Anatomic predictors for late mortality after standard endovascular aneurysm repair

Nelson F. G. Oliveira, MD,[a,b] Klaas Ultee, MD, PhD,[a] Marie Josee van Rijn, MD, PhD,[a] José Pedro Pinto, MD,[a,c] Sander Ten Raa, MD, PhD,[a] Frederico Bastos Gonçalves, MD, PhD,[a,d] Sanne E. Hoeks, PhD,[e] *and* Hence J. M. Verhagen, MD, PhD,[a] *Rotterdam, The Netherlands; and Ponta Delgada, Azores, Lisbon, and Porto, Portugal*

ABSTRACT

Objective: Abdominal aortic aneurysm (AAA) management involves a decision process that takes into account anatomic characteristics, surgical risks, patients' preferences, and expected survival. Whereas larger AAA diameter has been associated with increased mortality after both standard endovascular aneurysm repair (EVAR) and open repair, it is unclear whether survival after EVAR is influenced by other anatomic characteristics. The purpose of this study was to determine the importance of baseline anatomic features on survival after EVAR.

Methods: All patients treated at a tertiary teaching center with EVAR for intact standard infrarenal AAA from 2000 to 2014 were included. The civil data registry was queried to determine survival status; causes of death were obtained from death certificates. The primary study end point was to determine the impact of baseline morphologic features on all-cause and cardiovascular mortality after EVAR.

Results: This study included 404 EVAR patients (12.1% women; mean age, 73 years) with a median follow-up of 5.8 years (interquartile range, 3.1-7.4 years). The 5- and 10-year overall survival rates for the entire population after EVAR were 70% (95% confidence interval [CI], 66%-75%) and 43% (95% CI, 37%-50%), respectively. Only AAA diameter >70 mm (hazard ratio [HR], 1.75; 95% CI, 1.20-3.56) was identified as an independent anatomic predictor of all-cause mortality. Death due to cardiovascular causes occurred in 60 (38.5%) patients. Aneurysm-related mortality was responsible for six of the cardiovascular-related deaths. In multivariable analysis, both neck diameter ≥30 mm (HR, 2.16; 95% CI, 1.05-4.43) and AAA diameter >70 mm (HR, 2.45; 95% CI, 1.34-4.46) were identified as independent morphologic risk factors for cardiovascular mortality, whereas >25% circumferential neck thrombus (HR, 0.32; 95% CI, 0.13-0.77) was protective.

Conclusions: This study suggests that patients with AAA diameters >70 mm are at increased risk of all-cause and cardiovascular mortality. In addition, patients with infrarenal neck diameters ≥30 mm have a greater risk of cardiovascular mortality, although AAA-related deaths were not more frequent in this group of patients. Consequently, a more aggressive management of cardiovascular medical comorbidities may be warranted to improve survival after standard EVAR in these patients. (J Vasc Surg 2019;69:1444-51.)

Keywords: Aortic aneurysm; Abdominal; Mortality; Endovascular procedure; Blood vessel prosthesis implantation; Retrospective studies

Treatment of abdominal aortic aneurysms (AAAs) involves a decision-making process in which the patient's comorbidities, the anatomic characteristics, the procedure-specific outcomes, and the patient's preference are considered along with long-term survival expectancy. Whereas endovascular aneurysm repair (EVAR) has become the most common repair method, AAA patients still have a reduced survival compared with age- and sex-matched individuals.[1,2] This excessive mortality is mostly cardiovascular and cancer related and is inherent in the comorbidities and risk factors with which these patients are commonly burdened.[1-3]

Some vascular morphologic features have been associated with increased mortality in both general population-based studies and peripheral vascular surgery cohorts, such as patients with vascular

From the Department of Vascular Surgery[a] and Department of Anesthesiology,[e] Erasmus University Medical Center, Rotterdam; the Department of Angiology and Vascular Surgery, Hospital do Divino Espírito Santo, Ponta Delgada[b]; the Department of Angiology and Vascular Surgery, Hospital de São João, Porto[c]; and the Department of Angiology and Vascular Surgery, Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, Lisbon.[d]

Author conflict of interest: N.F.G.O. has received an educational research grant from the Lijf en Leven Foundation. F.B.G. is a consultant for Medtronic and W. L. Gore. S.E.H. has received an educational research grant from the Lijf en Leven Foundation. H.J.M.V. is a consultant for Medtronic, W. L. Gore, Endologix, Arsenal AAA, and Philips.

Presented in the International Fast-Talk session at the 2017 Vascular Annual Meeting of the Society for Vascular Surgery, San Diego, Calif, May 31-June 3, 2017.

Correspondence: Nelson F. G. Oliveira, MD, Erasmus University Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands (e-mail: n.gomesoliveira@erasmusmc.nl; nfgoliveira@sapo.pt).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2018.07.082

calcification.[4-7] Regarding EVAR patients, large preoperative AAA diameter and infrarenal neck diameter have been linked to worse survival.[8] Yet the impact of each of these features separately could not be established. Aortic thrombus has also been suggested to have a negative impact on survival, but the available data are scarce.[9] In addition to this, other anatomic characteristics of the aneurysm may also constitute an increased mortality risk after EVAR.

