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Endovascular aneurysm repair offers a survival advantage and is cost-effective compared with conservative management in patients physiologically unfit for open repair

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ABSTRACT

Objective: The endovascular aneurysm repair-2 (EVAR-2) trial suggested that EVAR in patients unfit for open surgical repair (OSR) failed to provide a significant overall survival advantage compared with conservative management. The aim is to compare survival and cost-effectiveness in patients with poor cardiopulmonary exercise test (CPET) metrics who underwent EVAR or were managed conservatively.

Methods: A prospective database of all CPETs (1435 patients) performed to assess preoperative fitness for abdominal aortic aneurysm repair was maintained. A total of 350 patients deemed unfit for OSR underwent EVAR or were managed conservatively. A 1:1 propensity-matched analysis incorporating age, gender, anaerobic threshold, and aneurysm size was used to compare survival. Cost-effectiveness analysis was based on the economic model for the National Institute for Health and Care Excellence clinical guideline on abdominal aortic aneurysm treatment.

Results: Propensity matching produced 122 pairs of patients in the EVAR and conservative management groups. The median overall survival for the EVAR group was significantly longer than that for the conservative management group (84 vs 30 months, $P < .001$). One-, three-, and five-year mortality in the EVAR group was 7%, 40%, and 68%, respectively, compared with 25%, 68%, and 82% in the conservative management group, all $P < .001$. The increment cost-effectiveness ratio for EVAR was £8023 (US$11,644) per quality-adjusted life year gained compared with £430,602 (US$624,967) in the National Institute for Health and Care Excellence guideline, which is based on EVAR-2 results.

Conclusions: EVAR offers a survival advantage and is cost-effective in selected patients deemed unfit for OSR based on CPET compared with conservative management. (J Vasc Surg 2023;77:386-95.)

Keywords: Endovascular aneurysm repair; EVAR; Survival; CPET; Open aneurysm repair

The introduction of endovascular aneurysm repair (EVAR) has revolutionized the management of abdominal aortic aneurysms (AAA). The EVAR-1 trial[1] and other more recent studies[2,3] showed that there is a short-term survival advantage for EVAR but inferior long-term survival compared with open surgical repair (OSR). In patients deemed physiologically unfit for OSR based on a "traffic light" system incorporating cardiac, respiratory, and renal factors, the EVAR-2 trial showed that EVAR was associated with inferior overall life expectancy compared with no intervention and superior outcomes in reducing aneurysmal mortality.[4] This was secondary to increased perioperative mortality in the EVAR group and the need for reintervention for endograft complications.[4] Current Society of Vascular Surgery guidelines recommend informing this cohort of patients of their Vascular Quality Initiative perioperative mortality risk score for them to make a decision to proceed with aneurysm repair.[5] Several recent published large cohort studies showed contradictory EVAR survival results to the EVAR-2 trial.[6,7] Advances in patient optimization, graft technology, improved operator skills, and

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percutaneous techniques in recent years might have been contributing factors to these improved outcomes.

Cardiopulmonary exercise testing (CPET) is the gold standard method for fitness and risk assessment in patients undergoing major intra-abdominal surgery[8] and is a predictor of mortality[9] and cardiovascular complications[10] after elective AAA repair. An anaerobic threshold (AT) below 10.2 mL/kg/min is a predictor of early death in open AAA repair[9] at 30 days, and peak VO2 less than 15 mL/kg/min is a predictor of 90-day mortality.

The National Institute for Health and Care Excellence (NICE) clinical guideline relating to the treatment of AAA[11] suggested that EVAR for patients who were unfit for OSR was not cost-effective. NICE typically uses a threshold of £30,000 (US$43,541) per quality-adjusted life year (QALY) gained to assess whether a treatment is cost-effective; the incremental cost-effectiveness ratio (ICER) for EVAR in this population was £430,602 (US$624,967) per QALY gained. However, it should be noted that a major driver for this high figure was the use of a hazard ratio (HR) estimate that suggested that EVAR increased the risk of death after 4.5 years compared with untreated patients; when no differential in deaths beyond 4.5 years was assumed (HR = 1), the ICER dropped to £66,801 (US$96,954).

