you today. I am so grateful for having had the opportunity to be educated and have worked with you and your group. You have been more to me than mere my professor. I want to thank you for your patience with me when I was doing clinical work and your trust in me that I would complete my PhD. Guess you were right!

Mijn copromotor, Dr. van Sambeek. Beste **Marc**, menig maal raadde jij me aan om mijn uitspraken in artikelen af te zwakken en dat advies zal ik ook hier ter harte nemen; Ik vind je fantastisch!! Vanaf dag één heb je me de ruimte gegeven dit project eigen te maken, maar als ik je nodig had was je er altijd. Bedankt dat je me naar Eindhoven hebt gehaald en me alle mogelijkheden hebt geboden om mezelf te ontplooien. Je bent zowel op professioneel als persoonlijk vlak een voorbeeld voor me. Onze gesprekken onder het genot van lunch in *Usine* en je eindeloze vertrouwen hebben veel voor me betekend. Ik zal altijd met veel plezier terugkijken op onze samenwerking en hoop dat we ook in de toekomst elkaar blijven tegenkomen.

Leden van de kleine commissie, hartelijk bedankt voor het beoordelen van mijn manuscript en uw bereidheid zitting te nemen in de commissie. Ik had me eerlijk waar geen leukere commissie kunnen wensen!

Prof. dr. Maas, beste **Angela**. Ik heb je vorig jaar op de Vaatdagen mogen ontmoeten tijdens de sekseverschillen sessie (met Midas Dekkers), maar wat was ik onder de indruk van jou! Bedankt voor je adviezen en het 'sparren' tijdens mijn bezoek aan Nijmegen, ook al leverde dat meer vragen op dan antwoorden. Ik denk dat we nog heel wat te doen hebben om sekseverschillen op de kaart te zetten. Hopelijk kunnen we daar samen aan werken.

Prof van der Lugt, beste **Aad**. Al vijf jaar kom ik je vooral tegen op de 'social events' van de Radiologie, en altijd is het gezellig! Even leek het erop dat we ook gingen samenwerken, maar helaas nam mijn onderzoek weer een andere wending. Ik wil je bedanken voor je luisterend oor en je adviezen. Jij begrijpt me als geen ander, gezien we dezelfde teleurstelling hebben moeten verwerken. Maar vandaag maken we er een feestje van!

Prof. dr. Verhagen, beste **Hence**. Ik moet toegeven dat ik in het begin de kat uit de boom heb gekeken. Voor mijn gevoel had je namelijk mijn promotietraject redelijk in de war gegooid. Maar al snel kwam ik er achter dat je een leuke vent bent! Ik heb met plezier met je samengewerkt (hetzij erg kort) en ook jou wil ik bedanken voor ons gesprek laatst. Ik weet nog

dat ik je kamer verliet met zoveel opties dat ik bijna niet wist waar te beginnen!

Dr. Hendriks, beste **Joke**, wat geweldig om ook jou in mijn commissie te mogen hebben! Jij bent dé specialist als het om de carotis gaat. Heerlijk om met jou te brainstormen over sekseverschillen bij de behandeling van de carotis stenose en hoe we deze het beste zouden kunnen onderzoeken. Jij kon tevens alle belangrijke artikelen en informatie zo uit je computer toveren. Heerlijk ook dat je zo dichtbij zat en je deur altijd voor me open stond, of het nu over mijn onderzoek ging of iets compleet anders. Jij bent hét voorbeeld dat vrouwen uitstekende chirurgen kunnen worden.