The purpose of this study was to assess the impact of baseline anatomic characteristics on long-term survival after standard EVAR for intact AAAs. In addition, the association between other patient factors (baseline demographics, comorbidities) and long-term mortality was investigated.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective, single-center cohort study
- **Key Findings:** Endovascular repair of abdominal aortic aneurysms in 404 patients resulted in 5- and 10-year survival of 70% and 43%. Preoperative aneurysm size >70 mm predicted all-cause and cardiovascular mortality, whereas aneurysm neck diameter >30 mm predicted cardiovascular mortality.
- **Take Home Message:** This study suggests that patients with larger abdominal aortic aneurysms with larger infrarenal necks have reduced life expectancy after endovascular aneurysm repair.

METHODS

Design and population. This retrospective study complies with the Declaration of Helsinki in research ethics. Informed consent was waived according to institutional policy on retrospective research. All patients undergoing standard infrarenal EVAR at a high-volume center in The Netherlands (Erasmus University Medical Center, Rotterdam) from January 2000 to December 2014 were included. Patients with anastomotic, infectious, or isolated iliac aneurysms were excluded from these analyses. In addition, patients who died during hospitalization for the initial EVAR or in whom a preoperative computed tomography (CT) image was no longer retrievable for analysis were excluded.

Measurements. All morphologic measurements were performed by two observers experienced in image analysis (N.F.G.O., F.B.G.) using dedicated postprocessing software (3mensio Vascular, Bilthoven, The Netherlands) following center lumen line reconstruction. These techniques have been extensively validated, demonstrating high rates of interobserver agreement for aortic diameters, proximal neck length, angulation, and aneurysm volume.[10-13] Neck diameters were measured in two perpendicular axes just distal to the lowermost renal artery ostium and at every 5 mm distally along the first 15 mm of the infrarenal neck on center lumen line reconstruction imaging.

Definitions. A patient was considered to have undergone standard EVAR if an infrarenal AAA had been treated with any of the commercially available standard infrarenal aortic endografts without planned adjuncts, such as endoanchoring, parallel stent techniques, and fenestrated or branched technology. Compliance with device instructions for use was not mandatory. The average of the two largest neck measurements obtained in the infrarenal neck was considered the reference neck diameter. For patients with a neck length <15 mm, the average of the first two measurements was taken as the reference diameter. This diameter was then used to select the study group (diameter ≥30 mm) and to calculate oversizing. Patients with a reference neck diameter <30 mm were considered controls. Neck configuration was classified according to published methods.[14] Aortic necks demonstrating progressive diameter increments ≥10% along their length were considered inverse-tapered neck (type II) configuration. Circumferential involvement of thrombus or calcification of the infrarenal neck was categorized into <25%, 25% to 50%, 50% to 75%, and >75%. Patients' comorbidities and aneurysm-related outcomes are presented according to the Society for Vascular Surgery reporting standards.[15,16] Accordingly, sac growth was defined as >5-mm-diameter increase after EVAR. Renal insufficiency was considered when the estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m^2.

Institutional AAA management and postoperative surveillance. During the study period, treatment selection was individualized but evolved toward a more primary EVAR practice, particularly in patients without significant anatomic restraints, patients with worse health status, or patients with previous abdominal surgery (hostile abdomen). The patient's preference was also considered. Typical follow-up protocols included 30-day and yearly CT angiography. However, according to the treating physician's expectation, in selected patients with an anticipated lower risk of complications or renal function impairment, CT angiography was replaced by color duplex ultrasound or noncontrast-enhanced CT.

Survival status and causes of death. Survival status and cause of death were retrieved from the Dutch Central Bureau of Statistics (study ID: 7465) for patients deceased to December 2014. Each patient's official death certificate report was matched to an anonymized database of the study population. As determined by Dutch privacy legislation, data analysis was allowed only to authorized researchers (K.U., F.B.G.) and performed inside a secure environment. All output was checked by the Central Bureau of Statistics for privacy violation before it was

cleared for publication. In The Netherlands, autopsy is not routinely performed, and the expected cause leading to the initial health deterioration before death was considered the true cause of death. The causes of death were grouped according to the *International Classification of Diseases, Tenth Revision* (ICD-10). The following codes were used: for cardiovascular death, I10-I79; for cancer-related death, C00-C43, C45-C97, D00-D03, and D05-09; and for AAA-related death, I71.3, I71.4, I71.8, I71.9, I72.3, and T82.7. The proportion of coding based on autopsy vs clinical evaluation could not be determined.

End points. The primary study end points were all-cause mortality and cardiovascular mortality. The secondary end point was AAA-related mortality.