The primary objective of this study was to compare overall and aneurysm-related survival in patients with poor CPET metrics who were deemed unfit for OSR based on CPET and multidisciplinary team (MDT) decision, who underwent EVAR or were managed conservatively. The secondary objective was to compare cost-effectiveness between the two groups.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single retrospective study of prospectively collected registry data
- **Key Findings:** In selected patients with abdominal aortic aneurysm unfit for open surgery, endovascular aneurysm repair was associated with longer survival (84 vs 30 months, $P < .001$) and is cost-effective compared with conservative management.
- **Take Home Message:** Endovascular aneurysm repair offers a survival advantage and is cost-effective in selected patients deemed unfit for open surgery based on cardiopulmonary exercise test compared with conservative management.

METHODS

Patients. A prospective database of all patients with AAA referred for CPET testing between November 2005 and December 2019 was maintained. Data included patient demographics, comorbidities, current medications, AAA size, CPET parameters, and survival status with date of death. The project was registered with the local clinical effectiveness unit (registration number 1492) and obtained institutional approval. As this study is retrospective, informed consent was not required. A retrospective analysis of this database was performed in addition to hospital electronic records and the radiology information system (CRIS) to identify short- and long-term outcomes, endograft complications, reinterventions, and survival using a census date of (January 20, 2020).

All patients were discussed in the MDT meeting with the presence of an interventional radiologist, vascular surgeon, and a consultant anesthetist. An AT ≥10.2 mL/kg/min was considered the cutoff value for being fit for OSR based on our departmental policy, based on Hartley et al[9] unless there was a technical or patient-related reason to consider EVAR. Patients with an AT < 10.2 mL/kg/min could be offered EVAR or managed conservatively based on MDT discussions, clinical assessment, and patient consultation. Unfit patients were considered for EVAR if they did not have a contraindication to EVAR such as anatomical factors (based on instructions for use [IFU]), advanced dementia, or advanced chronic obstructive pulmonary disease that might contraindicate regional anesthesia and was also based on patients' life expectancy. All EVARs were performed by an experienced team of interventional vascular radiologists and followed up in the vascular radiology outpatient clinic after their intervention with postoperative computed tomography scan at day 30, 6 months, and yearly afterward with no patients lost to follow-up. A group of patients not anatomically suitable for EVAR were considered for fenestrated EVAR. However, those patients were excluded from this analysis. Patients managed conservatively were established on best medical therapy and discharged to primary care with no routine secondary care follow-up. However, electronic hospital records and CRIS were updated with the survival status automatically on the notification of death.

Statistical analysis. Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range) as appropriate. Categorical data were presented as the number of subjects and percentage. Continuous variables were compared using the independent samples *t*-test. Categorical variables were compared using Pearson's χ^2 test. Propensity-matched analysis was performed to account for baseline differences between the EVAR and the conservative management groups to minimize confounding. A propensity-matched score for each patient was calculated using multivariable logistic regression analysis in which the treatment performed (EVAR or conservative) was regressed on four baseline characteristics (age, sex, AT, and aneurysm size) that were considered potential confounding factors and clearly affect the decision on treatment received and the outcome. Subjects were matched on the logit of the propensity score using 1:1 greedy nearest-neighbor matching with a caliper distance of 0.2

times of the SD of the logit of the propensity score. Pre- and post-matching propensity scores for both groups were compared using Kernel density estimation plots.

Survival was calculated from the date of CPET to date of death or census. All-cause and aneurysm-related survival was calculated using Kaplan-Meier survival curves and the log-rank test for comparison. Univariate Cox proportional hazard regression analysis was used to assess factors that influenced survival in the EVAR and the conservative management groups using the "enter" method and the calculation of HR and 95% confidence intervals (95% CI). Multivariate Cox proportional hazard regression analysis using the forward stepwise likelihood ratio method was performed for significant variables ($P < .200$) on univariate analysis.