Prof dr. Oscar Franco en Dr. Hanneke Takkenberg, bedankt voor uw bereidheid om als opponent zitting te nemen in de grote commissie

Lieve **ART-groep:** In de 5 jaar dat ik onderdeel heb uitgemaakt van deze groep heb ik vele mensen zien komen en gaan. Enkele mensen die ik in het bijzonder wil noemen:
Ylian, bedankt voor die eerste zomer, het me wegwijs maken op de afdeling, het heerlijk over eten kunnen praten en de vriendschap die we erop na gehouden hebben. **Ineke**, bedankt voor de vele gesprekken en koffiemomentjes, ik vind het bewonderenswaardig hoe jij hart voor je onderzoek hebt en hoe jij volhoudt. **Bart**, bedankt voor de vele discussies en hulp bij mijn projecten, ook voor het artikel dat we samen hebben geschreven, maar vooral voor de gezelligheid tijdens en buiten werk. Van Duffy in Paradiso tot North Sea Jazz in Rotterdam. **Bob**, jij bedankt voor je geduld als ik iets weer eens niet begreep (vaak op statistisch gebied!). Verder kan ik altijd heerlijk met je praten over van alles en nog wat en verzorgde je de nodige ontspanning. Kan nog steeds niet geloven dat ík degene was die jou voor het eerst meenam naar de FRANK borrel. Wat is er veel veranderd sindsdien! **Sandra** wil ik bedanken voor de jaarlijkse uitjes naar de Vaatdagen, heerlijk naar keiharde Amy Winehouse luisteren en altijd in de file op de terugweg.
Farzin, Edwin, Aletta, Raluca, Suman, Rachel en **Erica** wil ik ook bedanken voor de gezelligheid danwel op de kamer danwel tijdens de legendarische kerst-ART meetings.

Andere collega's van de 21ste wil ik bedanken voor de gezelligheid en het opzetten van de zgn. 21ste borrels, in het bijzonder de leden van de BIGR groep (**Renske, Fedde, Marius, Esben** en natuurlijk grote baas **Wiro**)

Chirurgen en collegae van de afdeling Heelkunde van het Erasmus MC wil ik bedanken voor het mij bijbrengen van de basis van de chirurgie. Vooral mijn tijd op 8Noord heeft mij een betere dokter gemaakt. In het bijzonder wil ik **Prof Tilanus**, Dr. **Bas** Wijnhoven en Dr. **Eric** Belt bedanken.

Chirurgen en collegae van de afdeling Heelkunde van het Ikazia Ziekenhuis hebben een allround assistent chirurgie van mij gemaakt. Het was een harde leerschool, maar ik ben er wijzer en sterker van geworden. Anne Marie en Ted, bedankt voor het stimuleren van mijn passie voor vaten. Verder wil ik ook de 'gipskamer', de 'IC', de 'SEH', de radiologie, Dr. Niers en de arts-assistenten van de Interne bedanken voor de gezelligheid, vooral tijdens de vele diensten.

My **RSM** years have left me with friends for life spread all over the world. Three classes (MBA04, MBA05, and MBA06) of around 150 students each are far too many people to thank personally, so below some I just had to.

Arindam: you are everything I expect a big brother to be, annoying as hell at times but we also have such fun and it's great to know that you always have my back. I'm so delighted that you are here today! **Carolina**; how I miss not having you right across the water and our weekly gym sessions. The Maas has been replaced by the Atlantic Ocean, but we manage nonetheless. Whether it be Paris or Buenos Aires we still find each other. Thanks for BA and making me part of your family (Irene y Eduardo, mis padres argentinos, gracias por todos!) Other people who have enriched my life in one way or another and I don't see as much as I would like to are **Sandra Leon**, **Cem Altıntaş**, **Sergio Sposato** and **Tore Rye**. I'm so fortunate to have you all in my life.

Argentina 2012; Querida Argentina, pais que quiero tanta y me dio tan buenos recuerdos, hasta pronto! Dear **Nicole**, **Marie** and **Mikkel**, what a coincidence to meet each other so far from home, we all fell in love with the beautiful city and country. I suggest a reunion in Buenos Aires (although New Mexico or Denmark sounds fun too). **Marcos**, querido amigo argentino, gracias por abrirme los ojos. Beso grande y mucha suerte con sus decisiones, nos vemos!!

