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CLINICAL RESEARCH
Cardiac and vascular surgery

Aneurysm growth, survival, and quality of life in untreated thoracic aortic aneurysms: the effective treatments for thoracic aortic aneurysms study

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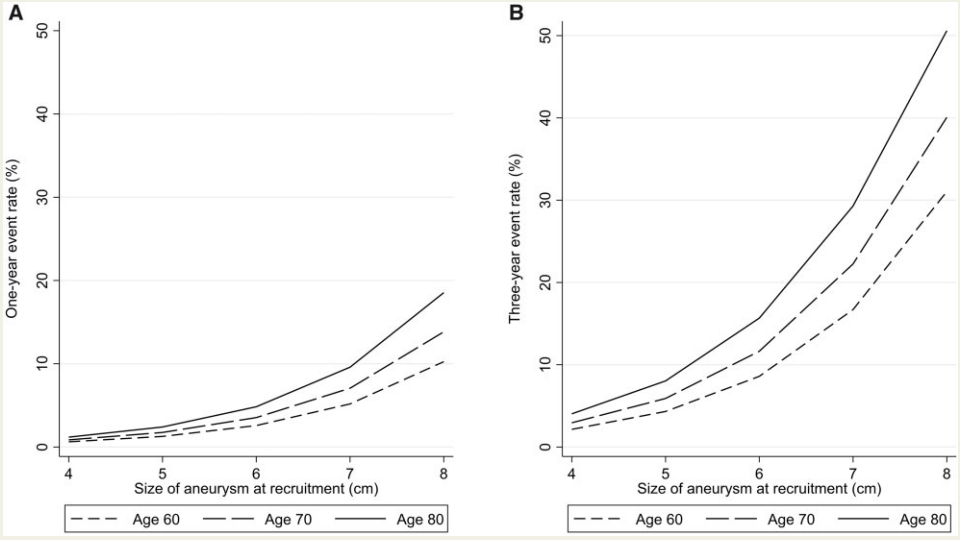
Graphical Abstract



Predicted incidence of an aneurysm-related event at 1 year (*A*) and 3 years (*B*) after recruitment by aneurysm size and age. One-year risk remains below 10% for aneurysms up to 7 cm for patients aged 60, 70, and 80 years.

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Aims To observe, describe, and evaluate management and timing of intervention for patients with untreated thoracic aortic aneurysms.

Methods and results Prospective study of UK National Health Service (NHS) patients aged ≥18 years, with new/existing arch or descending thoracic aortic aneurysms of ≥4 cm diameter, followed up until death, intervention, withdrawal, or July 2019. Outcomes were aneurysm growth, survival, quality of life (using the EQ-5D-5L utility index), and hospital admissions. Between 2014 and 2018, 886 patients were recruited from 30 NHS vascular/cardiothoracic units. Maximum aneurysm diameter was in the descending aorta in 725 (82%) patients, growing at 0.2 cm (0.17–0.24) per year. Aneurysms of ≥4 cm in the arch increased by 0.07 cm (0.02–0.12) per year. Baseline diameter was related to age and comorbidities, and no clinical correlates of growth were found. During follow-up, 129 patients died, 64 from aneurysm-related events. Adjusting for age, sex, and New York Heart Association dyspnoea index, risk of death increased with aneurysm size at baseline [hazard ratio (HR): 1.88 (95% confidence interval: 1.64–2.16) per cm, $P < 0.001$] and with growth [HR: 2.02 (1.70–2.41) per cm, $P < 0.001$]. Hospital admissions increased with aneurysm size [relative risk: 1.21 (1.05–1.38) per cm, $P = 0.008$]. Quality of life decreased annually for each 10-year increase in age [–0.013 (–0.019 to –0.007), $P < 0.001$] and for current smoking [–0.043 (–0.064 to –0.023), $P = 0.004$]. Aneurysm size was not associated with change in quality of life.

Conclusion International guidelines should consider increasing monitoring intervals to 12 months for small aneurysms and increasing intervention thresholds. Individualized decisions about surveillance/intervention should consider age, sex, size, growth, patient characteristics, and surgical risk.

Keywords Humans • Aortic aneurysm • Thoracic • Tomography • X-ray • Computed • Aorta and treatment outcome

Introduction

Chronic thoracic aortic aneurysm (CTAA) of the arch or descending thoracic aorta (DTA) is life-threatening if undiagnosed or neglected as aneurysms expand. Aneurysm growth is associated with dissection (tearing) or rupture of the aortic wall. In general, after diagnosis, 6-month mortality in treated and untreated patients with CTAA is estimated to be 17.7% and 30%, respectively.[1]

The condition is rare, but recorded incidence is rising. UK hospital admissions for thoracic aortic aneurysm increased from 4.4 to 9.0 per 100 000 inhabitants between 1999 and 2010.[2] This was probably secondary to greater availability of computed tomography (CT) scanning, in an increasingly elderly population.

Treatment of CTAA confers a significant risk of mortality and morbidity, significant post-operative recovery period, and cost.[3] Small aneurysms are monitored by CT or magnetic resonance imaging (MRI), and repair offered if perceived risk of rupture/dissection significantly increases. This follows rapid growth, worsening symptoms, or the CTAA reaching a critical size. In the infra-renal aorta, randomized controlled trials have demonstrated that surveillance is safe up to 5.5 cm[4] and these principles have informed current guidelines.[5] This is not the case for CTAA. Although guidelines have been formulated, evidence for the most effective surveillance and intervention strategies is sparse.[6,7] Previous registries have been limited by lack of prospective follow-up data.[8] As a result, there is substantial variation in practice. Evidence that informs robust surveillance strategies should highlight those at risk of aneurysm-related death and should inform optimal timing of repair for individuals. This information is needed urgently.

Using data from the Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study, the overall aim of this article is to describe the natural history of CTAA prior to intervention, document risks, and health-related quality of life (HRQoL) during surveillance and identify those at high-risk of aneurysm-related death. Specific objectives are: (i) to model growth over time, prior to any major intervention; (ii) to describe survival patterns and their relationship to changing aneurysm diameter and HRQoL in the absence of major interventions; (iii) to describe major aneurysm-related events of rupture and dissection; (iv) to model HRQoL over time, prior to any major intervention; and (v) to identify patient-specific or aneurysm-specific features that might predict poor outcome.

Methods

Patients

ETTAA is an observational cohort study of current clinical practice at the time of the study. The protocol is published and a funder's report will be released in 2022.[9,10] Patients aged ≥18 years, attending National Health Service (NHS) hospitals in England between March 2014 and July 2018, with previously or newly diagnosed aneurysms of ≥4 cm diameter in the arch or DTA (extending to thoraco-abdominal aorta) were eligible for ETTAA. These included aneurysms associated with atherosclerosis, acute dissection in adjacent segments, and aortopathy. Isolated ascending aortic aneurysms were not included. However, patients with ascending aortic aneurysm adjacent to arch aneurysms (over 4 cm) were included. Study centres provided a copy of the chest CT or MRI radiological scan nearest to recruitment and the accompanying report needed to confirm an

eligible aneurysm. Exclusion criteria were acute dissection with or without malperfusion syndromes and previous surgical intervention for an aneurysm in the same segment.