All statistical tests were two-sided, and a P value of less than .050 was considered statistically significant. A Statistical Package for the Social Sciences Program (SPSS) version 26 for Windows (SPSS Inc) and Stata version 16 (StataCorp) were used for statistical analysis and for propensity matching. GraphPad Prism 8.3.0 (GraphPad Software) software was used for presentation of data.

Cost-effectiveness analysis. The economic model developed for NICE clinical guideline (NG156) and its base case parameterization was used, with a small number of changes applied to reflect the new evidence base in relation to mortality and reintervention rates. Specifically, the following changes were made:

1. Perioperative mortality: the NICE guideline model used a rate of 7.3% from EVAR-2. This was replaced by a rate of 0.8% relating to the Sheffield cohort. The actual rate in the Sheffield cohort was 0%; however, this zero value returned an error message within the model, and so a single event was included (ie, 1/122).
2. No intervention survival curve: the NICE model extrapolated EVAR-2 survival data to describe lifetime survival. This was achieved by calibrating general population survival to the trial patients not receiving an intervention. This calibration was implemented by applying an HR of 3.539 to the relevant life tables up to 4.5 years and then 1.625 thereafter. Using the same approach to calibration (Appendix), the two HRs for the Sheffield cohort were re-estimated as 4.711 and 4.176, respectively.
3. Intervention survival curve: this was generated by applying treatment effects estimated using Cox proportional hazard regression models applied to the pre- and post-4.5-year time periods. In the NICE model, this produced EVAR HRs of 0.742 and 1.454 for the early and late periods, respectively. For the Sheffield cohort, these were re-estimated as 0.204 and 0.640.
4. Reintervention rate: in the NICE model, reinterventions in the EVAR arm were estimated as 0.253 and 0.038 per patient year for 0-6 months and >6 months, respectively. The split between life-threatening and serious but not life-threatening was 50:50. For the Sheffield cohort, the rates were estimated as 0.132 per patient year and 0.020 per patient year, with no life-threatening events.

Rupture rates for the no intervention arm could not be estimated from the Sheffield cohort due to missing data, and so the rate used in the NICE evaluation continued to be applied.

A scenario sensitivity analysis was undertaken to explore the impact of more conservative estimates of the initial treatment effect (<4.5 years) and the persistence of the treatment effect (>4.5 years). For the former, HR = 0.338 was chosen, as it is the upper 95% confidence limit on the central estimate used in the base case, whereas HR = 1 was used beyond 4.5 years as the central estimate was highly uncertain ($P = .223$). Both of these changes have the effect of making EVAR less cost-effective. The price level used for the NICE economic model was for the year 2015/2016, to which we applied the relevant purchasing power parity (0.689) to produce cost values in US$.

All parameters used in analyses are summarized in Supplementary Table I (online only). Further details of the calibration are given in the Appendix (online only).

RESULTS

Patients. The study flow is shown in Fig 1. Overall, 1435 patients with AAA (mean [SD] age: 75 [9] years, 260 [18%] female) were referred for CPET assessment. A total of 350 patients suitable for EVAR in terms of anatomy (within IFU) had infrarenal AAA size >5.5 cm and AT <10.2 mL/min/kg and were deemed unfit for OSR. A total of 135 patients underwent EVAR, and 215 patients were managed conservatively. Baseline characteristics of patients unfit for OSR before and after propensity score matching in the EVAR and conservative management groups are summarized in Table I. No significant difference between the two groups was observed after matching in age, sex, AAA size, AT, comorbidities, or cardiovascular risk factors. Pre- and post-matching propensity scores for both groups are shown in Fig 2 using Kernel density estimation plots.

