Maria Johanne Skjolde Fostervold

Re-intervention according to standard EVAR: Incidence and gender differences.

Review of operations at St Olav's hospital the last 10 years (2010-2020)

Graduate thesis in Medisin
Supervisor: Linn Nyrønning
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June 2023

Graduate thesis

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Norwegian University of Science and Technology
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Abstract

Objective: Female gender has been associated with higher 30-day mortality, increased rates of complications, and re-interventions compared to men after endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA). The evidence is scarce regarding gender difference in long-term survival and outcome. The aim of this study was to investigate the overall outcomes and gender differences in re-interventions and long term survival following conventional EVAR over the past 10 years at St. Olavs hospital.

Method: This quality improvement based retrospective study included 496 patients (17,5% women) who underwent conventional EVAR for intact AAA. Data are based on the Norwegian Vascular Surgery Registry (NORKAR) and the local vascular surgery registry (NORKAR lokalregister), in addition to medical record review. Variables including age, comorbidities, AAA diameter, indication and type of re-interventions, as well as survival and outcome, were collected and analysed to assess gender difference and overall outcomes. The primary end-point was re-intervention, while survival served as a secondary end-point. Pearson's Chi-square test, Fishers exact test, and the student's T-test were used to test difference between categorial and continuous variables. The impact of re-interventions and survival were assessed using the Kaplan-Meier method. Hazard ratios (HR) with 95% CI were calculated as estimates of relative risk in both univariable and multivariable Cox proportional hazard regression models.

Results: During a median follow-up period of 4.9 years, a total of 83 cases (12.6% women) of re-intervention following EVAR were observed. There were no significant difference in comorbidities, body mass index (BMI) and smoking status between the genders, and both men and women were of similar age (mean age; men 74.6 years, women 75.1 years). In the multivariable cox analysis, women had a 37% reduced hazard of re-interventions compared to men, although the result did not reach statistical significance (*P*=.48). There was a non-significant reduced risk of mortality among patients who underwent re-interventions (HR 0.84), and women had a non-significant 22% higher hazard of mortality compared to men. Women had an significantly smaller preoperative AAA diameter (*P*=.003), and the AAA diameter was also associated with an increased risk of mortality (*P*=.002).

Conclusion: A total of 83 (16.7%) patients required re-intervention after undergoing conventional EVAR. Of these, 72 (17.6%) were men and 11 (12.6%) women. Our results point towards a reduced risk of re-interventions for women compared to men, and that female gender is associated with an increased risk of mortality, even after adjusting for established risk factors.

However, the results did not reach statistical significance. It is possible that this was due to limited statistical power in our study.

Sammendrag

Bakgrunn: Kvinnelig kjønn har blitt assosiert med høyere 30-dagers dødelighet, samt flere komplikasjoner og re-intervensjoner sammenlignet med menn etter endovaskulær behandling (EVAR) for abdominalt aortaaneurisme (AAA). Få tidligere studier har undersøkt kjønnsforskjeller for utfall og langtidsoverlevelse. Målet med studien var å undersøke overordnet utfall og kjønnsforskjeller ved re-intervensjon og langtidsoverlevelse etter konvensjonell EVAR for intakte AAA gjennomført de siste 10 årene ved St. Olavs hospital.

Metode: I denne retrospektive kvalitetsstudien inkluderte vi 496 pasienter (17.5% kvinner) som gjennomgikk konvensjonell EVAR for intakt AAA. Data er hentet fra Norsk karkirurgisk register (NORKAR), i tillegg til journalgjennomgang. Variabler inkludert alder, komorbiditeter, AAA-diameter, indikasjon for og type re-intervensjoner, samt overlevelse og resultat, ble samlet inn og analysert for å vurdere kjønnsforskjeller og generelle utfall. Det primære endepunktet var re-intervensjon, mens overlevelse var det sekundære endepunktet. Pearson's Chi-square test, Fishers exact test og Student's T-test ble brukt for å teste forskjeller mellom kategoriske og kontinuerlige variabler. Overlevelsesanalyse og effekten av re-intervensjoner ble vurdert ved hjelp av Kaplan-Meier metoden. Hazard ratio (HR) med 95% konfidensintervall ble beregnet som estimater for relativ risiko i både univariable og multivariable Cox proporsjonal regresjonsmodeller.

Resultat: I løpet av en median oppfølgingstid på 4.9 år ble det observert totalt 83 tilfeller (12.6% kvinner) som gjennomfikk re-intervensjoner etter EVAR. Det var ingen signifikant forskjell i komorbiditeter, BMI eller røykestatus mellom kjønnene, og menn og kvinner var av tilnærmet like gamle (gjennomsnittlig alder; menn 74.6 år, kvinner 75.1 år). Justert for kovariater, så hadde kvinner 37% redusert hazard for re-intervensjoner sammenlignet med menn, men resultatet var ikke statistisk signifikant (P=.48). Vi fant en HR på 0.84 for risiko for død blant pasienter som gjennomgikk re-intervensjoner vs. ikke re-intervensjon, uten at resultatet var statistisk signifikant. Videre hadde kvinner hadde 22% høyere hazard for mortalitet sammenlignet med menn, men funnet nådde ikke statistisk signifikans. Kvinner hadde en signifikant mindre AAA-diameter (P=.003), og diameter i seg selv var assosiert med økt risiko for dødelighet (P=.002).

Konklusjon: Totalt 83 (16.7%) pasienter hadde behov for re-intervensjon etter konvensjonell EVAR i denne studien. 72 (17.6%) av pasientene var menn og 11 (12.6%) var kvinner. Våre funn peker i retning av at kvinner hadde lavere risiko for re-intervensjon sammenlignet med

menn, samt at kvinnelig kjønn var assosiert med høyere risiko for død, selv etter justering for etablerte risikofaktorer. Disse funnene nådde likevel ikke statistisk signifikans, noe som kan være relatert til begrenset statistisk styrke i studien.