At consent treating clinicians grouped patients according to intended management: *conservative management* (CM) if aneurysms were at risk of rupture, but surgical and endovascular procedures were not planned due to patient choice, comorbidities, or procedural risk; *watchful waiting* (WW) if aneurysms were small, at low risk of rupture, and surgical and endovascular procedures were not recommended but were options for future management; *endovascular stent grafting* (ESG); and *open surgical replacement* (OSR).

This paper reports on data from all patients in ETTAA before intervention. Patients assigned to WW, ESG, and OSR were collectively described as *intention to treat* (ITT). Changes in intended management during the study were recorded but there was no attempt to intervene in this observational study.

Data collection

Data were collected prospectively by local research staff, co-ordinated by Papworth Trials Unit Collaboration. Patient characteristics, maximum aneurysm diameter, clinical events, hospital admissions, cardiac or vascular surgery, and HRQoL were recorded at consent, 3, 6, 12, 18, 24, 36, and 48 months, until the end of the follow-up period on 31 July 2019.

Retrospective CT and MRI data were collected from sites for the measurement of aneurysm growth.

Patients contributed data from either date of diagnosis (aneurysm growth) or date of recruitment (HRQoL, survival, clinical events) until first intervention, death, major clinical event, withdrawal, or end of the study, whichever occurred first.

Outcomes

The four outcomes of interest were overall survival (primary), aneurysm-related survival, and longitudinal trajectories for aneurysm growth and HRQoL.

Survival time was calculated from centre-reported data, as date of consent to date of death. Surviving patients were censored at withdrawal, date of surgical treatment (ESG or OSR) for the aneurysm, or end of the study, whichever was first. For aneurysm-related survival, deaths from other causes were treated as censored.

Maximum aneurysm diameter was measured by CT or MRI during routine care, using local protocols. Anonymized CT/MRI scans were re-analysed at St George's Hospital (London, UK) or Papworth Hospital (Cambridge, UK) core labs to minimize observer differences. Five operators analysed CT scans [two at St Georges ($n = 269$ scans) and three at Papworth ($n = 1268$ scans)]. Centres agreed a standard protocol and used the same 3Mensio software, recording diameters from two-dimensional images (see Supplementary material online). MRI scans were analysed at Papworth by two radiology consultants ($n = 125$). If scans were not returned to core labs by the date of analysis, we took scan measurements provided by the participating hospital ($n = 70$). All available aneurysm measurements from recruited patients were included in the analysis, including those taken prior to recruitment. The maximum diameter observed was analysed, classified as upper thoracic aorta if the maximum diameter was located in the ascending aorta ($n = 93$, 10.5%) or arch ($n = 59$, 6.7%), and lower if it was in the DTA ($n = 725$, 81.8%) or thoraco-abdominal aorta ($n = 9$, 0.1%). Note that all aneurysms had a diameter of ≥4 cm in arch or DTA, although the maximum diameter may have been in an adjacent segment.

Aneurysm-related clinical events requiring hospital admission were collected by the local hospital. All events were reviewed centrally by ETTAA clinicians (P.S. and S.L.).

HRQoL was assessed by the EQ-5D-5L questionnaire at the local hospital.[11] Based on recommendations from the UK National Institute for Health and Care Excellence, responses were converted into EQ-5D-3L index values (value assigned to reported health state) using the crosswalk approach.[12] The index ranges from one (maximum health), through zero (equivalent to death), to –0.59; values < 0 indicate health states considered worse than death. This provides a simple, one-dimensional generic measure of HRQoL with an intuitive measurement scale.

Statistical methods

Full details of statistical methods are reported elsewhere.[10]

Sample size

Sample size calculations for ETTAA were based on comparing survival between patients who underwent ESG and OSR during the study, and are not relevant to the pre-intervention analysis here.

Exploratory analysis

Baseline measurements and missing data were summarized; ITT and CM groups were compared using Student's *t*-tests and Pearson's χ^2 test as appropriate. Time to event data were summarized using Kaplan–Meier estimates and compared using log-rank tests. Frequency and simple event rates per patient-year were summarized for deaths and hospital admissions, with ruptures, dissections, and neurological events reported separately.

Survival, hospital admissions, rupture, dissection, and neurological events

Cox proportional hazards models were developed to assess relationships between survival and baseline variables. Schoenfeld residual plots and tests verified proportional hazards assumptions. Centre effects were assessed using gamma frailty terms but were not significant and are not reported. The above analysis censors patients who have ESG and OSR on the date of the procedure; that is, we assume they have the same risk of death as people with similar aneurysms who remain in the ITT group. Because this assumption is unlikely to be true, we estimated risk factors for the composite outcome of death or intervention in a sensitivity analysis. Negative binomial regression was used to compare hospital admission rates, adjusted for age and sex.

Longitudinal data

For maximum aneurysm size, time zero was defined by the first recorded scan. HRQoL was analysed from the date of recruitment to ETTAA. Exploratory analysis involved plotting distributions and trajectories over time. Longitudinal measurements of aneurysm diameter and HRQoL were analysed using linear random effects models. Variables considered as fixed effects included time, sex, age, height, weight, body mass index, smoking (current, ex-smoker, never), hypertension, chronic obstructive pulmonary disease (COPD), connective tissue disorders, coronary artery disease, extra-cardiac arteriopathy, heart valve disease, type of scan (CT, MRI), and aneurysm location (arch/ascending, DTA/thoraco-abdominal aorta). Non-linear changes over time were assessed by including time-squared in the model, but were not significant. All continuous variables except time of assessment were centred at the mean. A linear term was included for New York Heart Association (NYHA) class. Patient and centre random effects (intercept and slope over time) were investigated, but only patient effects were significant in any analysis. For patients who were recruited with ≥4 cm arch aneurysms, models for growth in the ascending thoracic aorta and the arch diameter were also fitted separately.

Joint analysis of longitudinal measurements and survival

To investigate whether aneurysm diameter and HRQoL changes over time were related to overall or aneurysm-related deaths, we fitted joint random effects models for growth/HRQoL and time to death.[13] Based on analysis of longitudinal trajectories alone, linear models with normally-distributed residuals were assumed. Significant predictors identified in longitudinal and survival models were included in the joint model. Models were fitted using the *stjm* commands in Stata v16.[14]

Missing data

Mandated variables for ETTAA had few missing values (<8%) (*Appendix 1*). Variables with >25% missing data were not used in modelling. Complete case analysis was used for longitudinal data measurements since estimates from such models are unbiased provided that the data are missing at random (MAR) conditional on the observed data.[15] For survival models, sensitivity analysis assuming MAR used multiple imputation with chained equations and predictive mean matching. Imputation models included the outcome variable as well as all important covariates from exploratory analysis. Resulting models were combined using Rubin's rules.[16]

Results

ETTAA patient cohort

Between March 2014 and July 2018, 886 patients were recruited from 30 UK centres. At recruitment, 82 (9.3%) were assigned CM, either at patient request or clinician judgement. Six later underwent ESG or OSR, leaving 76 'true' CM patients at baseline. During follow-up, 36 additional patients were transferred to CM due to deterioration, comorbidities, or patient preference. Thus, 112 patients (12.6%) were ultimately assigned to CM. The remaining 774 (91.6%) patients were classified as ITT.

