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Tomee, S.M.; Bulder, R.M.A.; Meijer, C.A.; Berkum, I. van; Hinnen, J.W.; Schoones, J.W.; ... ; Lindeman, J.H.

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Excess Mortality for Abdominal Aortic Aneurysms and the Potential of Strict Implementation of Cardiovascular Risk Management: A Multifaceted Study Integrating Meta-Analysis, National Registry, and PHAST and TEDY Trial Data

Stephanie M. Tomee [a], Ruth M.A. Bulder [a], C. Arnoud Meijer [b], Ingrid van Berkum [a], Jan-Willem Hinnen [c], Jan W. Schoones [d], Jonathan Golledge [e,f], Esther Bastiaannet [g], Jon S. Matsumura [h], Jaap F. Hamming [a], Rebecka Hultgren [i], Jan H. Lindeman [a,*]

[a] Department of Vascular Surgery, Leiden University Medical Centre, Leiden, the Netherlands
[b] Department of Radiology, Martini Hospital, Groningen, the Netherlands
[c] Department of Vascular Surgery, Jeroen Bosch Hospital, 's-Hertogenbosch, GZ, the Netherlands
[d] Walaeus Library, Leiden University Medical Centre, Leiden, the Netherlands
[e] The Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Australia
[f] Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Australia
[g] Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands
[h] University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA
[i] Department of Vascular Surgery, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

WHAT THIS PAPER ADDS

While the primary concern with abdominal aortic aneurysms (AAAs) is rupture, and rupture risk is now adequately managed by screening and preventive aneurysm repair, a meta-analysis and evaluation of National data for Sweden shows that AAA disease is associated with a disquieting quadrupled (women) and doubled (men) five years residual mortality. This excess mortality may largely reflect the sharply increased cardiovascular risk. Cross sectional evaluation of the level of risk management of patients with AAA participating in the Pharmaceutical Aneurysm Stabilisation Trial (PHAST) and Pharmaceutical Aneurysm Stabilisation Trial (TEDY) trial shows that cardiovascular risk is generally, and particularly in women, suboptimally managed. Conclusions from a validated risk score algorithm stress the relevance of strict adherence to the guidelines for cardiovascular risk management for extremely high risk patients in managing patients with AAA.

Objective: Previous studies imply a profound residual mortality risk following successful abdominal aorta aneurysm (AAA) repair. This excess mortality is generally attributed to increased cardiovascular risk. The aim of this study was (1) to quantify the excess residual mortality for patients with AAA, (2) to evaluate the cross sectional level of cardiovascular risk management, and (3) to estimate the potential of optimised cardiovascular risk management to reduce the excess mortality in these patients.

Methods: Excess mortality was estimated through a systematic review and meta-analysis, and through data from the Swedish National Health Registry. Cardiovascular risk profiles were individually assessed during eligibility screening of patients with AAA for two multicentre pharmaceutical AAA stabilisation trials. The potential of full implementation of cardiovascular risk management was estimated through the validated Second Manifestations of ARTerial disease (SMART) risk scores algorithm.

Results: The meta-analysis showed a similarly impaired survival for patients who received early repair (small AAA) or regular repair ($\geq$ 55 mm), and a further impaired survival for patients under surveillance for a small AAA. Excess mortality was further quantified using Swedish population data. The data revealed a more than quadrupled and doubled five year mortality rate for women and men who had their AAA repaired, respectively. Evaluation of the level of risk management of 358 patients under surveillance in 16 Dutch hospitals showed that the majority of patients with AAA did not meet therapeutic targets set for risk management in high risk populations, and indicated a more pronounced prevention gap in women. Application of the SMART risk score algorithm predicted that optimal implementation of risk management guidelines would reduce the 10 year risk of major adverse cardiovascular events from 43% to 14%.

Conclusion: Independent of the rupture risk, AAA is associated with a worryingly compromised life expectancy with a particularly poor prognosis for women. Optimal implementation of cardiovascular risk prevention guidelines is predicted to profoundly reduce cardiovascular risk.

* Corresponding author. Department of Vascular Surgery K6-R, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands
E-mail address: Lindeman@lumc.nl (Jan H. Lindeman).

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INTRODUCTION

Rupture risk in abdominal aortic aneurysm (AAA) is now effectively managed by screening programmes and elective repair. Worryingly, the disease remains associated with a profound excess mortality[1–3] that appears largely independent of the rupture risk.[4–6] Epidemiological observations suggest that this excess (residual) mortality essentially relates to an increased cardiovascular risk,[7,8] and prevailing cardiovascular risk management guidelines classify patients with AAA as "at very high risk" patients.[9]

Notwithstanding, it is consistently concluded that the management of patients with AAA remains essentially rupture prevention focused, and that the accompanying excess cardiovascular risk, and the residual mortality risk receive less attention, or are in fact ignored.[2] The aim of this multifaceted study was threefold: (1) to provide an estimate of the residual mortality risk for patients with AAA; (2) to assess the level of cardiovascular risk management in patients with AAA in daily practice; and (3) to estimate the potential impact of a full implementation of the current cardiovascular prevention guidelines. The research strategy and the methodologies used in this study are summarised in Table 1.