Background

Abdominal aortic aneurysm (AAA) is a localised dilatation of the abdominal part of the aorta. An AAA is defined as an aortic widening with at least 50% increased diameter compared to a normal diameter, usually corresponding to a diameter of at least 30 mm or more[1]. AAA has a prevalence of 1-3% in the adult population[2] and the prevalence increases with age. The disease is 4-6 more common among men than women[1-4], and affects particularly men older than 60 years[5]. High age, male gender, smoking, heredity, hypertension and coronary artery disease are established as risk factors for developing AAA[1]. Smoking is considered the strongest risk factor for AAA with a higher association in women than men[6].

Most AAAs are asymptomatic and are incidentally detected. However, AAA is a potentially life-threatening disease and a ruptured AAA has a mortality of more than 75%, where approximately 50% die before they reach the hospital[1]. The risk of rupture increases with the diameter of the aneurysm[1, 5]. To prevent rupture, elective surgery is recommended in AAAs measuring 5 cm in women and 5.5. cm in men[7]. Women have about four times higher risk of rupture compared with men, and rupture occurs at smaller diameters[3, 6]. Female gender has also been associated with worse outcome after both elective and urgent surgery compared to men[3].

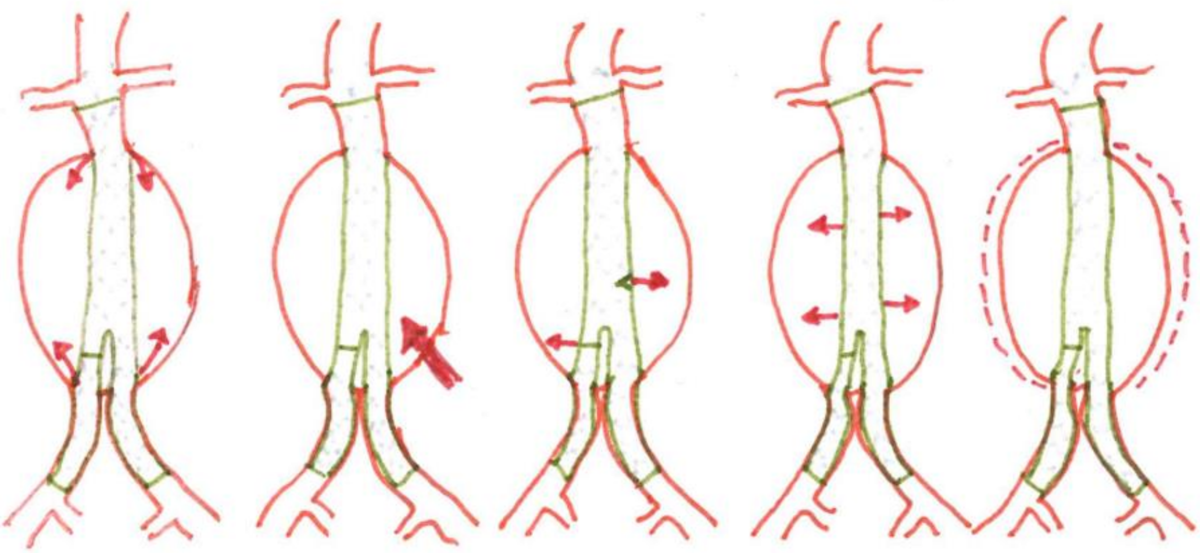
The only curative treatment for AAA is surgery. If the aneurysm is small, there is a smaller risk of rupture, and conservative treatment with monitoring, blood pressure control and cholesterol-lowering drugs such as statins is usually recommended. When the threshold is reached, AAAs can be treated surgically with Endovascular aneurysm repair (EVAR) or open repair (OAR). Open repair is a major operation where the surgeon opens the abdomen to access the aorta directly, and then clamp the aorta before they open the aneurysm and sew in a prosthetic graft[8]. EVAR was developed in 1991 by Parodi et al. as a minimally invasive alternative to open abdominal surgery[9, 10]. In EVAR a stent graft is introduced into the aorta through the femoral arteries, and positioned across the aneurysm with its proximal and distal limbs attached to the normal portion of the aorta and iliac arteries. The procedure aims to prevent enlargement and rupture of the AAA by excluding the aneurysm from the circulation[9]. The European guidelines grade open aortic repair as a high risk intervention, whereas EVAR is graded as an intermediate risk intervention[6]. EVAR results in less blood loss, requires a shorter hospital stay and faster recovery[11].

Long-term survival following elective AAA repair is influenced by several factors, including patient age at the time of repair, gender and comorbidities[1, 5, 6]. Elective EVAR repair has demonstrated lower 30-day mortality and morbidity rates compared to OAR in both male and female patients[2, 3, 5]. On the other hand, studies have indicated that the initial survival benefits following elective EVAR gradually decreases over time[5]. While the long-term mortality related to the aneurysm is low, it has been associated with secondary rupture of the aneurysm sac[5, 12]. Additionally, EVAR is associated with various complications such as endoleaks (leakage of blood outside the stent graft), stent graft migration, occlusions/thrombus, infection and stent fracture[12, 13]. These complications can lead to a need of re-interventions [12, 14]. Although mortality rates following EVAR are generally low, the occurrence of re-interventions and late complications appear to be more common[15].

Endoleaks are the most commonly observed complications following EVAR, responsible for approximately 70% of the re-interventions[12]. These leaks occur in approximately 25% of patients who have undergone successful EVAR[16]. Endoleak refers to the leakage of blood outside the lumen of the stent graft into the aneurysm sac, potentially leading to expansion of the aneurysm[16]. To detect potential complications such as endoleaks, patients undergoing EVAR are enrolled into regular follow-up programs[5, 12]. CTA is often the modality of choice for periodic follow up post EVAR, and is regarded as the gold standard for surveillance[6, 16]. There has been an increased trend in use of ultrasound for this purpose in recent years[17].

Endoleaks can be classified as primary, present at the time of repair, or secondary, occurring after an initially negative imaging[6]. There are five types of endoleaks based on their location, as shown in figure I[16]. The presence of endoleaks are important to detect as they potentially can increase the risk of secondary aneurysm rupture due to the pressure the aneurysm sac is exposed to. The management of endoleaks depends on their underlying cause[6]. Approximately half of the endoleaks, mainly type II, resolve spontaneously without requiring re-intervention[6]. Type II endoleak can be detected early after EVAR or occur later during follow-up. Type I endoleak is associated with high risk of aneurysm rupture, and should be treated promptly with the aim of excluding the aneurysm from pressurised circulation[6]. Type III endoleaks expose the aneurysm to direct aortic pressure with subsequent risk of rupture, just as type I endoleaks[6]. Therefore, immediate re-intervention is recommended, primarily by partial or total endovascular relining[6].