Median time between consent and leaving follow-up/end of study was 20.3 (0–61) months. Reasons for leaving follow-up were ESG/OSR ($n = 285$), death ($n = 129$), and withdrawal ($n = 30$); the remaining 442 patients were censored at the end of follow-up.

Baseline measurements

The ETTAA cohort included 321 (36.2%) women and 565 men, with mean [standard deviation (SD)] age of 70.9 (10.9) years. Comorbidities are listed in *Table 1*.

Survival

Eighty-three ITT patients (6.6% deaths per patient-year) and 46 CM patients (20.0% per patient-year) died during follow-up, for a total of 129 patients (8.6% per patient-year). Sixty-four (49.4%) deaths were aneurysm-related (45 ruptures, 11 dissections, 3 ruptured and dissected, and 5 aneurysm-related but specific event not reported). Thirty-nine aneurysm-related deaths were in ITT patients (3.0% per patient-year) and 25 in CM patients (11% per patient-year). Of 307 patients with aneurysms ≥6 cm, 76 died (23.1% per patient-year), of which 42 were aneurysm-related deaths (12.7% per patient-year).

One and 3-year survival rates were 92.4% (90.2–94.1) and 77.6% (73.4–81.2), respectively. Analogous figures for aneurysm-related death were 96.5% (94.8–97.6) and 88.3% (84.8–91.0), respectively. Nineteen ITT patients were recruited on the day of surgery and were excluded from this analysis.

In unadjusted analysis, ITT patients had significantly lower overall and aneurysm-related death rates compared with CM patients [hazard ratio (HR): 0.35 (95% confidence interval: 0.23–0.47) and 0.28 (0.17–0.47), respectively, $P < 0.001$ for both]. Patients with larger aneurysms at baseline, women, older age, formal/informal care, previous cardiac interventions, COPD, higher NYHA class, and those with smaller height and weight had significantly higher risk of death (*Appendix 2*).

In multivariable analysis, apart from age, sex, and (possibly) NYHA class, only maximum aneurysm size at baseline was a strong risk factor for overall and aneurysm-related death, approximately doubling risk for each centimetre increase in maximum diameter (*Table 2*). ITT and comorbidity markers were not significant once age, sex, aneurysm size, and NYHA were included. *Figure 1* shows predicted overall and aneurysm-related mortality rates by maximum aneurysm diameter at baseline, for people who had average values of age, sex, and NYHA class. Given average covariates, patients with aneurysms of maximum diameter 4–6 cm had predicted 1-year mortality below 10%, which increases to 12.4% and 22.2% for 7 cm and 8 cm aneurysms, respectively. By 3 years, patients with 6 cm aneurysms have predicted mortality of 21.3%, whilst probabilities for those with 7 cm and 8 cm aneurysms have increased to 36.5% and 57.7%, respectively. If we consider only deaths described as aneurysm-related, mortality rates were lower, with only large (>8 cm) aneurysms rising above 10% at 1 year and 40% at 3 years.

The *Graphical Abstract* shows additional effect of age on incidence of aneurysm-related death or non-fatal dissection/rupture at 1 and 3 years; incidence remains below 10% for aneurysms up to 7 cm even for 80-year olds, but increases rapidly in this age group between 1 and 3 years.

Multiple imputation for missing covariates gave almost identical results (*Appendix 1*).

Repeating the analysis for the composite outcome of death or intervention, the HRs for overall and aneurysm-related death for each 1 cm increase in maximum aneurysm diameter were 1.72 (1.59–1.86) and 1.81 (1.66–1.98), respectively (both $P < 0.001$).

Aneurysm diameters at baseline and growth over time

The largest aneurysm was in the DTA for 636 (82.2%) ITT patients and 89 (79.5%) CM patients. Mean (SD) maximum diameter at baseline was 5.6 cm (1.1) in ITT patients and 6.3 cm (1.2) in CM patients. After excluding scans using techniques other than CT or MRI ($n = 11$) and one scan dated 20 years before ETTAA, 1767 scans in 882 (99.5%) patients were included. Times between first and subsequent scans ranged from 3 days to 7.35 years.

The final model describing diameter measurement trajectories in the absence of treatment is shown in *Appendix 3*. Average (maximum) diameter in the DTA at baseline for a person of average age, with no comorbidities was 5.57 cm (5.48–5.67). At first scan, larger aneurysms were found for older patients [mean difference per 10-year increase in age = 0.18 cm (0.11–0.5), $P < 0.001$], connective tissue disorders [0.39 cm larger (0.06–0.72), $P = 0.019$], and COPD [0.21 cm larger (0.02–0.40), $P = 0.032$]. At baseline, adjusting for age, scan type, and comorbidities, the mean difference between maximum