MATERIALS AND METHODS

This multifaceted study is based on three pillars (Table 1). The first pillar evaluates the excess mortality risk of patients with AAA, the second pillar assesses the cross sectional level of cardiovascular risk management of patients with AAA, and the final third pillar estimates the potential of full implementation of prevailing cardiovascular prevention guidelines. Reporting of the observational data was in accordance with the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) checklists for observational data.

Aim 1. Estimation of the excess mortality of patients with abdominal aortic aneurysm

Systematic literature review of long term survival of patients with abdominal aortic aneurysm. Survival estimates for patients with AAA who had their larger (> 55 mm) aneurysm repaired were estimated on the basis of a previously published systematic review and meta-analysis of survival following respectively endovascular aneurysm repair (EVAR) or open repair performed by this group.[5] Because the meta-analysis showed similar survival following open or endovascular repair,[5] data were now pooled to obtain survival estimates for patients who had their larger AAA repaired.

Additional systematic reviews and meta-analyses were performed in order to estimate survival for patients with *small* (i.e., less than 55 mm) aneurysms. A first meta-analysis estimated post-repair survival of patients who underwent repair of a small aneurysm. The second analysis focused on patients under surveillance for a small AAA. Eligible studies were identified through a search using PubMed, Embase, Web of Science, and Cochrane central (the detailed search strategy is available in Supplementary File S1). The key inclusion criterion for the studies was the availability of long term survival data (at least one year survival) for patients with a small infrarenal AAA (< 5.5 cm). Excluded were studies involving ruptured or thoracic, mycotic or inflammatory aneurysms, or that studied medical stabilisation of their AAA (such as the Pharmaceutical Aneurysm Stabilisation Trial [PHAST] and TElmisartan in the management of abDominal aortic aneurysm [TEDY] trial),[10,11] as well as articles that were not available in full text or English literature, as well as editorials, letters, comments, or reviews. The final search update was performed on 6 July 2021. The systematic review was not registered.

The search strategy for the additional systematic review has been reported earlier.[5] For the current study, the specific components for surgical repair (EVAR or open repair) or surveillance strategies were omitted because this limited the search. Two authors reviewed the titles and abstracts for eligibility. When eligibility was unclear, full texts were reviewed. The screening process is summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Data extracted from the identified studies were inclusion criteria, characteristics of study population, duration of follow up, and overall survival at one, three, five, and 10 years when available. The overall survival was extracted from Kaplan–Meier graphs. In short, Kaplan–Meier graphs were magnified and printed on A3 paper. Survival was retrieved by reading the intersection point of lines drawn on the tick marks of the y axis (survival) *vs.* x axis (time points of one, three, five, and 10 years).[12] When authors presented their results in multiple studies, only the most recent publication was included in the meta-analysis.

To evaluate the risk of bias and quality of study the Cochrane Collaboration's tool (for randomised trials) or ROBINS-I tool (for non-randomised trials) was used for assessing risk of bias.[13,14] Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[15]

Table 1. Summary of the structure of this multifaceted study on excess mortality in patients with abdominal aortic aneurysms (AAA)

Study facets	Approach	Strategy
Aim 1: Estimation of the excess mortality of patients with AAA	(A) Systematic review and meta-analysis	Relative survival of (1) Patients under surveillance for a small AAA (2) Patients receiving early (<55 mm) repair (3) Patients who had regular elective AAA repair (>55 mm)
	(B) National (Swedish) registry data	Standardised excess five years mortality rate for patients with AAA (2006−2010 interval)
Aim 2: Inventory of the level of cardiovascular risk management in patients with AAA	Assessment of the level of risk management in patients with AAA participating in the PHAST[10] and TEDY[11] trial in 14 centres in The Netherlands	Prescription status of hypertensives and lipid lowering medication. Assessment of blood pressure and plasma lipid profiles
Aim 3: Impact of full implementation of the current cardiovascular prevention guidelines	Estimation of the additional impact of strict implementation of risk management on 10 year cardiovascular risk	Application of the European Society of Cardiology SMART risk estimation tool[12,13] on the population inventoried in aim 2

PHAST = Pharmaceutical Aneurysm Stabilisation Trial; TEDY = TElmisartan in the management of abDominal aortic aneurysm; SMART = Second Manifestations of ARTerial disease.

Standardised excess mortality of patients with abdominal aortic aneurysm. Since conclusions from the meta-analyses are summarised as relative survival estimates (relative survival) and are thus influenced by the baseline risk, more tangible risk estimates of additional relevance were considered. Standardised excess mortality, expressed as the number of observed deaths in a specific subpopulation divided by the number of expected deaths, is a strategy that provides a more qualitative estimate of the risks associated with a particular condition. Standardised excess mortality was estimated for the Swedish population using the National Patient Registry (NPR). Data for patients diagnosed with a repaired AAA were used to estimate the AAA associated standardised excess (residual) mortality. The NPR has a positive predictive value up to 96%, and 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.[6] Data were available for the 2000 − 2015 interval. Case identification was based on the registered diagnosis (intact AAA, International Classification of Diseases 9 or 10 codes). Standardised excess mortality was estimated for 2006 − 2010, representing the most recent interval for which five years survival was available. Patients with a diagnosis of ruptured AAA were excluded.