Figure I: The different types of endoleaks. Sketch by M.J.S. Fostervold.



Type I

Proximal or distal graft attachment site leaks

Type II

Retrograde flow into the aneurysm sac from aortic side-branches such as the lumbar or inferior mesenteric arteries

Type III

Caused by a defect in the graft either due to a fabric tear or disconnection of modular overlap

Type IV

Graft wall porosity

Type V

Increase in maximum aneurysm diameter with no identifiable endoleaks

Limb occlusions or kinking are other common complications after EVAR, requiring re-intervention in 1.4-8% of patients[6]. Risk factors for limb occlusion include iliac artery angulation, tortuosity, calcification and stent graft oversizing ≥ 15% in the iliac landing zone[6]. Approximately one third of stent graft limb occlusions are noted within the first 30 days post-EVAR, and about half of the patients present with symptoms of acute limb ischaemia[6]. Re-intervention is required for symptomatic limb occlusion or as a preventive intervention. Treatment includes graft thrombectomy, stenting in the presence of kinking, extra-anatomical bypass or endovascular thrombolytic treatment.

Migration is defined as movement of the stent graft > 10 mm compared with fixed anatomical landmarks or any migration resulting in symptoms or reinterventions[6]. Stent graft migration was a common complication with the early generation stent grafts, but the prevalence has decreased due to the improvements in modern stent grafts[6]. Migrations should be treated as it may result in type I endoleak, stent graft separation, kinking and graft occlusion. Risk factors for proximal migration are short proximal fixation, angulated neck, large aneurysm size and stent graft type. Migration may also occur at the distal landing zone of the stent graft due to changes in aneurysm morphology or shrinking of the aneurysm sack after EVAR[6].

The five year re-intervention rate after EVAR has been reported to be between 16-33%[11]. Some studies have reported that patients who undergo re-interventions following EVAR have higher cumulative 5-year survival rates compared to patients who do not undergo re-interventions[15]. These findings suggest that the occurrence of re-interventions may be associated with improved long-term survival outcomes.

Previous studies indicate that women who undergo EVAR have higher 30-day mortality, higher rates of complications and re-interventions compared to men [2-4, 18]. Although there have been an increasing number of reports analysing gender differences in AAA treatment over the last years, data on long-term survival and outcome in women remain scarce[4] and further investigation is needed.

Material and Methods

Aim and hypotheses

The aim of this master's thesis was to investigate total outcome and gender differences in re-interventions and long term survival following conventional EVAR over the past 10 years at St. Olavs hospital. The following hypothesis was investigated:

- Women have a higher rate of re-interventions following conventional EVAR compared to men.
- Women undergoing re-interventions have reduced long term survival compared to men.

Study design and population

This study is a quality improvement based retrospective study of patients who received conventional EVAR for elective AAA at St. Olavs hospital in Trondheim in 2010 through 2020.

We identified all patients who received conventional EVAR for intact AAA at St. Olavs hospital the last 10 years, through the Norwegian Vascular Surgery Registry (NORKAR). From 2010 through 2014, the data was only available from a local vascular surgery registry (NORKAR lokalregister), and contained a total of 126 patients.

A total of 545 patients underwent conventional EVAR, of these 496 were included in the study. 29 patients were excluded due to the presence of ruptured AAA, while 10 patients were excluded due to erroneous registration. Additionally, 6 patients who underwent EVAR as an re-intervention were also excluded, and 3 patients with suprarenal aneurysms were excluded. Inclusion and exclusion criteria are shown in Table 1.

Table I: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
ICD-10 code I71.4	Ruptured AAA (ICD-10: I71.3)
Conventional EVAR for intact AAA	Non-conventional EVAR

Follow-up and endpoints

The primary end-point was re-intervention, whereas survival was evaluated as a secondary end-point. Median follow-up time overall was 4.9 years (min-max, 0.02-13.07 years).

Study variables

Information regarding the following variables was collected from NORKAR: age, gender, date of birth, smoking status (never, ever), comorbidities (yes/no) (hypertension, heart disease, respiratory disease, diabetes, kidney failure, prior vascular surgery, BMI,), ASA-grade (mild systemic disease, severe systemic disease, severe life-threatening systemic disease), AAA diameter before surgery, presentation (elective, urgent non-ruptured), dates of surgery and re-intervention, type of re-intervention (coiling, relining, explantation, femoro-femoral-crossover bypass, percutaneous transluminal angioplasty (PTA), thrombectomy), indication for re-intervention (endoleaks, migration, infection, occlusions/thrombus), results of re-interventions (successful, need for additional measures), postoperative complications, blood loss and survival/outcome.

Data from the local registry (2010 to 2014) lacked information about some of the variables. This applied for the variables BMI and ASA-grade, and other variables that we decided not to include due to the amount of missing (i.e. use of antithrombotic medications before and after conventional EVAR). Smoking status was included in both registries, but with different variables. In the national NORKAR registry the smoking variable is encoded as never, current, and former smoker, whereas the local register only distinguished between non-smokers and smokers. In addition, patients who had ceased smoking for at least 5 years were categorized as non-smokers. To account for the inconsistency, we included the smoking variable in our current study as never/ever.

Information from medical records was needed to sufficiently identify re-interventions and survival data. Supplementary information was therefore collected from patient charts and the hospital register at St. Olavs hospital.

Statistical analysis

Descriptive statistics was analysed using frequencies for the categorical variables, and by mean and median for continuous variables. Pearson's Chi-square test and Fishers exact test were used to test difference between categorial variables, whereas the student's T-test was used for continuous variables. Histograms were constructed to evaluate continuous variables, and the variables were considered normally distributed. The Kaplan-Meier method was used to analyse overall survival and survival differences between genders, as well as the impact of re-interventions. The log-rank test was used to compare gender differences and survival rates between patients who underwent re-intervention and those who did not. Hazard ratios (HR) with 95% CI for survival were calculated as estimates of relative risk in univariable and multivariable Cox proportional hazard regression models. Covariates included in the multivariable model were gender, age, hypertension, heart disease, respiratory disease, smoking, AAA diameter, presentation and reintervention. Statistical significance was assumed if $p < .05$. All statistical analyses were preformed using SPSS IBM, version 28.