Statistical analysis. Baseline demographics, comorbidities, and morphologic variables are presented as means and standard deviation if continuous and normally distributed or as count and percentage if categorical. Differences were assessed using the Student *t*-test or Pearson χ^2 test. Continuous variables with a skewed distribution are presented as median and interquartile range and were compared using the Mann-Whitney *U* test for independent samples. The association between each of the baseline characteristics with all-cause mortality and cardiovascular mortality was tested in Cox proportional hazards regression univariable analyses. Variables with *P* value ≤.1 were then entered into a multivariable model, after which a final model was obtained using stepwise backward elimination of variables with a *P* value >.05. The 95% confidence intervals (CIs) were used, and statistical significance was considered for $\alpha < .05$. Survival curves were estimated by Kaplan-Meier methods, and equality was assessed with the Mantel-Cox log-rank test. All statistical analyses were performed using Statistical Package for Social Sciences 21.0 (IBM Corp, Chicago, Ill).

RESULTS

During the study period, 622 EVARs were performed; 82 ruptured AAAs, 33 anastomotic or other pseudoaneurysms, 16 isolated iliac aneurysms, and 9 infectious and 1 traumatic ruptures were excluded. Among the remaining cohort of 481 patients, 77 more patients were excluded; 4 patients died during the hospital admission for the primary procedure, and for 73, a complete anatomic data set was not obtainable as baseline imaging was no longer retrievable for analysis, leaving a final population of 404 patients treated for intact degenerative AAA with standard infrarenal EVAR. Baseline characteristics are depicted in Table I.

All-cause mortality. During a median follow-up of 5.8 years (interquartile range, 3.1-7.4 years; maximum, 16.1 years; total person-years of 2292.22), 181 patients died, resulting in a death incidence rate of 7.9 per 100 person-years. The 5- and 10-year overall survival rates for the entire population after EVAR were 70% (95% CI, 66%-75%) and 43% (95% CI, 37%-50%), respectively. In the univariable analysis, age, smoking, American Society of Anesthesiologists class 3 or class 4, eGFR <60 mL/min/1.73 m^2, AAA diameter >70 mm, infrarenal neck diameter ≥30 mm, and >25% circumferential neck thrombus were found to be risk factors for all-cause mortality. No association was found between postimplantation sac growth and overall mortality on univariable analysis ($P = .21$). Regarding anatomic characteristics, only baseline AAA diameter >70 mm remained significant in

Table I. Baseline demographic, anatomic, and device-related characteristics

Characteristics	(N = 404)
Age, years	72.6 (±7.7)
Male sex	355 (87.9)
Hypertension	281 (69.6)
Diabetes mellitus	68 (16.8)
eGFR <60 mL/min/1.73 m^2[a]	103 (25.5)
Previous history of smoking or continuous smoking at time of implantation[a]	287 (71.0)
Cardiac status ≥2[b]	76 (18.8)
ASA class 3/4[a]	207 (51.2)
AAA diameter >70 mm	86 (21.3)
Infrarenal neck diameter ≥30 mm	55 (13.6)
Infrarenal neck length, mm	29.9 (±14.4)
Reverse-tapered neck configuration	103 (25.5)
Neck thrombus >25%	369 (91.3)
Neck calcification >25%	372 (91.1)
α angle ≥45 degrees	46 (11.4)
β angle ≥60 degrees	77 (19.1)
Suprarenal fixation	221 (54.7)
Active (hooks) fixation	385 (95.3)
Endografts	
Endurant (Medtronic, Santa Rosa, Calif)	198 (49.0)
Excluder (W. L. Gore & Associates, Flagstaff, Ariz)	175 (43.3)
Talent (Medtronic)	12 (3.0)
Zenith (Cook Medical, Bloomington, Ind)	11 (2.7)
Others	8 (2.0)
Aneurysm sac growth	48 (11.9)
Endoleaks[c]	119 (29.5)
Type I or III	40 (9.9)
Type II	90 (22.3)

AAA, Abdominal aortic aneurysm; *ASA*, American Society of Anesthesiologists; *eGFR*, estimated glomerular filtration rate.
Continuous data are presented as mean (±standard deviation) and categorical data as count/number of patients with available data (percentage).
[a]Missing data for >3% to <6%.
[b]According to the Society for Vascular Surgery/American Association for Vascular Surgery medical comorbidity grading system.
[c]Count is given as number of patients developing each type of endoleak.

Table II. Risk factors for all-cause mortality

		All-cause mortality					
		First model			Final model		
Variables	Univariable *P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (per year)	<.001	1.06	1.03-1.08	<.001	1.06	1.04-1.09	<.001
Previous history of smoking or continuous smoking at time of implantation	.075	1.32	0.87-2.01	.184	–	–	–
ASA class 3/4	.029	1.71	1.17-2.51	.006	1.78	1.23-2.56	.002
Renal insufficiency	<.001	1.98	1.35-2.92	<.001	1.89	1.31-2.73	.001
AAA diameter >70 mm	.01	1.49	1.00-2.25	.050	1.75	1.20-3.56	.004
Infrarenal neck diameter ≥30 mm	.104	0.95	0.56-1.63	.862	–	–	–
Neck thrombus >25%	.016	0.54	0.26-1.12	.096	–	–	–