Standardised excess mortality was estimated by comparing the observed five years mortality of patients with an AAA with that of the corresponding (matched for age, sex, and year) Swedish general population.[16] National life tables (Statistics Sweden[17]) were used to estimate the expected five years mortality rate. The excess mortality rate was calculated by dividing the observed number of deaths of patients with AAA by the expected number of deaths for the corresponding general population for the index period.[16]

Use of the registry data 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 data handling followed the requirements of the EU data protection laws.

Aim 2. Inventory of the level of cardiovascular risk management in patients with abdominal aortic aneurysm

The level of risk management in patients under surveillance for a small AAA was inventoried in patients participating in the PHAST[10] and TEDY[11] trials in The Netherlands. Study protocols of both trials were approved by the Medical Ethical Review Board of the Leiden University Medical Centre and by the local review boards of the 16 participating centres. Written informed consent was obtained from all participants.

The PHAST trial tested the effectiveness of 18 months of doxycycline therapy or placebo in inhibiting AAA growth. The trial included 286 Dutch patients with an AAA measuring between 35 mm and 50 mm. The PHAST study was completed in June 2011 and has been reported previously.[10] The TEDY trial is an international randomised controlled trial testing the effect of telmisartan on aneurysm growth in patients with small AAAs (diameter 35 − 49 mm).[11] The 72 Dutch patients participating in the trial were included in this inventory.

This study is based on data collected at the eligibility screening for the PHAST and TEDY trials. For both trials, data with respect to current medication and smoking habits were collected during the eligibility screening and baseline visit. Moreover, standardised measurements were performed of height, weight, and systolic and diastolic blood pressure. Serum blood samples were analysed for lipid spectrum (low density lipoprotein [LDL], high density lipoprotein [HDL], total cholesterol, and triglycerides), the levels of creatinine, alanine transaminase, and (for TEDY only) glycated haemoglobin. The cholesterol/HDL ratio was estimated on the basis of total cholesterol and HDL levels, and the Modification of Diet in Renal Disease formula was used to estimate glomerular filtration rate.[18]

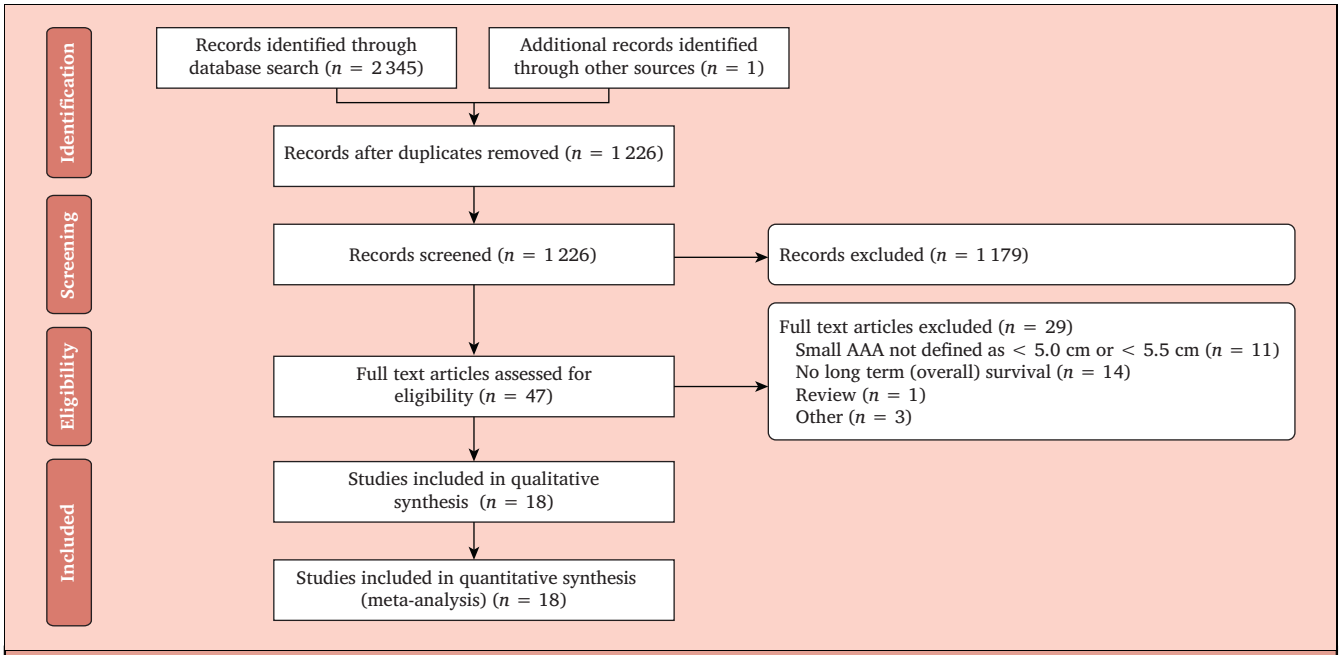

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting search and study selecting processes in this systematic review of long term survival of patients with small abdominal aortic aneurysms (AAA).