Ethical considerations

This study is classified as a clinical quality improvement study. The project was approved by the Research Council at the Department of Surgery. In addition, we submitted an application for an additional evaluation by the regional ethics committee who approved the study (REK nr 452363).

Results

Characteristics of the study population

A total of 496 (91%) patients in our study population underwent conventional EVAR for intact AAA at St. Olavs hospital between 2010-2020. Of these 409 (82.5%) were men and 87 (17.5%) were female (*P*< .001). Baseline characteristics for men and women are shown in Table II. There were no significant differences in comorbidities between men and women. The most common comorbidities in both genders were hypertension, heart disease, respiratory disease, diabetes and kidney failure. Moreover, women and men were of similar age (mean age; men 74.6 years, women 75.1 years, *P*=.52), and there were no differences in mean BMI in men and women before EVAR (mean BMI; men 27.4, women 26.9, *P*= .68). In both genders there were more smokers than those who had never smoked, 271 (66.3%) men and 57 (65.5%) women, but the difference was not significant (*P*=.79).

In total, 493 (88.5%) patients presented for elective repair and 57 (11.5%) for urgent non-ruptured aneurysms. Women had a significantly smaller mean aneurysm diameter compared with men (mean AAA diameter (mm); women 58.8 mm, men 62.5 mm, *P*= .003).

Both men and women had a similar operative blood loss (mean (L); men 0.28 L, women 0.22 L, *P*=.10), and there were no significant difference in the presence of any postoperative complication (men, 15.9%, women, 19.5%, *P*= .43).

Table II: Baseline characteristics for men and women

Characteristics	Total	Men	Women	*P*-value
Gender, n (%)	496	409 (82.5)	87 (17.5)	< .001
Age (years), mean (range)	74.7 (53-89)	74.6 (53-89)	75.1 (56-88)	.52
Smoking, n (%)				.79
Never	136 (27.4)	111 (29.1)	25 (30.5)	
Ever	328 (66.1)	271 (70.9)	57 (69.5)	
Hypertension, n (%)	288 (58.1)	231 (56.5)	57 (65.5)	.15
Heart disease, n (%)	247 (49.8)	210 (51.3)	37 (42.5)	.16
Respiratory disease, n (%)	128 (25.8)	100 (24.4)	28 (32.2)	.14
Diabetes, n (%)	65 (13.1)	56 (13.7)	9 (10.3)	.49
Kidney failure, n (%)	28 (5.7)	26 (6.5)	2 (2.3)	.20
BMI[5] (kg/m^2), mean (range)	27.3 (15.5-54.7)	27.4 (15.5-44.1)	26.9 (18.4-54.7)	0.68
ASA-grade[1], n (%)				.44
Mild systemic disease	43 (11.1)	35 (10.9)	8 (12.7)	
Severe systemic disease	307 (79.1)	260 (80.7)	47 (74.6)	
Severe, life-threatening systemic disease	35 (9.0)	27 (8.4)	8 (12.7)	
AAA diameter (mm), mean (range)	61.9 (7.0-120.0)	62.5 (35.0-120.0)	58.8 (7.0-94.0)	.003
Presentation, n (%)				.27
Urgent (non-ruptured)	57 (11.5)	44 (10.8)	13 (14.9)	
Elective	439 (88.5)	365 (89.2)	74 (85.1)	
Postoperative complications, n (%)	82 (16.5)	65 (15.9)	17 (19.5)	.43
Postoperative blood loss[1] (L), mean (range)	0.27 (0-2.0)	0.28 (0-2.0)	0.22 (0-1.2)	.10

Abbreviations: BMI, Body Mass Index; *ASA-grade*, The American society of Anesthesiologists (ASA) Physical status classification system; *AAA*, Abdominal Aortic Aneurysm.

[1] Reduced sample-size due to missing values in the local vascular register. Missing BMI n= 206, missing postoperative blood loss n= 132.

Indication for reintervention

In total, 83 (16.7%) patients underwent re-intervention after conventional EVAR. Among these 72 (17.6%) were men and 11 (12.6%) women, but the difference was not significant (*P*=.28). Descriptive characteristics for the re-interventions are shown in Table III. Endoleaks were the most common indication for re-intervention in both genders (57.8%), 54.2% of men and 81.8% of women. Among the different types of endoleaks, type 2 was the most common (53.9%), followed by type 1 (32.7%) and type 3 (11.5%). Other indications for re-interventions were stent graft limb occlusions (33.7%) and infection (2.4%). Limb occlusions were only present in males (n=28, 38.9%). Migration was not an indication alone for re-intervention in any of the patients, but was present in combination with endoleaks (total 4.8%) and limb occlusion (total 1.2%).

Type of reintervention

Relining was the most common type of re-intervention (total 42.2%), 41.7% of men and 45.5% of women. Coiling was the second most common type of reintervention with a total of 26 (31.3%) patients, 24 (33.3%) of men, but only 2 (18.2%) women. Other type of reinterventions were explantation (9.6%), femoro-femoral-crossover bypass (6.0%), PTA (1.2%), thrombectomy (1.2%) and combinations of types such as relining and thrombectomy (4.8%), relining and coiling (2.4%) and thrombectomy and PTA (1.2%). In both genders the re-interventions were mainly successful (80.7%), 80.6% of men and 81.8% of women.

Number of re-interventions

The median number of re-interventions was 1 for all patients, and there was no difference between men and women in numbers of re-interventions (min-max; men 1-5, women 1-6).