Table 1 Patient characteristics at recruitment according to intention to treat

Variables	Patient subgroup or summary	ITT ($n = 774$)	CM ($n = 112$)	Mean difference or odds ratio (95% CI) and P-values*
Age (years)	Mean (SD)	70.0 (10.7)	76.6 (9.9)	6.6 (4.5, 8.7)
	(min–max)	(31.6–92.5)	(26.1–92.5)	$P < 0.001$
Sex	Female, *n* (%)	273 (35.3)	48 (42.9)	0.73 (0.49–1.09)
	Male, *n* (%)	501 (64.7)	64 (57.1)	$P = 0.120$
Height (cm)	Mean (SD)	171.4 (10.5)	167.4 (12.5)	–4.03 (–6.24 to –1.81)
	(min–max)	(138–210)	(132–216)	$P < 0.001$
	Missing, *n* (%)	26 (3.4)	9 (8.0)	
Care	Formal/informal, *n* (%)	80 (10.3)	23 (20.6)	0.44 (0.27–0.74)
	None, *n* (%)	688 (88.9)	88 (78.6)	$P = 0.002$
	Missing, *n* (%)	6 (0.8)	1 (0.9)	
Smoking	Current, *n* (%)	99 (12.8)	14 (12.5)	1.27 (0.66–2.44)
	Past, *n* (%)	446 (57.6)	57 (50.9)	1.40 (0.91–2.17)
	Never, *n* (%)	223 (28.8)	40 (35.7)	–
	Missing, *n* (%)	6 (0.8)	1 (0.9)	$P = 0.307$
Connective tissue disorder	Yes, *n* (%)	52 (6.7)	3 (2.7)	2.62 (0.80–8.53)
	No, *n* (%)	722 (93.3)	109 (97.3)	$P = 0.098$
Coronary artery disease	CABG, *n* (%)	41 (3.3)	10 (8.9)	0.57 (0.27–1.17)
	PCI, *n* (%)	34 (4.4)	6 (5.4)	0.78 (0.32–1.92)
	Medication, *n* (%)	68 (8.8)	9 (8.0)	1.04 (0.50–2.17)
	No, *n* (%)	15 (1.9)	2 (1.8)	Reference
	Missing, *n* (%)	616 (79.6)	85 (75.9)	$P = 0.443$
Extracardiac arteriopathy	Yes, *n* (%)	113 (14.6)	20 (17.9)	1.26 (0.75–2.12)
	No, *n* (%)	647 (83.6)	91 (81.3)	$P = 0.389$
	Missing, *n* (%)	14 (1.8)	1 (0.9)	
Heart valve disease	Yes, *n* (%)	142 (18.3)	23 (20.5)	0.87 (0.53–1.42)
	No, *n* (%)	619 (80.0)	87 (77.7)	$P = 0.574$
	Missing, *n* (%)	13 (1.7)	2 (1.8)	
Left ventricular function (not mandated)	Good, *n* (%)	342 (44.2)	41 (36.6)	Reference
	Moderate, *n* (%)	62 (8.0)	14 (12.5)	0.53 (0.27–1.03)
	Poor, *n* (%)	13 (1.7)	2 (1.8)	0.78 (0.17–3.57)
	Not measured, *n* (%)	347 (44.8)	55 (49.1)	$P = 0.267$
	Missing, *n* (%)	10 (1.3)	0 (0.0)	
Diabetes[a]	Yes, *n* (%)	76 (9.8)	7 (6.3)	1.64 (0.74–3.65)
	No, *n* (%)	695 (89.8)	105 (93.8)	$P = 0.222$
	Missing, *n* (%)	3 (0.4)	0 (0.0)	
Documented hypertension	Yes, *n* (%)	678 (87.6)	97 (86.6)	1.12 (0.62–2.00)
	No, *n* (%)	94 (12.1)	15 (13.4)	$P = 0.714$
	Missing, *n* (%)	2 (0.3)	0 (0)	
Chronic obstructive pulmonary disease	Yes, *n* (%)	137 (17.7)	26 (23.2)	0.72 (0.45–1.15)
	No, *n* (%)	632 (81.7)	86 (76.8)	$P = 0.169$
	Missing, *n* (%)	5 (0.6)	0 (0.0)	
NYHA class	I, *n* (%)	320 (41.3)	39 (34.8)	Reference
	II, *n* (%)	274 (35.4)	41 (36.6)	0.81 (0.51–1.30)
	III, *n* (%)	123 (15.9)	27 (24.1)	0.56 (0.33–0.95)
	IV, *n* (%)	23 (3.0)	3 (2.7)	0.93 (0.27–3.26)
	Missing, *n* (%)	34 (4.4)	2 (1.8)	$P = 0.185$
Any anti-hypertensive medication	Yes, *n* (%)	659 (85.1)	94 (83.9)	1.10 (0.64–1.89)
	No, *n* (%)	115 (14.9)	18 (16.1)	$P = 0.737$
Statins	Yes, *n* (%)	440 (56.8)	72 (64.3)	0.74 (0.49–1.11)
	No, *n* (%)	332 (42.9)	40 (35.7)	$P = 0.144$
	Missing, *n* (%)	2 (0.3)	0 (0.0)	

CI, confidence interval; CM, conservative management; IDDM, insulin-dependent diabetes mellitus; ITT, intention to treat.
[a]Three cases of IDDM in ITT groups, all others non-IDDM.
*P-value from hypothesis test of zero mean difference or odds-ratio = 1.

Table 2 Multivariable Cox regression results for all-cause and aneurysm-related deaths, complete case analysis

	All-cause deaths		Aneurysm-related deaths	
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Female sex	1.78 (1.24–2.54)	0.002	2.60 (1.58–4.29)	<0.001
Age at consent (per decade)	1.80 (1.42–2.27)	<0.001	1.50 (1.09–2.05)	0.012
Baseline NYHA per class	1.23 (1.00–1.52)	0.054		
Baseline maximum aneurysm size per cm	1.88 (1.64–2.16)	<0.001	2.16 (1.79–2.61)	<0.001

CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

diameter in upper and lower sections of the thoracic aorta was small [–0.10 cm (–0.30 to 0.09), $P = 0.296$].

Maximal aneurysms in the DTA grew by 0.20 cm per year (0.17–0.24) ($P < 0.001$); those in the upper thoracic aorta did not grow on average [–0.007 cm (–0.08 to 0.07), $P = 0.850$]. *Figure 2* summarizes average growth trajectories in each section. In additional analysis, annual growth rate in the large (≥4 cm) arch aneurysms alone was 0.068 cm (0.017–0.118) ($P = 0.009$), whilst aneurysm diameter in the ascending thoracic aorta did not increase [–0.070 cm (–0.149 to 0.010), $P = 0.085$]. There was no evidence that aneurysm growth accelerated or decelerated during follow-up. After adjusting for baseline variables, there was significant between-patient variation in maximum aneurysm size (random effects SD: 1.06 cm). Additionally, there was significant unexplained (by available covariates) between-patient variation in growth rate (random effects SD: 0.17 cm/year). Adjusting for covariates, patients with larger maximal diameters at baseline also had faster growth (correlation: 0.40). At first scan, there was no difference between aneurysm diameters measured by CT and MRI, all other variables being equal. However, the average difference between diameters measured by the two modalities increased over time by 0.14 cm per year (0.08–0.21) ($P < 0.001$), with MRI measurements being smaller (*Appendix 3*).

Joint analysis of growth and survival

Adjusting for location of the aneurysm with maximal diameter and intended management, current (rather than baseline) diameter was significantly associated with overall survival (*Appendix 4*). Each 1 cm increase in the maximal diameter within a patient more than doubled the risk of overall death [HR: 2.02 (1.70–2.41)] and aneurysm-related death [HR: 2.35 (1.85–2.99)] for that individual (both $P < 0.001$). Baseline diameter and current diameter were correlated, and models including both suggested that current aneurysm size is a more important risk factor than size when presenting at multi-disciplinary team meetings.

Hospital admissions

Centres reported 363 hospital admissions in 222 patients during follow-up (*Table 3*). Admission rates were related to maximum aneurysm diameter, increasing by 21% per cm increase in size at baseline [relative rate 1.21 (1.05–1.38), $P = 0.008$]. ITT patients were less likely to be readmitted than CM patients [odds ratio: 0.53 (0.35–0.80)], although admission rates per person were not significantly higher. Fifty-two (definitely/probably) aneurysm-related hospital admissions were recorded for 39 patients. Although aneurysm-related admissions increased by aneurysm size [relative rate: 1.48 per cm (0.93–2.26), $P = 0.10$], this was not statistically significant (at 5%). Nine non-fatal aneurysm-related events were reported (two ruptures, seven dissections): three had CT scans in the previous month, maximum aneurysm diameters were 5.64 cm, 6.91 cm, and 8.29 cm; the six with no scans within the previous 6 months, maximum diameters ranged from 4.56 cm to 6.98 cm. Eight non-fatal neurological events were reported.