Ka'tje en Jen. In 2001 zijn we samen aan Geneeskunde begonnen, meer dan 10 jaar later nog steeds in Rotterdam, maar belangrijker nog, nog steeds vriendinnen!! Hoelang we allemaal nog in Rotterdam blijven is de vraag, maar wij vinden elkaar overal ter wereld wel. Bedankt voor de vele lunches, etentjes, feestjes, kite-surf sessies, pleegkatten en het feit dat ondanks dat we elkaar soms een tijd niet zien ik weet dat ik altijd op jullie kan rekenen. Op heel veel meer van dit moois!!

Geert en Erlijne: Geert, jou ken ik alweer 25 jaar lang en afgezien van 1 jaar 'ruzie' op de middelbare school zijn we altijd vrienden gebleven en doen we vanalles samen. Van hardlopen in Ommoord en avondritjes naar de Mac (waarom ook alweer?!) tot weekendjes Rome en Zeeland, museumbezoeken en heerlijk eten in onze gezamenlijk favoriete restaurant, het Wereldmuseum. Erlijne, wat ben jij een aanwinst! Ik vertel Geert regelmatig dat hij in zijn handjes mag knijpen met jou ;) Ik zie jou niet alleen als de vriendin van Geert, maar vooral als een vriendin van mij! Heel benieuwd waar je werk jullie gaat brengen. Een ding staat vast: ik kom op bezoek!

Lieve **Sab**, al 27 jaar vriendinnen en wat hebben we veel meegemaakt en gezien. Te veel om op te noemen eigenlijk, maar of we nu door diepe dalen gaan (liefdesverdriet danwel New Delhi ;)) of ergens op een eiland zitten (Curaçao danwel Schiermonnikoog) er wordt ALTIJD veel gelachen en we zijn NOOIT uitgepraat. Ik kan niet wachten op onze 30ste Birthday party, het wordt GROOTS!!!

Mijn paranimfen maar vooral vriendinnen voor het leven 'Genders' en 'Drex'.
Lieve **Tessa**, yep, ik vond je in het begin maar rrrrraar. Maar gelukkig trok je snel bij ;). Jij was mijn 'roomie' bij uitstek zowel in letterlijke zin op de 21ste als in figuurlijke zin, want naast werk gingen we ook samen 'heerlijk' naar de sportschool of hardlopen, boodschappen doen, koken (yumyum), winkelen (Breda was geen succes, Antwerpen al een heel stuk beter), weekendjes weg en stappen!! Het mooie is dat de promoties er nu op zitten en we alleen nog maar de leuke dingen samen gaan doen. Je bent als vriendin een rots in de branding en ondanks dat je 100 jaar jonger bent dan ik, bewonder ik je zelfdiscipline en wijsheid. Ik kan nog het een en ander van je leren ;)

Ik ben heel benieuwd waar we over een paar jaar zitten, maar ik maak in ieder geval voor jou en **Aaron** de uitzondering om naar Amerika te komen, om die tuin met dat witte hek, die bbq, die schommel en die ..... te zien!!
Lieve **Roos**, al 11 jaar vriendinnen en op de een of andere manier komen we elkaar professioneel ook steeds tegen. Eerst een paar jaar lang dagelijks 'werkoverleg' in de koffiebar tijdens ons promotieonderzoek en vervolgens dit voort kunnen zetten tijdens onze dagelijkse 'intercollegiale overleggen' in het Ikazia Ziekenhuis. Maar buiten werk doen we toch echt de leukste dingen. New York, onze jaarlijkse Parijs tripjes en dit jaar Argentinië en Rio de Janeiro. Ik weet niet precies meer wat de stand is maar wat hebben we daar onder het genot van menig wijntje het een en ander afgehuild maar vooral gelachen! Wat ben ik blij dat nu ook mijn promotie er op zit en dat jij hier naast me staat.

My family abroad, dear Elche, John, Simone and Jonathan, dear Carla, Tom, Kim and Guy, even though we see each other very infrequently, when we do it is as if time stood still! You are often in my thoughts and I love you all very much.