AAA, Abdominal aortic aneurysm; *ASA*, American Society of Anesthesiologists; *CI*, confidence interval; *HR*, hazard ratio.
Multivariable regression performed with progressive backward stepwise modeling including variables with $\alpha < .1$ in the first model and variables $\alpha < .05$ in the final model.

multivariable analysis (hazard ratio [HR], 1.75; 95% CI, 1.20-3.56; Table II). In addition, age (HR, 1.06; 95% CI, 1.04-1.09 per year), American Society of Anesthesiologists class ≥3 (HR, 1.78; 95% CI, 1.23-2.56), and eGFR <60 mL/min/1.73 m^2 (HR, 1.89; 95% CI, 1.31-2.73) were significantly associated with decreased survival.

Cardiovascular mortality. The cause of death was obtainable for patients who died before the beginning of 2015. Up to then, 158 patients had died among the study cohort, and the cause of death was known for 156 of these patients (98.7%). Cardiovascular causes were responsible for 60 deaths (38.5%), which included 6 aneurysm-related deaths (1.5%). In addition, 47 (30.1%) were related to cancer, and 49 (31.4%) were due to other causes. In the univariable analysis, age, male sex, eGFR <60 mL/min/1.73 m^2, AAA diameter >70 mm, infrarenal neck diameter ≥30 mm, reverse-tapered neck configuration, neck thrombus >25%, and α angle ≥45 degrees were found to be risk factors for cardiovascular mortality (Table III). Postimplantation sac growth was not associated with cardiovascular-related mortality in univariable analysis ($P = .25$). In the final multivariable regression model, AAA diameter >70 mm (HR, 2.45; 95% CI, 1.34-4.46) and neck diameter ≥30 mm (HR, 2.16; 95% CI, 1.05-4.43) were associated with an increased risk of cardiovascular mortality. Other independent predictors of cardiovascular mortality were age (HR, 1.66; 95% CI, 1.15-2.41 per year), eGFR <60 mL/min/1.73 m^2 (HR, 2.09; 95% CI, 1.19-3.65), and female sex (HR, 2.04; 95% CI, 1.08-4.00). Infrarenal neck thrombus ≥25% (HR, 0.32; 95% CI, 0.13-0.77) was found to have a protective association.

Aneurysm-related mortality. Aneurysm-related causes were responsible for six of the deaths (incidence rate of 0.29 per 100 person-years). For two patients, the reported main cause of death was vascular graft infection (ICD-10 code T82.7). These patients developed a type IA endoleak and aneurysm rupture and died in the perioperative period after open conversion. Another two patients had postprocedural complications of the circulatory system, unspecified (ICD-10 code I97.9). One of these patients had developed a type IA endoleak and underwent open conversion. This patient died 4 months later after having been transferred to another health care institution, but the exact cause of death could not be obtained. The other patient presented with acute limb ischemia due to endograft limb occlusion and died of myocardial infarction in the perioperative period after a successful thrombectomy. Finally, the cause of death of the remaining two patients was classified as sequelae of complications of surgical and medical care (ICD-10 code T98.3). One of these patients had undergone a femoral-femoral bypass because of acute limb ischemia a month before and presented with thrombosis of the crossover bypass. During the thrombectomy procedure, this patient died of heart failure. The last patient with a type IB endoleak detected on routine imaging surveillance developed a type IA endoleak and AAA rupture while awaiting treatment. As the type IA endoleak was considered unsuitable to endovascular repair and the patient was unfit for open repair, no intervention was performed.

DISCUSSION

This study suggests that after standard EVAR for intact AAA, the main causes of death are cardiovascular diseases and cancer. Baseline AAA diameter >70 mm was associated with both an increased risk of all-cause and cardiovascular mortality after standard EVAR for intact degenerative AAA. In addition, an increased risk of cardiovascular mortality was found among patients with neck diameters ≥30 mm, which was independent from preoperative AAA diameter. However, this relative excess of cardiovascular-related mortality in the wide infrarenal neck group was not AAA related, implicating that preoperative presence of a wide proximal neck diameter did

Table III. Risk factors for cardiovascular-related mortality

		Cardiovascular mortality					
		First model			Final model		
Variables	Univariable *P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (per year)	.001	1.62	1.12-2.35	.011	1.66	1.15-2.41	.007
Female sex	.026	0.48	0.25-0.92	.027	2.04	1.08-4.00	.030
Renal insufficiency	.003	2.03	1.16-3.56	.013	2.09	1.19-3.65	.010
AAA diameter >70 mm	.005	2.20	1.16-4.16	.016	2.45	1.34-4.46	.003
Infrarenal neck diameter ≥30 mm	.104	1.98	1.00-4.10	.05	2.16	1.05-4.43	.037
Reverse-tapered neck configuration	.054	1.44	0.80-2.61	.227	–	–	–
Neck thrombus >25%	.004	0.31	0.12-0.76	.011	0.32	0.13-0.77	.011
α angle ≥45 degrees	.054	1.39	0.66-2.94	.39	–	–	–

AAA, Abdominal aortic aneurysm; *CI*, confidence interval; *HR*, hazard ratio.
Multivariable regression performed with progressive backward stepwise modeling including variables with $\alpha < .1$ in the first model and variables $\alpha < .05$ in the final model.
Cause of death was known for 156 of 158 patients who were deceased to the end of 2014, 19 in the ≥30-mm neck diameter group and 139 in the control group.

not result in more AAA ruptures of other AAA-related life-threatening complications.