HRQoL pre-intervention

During ETTAA, 3732 HRQoL questionnaires were returned by 886 patients. After excluding blank forms ($n = 256$), duplicate entries ($n = 11$), and incomplete forms ($n = 35$), 3492 (93.6%) remained. Overall 855 of 886 (96.5%) patients completed between one and nine EQ-5D-5L questionnaires. Mean (SD) utilities at baseline for ITT and CM patients were 0.73 (0.24) and 0.68 (0.25), respectively.

The final model describing HRQoL trajectories in the absence of ESG or OSR is shown in *Appendix 5*. At recruitment (time zero), mean HRQoL was 0.84 (0.81–0.86) for a person of average age (70.9 years), in NYHA class I, who has never smoked, and did not have formal/informal care. Baseline HRQoL decreased as NYHA class increased [I—0.84 (0.81–0.86); II—0.74 (0.71–0.76); III—0.63 (0.60–0.67); IV—0.53 (0.49–0.58), $P < 0.001$] (all else equal). Reported requirement for formal/informal care was associated with large deficit in HRQoL at recruitment [mean = 0.66 (0.61–0.70), $P < 0.001$]. Average age at recruitment was 70.9 years, and HRQoL at recruitment was slightly larger for older patients by 0.010 (–0.003 to 0.022) ($P = 0.122$) per decade, possibly due to selection policies. Current smokers had worse HRQoL at recruitment of 0.79 (0.75–0.83) compared with ex-smokers [0.84 (0.82–0.86)] and never smokers [0.84 (0.81–0.86), $P = 0.057$].

For relatively fit, non-smoking patients, of average age, mean HRQoL did not change significantly over time, estimated decrease was –0.010 (–0.022 to 0.003) ($P = 0.132$ per year). However, the interaction between follow-up time and age showed that if two patients differed in age by 10 years, the older patient would have a faster decrease in HRQoL of –0.013 (–0.019 to –0.007; $P < 0.001$ per year) (all else being equal). As a result, the difference between age groups increased over time thereafter. Current smokers had a faster decline in HRQoL over time [–0.043 (–0.064 to –0.023), $P = 0.004$ per year]. *Figure 3* shows that, for this cohort, current smoking had a much greater influence on HRQoL than a 10-year increase in age.

Significant random effects indicated that HRQoL varied between patients both at recruitment and in the rate of decline over time, in

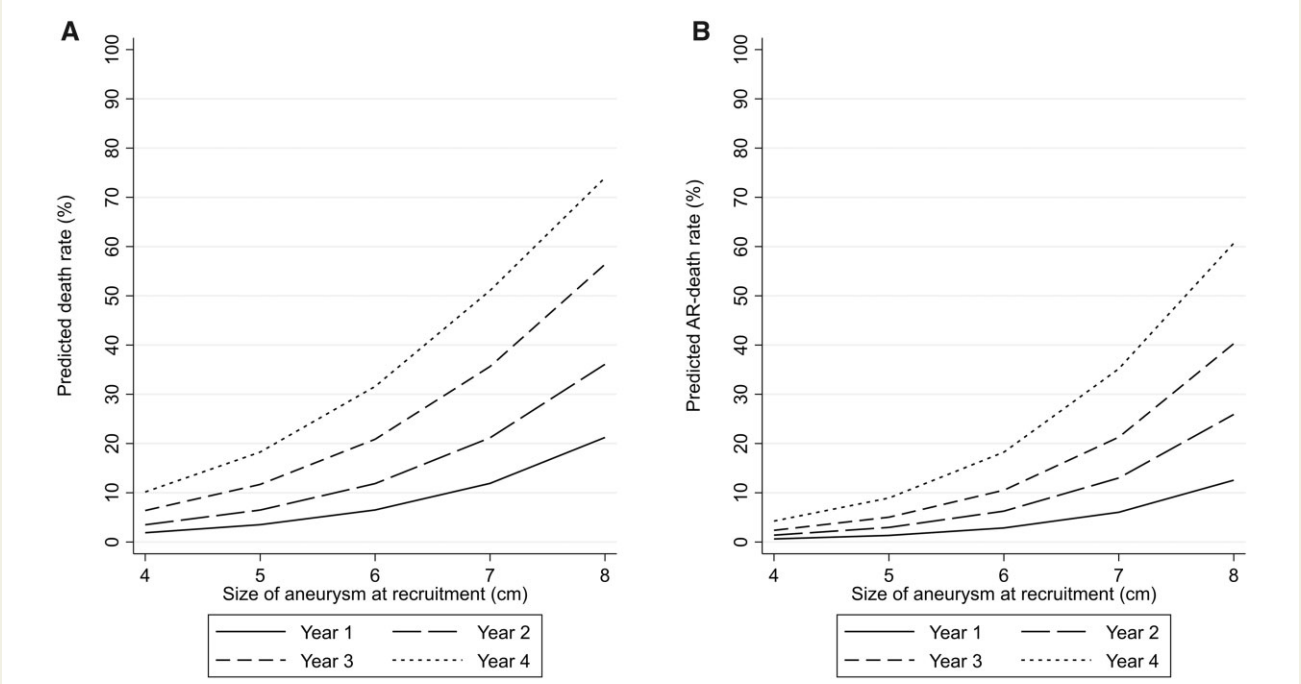

Figure 1 Predicted proportion dying from any cause (*A*) and aneurysm-related causes (*B*) using fitted Cox regression models by maximum aneurysm diameter at baseline, with age, sex, and New York Heart Association class set to the average values.

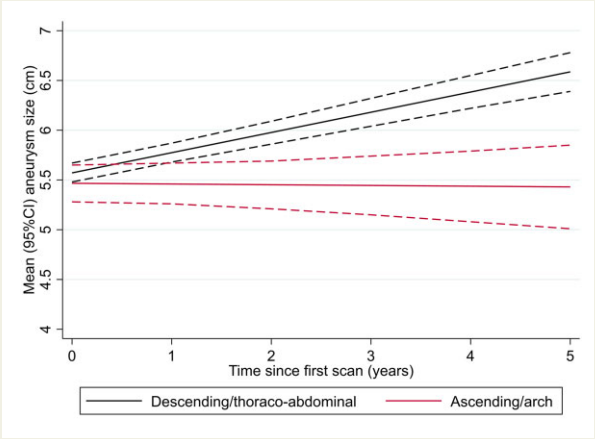

Figure 2 Estimated mean (95% confidence interval) aneurysm diameter over time by site of maximum measurement.

addition to the variation that could be attributed to the variables in the model.

Joint analysis of changes in HRQoL and survival

After adjusting for age, sex, aneurysm size, and NYHA class, there was weak evidence that current HRQoL was associated with overall death [HR per 0.1 unit decrease in HRQoL: 0.90 (0.82–0.99), $P = 0.032$], but not aneurysm-related death [HR: 1.00 (0.86–1.16), $P = 0.963$] (*Appendix 6*).

Discussion

Summary of findings

This paper reported aneurysm growth, hospital admissions, survival, and HRQoL in a large group of patients.