Table III: Re-interventions characteristics for men and women

Characteristics	Total	Men	Women
Re-intervention, n (%)	83 (16.7)	72 (17.6)	11 (12.6)
Indication for re-intervention, n (%)			
Endoleaks	48 (57.8)	39 (54.2)	9 (81.8)
Limb occlusions	28 (33.7)	28 (38.9)	-
Endoleaks and migration	4 (4.8)	3 (4.2)	1 (9.1)
Infection	2 (2.4)	1 (1.4)	1 (9.1)
Migration and occlusion	1 (1.2)	1 (1.4)	-
Type of re-intervention, n (%)			
Relining	35 (42.2)	30 (41.7)	5 (45.5)
Coiling	26 (31.3)	24 (33.3)	2 (18.2)
Explantation	8 (9.6)	5 (6.9)	3 (27.3)
Femoro-femoral-crossover bypass	5 (6.0)	5 (6.9)	-
Relining and thrombectomy	4 (4.8)	4 (5.6)	-
PTA	1 (1.2)	1 (1.4)	-
Thrombectomy	1 (1.2)	1 (1.4)	-
Relining and coiling	2 (2.4)	1 (1.4)	1 (9.1)
Thrombectomy and PTA	1 (1.2)	1 (1.4)	-
Results of re-interventions, n (%)			
Successful	67 (80.7)	58 (80.6)	9 (81.8)
Need for additional measures	16 (19.3)	14 (19.4)	2 (18.2)

Abbreviations: PTA, percutaneous transluminal angioplasty

Survival analyses

Kaplan-Meier curves

Figure II shows the survival difference between patients who underwent re-interventions and those who did not. After approximately 5 years the curve separates with a tendency of impaired survival in the non-reintervention group. The median survival time after conventional EVAR was 8.7 years for patients who did not undergo re-interventions, while patients who underwent re-interventions had a median survival time of 11.1 years. A log rank test was conducted to determine if there were differences in the survival distributions for patients who underwent re-interventions and not. The survival distributions were not significantly different (*P*=.17).

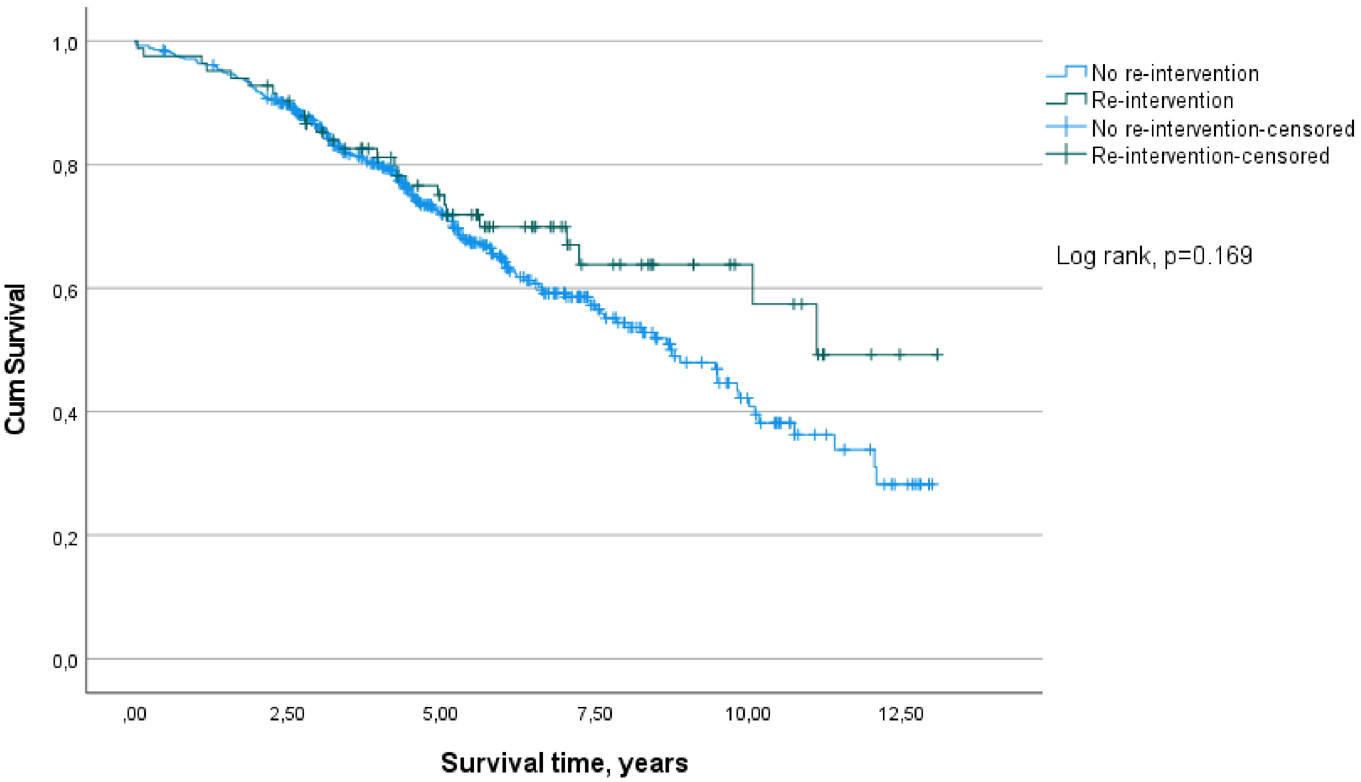


Figure II: The Kaplan-Meier curve of survival differences between patients who underwent re-interventions and patients who did not undergo re-intervention.

Figure III presents the overall survival difference between the genders. Following conventional EVAR, the median survival time was found to be 9.5 years for men and 8 years for women. After approximately 5 years the curve separates with a tendency of impaired survival in women. To evaluate whether there were statistically significant differences in survival distributions between genders, a log-rank test was performed. The results revealed that the survival distributions were not significantly different (*P*=.29).