Contemporary management of AAA patients who reach a repair threshold involves a complex decision-making process in which demographics, comorbidities, anatomic features, operative risk, vital prognosis, and patients' preferences are considered. The reduced overall survival of AAA patients after repair compared with age- and sex-matched counterparts has been reported and has been attributed to cardiovascular events.[1,17] More recently, some studies have suggested a change in the epidemiology, with other competing health risks, such as cancer, gaining a greater preponderance among death causes of AAA patients.[2] Yet, as arterial aneurysmal disease and atherosclerosis share most of the previously established risk factors, it is not surprising that cardiovascular diseases are still one of the main causes of death among these patients.[18,19] In a systematic review from Khashram et al,[3] several risk factors (hypertension, hyperlipidemia, tobacco abuse) and comorbidities (cardiac disease, cerebrovascular disease, renal insufficiency, pulmonary disease) were independently linked to the excessive mortality found in AAA patients, which parallels the results reported in our study. In addition, sex-related disparities have been extensively reported regarding perioperative EVAR outcomes and long-term survival, generally disfavorable for women.[20,21] In our report, female sex was also associated with an increased risk of cardiovascular mortality.

In addition to demographics and patients' comorbidities, some anatomic features, such as arterial calcification and in particular abdominal aortic calcification, have been found to influence survival in the general population as well as in populations with aortic aneurysms.[7,22,23] In our study, only aortic neck calcification was assessed, with no association with survival found.

More important, AAA diameter has also been associated with a worse survival by several authors, including a systematic review and meta-analysis from Bahia et al.[24,25] Among EVAR patients, Huang et al[26] observed an increased risk of mortality in adjusted analyses of patients with AAA diameters >6.0 cm (HR, 2.0; 95% CI, 1.4-2.9). Similarly, Leurs et al[27] had found an 8-year survival rate of 49.6% among patients with AAA diameters ≥55 mm (n = 609), which was also significantly shorter compared with the remaining cohort (74.5% [n = 581]; $P < .001$). However, in the report from Leurs et al, an excess of aneurysm-related mortality was reported among the ≥55-mm AAA diameter group (21.2% vs 5.7% in the <55-mm group; $P < .001$), which contributed to the observed survival difference, possibly related to the inclusion of older generation devices that were more prone to fail compared with more recent endografts.[28] To overcome this limitation, Waasdorp et al[8] analysed a subgroup of patients from the European Collaborators on Stent/graft Techniques for aortic Aneurysm Repair (EUROSTAR) registry treated only with a single second-generation device (Talent; Medtronic, Santa Rosa, Calif). Still, an increased mortality was reported among patients with AAA diameters >60 mm and infrarenal neck diameters >26 mm ($P = .002$). Nevertheless, these patients also suffered from a higher rate of aneurysm-related complications, including type I endoleaks, open conversion, and aneurysm rupture. Interestingly, in a study from Brady et al[29] reporting on the UK Small Aneurysm Trial and study cohort, patients with larger AAA diameters were found to have a higher risk of cardiovascular mortality (not aneurysm related) both before (odds ratio, 1.3; 95% CI, 1.0-1.8 per 0.8 cm of AAA diameter increase) and after AAA repair (odds ratio, 1.3; 95% CI, 1.1-1.6 per 0.8 cm of AAA diameter increase). Importantly, in this study, all aneurysm-related deaths had been excluded from the analyses. Similarly, in our study, AAA

diameter was associated with both decreased overall survival and increased risk of cardiovascular death. Noteworthy, our analyses adjusted not only for differences in demographics and comorbidities but also for other morphologic characteristics as well. Consequently, our results suggest that factors related to the size of the aneurysm itself may play a role in the excessive mortality found among these patients. Increased wall inflammation and serum level of high-sensitivity C-reactive protein have been identified among patients with larger aortic aneurysms.[30,31] Furthermore, systemic inflammation has been associated with increased mortality in the long term among patients with atherosclerotic disease.[32] Consequently, one may speculate that the survival disadvantage found among patients with larger AAA diameters suggests that the aneurysm itself may play a biologically active role as a source of inflammation. Still, although more robust data are not available, patients with large AAA size still have a shorter survival compared with patients with smaller AAA diameters, greatly related to a higher risk of cardiovascular death. Consequently, although it is not recommended in practice guidelines, a more intensive management of these patients' comorbidities with inclusion of routine high-dose statin therapy with the purpose of lowering cardiovascular risk may be justified in this particular group of AAA patients.[33] In this report, we also investigated the importance of infrarenal neck diameter. The association between large (>26 mm) infrarenal aortic necks and worse survival had been previously reported by Waasdorp et al. However, along with the limitations listed before, the exact causes of death of these patients were not reported. More important, the authors included patients with both infrarenal neck diameter >26 mm and AAA diameter >60 mm but did not perform multivariable analysis, so the independent influence of each of these characteristics on survival could not be determined. In our study, the reported causes of death were obtained. Furthermore, infrarenal aortic neck diameter was found to be related to an increased risk of cardiovascular mortality, which was not AAA related. Moreover, this effect was independent from AAA diameter. Therefore, our results suggest that larger infrarenal neck diameters are an additional anatomic marker of a more frail overall health status. Like patients with large AAA diameters, these patients might also benefit from a more intensive management of their comorbidities and from routine high-dose statin therapy.