Aneurysms with maximum diameter in the DTA grew significantly faster, and (adjusting for comorbidity and aneurysm location) patients with larger aneurysms at baseline had faster growth (*Appendix 3*, correlation 0.4). No clinical risk factors for accelerated growth were identified, despite significant between-patient variation. This may result from short and infrequent follow-up, the relatively stable nature of most patients and selection of high-risk patients for ESG or OSR.

The cohort required frequent hospital admissions and there was high risk of death before intervention even in those undergoing surveillance with a view to treatment (8.6% per year overall and 6.6% per year in the ITT group). There were few non-fatal dissections and ruptures. After adjusting for age, sex, and NYHA class, aneurysm size at baseline and growth were the most significant variables affecting overall and aneurysm-related survival. A 1 cm increase in size, either between patients at baseline, or growth within a patient, doubled the hazard of death. Admissions to hospital also increased with aneurysm size. HRQoL (measured by EQ-5D-5L) was not related to aneurysm size, and remained high in 'healthy' patients. Baseline HRQoL was related to need for supportive care, NYHA class, and smoking

Table 3 Clinical events and hospital admissions prior to any surgical or endovascular interventions

Patient subgroup	ITT (n = 774)	CM (n = 112)	Simple comparisons (n = 886)
Total time at risk (years)	1268.3	229.9	
Median follow-up (years)	1.35	2.06	–
(minimum–maximum)	(0–5.11)	(0.003–4.54)	
All admissions, n (rate/patient-year)			Relative admission rate
	292 (0.23)	71 (0.31)	0.77 (0.56–1.07)
			P = 0.116
Admissions, definitely/probably aneurysm-related, n (rate/patient-year)			Relative admission rate
	41 (0.03)	11 (0.05)	0.59 (0.28–1.24)
			P = 0.165
People with at least one admission, n (%)			Odds ratio
	181 (23.4)	41 (36.6)	0.53 (0.35–0.80)
			P = 0.003
Patients admitted, definitely/probably aneurysm-related, n (%)			Odds ratio
	30 (3.9)	9 (8.0)	0.46 (0.21–1.00)
			P = 0.050
Non-fatal ruptured aneurysms	2	0	–
Non-fatal dissected aneurysms	6	1	–
Non-fatal neurological events	7	1	–

CM, conservative management; ITT, intention to treat.

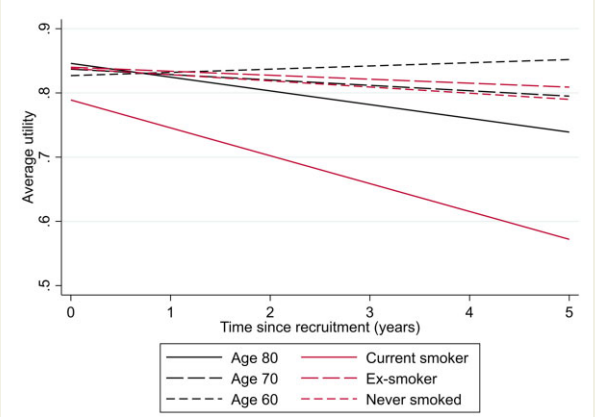

Figure 3 Average utility trajectories over time by age and smoking habits.

activity. Decline in HRQoL over time was related to increasing age and current smoking.

Relationship to external evidence and interpretation of results

All-cause death rate in ETTAA was 8.6% per patient-year, with 3-year survival of 77.6%. According to UK Government 2015–17 statistics, the 1-year probability of death for English men and women aged 71 years, in the general population, was 2.1% and 1.4%, respectively, with 3-year survival of 93.4% and 95.5%, respectively, substantially higher than reported in this study.[17] Only half the observed deaths were aneurysm-related, suggesting that the ETTAA population also had higher risk of death from causes not related to the aneurysm, such as comorbidities with similar risk factors (e.g. smoking, hypertension). These comorbidities also partly explain high rates of hospital admission. Attention to treatment of significant comorbidity and cardiovascular risk factor control to reduce the risk of major cardiac, cerebral, and other arterial events is important in this group of patients.

Survival outcomes

ETTAA results suggest that large aneurysms should be treated with minimum delay since 3-year probability of death jumps from just under 12% for 'average' patients with 5 cm aneurysms to over 35% if the aneurysm increases to 7 cm (*Figure 1*). These increases will be greater for women and older patients. Similarly, 3-year risk of aneurysm-related death jumps from approximately 5% for aneurysms of 5 cm to over 20% for aneurysms of 7 cm.

The increase in mortality with age was expected. The higher risk of death for women in ETTAA is more difficult to explain. Women may present at a later stage in their disease or when they also have other life-threatening comorbidities, but this should not be assumed. It may be that comorbidities in women are less well investigated or treated or that aneurysm behaviours are different. There was no evidence that women had longer follow-up after consent than men, so that any delays were likely to occur prior to referral to participating multidisciplinary teams. Further investigation into causes of differences in outcomes between sexes is warranted.

Comparisons of CM and ITT patients showed that clinicians successfully identify high-risk patients based on demographic, clinical, and aneurysm characteristics. However, transfer of patients between management groups in a relatively short follow-up period and the

high death rate suggests remaining uncertainty about whether and when to intervene. Better risk profiling methods are needed for these aneurysms to guide clinicians.

Aneurysm size and growth

ETTAA raises questions regarding current guidance. Updated guidelines from the AHA/ACC suggest reimaging arch aneurysms to detect enlargement at 12-month intervals if <4.0 cm diameter and 6-month intervals for 4.0–5.4 cm diameter.[18] In ETTAA, average growth rates were 0.20 cm (0.17–0.24) per year in the DTA and lower in the arch, so that yearly scanning may be more appropriate for small aneurysms, even in the arch.

European and American Society guidelines for vascular and cardiac surgery recommend consideration of ESG in patients with suitable anatomy and maximal diameter ≥5.5 cm and open surgery for patients with unsuitable anatomy at 5.5–6.0 cm.[6,7] For DTA/thoracoabdominal aneurysms, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or if a connective tissue disorder is present. The European Society for Vascular Surgery stated that 'An initial diameter of 60 mm carries an annual risk of rupture of 10%'.[19] In ETTAA, predicted 1-year aneurysm-related event probabilities for average ETTAA patients with aortic aneurysms of 6 cm, 7 cm, and 8 cm were 3.5%, 7.1% and 13.8%, respectively. Furthermore, the location of the maximum diameter aneurysm was not significantly associated with survival [HR for descending relative to arch/ascending: 1.33 (0.92–1.93), $P = 0.128$], although size and growth were greater for aneurysms in the DTA. These results from ETTAA suggest that the threshold aneurysm size for repair could be revised for stable patients of average age. For older patients, women, and those with higher NYHA class, ETTAA data are largely consistent with guidelines in the short term. These factors, together with the need for concomitant procedures and risk of surgery, can inform personalized management strategies.