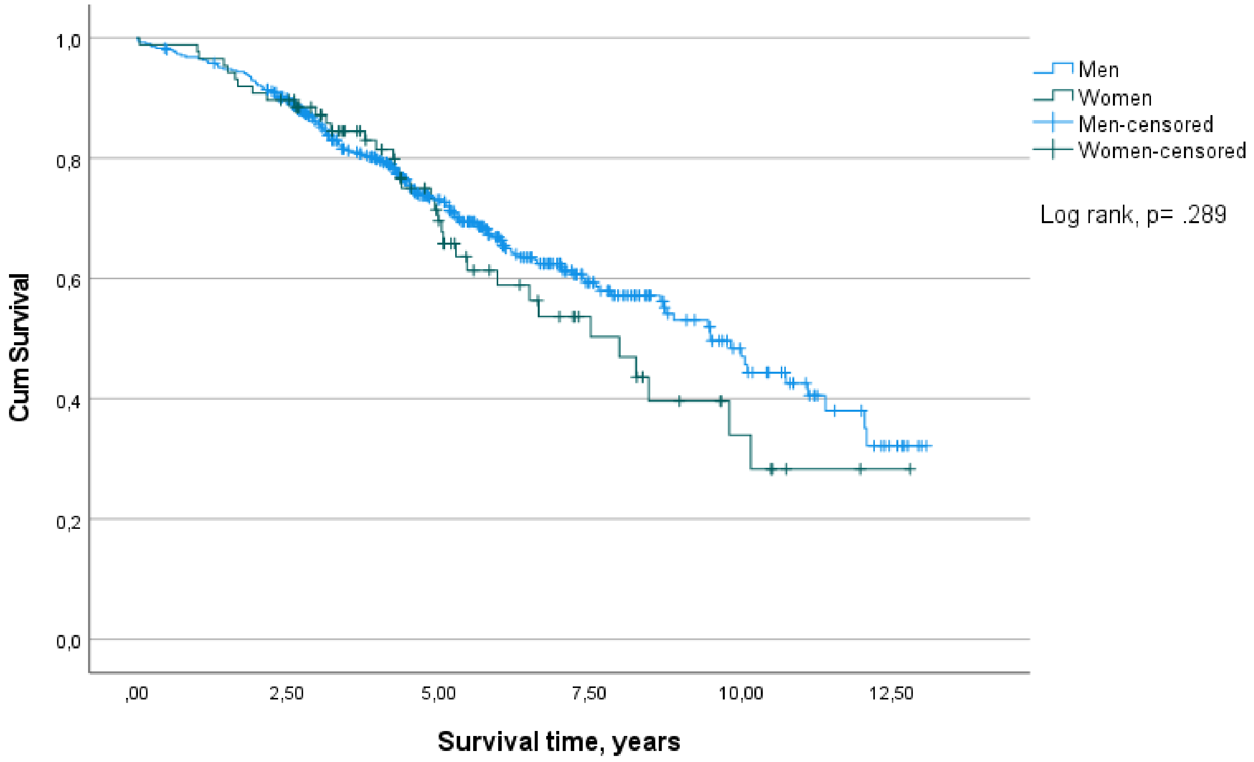


Figure III: The Kaplan-Meier curve of overall survival differences between men and women

Figure IV shows the survival difference between men and women who underwent re-interventions. The log rank test indicated no statistically significant differences between the genders (*P*=.48), and the curves illustrates that the number of women was very low.

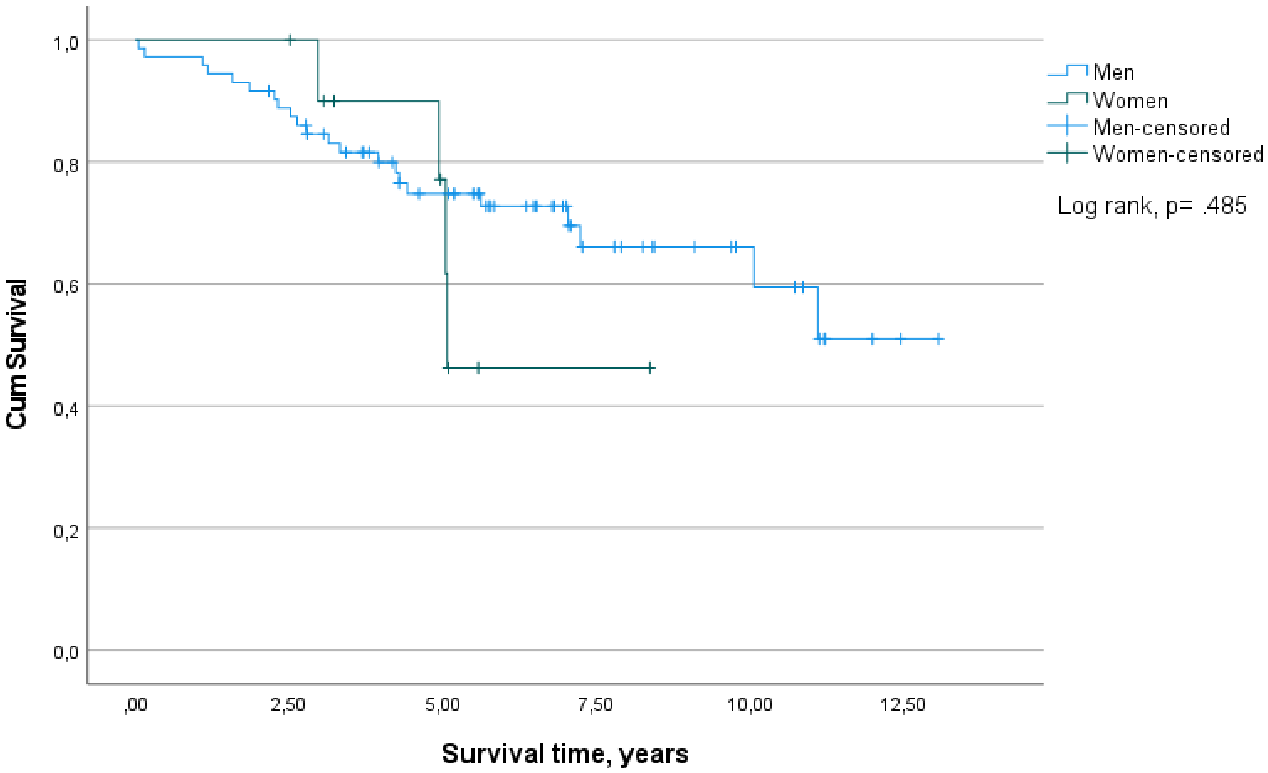


Figure IV: The Kaplan-Meier curve of survival differences between men and women who underwent re-interventions.