Aortic thrombus is another characteristic that has been associated with decreased survival after EVAR.[9,34] In a report from Parr et al[34] (N = 98), AAA thrombus volume ≥25 cm^3 was identified as an independent risk factor for cardiovascular events (relative risk, 2.3; 95% CI, 1.0-5.2). Nevertheless, as reported by the same group in a separate publication, thrombus volume and AAA size are highly correlated ($r = 0.74$; $P < .0001$), which limits their results, as they suggest that significant interaction may have been present in their multivariable modeling.[34,35] In another report focusing on mural thrombus of the thoracic and visceral aorta, Kwon et al[9] reported a shorter overall survival (mean, 64.1 ± 5.7 months) for patients with greater aortic thrombus burdens ("shaggy aorta") compared with the remaining cohort (mean, 81.5 ± 1.5 months; $P = .005$). However, these findings lost their statistical significance in multivariable analyses, suggesting that potential confounders may be responsible for their findings. Paradoxically, in our study, patients with >25% circumferential thrombus in the infrarenal aortic neck were found to have a decreased risk of cardiovascular death in multivariable analysis, which was not anticipated and warrants caution in interpretation. However, as we did not assess the presence of aortic thrombus in other segments, we cannot determine whether infrarenal neck thrombus was associated with greater thrombus burden in the thoracic and suprarenal abdominal aorta. Future investigation should be performed to clarify these findings.

The reported crude death rates after EVAR for intact AAA are subject to some variation throughout the literature. Among the randomized controlled trials (RCTs), the overall mortality was 11.3% in the Anevrysme de l'aorte abdominale: Chirurgie versus Endoprothese (ACE) trial during a median follow-up of 3 years, 31.1% in the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial after a median follow-up of 6.4 years, 39.2% in the Open Versus Endovascular Repair (OVER) trial at a mean follow-up of 5.2 years, and 53% beyond the eighth year of follow-up in the UK EndoVascular Aneurysm Repair (EVAR 1) trial.[36-39] Regarding registry databases, Schermerhorn et al[40] reported an 8-year death rate of 54.9% among 39,966 Medicare patients treated by EVAR, which parallels the EVAR 1 trial data. In the Swedish population, Mani et al[1] found a 5-year death rate of 25.9% among 855 EVAR patients, which was lower than in the previously cited studies and suggested that long-term survival had improved in more recent years. In two separate meta-analyses including the aforementioned reports, the overall mortality was found to be 31% at 5-year follow-up and 34.7% at 4-year follow-up, respectively.[3,41] In our study, the crude mortality rate (mean, 7.7%/y) is within the range of the reported meta-analyses but higher than in the RCTs, which may be the consequence of comorbidities and life expectancy differences in these populations.

Aneurysm-related mortality was responsible for 1.5% of the deaths in our population, which is similar to the rates reported in the RCTs. In the ACE trial, 2% of the EVAR patients died of aneurysm-related causes, whereas in the OVER trial, a comparable 1.8% of aneurysm-related deaths was also found but during a longer follow-up time (median of 3 years vs mean of 5.2 years, respectively). In the EVAR 1 trial, the incidence rate of aneurysm-related mortality was 0.6 per 100 person-years from 6 months to

4-year follow-up and increased to 0.9 per 100 person-years during the 4- to 8-year period. In comparison to the EVAR 1 trial, our study shows a lower rate of aneurysm-related deaths (0.29 per 100 person-years). This discrepancy may well be due to improved selection of patients and better performance of later generation endografts.[28] However, these data should be interpreted with caution because of the low number of events and because four perioperative (AAA-related) deaths were excluded from our analysis. Consequently we were not able to determine the importance of each of the studied morphologic characteristics on aneurysm-related mortality.

