Endovascular stent grafting and open surgical replacement for chronic thoracic aortic aneurysms: a systematic review and prospective cohort study

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Scientific summary

Chronic thoracic aortic aneurysms

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Scientific summary

Background

Chronic thoracic aortic aneurysm (CTAA) is a long-term condition in which the aorta dilates beyond 50% of its normal diameter. If untreated, aneurysms expand, stretching vessel walls until the aorta tears (dissection) or ruptures. Both are life-threatening events.

The management of smaller aneurysms comprises watchful waiting (WW) if future intervention is envisaged and conservative management (CM) if patients are unfit for or refuse surgery. With larger aneurysms, intervention involves either endovascular stent grafting (ESG), in which stent(s) are placed into the aorta, or open surgical repair (OSR), where the chest is opened and the diseased segment is replaced. Both interventions are effective in some patients, but both are associated with significant postoperative recovery period, complications and cost.

Objectives

- To review the literature comparing ESG and OSR.
- To explore clinicians' views on optimal patient management.
- To prospectively record management and outcomes (aneurysm growth, survival, clinical events and quality of life).
- To identify the features predicting poor outcome.
- To estimate the clinical effectiveness and cost-effectiveness of competing treatments for patients suitable for more than one treatment.

Methods

Systematic review

Electronic databases were searched for studies between January 1994 and March 2020 to identify randomised controlled trials and non-randomised controlled trial comparative studies comparing ESG and OSR for the elective treatment of arch/descending aortic aneurysm. Studies that included other aortic conditions such as dissection were excluded if elective aneurysm treatment was not reported separately. The ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool was used to assess risk of bias, with results reported narratively and meta-analysis used where appropriate.

Delphi study methods

Based on five key criteria [connective tissue disorder (CTD), age, aneurysm size, aneurysm location and operative risk], 360 hypothetical case scenarios were defined. Expert panels (including an anaesthetist, an interventional radiologist, and cardiac and vascular surgeons) assessed each scenario for appropriate patient management to provide consensus, equipoise between two options or no consensus.

Observational study design

Inclusion

Patients aged ≥ 18 years presenting to NHS hospitals with existing or new aneurysms of ≥ 4 cm in diameter in the arch, descending or thoracoabdominal aorta (including aneurysms secondary to atherosclerotic degeneration, after acute dissection and secondary to aortopathy).

Exclusion

Patients suffering from acute dissection with or without malperfusion syndromes or who had previous intervention for the same aneurysm.

Study groups

The study groups were WW, CM, ESG and OSR.

Data collection

Patient characteristics, medical history, health-related quality of life and NHS resource use were recorded at consent and at 3, 6, 12, 18, 24, 36 and 48 months (plus 1 month post intervention). Aneurysm growth was monitored using thoracic computerised tomography (CT) or magnetic resonance images in accordance with local protocols.

Outcomes

Aneurysm diameter growth, pre-/post-intervention survival, clinical events, hospital admissions and quality of life. An estimation of incremental cost per quality-adjusted life-years (QALYs) gained was planned.

Statistical methods

The sample size of 170 ESG and 112 OSR patients was based on identifying moderate to large effects on survival [hazard ratio (HR) > 0.5)], with 5% significance and 80% power. This allowed an estimation of EuroQoL-5 Dimensions, five-level version (EQ-5D-5L) utility differences of 0.1, with 90% power.

Main data analysis methods

Analysis included Cox regression for predictors of survival, negative binomial regression to compare event rates and longitudinal mixed effects for aneurysm growth and quality-of-life trajectories. Sensitivity to assumptions about missing covariates was assessed using multiple imputation. In sensitivity analyses, patients with a contraindication to either intervention were excluded and the analyses were repeated based on propensity scores.

Health economic analysis

Within-study and model-based analyses were planned but were revised to a description of quality-adjusted life-years and costs from an NHS and Personal Social Services (PSS) perspective. Further analysis involved the exploration of the drivers of costs and the prediction of the value of information (VoI) of future research. Costs were reported in 2018 Great British pounds and QALYs were estimated from responses to the EQ-5D-5L.

Results

Systematic review

The review identified five comparative cohort studies (ESG patients, $n = 3955$; OSR patients, $n = 21{,}197$). Risk of bias was rated as being moderate to severe across all studies. Pooled short-term all-cause mortality favoured ESG [odds ratio 0.71, 95% confidence interval (CI) 0.51 to 0.98; no heterogeneity]. Data on survival beyond 30 days were mixed. Fewer short-term complications were reported with ESG.