Cox regression analyses

Risk of re-intervention

Table IV presents the estimated relative risk in both univariable and multivariable Cox regression models, aiming to investigate the association between re-intervention and various risk factors.

In the univariable analysis, women had a 28% reduced hazard of re-intervention compared to men (HR 0.72, 95% CI 0.38-1.36). After adjusting for additional variables in the multivariable model (age, hypertension, heart disease, respiratory disease, smoking, AAA diameter, presentation), women had a 37% reduced hazard of re-interventions compared to men (HR 0.63, 95% CI 0.30-1.33). The association between gender and risk of re-intervention did not reach statistical significance in either the univariable analysis (*P*=.31) or the multivariable analysis (*P*=.48).

No significant associations were found between age, smoking, AAA diameter, hypertension, heart disease, respiratory disease or presentation and risk of re-intervention in either the univariable or multivariable models.

Table IV: Cox regression analysis with 95% CI for analysis of risk factors for reintervention (time to reintervention, median follow-up time 4,4 years (min-max, 0.00-12.99 years).

Variables	Univariable HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*- value
Gender				
Male	1.00 (REF)	.31	1.00 (REF)	.23
Female	0.72 (0.38-1.36)		0.63 (0.30-1.33)	
Age	0.99 (0.96-1.02)	.65	0.99 (0.96-1.02)	.48
Hypertension	0.74 (0.48-1.14)	.17	0.70 (0.44-1.10)	.12
Heart disease	1.27 (0.82-1.95)	.28	1.15 (0.72-1.82)	.57
Respiratory disease	0.71 (0.41-1.22)	.22	0.65 (0.36-1.18)	.15
Smoking	1.06 (0.65-1.71)	.83	1.10 (0.67-1.83)	.71
AAA diameter	1.01 (0.99-1.03)	.20	1.01 (0.99-1.04)	.28
Presentation				
Urgent, non-ruptured	1.00 (REF)	.95	1.00 (REF)	.82
Elective	0.98 (0.49-1.96)		1.09 (0.51-2.34)	

Abbreviation: AAA, Abdominal Aortic Aneurysm. *Smoking*, Never/ever. *HR*, Hazard ratio. *CI*, confidence interval.

Survival analysis

Table V shows the estimated relative risk in both univariable and multivariable Cox regression models, examining the association between gender, various risk factors and overall survival.

In the univariable analysis, women had a 22% higher hazard of mortality compared to men (HR 1.22, 95% CI 0.84-1.77). After adjusting for other variables in the multivariable model, women had a 38% higher hazard of mortality than men (HR 1.38, 95% CI 0.94-2.03). The association between gender and survival did not reach statistical significance in either the univariable analysis or the multivariable analysis.

Re-intervention was associated with a reduced risk of mortality in both models (univariable, HR 0.75 95% CI 0.49-1.13; multivariable, HR 0.84, 95% CI 0.54-1.31), but the associations were not statistically significant.

Age demonstrated a significant association with an increased risk of mortality in both the univariable (HR 1.07 95% CI 1.04-1.09) and the multivariable model (HR 1.07 95% CI 1.04-1.09). Smoking was associated with an increased risk of mortality, reaching statistical significance only in the multivariable model (HR 1.53 95% CI 1.09-2.15). AAA diameter demonstrated a slight, but significant increase in the risk of mortality in both models (univariable, HR 1.02 95% CI 1.01-1.04; multivariable HR 1.02 95% CI 1.01-1.04). No significant associations were found between hypertension, heart disease, respiratory disease and presentation in either the univariable or multivariable models.

Table V: Cox regression analysis with 95% CI for association between survival in patients who underwent conventional EVAR and risk factors (median follow-up time 4,9 years (min-max, 0.02-13.07).

Variables	**Univariable HR (95% CI)**	***P*-value**	**Multivariable HR (95% CI)**	***P*- value**
Gender				
Male	1.00 (REF)	.29	1.00 (REF)	.103
Female	1.22 (0.84-1.77)		1.38 (0.94 – 2.04)	
Age	1.07 (1.04-1.09)	< .001	1.07 (1.04 – 1.09)	< .001
Re-intervention	0.75 (0.49-1.13)	.17	0.84 (0.54 – 1.31)	.44
Hypertension	1.12 (0.84-1.51)	.45	1.10 (0.81 – 1.50)	.55
Heart disease	1.24 (0.93-1.66)	.14	1.03 (0.76 – 1.39)	.87
Respiratory disease	1.07 (0.76-1.50)	.70	0.94 (0.66 – 1.35)	.75
Smoking	1.31 (0.94-1.82)	.11	1.53 (1.09 – 2.15)	.02
AAA diameter	1.02 (1.01-1.04)	< .001	1.02 (1.01 – 1.04)	.002
Presentation				
Urgent, non-ruptured	1.00 (REF)	.09	1.00 (REF)	.88
Elective	0.69 (0.45-1.06)		0.97 (0.60 – 1.54)	

Abbreviation: AAA, Abdominal Aortic Aneurysm. *Smoking*, Never/ever. *HR*, Hazard ratio. *CI*, confidence interval.

Discussion

This quality improvement based retrospective study with a median follow-up time of 4.9 years included a total of 496 (17.5 % women) patients who underwent conventional EVAR for intact AAA. A total of 83 (16.7%) patients required re-intervention. Of these, 72 (17.6%) were men and 11 (12.6%) women. There were no significant differences in re-intervention rates between the genders.

Overall, the study population consisted of a significantly higher proportion of men (82.5%) compared to women (17.5%), and the number of women in the re-intervention group was very low. Women had a 37% reduced hazard of re-interventions compared to men in the multivariable regression analysis, but the results did not reach statistical significance.

The Kaplan-Meier analysis illustrated that after approximately 5 years, survival rates seemed to be higher among patients who underwent re-interventions. However, the result was not significant. Moreover, as another Kaplan-Meier plot illustrated, our study lacked statistical power to properly evaluate gender differences in the risk of mortality in patients who underwent re-interventions.