Other noteworthy limitations of this study include its retrospective design and the inclusion of patients treated at a single center, which may have introduced a selection bias. In addition, autopsies are not routinely performed in The Netherlands, which may have limited the diagnostic accuracy and consequent codification of cause of death, particularly for the AAA-related deaths. It was not possible to determine the proportion of deaths coded on the basis of autopsy in this study. Nevertheless, the causes of death were obtained from the Central Bureau of Statistics and were available for 99% of those patients who died before the start of 2015; these are the most reliable mortality data available in The Netherlands, a country with a recognized strict policy of rigor in reporting causes of death. The accuracy of cause of death coding in The Netherlands has been previously investigated and was found to be higher than 90%.[42] Still, we suggest that data regarding cause of death be carefully interpreted, taking into account the potential for some degree of misdiagnosis to be present. Also, our results may not be applicable to non-Western European populations with different genetic and environmental backgrounds, to other populations in whom secondary prevention differs from the standards of practice in The Netherlands, or to other populations with greatly different disease incidences. Also important, the exclusion of patients who died during the index hospitalization for EVAR or for whom a preoperative CT image was not retrievable for analysis may constitute a selection bias. Finally, all patients included were from a tertiary center with expertise in AAA management, which may limit the generalizability of our findings to other centers.

CONCLUSIONS

This study suggests that patients with AAA diameters >70 mm are at increased risk of all-cause and cardiovascular mortality. In addition, patients with infrarenal neck diameters ≥30 mm had a greater risk of cardiovascular mortality. Importantly, this relative excess of cardiovascular mortality was not AAA related. Consequently, patients with large AAA diameter and wider neck diameters may warrant a more aggressive management of their medical comorbidities to improve survival after EVAR.

AUTHOR CONTRIBUTIONS

Conception and design: NO, HV
Analysis and interpretation: NO, KU, MR, JP, SR, FG, SH, HV
Data collection: NO, KU, FG
Writing the article: NO, KU
Critical revision of the article: NO, KU, MR, JP, SR, FG, SH, HV
Final approval of the article: NO, KU, MR, JP, SR, FG, SH, HV
Statistical analysis: NO, KU, SH
Obtained funding: Not applicable
Overall responsibility: HV
NO and KU contributed equally to this article and share co-first authorship.

REFERENCES

1. Mani K, Bjorck M, Lundkvist J, Wanhainen A. Improved long-term survival after abdominal aortic aneurysm repair. Circulation 2009;120:201-11.
2. Bastos Goncalves F, Ultee KH, Hoeks SE, Stolker RJ, Verhagen HJ. Life expectancy and causes of death after repair of intact and ruptured abdominal aortic aneurysms. J Vasc Surg 2016;63:610-6.
3. Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Systematic review and meta-analysis of factors influencing survival following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2016;51:203-15.
4. Witteman JC, Kok FJ, van Saase JL, Valkenburg HA. Aortic calcification as a predictor of cardiovascular mortality. Lancet 1986;2:1120-2.
5. Witteman JC, Kannel WB, Wolf PA, Grobbee DE, Hofman A, D'Agostino RB, et al. Aortic calcified plaques and cardiovascular disease (the Framingham Study). Am J Cardiol 1990;66:1060-4.
6. Buijs RV, Willems TP, Tio RA, Boersma HH, Tielliu IF, Slart RH, et al. Calcification as a risk factor for rupture of abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2013;46:542-8.
7. Valentijn TM, Hoeks SE, Bakker EJ, Voute MT, Chonchol M, van de Luijtgaarden KM, et al. Influence of aortic valve calcium on outcome in patients undergoing peripheral vascular surgery. Am J Cardiol 2012;110:1195-9.
8. Waasdorp EJ, de Vries JP, Hobo R, Leurs LJ, Buth J, Moll FL, et al. Aneurysm diameter and proximal aortic neck diameter influence clinical outcome of endovascular abdominal aortic repair: a 4-year EUROSTAR experience. Ann Vasc Surg 2005;19:755-61.
9. Kwon H, Han Y, Noh M, Gwon JG, Cho YP, Kwon TW. Impact of shaggy aorta in patients with abdominal aortic aneurysm following open or endovascular aneurysm repair. Eur J Vasc Endovasc Surg 2016;52:613-9.
10. Bastos Goncalves F, van de Luijtgaarden KM, Hoeks SE, Hendriks JM, ten Raa S, Rouwet EV, et al. Adequate seal and no endoleak on the first postoperative computed tomography angiography as criteria for no additional imaging up to 5 years after endovascular aneurysm repair. J Vasc Surg 2013;57:1503-11.
11. van Prehn J, van der Wal MB, Vincken K, Bartels LW, Moll FL, van Herwaarden JA. Intra- and interobserver variability of aortic aneurysm volume measurement with fast CTA post-processing software. J Endovasc Ther 2008;15:504-10.
12. van Keulen JW, Moll FL, Tolenaar JL, Verhagen HJ, van Herwaarden JA. Validation of a new standardized method to measure proximal aneurysm neck angulation. J Vasc Surg 2010;51:821-8.
13. Oliveira NF, Bastos Goncalves FM, Van Rijn MJ, de Ruiter Q, Hoeks S, de Vries JP, et al. Standard endovascular aneurysm