Delphi study

Twenty experts from 13 centres took part. Among 360 scenarios, consensus was reached in 247 (69%) and equipoise in 34 (9%), leaving neither consensus nor equipoise in 79 (22%).

For patients with smaller aneurysms, of ≤ 6.0 cm in diameter (110/144, 76% scenarios), WW was generally the preferred management; the main exceptions were older or high-risk patients (CM) and patients with CTDs (OSR). Equipoise between WW and OSR was evident for a small number of scenarios. There was no consensus for low-/medium-risk patients aged > 85 years or for patients aged < 65 years with CTDs.

For patients with aneurysms of > 6.0 cm in diameter, experts generally favoured OSR in the arch, except in older/high-risk patients, and in the descending thoracic aorta if patients had CTDs. Otherwise ESG was preferred. Experts expressed equipoise between OSR and ESG for medium-risk patients aged 65–75 years with aneurysms in the arch of > 6.0 cm in diameter and for patients with CTDs at low/medium surgical risk and aged 75–85 years.

Effective Treatments for Thoracic Aortic Aneurysms patient cohort

Between March 2014 and July 2018, 886 patients were recruited from 30 English centres [WW, *n* = 489 (55.2%); CM, *n* = 112 (12.6%); ESG, *n* = 150 (16.9%); OSR, *n* = 135 (15.2%)]. The mean time between diagnosis and recruitment was 2 (range 0–22) years.

Baseline predictors

A total of 321 (36.2%) patients were women and 565 were men; patients' mean age was 70.9 [standard deviation (SD) 10.9] years, and 86–96% had treated hypertension. Patients receiving CM were significantly older and more likely to have comorbidities. OSR patients were significantly younger. There were significant differences between the groups in the prevalence of some comorbidities, biomarkers and cardiac medication.

Details of procedures

A total of 150 patients underwent ESG and 135 underwent OSR. Thirty-seven OSR patients had concomitant cardiac procedures that could have been completed only during open surgery. Aneurysms were more likely to be treated with OSR if they were in the arch (103/139) and less likely to be treated with OSR if they were in the descending aorta (82/221). Aneurysms involving the ascending aorta were always treated with OSR. Twelve ESG patients and 25 OSR patients had a second procedure; three progressed to a third.

Pre-procedure survival, clinical events, readmissions, aneurysm growth and quality of life

Aneurysm growth

Analysis included 1767 scans that allowed for 6433 aneurysm diameter measurements to be taken in 886 patients. The mean baseline aneurysm diameters (cm) in patients with repeated measurements were 4.11 (SD 0.87) in the ascending aorta, 3.98 (SD 0.85) in the arch of the aorta, 5.26 (SD 1.09) in the descending aorta and 3.48 (SD 0.81) in the thoracoabdominal aorta. Baseline aneurysm diameter was higher in older patients, current smokers and patients with CTDs, chronic obstructive pulmonary disease (COPD) or valve disease. On average each year, aneurysms grew by 0.04 cm in the arch, 0.07 cm in the descending aorta and 0.10 cm in the thoracoabdominal aorta.

Survival

Pre intervention, 129 patients died during 1498.2 patient-years of follow-up (8.6% per patient-year); 64 (49.6%) deaths were aneurysm related. In unadjusted Cox regression for overall survival, the hazard ratio (HR) for CM was 3.05 (95% CI 2.12 to 4.37; $p < 0.001$). In multivariable analysis, the hazard of death from any cause was higher for women (HR 1.79, 95% CI 1.25 to 2.57; $p = 0.001$) and older patients (HR 2.50, 95% CI 0.76 to 5.43, age 61–70 years; HR 3.49, 95% CI 1.26 to 9.66, age 71–80 years; HR 7.01, 95% CI 2.50 to 19.62, age > 80 years; $p < 0.001$) and per 1-cm increase in aneurysm diameter (HR 1.90, 95% CI 1.65 to 2.18; $p = 0.001$). Weak evidence suggested that New York Heart Association (NYHA) class was associated with increasing risk of all-cause death (HR 1.23 per class, 95% CI 1.00 to 1.52 per class; $p = 0.052$). Similar results were found for aneurysm-related deaths. Predictions from this analysis suggest that intervention should be discussed once aneurysms exceed 6 cm in diameter if the operative risk is low/moderate.