Aneurysm growth within a person was also a significant (perhaps stronger) predictor of death. Thus, both current aneurysms with diameters >6 cm, and aneurysms growing at a rate such that they will exceed 6 cm soon should be weighed up against operative risks when deciding on the nature and timing of intervention. Risk of death doubled per 1 cm increase in aneurysms size, and this can be used to predict when aneurysm risk exceeds operative risk for an individual. This is not stated as an indication for repair in current international guidelines but should be considered.[7,19]

Patients presented with widely varying aneurysm sizes, some of which were attributed to patient age, size, smoking history, comorbidities, and location of the aneurysm. Faster growth in the DTA may be related to differences in pathology in different sections of the aorta. The more linear anatomy of this segment may also allow greater expansion before the patient presents clinically. It may equally be because growth of arch aneurysms was modified by previous repair in adjacent segments (from type A dissection). This raises the question of whether aneurysms in the arch and DTA require different scanning protocols and surveillance intervals. Further investigation of these issues should be undertaken.

Health-related quality of life

At baseline, ITT and CM patients had mean (SD) HRQoL of 0.73 (0.24) and 0.68 (0.25), respectively, which is somewhat lower than the population average in the UK (0.785 for people aged 65–74 and 0.734 for people aged ≥75 years), although individuals varied widely.[20] Importantly, HRQoL remained relatively stable over time for non-smokers and therefore one might consider surveillance appropriate for this cohort. Comorbidities such as COPD, coronary heart disease, and heart valve disease might be expected to reduce HRQoL, but were not included in the multivariable model. These comorbidities are correlated with age and frailty (indicated by use of formal/informal care), which may have acted as surrogates since they reflect a wider perspective on quality of life. Current smoking had the greatest effect on HRQoL over time. In order to improve the HRQoL of patients undergoing surveillance, smoking cessation may be important.[21]

Limitations

In this observational study, data reflected routine clinical practice and causal relationships between aneurysm diameter, growth, patient clinical history, HRQoL, and survival cannot be concluded. No attempt was made to alter routine practice so that management varied and the population was heterogeneous. The relatively short follow-up in ETTAA and the 1-year interval between CT scans meant that only linear growth was apparent but we cannot exclude acceleration in growth, particularly if it occurs between scans and immediately before dissection or rupture. If this was the case, we might speculate that there are triggers for these clinical events.

Although hypertension is an established risk factor for poor outcome, we have not included it because almost all patients (88%) had hypertension and were treated with one or more anti-hypertensive medications, and the observational nature of the study may also result in treatment by indication bias, where higher-risk patients are treated with more powerful drugs. Such bias is impossible to adjust for without detailed information on rationale for single/combination drug management.

Results were not sensitive to missing data, provided that the assumption of MAR holds. If there are unknown missing data mechanisms, some bias in results could obtain. We consider this unlikely given the comprehensive covariate adjustment in the imputation process.

Strengths

A major strength of ETTAA is the large prospectively collected sample, with data provided by 30 specialist centres across England, which ensures results are generalizable to similar populations with access to specialist multi-disciplinary teams. Despite the observational study design, we used rigorous scientific methods for data collection and analysis, including core labs to minimize observer bias. We jointly analysed aneurysm growth and survival in a single model, providing new insight into the relative importance of initial size and rate of growth.

Further research

There was substantial variation in maximum aneurysm size and growth, not explained by recorded variables. Further studies should explore genetic, physiological, and lifestyle factors that explain this variation. Longer follow-up may help to clarify determinants of growth. Differences in outcomes between men and women should be investigated to eradicate possible inequalities in the care system.

Similarly, the (largely clinical) covariates in this study did not completely explain variation in HRQoL, which results from a range of patient-specific concerns around health and well-being. Better understanding of these concerns may help patients decide whether intervention will have worthwhile impact on their HRQoL.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the senior author S.L.

Declaration of Helsinki

The authors confirm that the ETTAA study complies with the Declaration of Helsinki; that the West Midlands—South Birmingham Research Ethical Committee approved the research protocol and that informed consent was obtained from all participants.

Appendices

Appendix 1: Treatment of missing covariates

Missing values for variables included in multiple imputation are tabulated by treatment group below.

Frequencies of missing covariates at baseline by planned management group

Overall 788 (88.9%) patients had complete data.

Patient subgroup (number of patients)	CM ($n = 112$)	ITT ($n = 774$)
Age, *n*	0	0
Sex, *n*	0	0
Height, *n* (%)	9 (8.0)	26 (3.4)
Weight, *n* (%)	8 (7.1)	30 (3.9)
BMI, *n* (%)	9 (8.0)	33 (4.3)
Care, *n* (%)	1 (0.9)	6 (0.8)
Smoker, *n* (%)	1 (0.9)	6 (0.8)
Connective tissue disorder	0	0
Extracardiac arteriopathy, *n* (%)	0	0
Valvular heart disease, *n* (%)	2 (1.8)	13 (1.7)
Coronary artery disease, *n* (%)	2 (1.8)	15 (1.9)
LV function, *n* (%)	0	10 (1.3)
LV function not measured, *n* (%)	55 (49.1)	347 (44.8)
Diabetes, *n* (%)	0	3 (0.4)
Hypertension, *n* (%)	0	2 (0.3)

Continued

Continued

Patient subgroup (number of patients)	CM ($n = 112$)	ITT ($n = 774$)
COPD, *n* (%)	0	5 (0.6)
NYHA, *n* (%)	2 (1.8)	34 (4.4)
Beta blockers, *n* (%)	0	0
ACE inhibitors, *n* (%)	0	0
Angiotensin receptor blockers, *n* (%)	0	0
Calcium channel blocker use, *n* (%)	0	0
Other anti-hypertensives, *n* (%)	0	0
Any anti-hypertensives, *n* (%)	0	0
Statins, *n* (%)	0	2 (0.3)
Serum creatinine, *n* (%)	60 (53.6)	399 (51.6)
Haemoglobin, *n* (%)	64 (57.1)	420 (54.3)
Maximum aneurysm location, *n* (%)	0	0
Maximum aneurysm size, *n* (%)	0	0

Missing data mechanisms

Little's test for continuous covariates (age, height, weight, BMI, maximum aneurysm diameter) found weak evidence that they were not Missing Completely At Random ($P = 0.027$).[22] For other variables, there was evidence that survival was significantly related to missing covariate status for weight, BMI, use of formal/informal care, hypertension, and extracardiac arteriopathy. NYHA missingness was significantly associated with treatment group. These exploratory analyses suggested that imputation models could be informed by related measured covariates in the dataset.

Development of imputation model

For survival, treatment group, pre-procedure survival time from consent, whether aneurysm was related to death or not, death status before the index procedure, and all pre-procedure variables were included in the imputation models. Within the Multivariate Imputation by Chained Equations procedure,[23] we used predictive mean matching for all covariates included in imputation models except BMI. For imputation of missing BMI, a fixed formula was used. We therefore set the number of imputations to 12. During the imputation process, we ran 10 imputation iterations for each imputed variable. The imputed values in the last iteration were used for generating an imputation dataset. Those imputed values generated during the process were used for checking whether the values converged or not by inspecting the trajectories.