All blood samples were analysed in a certified laboratory (the Department of Clinical Chemistry, Leiden University Medical Centre).

AIM 3. The potential of full implementation of the current cardiovascular prevention guidelines

The Second Manifestations of ARTerial disease (SMART) risk score,[19] an online tool offered by the European Society of Cardiology,[20] estimates 10 year risk of recurrent vascular events in patients with manifest cardiovascular disease. The tool was used to estimate the cardiovascular risk, and the anticipated risk reduction through optimised risk management (relative risk reduction and number needed to treat) for each individual AAA patient participating in the PHAST or TEDY trial. Optimised targets were systolic blood pressure < 140 mmHg, LDL < 1.8 mmol/L, cessation of smoking, or a combination of the different targets.[12,13] Missing values were considered as missing at random.

Statistical analyses

Meta-analysis and survival analyses were performed using Stata/SE, version 12.0 (StataCorp, College Station, TX, USA). I^2 statistics were used to estimate heterogeneity.[21] A value of $> 50\%$ was considered to indicate significant heterogeneity.[21] Relative survival for studies included in the meta-analysis was achieved by calculating the observed expected ratios and their 95% confident intervals followed by transformation to their natural logarithms. Pooled observed expected ratios were estimated for patients undergoing elective surgical repair (EVAR and open repair) and those

Table 2. Relative survival of patients with abdominal aortic aneurysms (AAA) included in this systematic review and meta-analysis of the available literature, including a total of 18 studies and 20 364 patients. Relative survival reflects the observed survival of the study population divided by the expected survival of the reference population (i.e., general population matched for age, sex year of operation, and country). A relative survival of 100% respectively. 50% reflects a survival equal to, respectively one half of that of the reference population

Follow up − y	Relative survival − %		
	Small AAA (<5.5 cm)		AAA (>5.5 cm)
	Intervention (*n* = 18 500)	Surveillance (*n* = 1 864)	Intervention (*n* = 131 925)
1	97 (96–97)	100 (100–100)	–
3	97 (96–97)	98 (96–99)	94 (94–95)
5	84 (79–90)	70 (60–82)	90 (88–91)
10	62 (49–80)*	65 (62–68)†	76 (71–82)

Data are presented as median (95% confidence interval).
* 10 year survival data only available for two studies ($n = 1\ 197$).[21,26]
† 10 year survival data only available for two studies ($n = 1\ 224$).[21,36]

Table 3. Rupture censored five years excess mortality for 11 351 patients with abdominal aortic aneurysms (AAA; both small and large) included in the Swedish National Registry between 2006 and 2010

Data at five years	Males (n = 8 940)			Females (n = 2 411)		
	<70 y	70–79 y	≥80 y	<70 y	70–79 y	≥80 y
Patients with AAA at risk – n*	3 332	3 691	1 917	584	1 042	785
Observed mortality in the AAA population	545 (16.4)	1 258 (34.1)	1 245 (64.9)	109 (18.7)	426 (40.1)	521 (66.4)
Expected mortality for the age and sex matched population†	216 (6.5)	617 (16.7)	707 (36.9)	23 (3.9)	108 (10.4)	199 (25.4)
Excess mortality for patients with AAA‡	329 (9.9)	641 (17.4)	538 (28.1)	86 (14.7)	318 (30.5)	322 (41.0)
Excess mortality rate for patients with AAA§	2.52	2.04	1.76	4.74	3.76	2.62

Data are presented as n (%).
* Number of patients with AAA at risk represents the number of patients with AAA in the Swedish national registry.
† Expected mortality = anticipated mortality based on the number at risk, and the mortality for the age and sex matched Swedish general population (this number reflects the reference population).
‡ Excess mortality = observed mortality minus expected mortality.
§ Excess mortality rate = observed mortality divided by the expected mortality.

with a small aneurysm using the random effects model of DerSimonian and Laird.[22]

Relative survival for patients in the Swedish National Patients Registry was calculated by dividing the observed survival of the study population and the expected survival of a general population matched for age, sex, and year of operation.[5]

Descriptive statistics regarding the levels of risk management were performed using SPSS (version 25, IBM, Amsterdam, The Netherlands). Continuous data are presented as mean (standard deviation [SD]) or as median (interquartile range). Differences between groups were estimated using the independent t test. Categorical data are presented as percentages and tested using the chi square statistic. A p value of $< .050$ was considered to be statistically significant.