Perioperative outcomes. Overall, 135 (39%) patients underwent EVAR. A total of 26 (19%) patients had surgical cut down for common femoral artery access, 81 (60%) had percutaneous access, and 28 (21%) had both. A total of 22 (16%) patients underwent EVAR under general anesthesia, 32 (24%) under regional epidural anesthesia, 25 (19%) under regional spinal anesthesia, and 56 (41%) under local anesthesia. Endurant (Medtronic Ltd) was used in 101 (75%) patients, Ovation (Trivascular Inc) in 12 (9%), Zenith (Cook Medical) in 10 (7%), Aorfix (Lombard Medical) in 2 (1%), AFX (Endologix Inc) in 1 (1%), Nellix (Endologix Inc) in 7 (4%), Incraft (Cordis Corp) in 3 (2%), and Excluder (Gore Medical) in 1 (1%). Reinterventions based on time from EVAR are summarized in

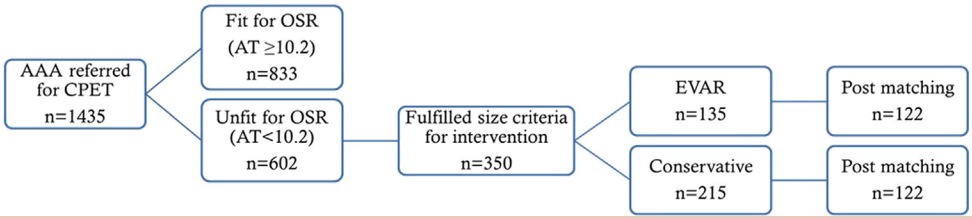

Fig 1. Consort diagram for patients included in the study with the number of patients before and after propensity-matched analysis. *AAA*, Abdominal aortic aneurysm; *AT*, anaerobic threshold; *CPET*, cardiopulmonary exercise testing; *EVAR*, endovascular aneurysm repair; *OSR*, open surgical repair.

Supplementary Table II (online only). A total of 25 reinterventions occurred in 21 (17%) patients. All reinterventions were classed as serious. No life-threatening reinterventions occurred. The mean (SD) length of hospital stay for patients who underwent EVAR was 2 (3) days.

All-cause survival. During a mean (range) follow-up period of 9 (1-12.5) years, 205 (59%) patients (39 [11%] in the EVAR group and 106 [49%] in the conservative group) died. The median (95% CI) all-cause survival for the whole cohort after propensity score matching (244 patients) was 58 (46-69) months. The median (95% CI) survival for the EVAR group was longer than that for the conservative management group (84 [58-109] months vs 30 [23-37] months, respectively; $P < .001$; Fig 3, *A*). All-cause mortalities at 30 and 90 days were lower in the EVAR group compared with the conservative management group (0% vs 2%; $P = .156$ and 0% vs 6%; $P = .006$, respectively). The 1-, 3-, and 5-year all-cause mortality rates were lower in the EVAR group compared with the conservative management group (7% vs 25%; $P < .001$, 40% vs 68%; $P < .001$, and 68% vs 82%; $P = .010$, respectively).

Aneurysm-specific mortality. Data on aneurysm-specific mortality were available for 180 of the 244 patients including post-matching (74%) patients (97 [54%] in the EVAR group and 83 [46%] in the conservative management group). Overall, 70 (39%) patients (12 [7%] in the EVAR group and 58 [32%] in the conservative group) died during the follow-up period. The median (95% CI) aneurysm-specific survival for the whole cohort after propensity score matching was 77 (58-96) months. The median survival for the EVAR group could not be estimated, and the 75th percentile survival was calculated. The 75th percentile aneurysm-specific survival for the EVAR group was longer than that for the conservative management group (84 months vs 15 months, respectively; $P < .001$; Fig 3, *B*). Aneurysm-specific mortalities at 30 and 90 days were lower in the EVAR group compared with the conservative management group (0% vs 1%; $P = .278$ and 0% vs 5%; $P = .029$, respectively). The 1-, 3-, and 5-year aneurysm-related mortality rates were lower in the EVAR group compared with the conservative management group (6% vs 24%; $P = .001$, 43% vs 65%; $P = .004$, and 68% vs 83%; $P = .020$, respectively).

