Elective Abdominal Aortic Aneurysm (AAA) repair: challenges remain

Bulder, R.M.A.

Chapter 3

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

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

Annals of Surgery 2020

ABSTRACT

Objective

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

Background

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

Methods

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

Results

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

Conclusions

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

INTRODUCTION

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

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

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

METHODS

Ethical Approval

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

Registry Data

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

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

Time-resolved Analysis

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

Outcome Measures

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

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

Statistical Analysis

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

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

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

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

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

RESULTS

Changes in AAA Management

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

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

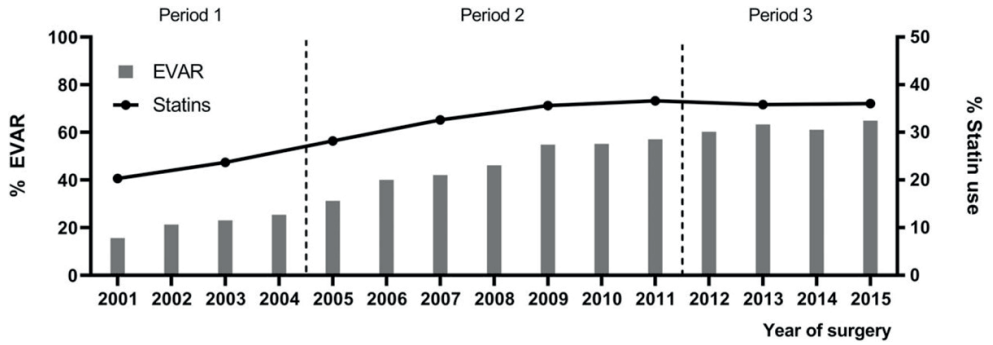


Figure 1. Developments in AAA management between 2001 and 2015. Percentage of EVAR procedures for patients with AAA repair and statin use for the general Swedish population.

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

Patient Characteristics

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

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

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

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

Procedural Mortality (Short-term Survival)

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

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

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

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

Relative Survival (Long-term Survival)

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

Cause of Death

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

Sex Differences

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

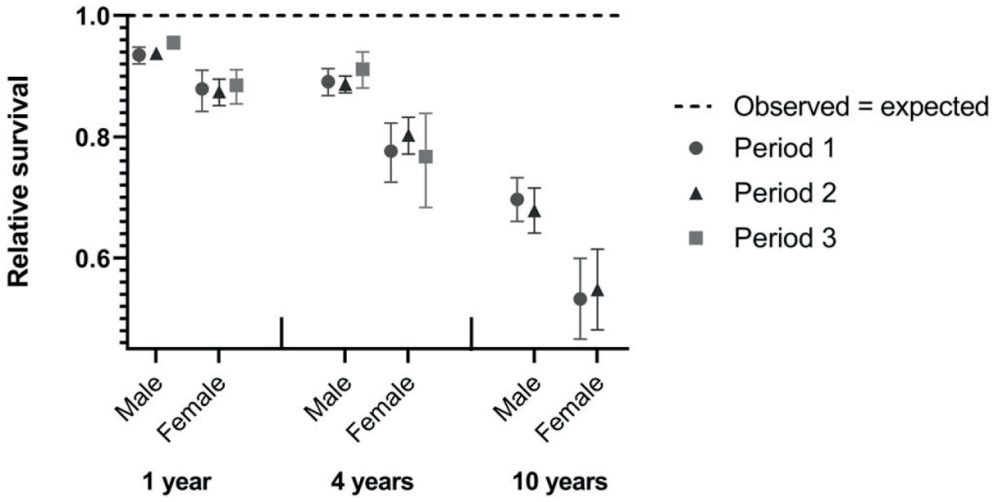


Figure 2. Relative survival for males and females for respectively period 1, period 2, and period 3 at 1, 4, 10 year survival.