Table 4. Baseline characteristics of the 358 patients with small abdominal aortic aneurysms included in the Pharmaceutical Aneurysm Stabilisation Trial (PHAST) and TElmisartan in the management of abDominal aortic aneurysm (TEDY) trial

Baseline characteristics	Patients with small AAA (n = 358)
Male	318 (88.8)
Female	40 (11.2)
Body mass index >25 kg/m²	
Male	124 (39)
Female	10 (25)
Smoking	
Never	30 (8.4)
Current	125 (34.9)
Former	203 (56.7)
Pack years	42.5 ± 27.4
Systolic blood pressure – mmHg	144.4 ± 19.9
Diastolic blood pressure – mmHg	83.5 ± 8.9
Low density lipoprotein cholesterol – mmol/L	2.66 ± 1.03
Total cholesterol – mmol/L	4.63 ± 1.06
Triglycerides – mmol/L	1.93 ± 1.16
HDL cholesterol – mmol/L	1.12 ± 0.34
Total cholesterol/HDL ratio	4.44 ± 1.51
Glycated haemoglobin – mmol/mole	39.7 ± 5.2
*eGFR – mL/min/1.73 m²**	
Male	73.3 ± 18.1
Female	68.1 ± 16.3
Alanine transaminase – U/L	26.3 ± 13.4

Data are presented as n (%) or mean ± standard deviation. eGFR= estimated glomerular filtration rate; HDL = high density lipoprotein.
* Modification of diet in renal disease formula.

RESULTS

Aim 1. Estimation of the excess mortality of patients with abdominal aortic aneurysm

Systematic literature review of long term survival of patients with abdominal aortic aneurysm. Survival estimates for patients with a smaller AAA (< 5.5 cm) were based on a systematic review of reported survival data. A literature search identified 2 345 articles, of which 18 articles met inclusion criteria.[23–40] The screening process is summarised in the PRISMA flow diagram in Figure 1. Four of the included articles were randomised controlled trials (22%)[23–26] and 14 were retrospective studies (78%).[27–40] All included studies are summarised in Supplementary Table S1. This meta-analysis incorporated 20 364 patients: 18 500 (91%) treated by surgical repair of a small AAA, and 1 864 (9%) under surveillance for small AAA. GRADE assessment showed a moderate certainty of evidence for all 10 year survival outcomes due to the long follow up length, loss to follow up, and correlation with mortality. For all other outcomes (one, three, five year survival), certainty of evidence was classified as high. Full GRADE assessment and evidence profiles per outcome are illustrated in Supplementary Table S2.

Survival estimates for patients with larger (> 5.5 cm) AAA shown in Table 1 reflect the aggregated data for 131 925 patients included in an earlier meta-analysis of long term survival following open or endovascular repair of a larger AAA.[5] Survival data were transformed to relative survival in order to correct for variances in age and sex in the study cohorts, for putative age differences between patients with small and larger AAA, and for regional and time related differences in life expectancy. Relative survival estimates are summarised in Table 2. Relative survival estimates were similar for patients with a small AAA who received early repair, and for patients who had their larger AAA repaired (5 years relative survival: 84%, 95% CI 79 – 90%; and 90%,

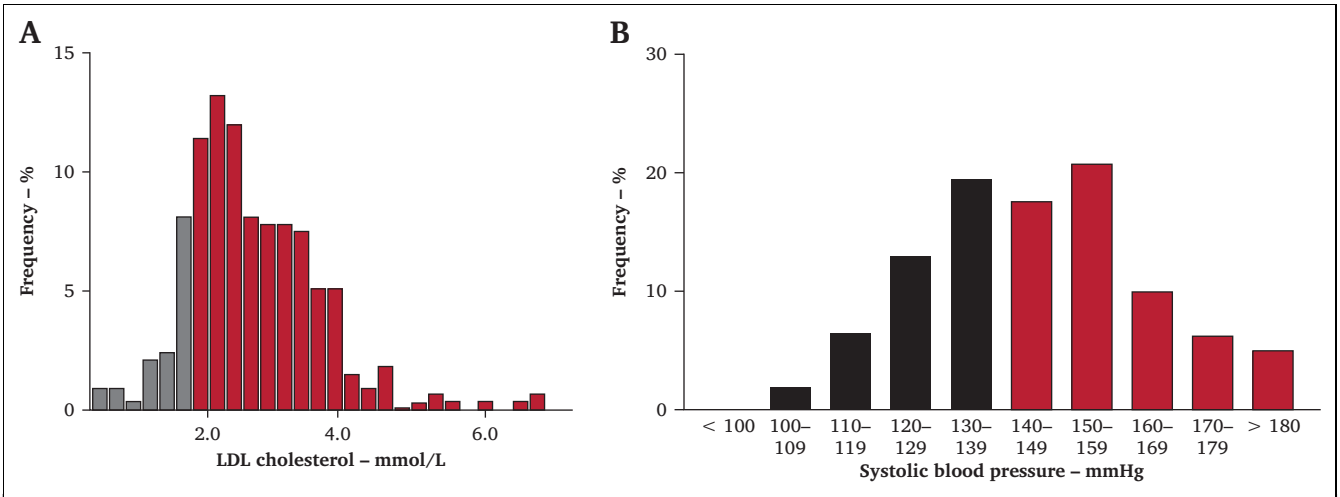

Figure 2. Distribution of (A) low density lipoprotein (LDL) cholesterol levels (mmol/L) and (B) systolic blood pressure in patients with a small (<50 mm) abdominal aortic aneurysm participating in Pharmaceutical Aneurysm Stabilisation Trial (PHAST) and TElmisartan in the management of abDominal aortic aneurysm (TEDY) trials ($n = 358$). Red bars depict individuals with LDL levels or systolic blood pressure above the target levels for high risk patients (1.8 mmol/L and 140 mmHg, respectively). Note the different scales used in A and B.