Hospital admissions

Pre procedure, 363 admissions were reported for 222 patients; 52 admissions for 39 patients were aneurysm related. Adjusting for age and sex, and taking WW as the reference group, the relative admission rate was 1.31 (95% CI 0.89 to 1.92) for CM patients, 2.10 (95% CI 1.30 to 3.42) for ESG recipients and 0.90 (95% CI 0.46 to 1.76) for OSR recipients ($p = 0.016$). Two non-fatal ruptures and seven dissections were reported. Combining fatal and non-fatal events, there were 69 ruptures/dissections in 1489 years of patient follow-up: 4.6% per patient-year. Eight non-fatal neurological events were reported.

Quality of life pre intervention

The analysis included 3492 EQ-5D-5L utilities from 855 patients. The mean utility at baseline was 0.73 (SD 0.23) for WW patients, 0.68 (SD 0.25) for CM patients, 0.77 (SD 0.24) for ESG patients and 0.76 (SD 0.18) for OSR patients. For patients who had average covariates at baseline, the mean utility was 0.85 (95% CI 0.82 to 0.88), decreasing for patients who required formal/informal care (decrement –0.206, 95% CI –0.255 to –0.156; $p < 0.001$) and with each increase in NYHA class (decrement –0.089, 95% CI –0.108 to –0.069; $p < 0.001$). There was little change in quality of life pre intervention (decrement –0.010 per year, 95% CI –0.022 to 0.003 per year; $p = 0.128$) for average patients. The decline per year in quality of life was greater for older patients (additional change –0.013 per decade increase in age, –0.019 to –0.007; $p < 0.001$) and smokers (additional change compared with non-smokers: 0.003, 95% CI –0.026 to 0.032, for ex-smokers, and –0.034, 95% CI –0.057 to –0.01, for current smokers; $p = 0.004$).

Post-intervention survival, clinical outcomes and quality of life

Baseline predictors

The key differences between the ESG and OSR patients at the time of the procedure were that ESG patients were older (mean age difference 7.1 years, 95% CI 4.7 to 9.5 years; $p < 0.001$) and more likely to be current smokers or ex-smokers (75.8% vs. 66.4%; $p = 0.080$), have valve disease (89.9% vs. 71.6%; $p < 0.0001$), have COPD (21.3% vs. 13.3%; $p = 0.087$), be at NYHA class III/IV (22.3% vs. 16.0%; $p = 0.217$), have lower average levels of haemoglobin (mean difference –6.8 g/l, 95% CI –11.2 to –2.4 g/l; $p = 0.003$) and take statins (69.3% vs. 42.2%; $p < 0.0001$). Patients with CTDs primarily underwent OSR (14.8% vs. 1.3%; $p < 0.001$).

Outcomes after procedure

Ten (6.7%) ESG and 15 (11.1%) OSR patients died within 30 days of the procedure ($p = 0.2107$). OSR patients required a significantly longer stay in the intensive care unit (median 5 vs. 0.5 days; $p < 0.0001$) and a longer stay in hospital (median 16 vs. 7 days; $p < 0.0001$) than ESG patients. OSR patients also had more complications (240 vs. 98; relative rate 2.72, 95% CI 2.04 to 3.68; $p < 0.001$). Overall, 58 (38.7%) ESG and 103 (76.3%) OSR patients experienced adverse events during the index procedure admission ($p < 0.001$).

Survival post procedure

During follow-up, 40 ESG and 36 OSR patients died, 17 and 25, respectively, from aneurysm-related causes. One-year overall survival rate was 82.5% (95% CI 75.2% to 87.8%) after ESG and 79.3% (95% CI 71.1% to 85.4%) after OSR (log-rank $p = 0.9918$). One-year aneurysm-related survival rate was 89.8% (95% CI 83.4% to 93.8%) after ESG and 87.7% (95% CI 75.9% to 89.1%) after OSR (log-rank $p = 0.1107$). There was a non-significant higher hazard of all-cause and aneurysm-related deaths for OSR patients (HR 1.27, 95% CI 0.78 to 2.09; $p = 0.332$; and HR 1.59, 95% CI 0.86 to 2.96; $p = 0.140$). The variables affecting survival were aneurysm location, age, NYHA class and time waiting for procedure.

Readmissions after discharge from index procedure

In the first 3 months after discharge, ESG patients were more likely to be readmitted; thereafter, readmission rates in both groups were similar. During follow-up, 40.7% of ESG and 31.9% of OSR patients were readmitted ($p = 0.1398$). A similar pattern was observed for aneurysm-related readmissions. No readmissions were reported for rupture and one readmission was reported for dissection.