repair in patients with wide infrarenal aneurysm necks is associated with increased risk of adverse events. J Vasc Surg 2017;65:1608-16.
14. Balm R, Stokking R, Kaatee R, Blankensteijn JD, Eikelboom BC, van Leeuwen MS. Computed tomographic angiographic imaging of abdominal aortic aneurysms: implications for transfemoral endovascular aneurysm management. J Vasc Surg 1997;26:231-7.
15. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002;35:1048-60.
16. Chaikof EL, Fillinger MF, Matsumura JS, Rutherford RB, White GH, Blankensteijn JD, et al. Identifying and grading factors that modify the outcome of endovascular aortic aneurysm repair. J Vasc Surg 2002;35:1061-6.
17. Batt M, Staccini P, Pittaluga P, Ferrari E, Hassen-Khodja R, Declemy S. Late survival after abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 1999;17:338-42.
18. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
19. Ohrlander T, Dencker M, Dias NV, Gottsater A, Acosta S. Cardiovascular predictors for long-term mortality after EVAR for AAA. Vasc Med 2011;16:422-7.
20. Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT; SWAN collaborators. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet 2017;389:2482-91.
21. Desai M, Choke E, Sayers RD, Nath M, Bown MJ. Sex-related trends in mortality after elective abdominal aortic aneurysm surgery between 2002 and 2013 at National Health Service hospitals in England: less benefit for women compared with men. Eur Heart J 2016;37:3452-60.
22. Bastos Goncalves F, Voute MT, Hoeks SE, Chonchol MB, Boersma EE, Stolker RJ, et al. Calcification of the abdominal aorta as an independent predictor of cardiovascular events: a meta-analysis. Heart 2012;98:988-94.
23. Chowdhury MM, Zielinski LP, Sun JJ, Lambracos S, Boyle JR, Harrison SC, et al. Editor's choice—calcification of thoracic and abdominal aneurysms is associated with mortality and morbidity. Eur J Vasc Endovasc Surg 2018;55:101-8.
24. Forsdahl SH, Solberg S, Singh K, Jacobsen BK. Abdominal aortic aneurysms, or a relatively large diameter of non-aneurysmal aortas, increase total and cardiovascular mortality: the Tromsø study. Int J Epidemiol 2010;39:225-32.
25. Bahia SS, Holt PJ, Jackson D, Patterson BO, Hinchliffe RJ, Thompson MM, et al. Systematic review and meta-analysis of long-term survival after elective infrarenal abdominal aortic aneurysm repair 1969-2011: 5 year survival remains poor despite advances in medical care and treatment strategies. Eur J Vasc Endovasc Surg 2015;50:320-30.
26. Huang Y, Gloviczki P, Duncan AA, Kalra M, Oderich GS, Fleming MD, et al. Maximal aortic diameter affects outcome after endovascular repair of abdominal aortic aneurysms. J Vasc Surg 2017;65:1313-22.e4.
27. Leurs LJ, Buth J, Laheij RJ. Long-term results of endovascular abdominal aortic aneurysm treatment with the first generation of commercially available stent grafts. Arch Surg 2007;142:33-41; discussion: 42.
28. Tadros RO, Faries PL, Ellozy SH, Lookstein RA, Vouyouka AG, Schrier R, et al. The impact of stent graft evolution on the results of endovascular abdominal aortic aneurysm repair. J Vasc Surg 2014;59:1518-27.
29. Brady AR, Fowkes FG, Thompson SG, Powell JT. Aortic aneurysm diameter and risk of cardiovascular mortality. Arterioscler Thromb Vasc Biol 2001;21:1203-7.
30. MA3RS Study Investigators. Aortic wall inflammation predicts abdominal aortic aneurysm expansion, rupture, and need for surgical repair. Circulation 2017;136:787-97.
31. Vainas T, Lubbers T, Stassen FR, Herngreen SB, van Dieijen-Visser MP, Bruggeman CA, et al. Serum C-reactive protein level is associated with abdominal aortic aneurysm size and may be produced by aneurysmal tissue. Circulation 2003;107:1103-5.
32. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018;391:319-28.
33. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg 2018;67:2-77.e2.
34. Parr A, McCann M, Bradshaw B, Shahzad A, Buttner P, Golledge J. Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms. J Vasc Surg 2011;53:28-35.
35. Golledge J, Wolanski P, Parr A, Buttner P. Measurement and determinants of infrarenal aortic thrombus volume. Eur Radiol 2008;18:1987-94.
36. Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P, et al. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. J Vasc Surg 2011;53:1167-73.e1.
37. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1881-9.
38. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012;367:1988-97.
39. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG; EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet 2004;364:843-8.
40. Schermerhorn ML, Buck DB, Curran T, McCallum JC, O'Malley AJ, Cotterill P, et al. Long-term outcomes and temporal trends with endovascular vs open repair of abdominal aortic aneurysms in the Medicare population. J Vasc Surg 2014;60:830.
41. Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg 2013;100:863-72.
42. Harteloh P, de Bruin K, Kardaun J. The reliability of cause-of-death coding in The Netherlands. Eur J Epidemiol 2010;25:531-8.

Submitted Apr 22, 2018; accepted Jul 29, 2018.