95% CI 88 — 91% respectively), and worse for patients under surveillance for a small AAA (70%, 95% CI 60 — 82%).

Standardised excess mortality of patients with abdominal aortic aneurysm. Because most studies included in the above meta-analyses report aggregated normalised data, and consequently lack sex and age specific information as well as reference values, a second, more granular survival analysis of five year survival data of all patients with an intact AAA was performed for the Swedish AAA population (Table 3). Data are presented as standardised excess mortality as this provides both reference data (included in the table as "Expected mortality for the age/sex matched population") and a more direct estimate of the AAA associated excess mortality. Results in Table 3 clearly illustrate the profound residual impact of AAA disease on five year survival, with a quadrupled (for females) and more than doubled (for males) five year mortality risk for patients under 80 with an AAA (Table 3).

Aim 2. Inventory of the level of cardiovascular risk management in patients with abdominal aortic aneurysm

This evaluation included 358 patients from 16 different hospitals in The Netherlands. The mean ± SD age of these patients was 70.3 ± 7.4 years, and 89% were male. Further characteristics of the patient cohort are presented in Table 4.

The mean ± SD body mass index (BMI) of male and female patients was 27.4 ± 3.6) kg/m^2, and 25.8 kg/m^2, respectively, and 23% and 19% of the patients were classified as obese (BMI > 30 kg/m^2). Among men, 32.7% were a current smoker, 58.8% a former smoker, and 8.5% had never smoked. Women had worse smoking habits than men: 52.5% were classified as current smokers, 40% former smokers, and 7.5% had never smoked ($\chi^2 = 6.25$, $p < .050$).

Plasma LDL cholesterol and systolic blood pressure frequency distributions are summarised in Figure 2. Mean ± SD systolic and diastolic blood pressure was 144 ± 20.1 and 83 ± 9.1 mmHg and 149±18 and 84 ± 7.8 mmHg for men and women, respectively. Thirty-eight per cent and 29% of the male and female patients with AAA had a normal blood pressure without use of antihypertensives. Sixty-three per cent of the patients reported use of antihypertensive medication. Of those prescribed antihypertensives, 57% (males) and 73% (females) had a systolic blood pressure above 140 mmHg. Diastolic blood pressure exceeded 85 mmHg in 69% of patients (similar for both sexes).

Seventy per cent of the patients used lipid lowering medication (statins). Cholesterol levels were lower in those using *vs*. not using statins; (mean ± SD LDL cholesterol, 2.33 ± 0.88 *vs.* 3.5 ± 0.91 mmol/L; total cholesterol levels, 4.3 ± 0.92) *vs.* 5.46 ± 0.96 mmol/L, both $p < .001$. Of patients receiving statin treatment 18% of males and 11% of females were on target with an LDL level of < 1.8 mmol/L.

Plasma HDL and triglycerides levels were similar between statin and non-statin users: 1.1 ± 0.4 and 2.0 ± 1.3; and 1.1 ± 0.3 and 1.8 ± 0.8, respectively.

AIM 3. The potential of full implementation of the current cardiovascular prevention guidelines

The SMART risk tool[19,20] was applied to estimate 10 year cardiovascular risk and theoretically modifiable 10 year cardiovascular risk (treatment gap) for the 304 AAA patients for whom a full risk profile was available. Predicted individual 10 years cardiovascular risk ranged from 17% to 91% (mean predicted 10 years risk, 43%). The potential impacts of the different risk reduction interventions on cardiovascular risk (smoking cessation, lipid lowering (LDL < 1.8 mmol/L), and blood pressure control (systolic blood pressure < 140 mmHg) on the estimated 10 years cardiovascular risk are summarised in Table 5. Based on the SMART risk estimation tool,[19,20] it is estimated that if optimised risk management were fully implemented in the 304 patients with AAA, this would result in 29 ± 11.3% (mean ± SD)

Table 5. Estimated risk reductions achieved by implementing cardiovascular risk management guidelines in 358 patients with a small aneurysm under surveillance in 16 hospitals in The Netherlands using the Second Manifestations of ARTerial disease (SMART) risk scores (estimated 10 year risk of cardiovascular event)