Refitting the final models using the methods above gave almost identical point estimates and confidence intervals to the complete case analysis.

Appendix 2: Univariable Cox regression results for all cause and aneurysm-related deaths, complete case analysis

	All-cause deaths		Aneurysm-related deaths	
Variable	**HR (95% CI)**	***Z*-test**	**HR (95% CI)**	***Z*-test**
ITT	0.35 (0.23–0.47)	$P < 0.001$	0.28 (0.17–0.47)	$P < 0.001$
Female sex	1.93 (1.36–2.72)	$P < 0.001$	2.61 (1.59–4.29)	$P < 0.001$
Use of formal/informal care	2.15 (1.40–3.29)	$P < 0.001$	1.92 (1.02–3.61)	$P = 0.042$
Previous cardiac interventions CABG/PCI	2.17 (1.43–3.29)	$P < 0.001$	1.28 (0.63–2.59)	$P = 0.492$
COPD	2.28 (1.56–3.34)	$P < 0.001$	2.14 (1.24–3.69)	$P = 0.007$
NYHA per class	1.47 (1.21–1.79)	$P < 0.001$	1.35 (1.02–1.79)	$P = 0.037$
Maximum aneurysm size per cm	1.94 (1.71–2.21)	$P < 0.001$	2.16 (1.81–2.59)	$P < 0.001$
Age at consent (per decade)	2.02 (1.62–2.51)	$P < 0.001$	1.73 (1.29–2.32)	$P < 0.001$
Height per 10 cm	0.66 (0.56–0.77)	$P < 0.001$	0.60 (0.48–0.76)	$P < 0.001$
Weight per kg	0.97 (0.96–0.98)	$P < 0.001$	0.96 (0.94–0.98)	$P < 0.001$
BMI per kg/m^2	0.95 (0.91–0.99)	$P = 0.008$	0.91 (0.86–0.97)	$P = 0.002$

Appendix 3: Pre-intervention longitudinal model for relation between maximum aneurysm diameter over time and covariates

Parameter fixed effects	**Coefficient (SE)**	**95% confidence interval**	***P*-Value (*Z*-test)**
Main effects			
Intercept (descending/thoracic abdominal)	5.57 (0.05)	(5.48–5.67)	<0.001
Arch/ascending aneurysms	–0.10 (0.10)	(–0.30 to 0.09)	0.296
Time per year for lower section	0.20 (0.02)	(0.17–0.24)	<0.001
Age at scan per decade (centred about mean age of 70.9)	0.18 (0.04)	(0.11–0.25)	<0.001
Connective tissue disorder	0.39 (0.17)	(0.06–0.72)	0.019
Chronic obstructive pulmonary disease	0.21 (0.10)	(0.02–0.40)	0.032
MRI relative to CT	–0.01 (0.04)	(–0.09 to 0.07)	0.807
Interactions			
Additional time effect per year for MRI	–0.14 (0.3)	(–0.21 to –0.08)	<0.001
Additional time effect per year for arch/ascending aneurysms	–0.21 (0.04)	(–0.29 to –0.13)	<0.001
Random effects			
Standard deviation(intercept)	1.06		
Standard deviation (slope)	0.17		
Correlation (intercept-slope)	0.40		
Residual standard deviation	0.38		

Appendix 4: Joint model for longitudinal measurements of aneurysm diameter and overall survival

	Coefficient	95% confidence interval	*P*-Value[a]
Maximum aneurysm diameter (cm)			
Intercept (descending/thoraco-abdominal)	6.27	(6.05 to 6.48)	<0.001
Arch/ascending aneurysms	–0.18	(–0.38 to 0.02)	0.085
Intention to treat (relative to CM)	–0.70	(–0.93 to –0.48)	<0.001
Time (per year)	0.08	(0.04 to 0.11)	<0.001
Overall survival	**Hazard ratio**	**95% confidence interval**	***P*-Value[a]**
Current diameter (per cm)	2.02	(1.70 to 2.41)	<0.001
Arch/ascending aneurysms	0.74	(0.42 to 1.28)	0.283
Intention to treat (relative to CM)	0.87	(0.57 to 1.32)	0.506
Female (relative to male)	1.84	(1.27 to 2.65)	0.001
Age at consent (per decade)	1.84	(1.44 to 2.35)	<0.001
NYHA (per class)	1.23	(0.99 to 1.53)	0.060
Random effects	**Estimate**	**95% confidence interval**	
Standard deviation (intercept)	1.02	(0.96 to 1.08)	
Standard deviation (time)	0.09	(0.05 to 0.19)	
Correlation (intercept, time)	0.61	(–0.36 to 0.95)	

[a]From Wald test.

Appendix 5: Final models estimates for relation between HRQoL over time and baseline covariates

Parameter fixed effects	Coefficient (SE)	95% confidence interval	*P*-Value (*Z*-test)
Main effects			
Intercept	0.838 (0.013)	(0.812–0.863)	<0.001
Time per year	–0.010 (0.006)	(–0.022 to 0.002)	0.132
(non smoker and average age)			
Age per decade	0.010 (0.006)	(–0.003 to 0.022)	0.122
(centred about mean of 70.9 years)			
Formal/informal care	–0.179 (0.020)	(–0.219 to –0.140)	<0.001
NYHA per class above I	–0.102 (0.008)	(–0.118 to -0.086)	<0.001
Smoking history			0.057
Current smoker	–0.049 (0.022)	(–0.093 to –0.005)	
Ex-smoker	0.003 (0.015)	(–0.027 to 0.032)	
Interactions			
Additional change over time per decade increase in age	–0.013 (0.003)	(–0.019 to –0.007)	<0.001
Additional change by smoking history			0.004
Current smoker	–0.034 (0.012)	(–0.058 to –0.010)	
Ex smoker	0.003 (0.008)	(–0.012 to 0.018)	
Random effects			
Standard deviation (intercept)	0.166		
Standard deviation (slope)	0.040		
Correlation (intercept-slope)	–0.070		
Residual standard deviation	0.124		

Appendix 6: Joint model for longitudinal measurements of HRQoL (EQ5D-5L) and overall survival

	Coefficient	95% confidence interval	*P*-Value[a]
HRQoL measured by EQ5D-5L index utility			
Intercept	0.727	(0.712–0.743)	<0.001
Time (per year)	–0.011	(–0.019 to –0.003)	0.008
Overall survival	**Hazard ratio**	**95% confidence interval**	***P*-Value[a]**
Current HRQoL	0.35	(0.13–0.92)	0.034
Maximum aneurysm diameter (per cm)	1.76	(1.51–2.08)	<0.001
Female (relative to male)	1.61	(1.12–2.32)	0.010
Age at consent (per decade)	1.64	(1.30–2.07)	<0.001
NYHA (per class)	1.10	(0.87–1.39)	0.437
Random effects	**Estimate**	**95% confidence interval**	
Standard deviation (intercept)	0.205	(0.193–0.217)	
Standard deviation (time)	0.047	(0.037–0.060)	
Correlation (intercept, time)	–0.064	(–0.255 to 0.132)	

[a]From Wald test.

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