My 2nd family, the **Jacobs family**, dear Veronica & Leon, dear Erica & Andrew and Ben, Bas and Nina, dear Marika & Andrew and Alex and Adam, and last but definitely not least, dear Leon-Eric & Alida. How I love spending time with you guys whether in Namibia, Rooiels, Cape Town, East London or the Hogsback. I can't wait for the kids to grow up and come visit their 'aunt' in Europe. The parents and grandparents are of course also more than welcome!

Dear '**Aunties**', you have done so much for me and still do. You looked after me while I lived with you guys during my surgery internship because I was too exhausted to cross the Erasmus Bridge. We also had fantastic holidays in France, either at mom's house or in Normandy. Then of course the many dinners followed by serious loud music playing and dancing through the house. Thanks for everything and here is to many more fun times together.

Dear **mom**, I know that we don't always see eye to eye, but that's probably because we are more alike than we think, or like to acknowledge ;). Thanks for giving me all the possibilities in the world even when times were hard. Thanks also for your unconditional support, even though you did not always understand exactly what I was doing, without your support I would not be where I am today. I know we often discuss which characteristics I got from you and which from dad, but one thing is for sure; you taught me how to party!
Beste **Herman**, bedankt voor je jarenlange steun en het verzorgen van de mooiste bolides om in te rijden en nogmaals excuses voor mijn puberteit ;). **Scally Wags** and **Honey Bunny**, your older sister loves you!

Dear **dad**, three years later than you, but I made it! I had many doubts but you never had any (or at least didn't show them) Thanks for showing me the world, accompanying me to seriously strange places such as Merthyr Tydfil, looking after me when I was struck by the Noro-virus and picking up the pieces when I didn't get the job. I am so looking forward to our combined 100th anniversary and think we should celebrate it by going back to the Kruger for another safari walking trail, because that was pure magic. Thanks for your guidance and everlasting confidence in me.

List of publications

Grootenboer N, Bosch JL, Hendriks JM, van Sambeek MR. Epidemiology, aetiology, risk of rupture and treatment of abdominal aortic aneurysms: Does sex matter? Eur J Vasc Endovasc Surg. 2009 Sep;38(3):278-84. Epub 2009 Jun 21. Review.

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 Aug;97(8):1169-79. Review.

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Grootenboer N , Hunink MG, Hoeks S, Hendriks JM, van Sambeek MR, Poldermans D. The impact of gender on prognosis after non-cardiac vascular surgery. *Eur J Vasc Endovasc Surg.* 2011 Oct;42(4):510-6. Epub 2011 Jul 26.

Ferket BS, **Grootenboer N,** Colkesen EB, Visser JJ, van Sambeek MR, Spronk S, Steyerberg EW, Hunink MG. Systematic review of guidelines on abdominal aortic aneurysm screening. *J Vasc Surg*. 2012 May;55(5):1296-1304. Epub 2011 Feb 16. Review.

Grootenboer N, Hunink MG, Hendriks JM, van Sambeek MRHM, Buth J. Gender differences in 30-day and long-term outcomes after endovascular repair of abdominal aortic aneurysms: Results from the EUROSTAR study. Submitted.

Grootenboer N, Hunink MG, van Sambeek MR, Hendriks JM, Kennedy KF, House JA, White CJ. Sex differences in short-term outcome after carotid endarterectomy or carotid angioplasty and stenting: The CARE-Registry. Submitted.

PhD Portfolio

Name PhD student:	Nathalie Grootenboer
Erasmus MC Department:	Epidemiology and Radiology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	November 2007 – November 2012
Promotor(s):	Prof. dr. M.G. Myriam Hunink
Supervisor:	Dr. Marc R.H.M. van Sambeek