In the multivariable regression analysis, women had a 38% higher hazard of mortality compared to men, but the difference in survival was not statistically significant. Of note, the age of women and men in the study was similar, and age was found to have a significant association with increased risk of mortality.

Our findings in relation to previous research

Our study found a re-intervention rate of 16.7% among patients who underwent EVAR. This compares well with the range of re-interventions of 16-33% reported in previous studies[11], indicating that the quality of EVAR procedures at St. Olavs hospital is comparable to other hospitals globally. These findings suggest that the outcome of EVAR procedures at our institution are in line with the established standards in the field.

The study population consisted of a higher proportion of male patients, which is consistent with previous research indicating a 4-6 times higher prevalence of AAA among men compared to women[1-4].

High age, male gender, smoking, heredity, hypertension and coronary artery disease are well-established risk factors for developing AAA[1]. Smoking, in particular, is indisputably the major risk factor for AAA, with a higher association observed in women compared to men[6, 19]. Factors associated with risk of re-intervention may differ from risk of AAA. Despite having a higher number of patients in the smoker group compared to non-smokers, we did not find any association between smoking and the risk of re-intervention. There are other factors that may also contribute to the risk of re-interventions, such as the use of antithrombotic medications before and after conventional EVAR [20, 21]. However, these data were not available in our study due to a considerable amount of missing in the local vascular surgery registry.

Previous research suggest that female gender is associated with a higher risk of surgical re-intervention[22]. Our study results do not support these findings. Although the results were not statistically significant, we observed a reduced hazard ratio of re-intervention among women in both the univariable and the multivariable models. This discrepancy could be attributed to the low statistical power resulting from the limited overall number of women in our study population. Furthermore, the lack of statistical significance in our findings may be attributed to the small number of women in the re-intervention group, as evident in the Kaplan-Meier analysis. With a larger study population, we might have obtained different and potentially significant results.

Another potential factor of interest to explore as a risk factor for re-intervention is the AAA diameter. In our study, similar to previous research and as expected, we observed that women had a smaller AAA diameter compared to men at the time of conventional EVAR[3, 6, 23]. Diameter was also associated with increased risk of mortality, as reported in other studies[1, 3, 5, 6]. However, in our analysis, we did not find any significant associations between AAA diameter at the time of EVAR and the risk of re-interventions, neither in the univariable nor multivariable models. Of note, our study only had data on the diameter before patients underwent conventional EVAR and lacked data on AAA diameter prior to re-interventions. Endoleaks were identified as the most common indication for re-intervention in both genders, and an increasing diameter could potentially indicate the presence of an endoleak due to the increased pressure on the aneurysm sac[6]. Diameter, therefore, is an important criterion to consider when contemplating re-intervention[23], and may contribute to the overall risk of re-interventions[24].

In our study, the hazard ratio indicated a reduction in the risk of mortality among patients who underwent re-interventions. The non-significant result could potentially be attributed to selection bias[25]. Patients who underwent reinterventions were those who required intervention and were considered fit for surgery, while those who did not undergo re-intervention represented a mixture of patients who did not require further interventions and those who may have needed re-intervention, but were considered inoperable. Moreover, with a larger sample size, we might have obtained a significant result. As shown in figure IV, the number of women in the re-intervention group was notably low. Some studies have reported that patients who undergo re-interventions following EVAR exhibit higher cumulative 5-year survival rates compared to those who do not undergo re-interventions[15]. These findings provide support for the potential association between the occurrence of re-interventions and improved long-term survival outcomes, as indicated in our study.

While the results from our study did not reach statistical significance for the association between gender and mortality, numerous other studies have demonstrated an independent association between female gender and worse outcome following elective surgery compared to men[3, 26]. The findings of our study are consistent with previous research[4], indicating that women have inferior outcomes despite presenting at a similar age, with smaller aneurysm diameters and similar medical comorbidities. However, the low number of women in our study population has limited the statistical power, potentially obscuring the detection of a significant result. With a larger sample size, we might have detected a significant difference in long-term survival between the genders.

Age was identified as a significant factor associated with an increased risk of mortality, which could help explain the higher mortality risk observed in women compared to men. However, in our study, women and men were of similar age. The discrepancy in outcome suggests that factors other than age alone contribute to the observed differences in mortality risk between genders. One explanation, supported by previous research, is that women tend to exhibit a higher degree of frailty compared to men[26]. This suggest that frailty, along with other factors, may contribute to the divergent mortality outcomes between genders, an needs further investigations.

Strengths and limitations

Our study has several strengths, including a long duration of follow-up, manual verification of data, and adjustment for numerous risk factors associated with both AAA surgery and mortality.

However, there are some limitations that should be addressed. The retrospective design of our study introduces inherent limitations, such as the possibility of missing data and insufficient patients numbers[27]. The local vascular registry had the highest amount of missing data, which could potentially lead to an underestimation of the occurrence of risk factors. We did not have relevant information about for instance antithrombotic therapy and AAA diameter at time of reintervention. Additionally, the quality and accuracy of the data may vary across different data sources, introducing measurements errors and biases[28].

Our study population exhibited an imbalance in the gender distribution, with a considerably higher proportion of men compared to women. Although this is commonly observed in the patients group, it limits our statistical power and may affect the generalizability of our results to a broader population. Additionally, the small number of women in the re-intervention group limited our ability to draw conclusions about the association between gender, re-interventions, and outcomes. The limited sample size in particular variables also prevented the calculation of reliable *p*-values in Table III. Moreover, the limited sample size compromises the statistical power to detect significant differences or associations, increasing the risk of type II errors[29, 30], where true associations may go undetected.

Conclusions and future perspectives

In our retrospective study, a total of 83 (16.7%) patients required re-intervention after undergoing conventional EVAR. Of these, 72 (17.6%) were men and 11 (12.6%) were women. Women had a 37% reduced hazard of re-interventions compared to men., but the result was not statistically significant. The number of women in the re-intervention group was very low, which limits the statistical power. With an adjusted hazard ratio of 1.38, the risk of death appeared higher for women compared to men. However, the association was not significant, perhaps due to limited statistical power.

To gain a deeper understanding of the relationship between gender, re-intervention, and outcomes, future studies with larger sample sizes and a prospective design are necessary.

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