Post-procedure quality of life

For ESG, utility did not change over time, apart from a small decrease of –0.017 (95% CI –0.062 to 0.027) in weeks 0–6. For OSR patients, there was a substantial decrease in utility of –0.160 (95% CI –0.199 to –0.121; $p < 0.001$) up to 6 weeks. Otherwise, the difference in utility between the two procedures during follow-up for survivors was not significant. Women had a small increase in quality of life over time ($p = 0.029$), whereas men's quality of life did not change after 6 weeks. Current smokers and patients in higher NYHA classes had significantly lower quality of life throughout.

Direct comparison between groups suitable for both interventions

In total, 115 ESG and 35 OSR patients were considered suitable for both procedures. Despite the exclusion of patients who had contraindications to either treatment, important differences in baseline variables remained between the groups. Importantly, the age difference between the groups increased, with ESG patients a mean of 10.5 years older (95% CI 6.9 to 14.1 years older).

Survival and hospital readmissions

Eight (7.0%) ESG and three (8.6%) OSR patients died within 30 days of the procedure. The HR for OSR ranged from 0.87 to 1.43 for all-cause deaths and from 1.20 to 1.59 for aneurysm-related deaths; none was statistically significant. Hospital admission rates showed similar patterns to the full post-procedure cohort.

Post-procedure quality of life

Quality of life was available for 129 out of 150 patients, who completed a total of 548 questionnaires. The results of refitting quality-of-life models showed a larger decrease in quality of life for OSR patients throughout, which was significant across most models, but is likely to have been exaggerated by small-sample bias.

Health economic analysis

No formal comparative economic analysis was possible. However, an analysis of patients by arm showed that, on average, ESG procedures were more costly than OSR (£26,536, SD £9877, vs. £17,239, SD £8043) but incurred lower hospital costs (£7484, SD £7848, vs. £28,636, SD £23,083) and follow-up costs to 12 months (£6642, SD £11,927, vs. £15,989, SD £38,247). The main drivers of costs were the stents for ESG and hospital stays for OSR. The EQ-5D-5L scores in the OSR group were generally lower. At 12 months, the mean number of QALYs gained was, on average, 0.62 (SD 0.32) for ESG and 0.46 (SD 0.35) for OSR. VoI was, at most, £500,000.

Conclusions

The current literature comparing ESG and OSR is dated and of limited quality. The incidence of diagnosed CTAAs is low but may rise as the UK population ages, comorbidities become more prevalent and CT scanning becomes more prevalent. Patients have a high risk of death compared with the age-matched population, and have a range of comorbidities. With small aneurysms, the risk of rupture is low and monitoring with detailed cross-sectional imaging is appropriate, in addition to risk factor modification. Interventions often involve more than one aortic segment; 11.2% also require concomitant cardiac procedures and 4.6% require hybrid procedures. Recommending the type and the timing of intervention is challenging, but strong expert consensus is evident. The timing of intervention is driven primarily by aneurysm size and location, and intervention type is driven primarily by age, operative risk and presence of CTDs. Both ESG and OSR are successful in the medium term for carefully selected patients. Both interventions are expensive, but no cost-effectiveness comparison could be completed. The results indicate that a randomised trial is not feasible, and nor would such a study be of sufficient value in the UK.

Strengths and weaknesses

The main strength of the Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study was the engagement of 30 centres that had specialist aortic aneurysm provision and rigorously applied research methods. The biggest limitations were the relatively small number of patients and, thus, the low power to detect differences in outcomes and limited adjustment for confounding.

Implications for service

1. The complex needs and relative rarity of CTAAs suggest that care may be best delivered by specialist centres with multidisciplinary teams.
2. For small aneurysms (4–5.5 cm in diameter) current strategies, including blood pressure management, optimal management of breathlessness and encouragement to reduce smoking and maintain an active lifestyle, appear to work well.
3. Larger aneurysms (≥ 6 cm in diameter) require intervention without long delays. Timing of intervention remains challenging, but should be discussed when aneurysms reach 6 cm in diameter if operative risk is low or moderate.
4. ESG and OSR are successful for carefully selected patients, based on age, sex, operative risk and aneurysm diameter.

Further research

1. More detailed analysis of diameter, length and volume of aneurysms, and other anatomical features, to refine decisions around when and how to intervene.
2. Definition of low-, medium- and high-risk patients within each intervention group.
3. Combine ETTAA and long-term routine electronic data to elucidate longer-term survival and hospital admissions and identify predictors of clinical outcomes and cost.
4. Establish a prospective registry, involving specialist centres, to record the outcomes of and predictors for ESG and OSR, allowing the longer-term follow-up of patients pre/post intervention.

Trial registration

This trial is registered as ISRCTN04044627 and NCT02010892.

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