1. PhD training

	Year	Workload (Hours/ECTS)
Research skills		
Master of Science in Health Sciences specialisation Clinical Epidemiology, NIHES, Rotterdam	2007 - 2009	120 ECTS
Seminars and workshops		
Gender Medicine 2010, EUGIM & Margherita von Brentano Summer School, Berlin, Germany	2010	30 hours
Presentations		
Abdominal Aortic Aneurysms. Gender differences in Disease Presentation Symposium, Erasmus MC Rotterdam	29 jan 2008	1 ECTS
Invloed van Geslacht op Mortaliteit na Behandeling van het Aneurysma van de Abdominale Aorta: Een systematisch literatuur onderzoek", Vaatdagen, Noordwijkerhout	7 april 2008	1 ECTS
Gender differences in short-term outcome after carotid revascularization: The CARE-registry" American Heart Association Scientific Sessions 2009, Orlando, Florida, USA	16 Nov 2009	1 ECTS
The impact of gender on prognosis after non-cardiac vascular surgery, EUGIM & Margherita von Brentano Summer School, Berlin, Germany	22 Sep 2010	1 ECTS
Komt een vrouw bij de vaatchirurg, Vaatdagen, Noordwijkerhout, The Netherlands	19 april 2011	1 ECTS

(Inter)national conferences		
Vaatdagen, Noordwijkerhout, the Netherlands	2008	1 ECTS
Vaatdagen, Noordwijkerhout, the Netherlands	2009	1 ECTS
American Heart Association, Scientific Sessions 2009, Orlando, Florida, USA	2009	1 ECTS
Vaatdagen, Noordwijkerhout, the Netherlands	2010	1 ECTS
Vaatdagen, Noordwijkerhout, the Netherlands	2011	1 ECTS
Chair		
Chair of the "Sexe verschillen in de vaatpatiënt': bestaat dit en wat betekent dit" session at the Vaatdagen, Noordwijkerhout, the Netherlands	2011	-

2. Teaching

	Year	Workload (Hours/ ECTS)
Lecturing		
Teaching 5th year medical students about " Evidence Based Radiology" during their Radiology internship at the Erasmus University Medical Center, Rotterdam, the Netherlands	2008-2011	40 hours
Supervising practicals and excursions, tutoring		
Teaching 4th year medical students during; " Sensitivity, specificity, predictive values, Bayesian revision, likelihood ratios and ROC curves", " Medical decision-making + no treat-test/ tes- treat thresholds, and "How to read a scientic paper?"	2007-2010	32 hours

About the author

Nathalie Grootenboer was born on 5 February 1983 in Jeddah, Saudi Arabia. She was born to Leslee Deacon (South Africa) and Jan Grootenboer (The Netherlands) who happened to be in Saudi Arabia performing geological surveys.

At the age of two she moved to Rotterdam, the Netherlands where she received all her education up till now. She received her primary education at the Albert Plesman School and her secondary education at the Marnix Gymnasium, from which she graduated in 2001. In the same year she started studying Medicine at the Erasmus University. During her rotations (4th year) she discovered the wonderful world of vascular surgery and after obtaining her medical degree in October 2007 she embarked on a PhD in this field. She started by entering the Master of Science program in Clinical Epidemiology at the Netherlands' Institute for Health Sciences (NIHES), from which she graduated in 2009.

Nathalie worked on her PhD-thesis at the departments of Epidemiology and Radiology at the Erasmus University Medical Center, under the supervision of Prof dr. M.G. Myriam Hunink and at the department of Surgery at the Catharina Hospital Eindhoven, under the supervision of Dr. Marc R.H.M. van Sambeek. Her work looks at gender differences in the presentation of cardiovascular disease and clinical outcome after vascular surgery, focusing on abdominal aortic aneurysm repair and the treatment of carotid artery stenosis. During her research period she also worked at the out-patient clinic of the Catharina Hospital Eindhoven to retain her clinical touch and preserve the clinical relevance of her work. In November 2010 she started working full-time at the department of Surgery at the Erasmus MC and in June 2011 at the department of Surgery at the Ikazia hospital, also in Rotterdam.

In June 2012 she ventured off to Argentina, where she travelled extensively, brushed up on her Spanish and finished writing her PhD.

Currently, Nathalie is in the process of finally leaving her 'much loved' Rotterdam for a new adventure abroad.