Treatment target	Men		Women	
	n	Estimated 10 year risk reduction	*n*	Estimated 10 year risk reduction
Estimated impact on patients not on target[*]				
Systolic blood pressure <140 mmHg	139	8.2 (5.3–14.5)	21	10.8 (6.1–15.9)
LDL cholesterol < 1.8 mg/dL	225	6.1 (3.1–11.3)	30	7.7 (4.2–12.8)
Smoking cessation	90	16.6 (11.5–16.4)	18	13.0 (10.8–17.3)
Systolic blood pressure <140 mmHg + LDL cholesterol <1.8 mg/dL	118	16.9 (10.6–22.6)	19	14.9 (12.9–20.2)
Systolic blood pressure <140 mmHg + smoking cessation	43	22.9 (16.5–26.7)	13	20.6 (16.6–31.2)
LDL cholesterol <1.8 mg/dL + Smoking cessation	77	19.9 (15.5–26.1)	16	16.6 (14.0–24.1)
Systolic blood pressure <140 mmHg + LDL cholesterol <1.8 mg/dL + Smoking cessation	36	27.0 (21.9–35.2)	12	24.4 (21.5–34.8)
Estimated overall impact (full cohort)				
Systolic blood pressure <140 mmHg	270	1.6 (0.0–9.1)	34	5.6 (0.0–11.5)
LDL cholesterol <1.8 mg/dL	270	4.9 (1.7–9.9)	34	6.4 (3.1–11.2)
Smoking cessation	270	0.0 (0.0–11.5)	34	9.0 (0–13.5)
Systolic blood pressure <140 mmHg + LDL cholesterol <1.8 mg/dL	270	6.8 (0.6–16.6)	34	14.4 (8.8–20.5)
Systolic blood pressure <140 mmHg + Smoking cessation	270	0.0 (0.0–12.6)	34	10.2 (0.0–20.1)
LDL cholesterol <1.8 mg/dL + smoking cessation	270	7.2 (1.8–16.1)	34	13.7 (5.4–19.1)
Systolic blood pressure <140 mmHg + LDL cholesterol <1.8 mg/dL + smoking cessation	270	7.0 (0.6–18.5)	34	18.3 (8.8–25.6)

Data are presented as median (interquartile range). LDL = low density lipoprotein.
* *n* = number of patients not on target.

reduction in 10 years risk of cardiovascular events. It was further concluded that full implementation of risk management would result in a 10 years cardiovascular risk that is approximately 14% higher than that of the general population.

DISCUSSION

The meta-analyses of reported survival data for patients with AAA included in this study, and a comparison of survival data of Swedish patients with AAA with that of the general Swedish population show an extreme impact of AAA disease on life expectancy. This excess mortality appears largely independent of rupture risk, and is assumed to relate to a sharply increased cardiovascular risk.[2,7,8] Systematic evaluation of the levels of risk management in patients under surveillance for small AAA shows that, for the majority of patients, the level of management does not meet the targets for high risk cardiovascular patients.[9] Estimation of the theoretical therapeutic gap through the SMART risk score[19,20] illustrated the profound potential of strict implementation of cardiovascular risk management in patients with AAA.

While the primary focus in AAA management is on rupture prevention, a meta-analysis of patient survival following elective open or endovascular repair shows a profound residual mortality risk for patients who had had their AAA repaired.[5] Extension of this evaluation to patients with a small (< 55 mm) AAA in the meta-analyses performed herein show an equal excess mortality for patients who underwent early repair, and an even worse prognosis for those under surveillance. Although the latter may reflect the (slight) rupture risk of small AAA, any conclusion is interfered with by medical decision making (selection bias). To be more specific: the surveillance population also includes patients deemed unfit or non-eligible for AAA repair, and or those who did not meet the inclusion criteria for randomised controlled trials. Consequently, it is likely that frail patients and other patients with an anticipated compromised life expectancy are asymmetrically represented in surveillance studies.

The relative survival analysis is based on aggregated survival information[41] from the meta-analyses and provides an estimate of exposure related deaths (i.e., in this study, disease specific mortality of patients with AAA).[42] It corrects for general interfering factors such as differences in age at the time of surgery, sex, population, and year of data collection (index years). Consequently, while this provides a global and robust overall survival estimate, age and sex specific information (women!) is lacking. To overcome this information gap, an additional analysis of Swedish national data was performed. In this analysis it was decided to apply standardised five years mortality rates rather than relative survival, as these provide more tangible reflections of AAA associated mortality.[16] This national evaluation not only confirmed the profound disease specific excess mortality observed in the meta-analysis data, but also revealed an extreme sex disparity and an age effect with a reduced excess mortality in older patients. The observed mitigation of excess mortality with increasing age presumably relates to increases in competitive deaths,[43] selective loss of vulnerable patients during ageing, and or confounding by indication (e.g., frail, older patients may not be referred for

evaluation of their AAA). The observed quadrupled five year mortality for women under 80 years provides a worrying quantification of the acknowledged poorer outcomes for female patients with AAA.[6,44]

Persistently compromised survival following AAA repair (and thus minimisation of rupture risk) implies that the excess mortality in the AAA population is largely independent of rupture risk.[45] This observation is supported by Danish population based data that reported a 2.4 fold increase in all cause mortality for the 11 094 patients with AAA who underwent acute or elective open repair.[46] The excess profound residual mortality rate is largely attributed to increased cardiovascular risk.[1,2] In fact, cardiovascular death accounts for approximately 50% of all deaths in Swedish patients with an AAA, with neoplasm-related deaths being the second most common cause of death (approximately 20 — 25% of all deaths).[6] The increased cardiovascular risk is well acknowledged, and patients with AAA are categorised as being very high risk in the current AAA and cardiovascular risk management guidelines,[9,47] and classify for intensified cardiovascular risk management accordingly.