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

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

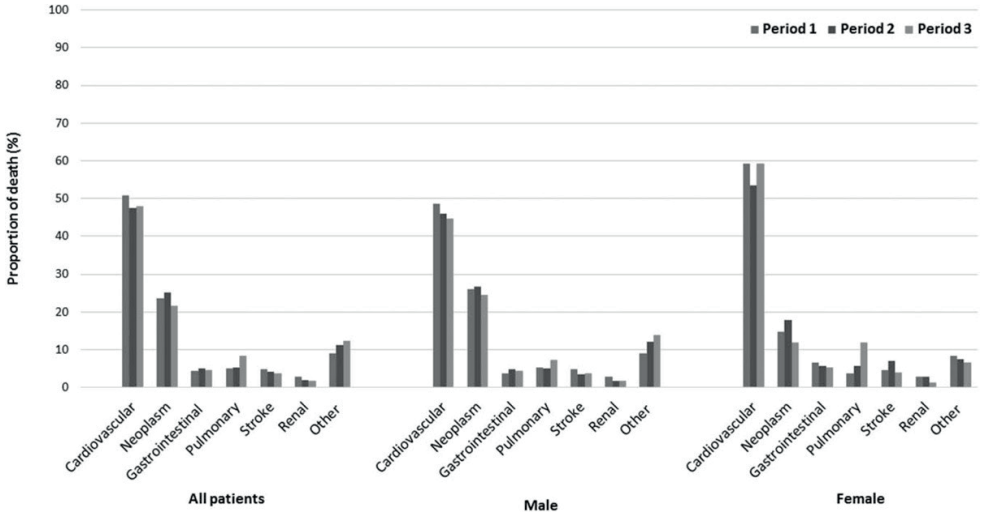


Figure 3. Long-term causes of death (proportions), including all patients who died after 90 days and within 4 year after elective infrarenal AAA repair.

AAA, abdominal aortic aneurysm.

Potential Bias Due to Change of Patient Selection Over Time

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

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

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

DISCUSSION

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

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

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

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

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

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

Limitations

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

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

CONCLUSION

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

REFERENCES

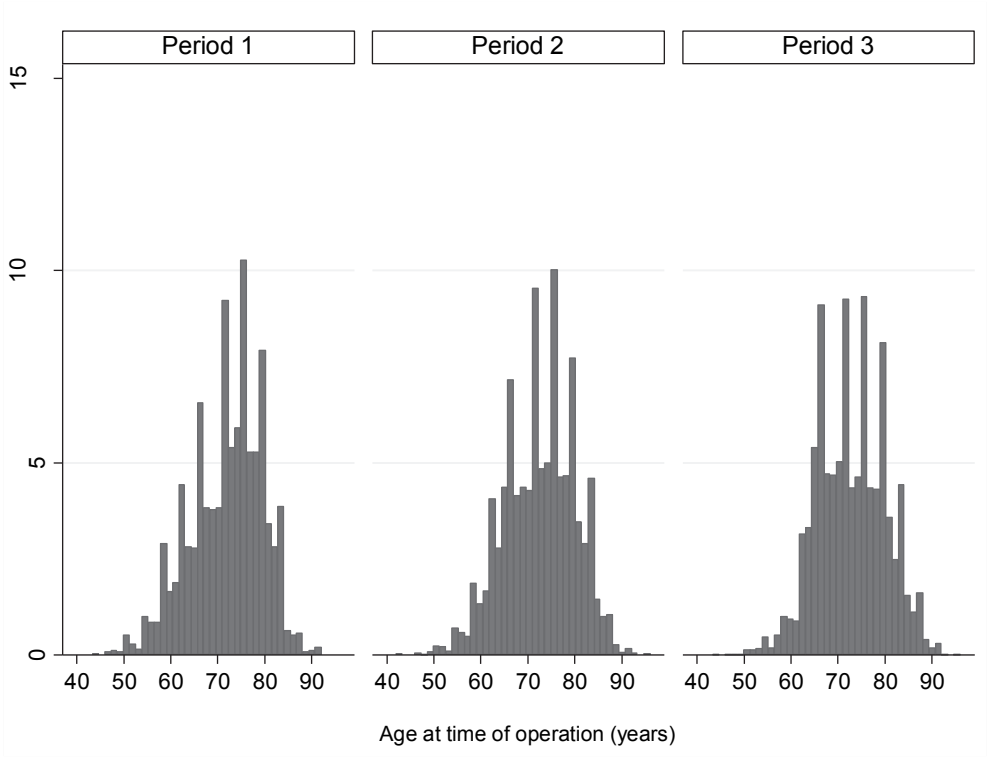
1. Rich N, Tucker LY, Okuhn S, et al. Long-term freedom from aneurysm-related mortality remains favorable after endovascular abdominal aortic aneurysm repair in a 15-year multicenter registry. J Vasc Surg. 2020;71:790–798.
2. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. Lancet. 2005;365:1577–1589.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

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

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

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

SUPPLEMENTAL MATERIAL



Supplemental Figure 1. Age distribution per period.

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

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

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

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

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

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

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

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

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

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

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

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