Conclusions from the national, cross sectional inventory of the levels of risk management presented herein show that, while the great majority of patients with AAA receive some form of risk management, the overall level of risk management achieved does generally not meet the criteria for high risk patients.[9] It is unlikely that these observations are specific for the Dutch health system. In fact, multiple reports indicate suboptimal pharmaceutical risk management and smoking cessation in patients with AAA and conclude that the majority of patients with AAA are undertreated and or insufficiently monitored.[46,48]

An alarming observation is the more pronounced prevention gap in women. Although the number of women in the inventory in this study is limited, data indicate that women present with worse cardiovascular risk profiles than men. This poorer level of risk management in women is not an isolated observation for AAA patients: a Dutch evaluation of medical therapy adherence following STEMI (ST segment elevation myocardial infarction) and non-STEMI concluded that treatment adherence was lower in women,[49] and similar real world conclusions were also reached in other cohort studies.[50—52]

Available evidence suggests that patients with AAA would benefit from optimised management (treat to target), and in this context AAA screening could be considered a two edged sword by also identifying patients at a high cardiovascular risk. The report by Bahia *et al.* indicated superior five years survival for patients with AAA receiving statins, antiplatelet agents, or antihypertensive medication compared with patients not receiving either one of these therapeutic agents.[46] Similarly, multiple studies have shown that irrespective of the repair status, statin therapy is associated with superior survival in patients with AAA.[53,54] However, it is unclear whether these observations relate to a superior risk management or non-exclusively reflect confounding, caused by an association between therapy compliance and superior survival.[55]

In an effort to estimate the bridgeable prevention gap for patients with AAA (what would be gained by strict implementation of cardiovascular risk management?), the SMART risk score tool was applied.[19,20] Outcomes from the algorithm illustrated the profound potential of optimal cardiovascular risk management, with an average 25% reduction in 10 years cardiovascular risk. Notwithstanding, the data also indicate persistence of considerable residual risk.

All in all, these data illustrate the need and theoretical potential of optimised cardiovascular risk management in patients with AAA. Although the relative undermanagement may obviously relate to poor patient compliance or adherence,[49—52] or a lack of accurate disease knowledge,[56] underuse also involves iatrogenic aspects. In fact, an inventory of statin underuse identified a lack of awareness among care providers to be a preventable and major cause (i.e., more than half of patients eligible for statin therapy but not on treatment reported never being offered a statin by their doctor).[57] This observation may particularly apply to patients with AAA for whom the primary focus is surgical (i.e., management of rupture risk and the adequacy of repair). In this respect, it is concluded that patients with AAA perceive their disease as a "bodily" defect and not as a health condition with an associated risk.[58] Hence, interventions aimed at mitigating the extreme cardiovascular risk presumably also need to address a gap in health self efficacy.

Limitations

The inventory of the level of risk management was performed in patients participating in the TEDY or PHAST trials. Participants in clinical trials generally tend to be "healthier" and more motivated than general patient populations, as a consequence the data may overestimate the level of risk management. Along these lines, use of an angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist was an exclusion criterion in the TEDY trial. Since these groups of antihypertensives are considered second line antihypertensive treatment, patients with severe hypertension may be under represented in the trial. Detailed data on antiplatelet therapy were not available for patients in the PHAST study, and this therapy was therefore not incorporated as a variable in the cardiovascular risk profiles and was excluded from SMART risk analysis as a potential cardiovascular risk modifier.

The SMART risk score is a validated tool for the calculation of individual cardiovascular risk of several vascular patient groups in clinical practice.[19,20] Although the tool is validated, differences between populations are observed.[60] Finally, although the SMART risk model provides a risk estimate for recurrent cardiovascular events, it is unclear whether the risk reductions will translate to improved long term survival of patients with AAA and reduce their excess mortality.

Conclusions

Independent of rupture risk, AAA is associated with a more than doubled (men) or quadrupled (women) five year

mortality risk, a risk that far exceeds the mortality risk of patients with a previous myocardial infarction.[59] This non-aneurysmal, residual excess risk is largely amendable by cardiovascular risk prevention. Conclusions from this study suggest that cardiovascular risk management should be considered equal to or even more relevant than rupture prevention, and the level of risk management should be included as a quality parameter for the management of patients with AAA. The extremely poor outcomes for female patients with AAA are particularly worrying. Considering the traditional focus on male patients with AAA, studies focusing on female patients are urgently required.

CONFLICT OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

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