Predictors of all-cause mortality. Results of univariate Cox regression analysis of predictors of all-cause mortality are summarized in Fig 4. A lower rate of vascular intervention (EVAR) ($P < .001$), increasing age ($P = .002$), lower body mass index ($P = .003$), and higher frailty score >4 ($P = .011$) were associated with increased all-cause mortality on univariate Cox regression analysis. Lower rate of vascular intervention (EVAR) (HR = 0.224, 95% CI [0.150-0.334]; $P < .001$) and increasing age (HR = 1.047, 95% CI [1.022-1.073]; $P < .001$) were associated with increased all-cause mortality on multivariate Cox regression analysis. Patients managed conservatively were four times more likely to die from any cause compared with patients who underwent EVAR (HR [95% CI] = 4.464 [3.030-6.666], $P < .001$).

Predictors of aneurysm-specific mortality. Results of univariate Cox regression analysis of predictors of aneurysm-specific mortality are summarized in Fig 4. A lower rate of vascular intervention (EVAR) ($P < .001$), increasing age ($P = .003$), lower body mass index ($P = .008$), higher frailty score >4 ($P = .021$), and higher revised cardiac risk index (RCRI) ≥ 3 ($P = .044$) were associated with increased aneurysm-specific mortality on univariate analysis. A lower rate of vascular intervention (EVAR) (HR = 0.121, 95% CI [0.064-0.228]; $P < .001$) and increasing age (HR = 1.055, 95% CI [1.020-1.091]; $P = .002$) were associated with increased aneurysm-specific mortality on multivariate Cox regression analysis. Patients managed conservatively were eight times more likely to die from aneurysm-related complications compared with patients who underwent EVAR (HR [95% CI] = 8.264 [4.385-15.625], $P < .001$).

Base case cost-effectiveness analysis. Results of the base case cost-effectiveness and sensitivity analysis are summarized in Table II. Mean costs of EVAR were estimated at £13,763 (US$19,975) compared with £14,063 (US$20,411) in the NICE model. EVAR provides an average

Table I. Patients baseline characteristics and results of baseline investigations for the whole cohort and the endovascular aneurysm repair (*EVAR*) and conservative management groups before and after matching

	Before propensity score matching				After propensity score matching			
Baseline characteristic[a]	All patients (n = 350)	EVAR (n = 135)	Conservative (n = 215)	*P* value[b]	All patients (n = 244)	EVAR (n = 122)	Conservative (n = 122)	*P* value[b]
Demographics								
Age, years	76 (8)	75 (6)	78 (7)	.033	76 (7)	76 (6)	76 (8)	.836
Female, n (%)	91 (26)	24 (18)	67 (31)	.006	53 (22)	24 (20)	29 (24)	.535
AAA size, cm	5.9 (2)	5.9 (1)	5.8 (2)	.580	5.9 (2)	6 (1)	5.6 (2)	.109
BMI, kg/m^2	28 (6)	29 (6)	27 (5)	<.001	28 (6)	30 (7)	27 (6)	.002
AAA characteristics								
Neck diameter, mm	26 (6)	26 (5)	28 (6)	<.001	26 (4)	25 (4)	27 (4)	<.001
Neck length, mm	32 (12)	33 (10)	29 (12)	.005	30 (11)	32 (11)	27 (10)	.002
CIA involvement, n (%)	42 (12)	25 (19)	17 (13)	.554	30 (12)	17 (14)	13 (11)	.606
Adverse anatomy, n (%)	102 (29)	52 (38)	50 (37)	.422	78 (32)	44 (36)	34 (28)	.176
Medications, n (%)								
β-Blockers	104 (30)	46 (34)	58 (27)	.005	75 (31)	43 (35)	32 (26)	.001
Statins	200 (57)	84 (62)	116 (54)	.003	140 (57)	77 (63)	63 (52)	<.001
Aspirin	184 (53)	73 (54)	111 (52)	.740	132 (54)	68 (56)	64 (52)	.539
Comorbidities, n (%)								
Coronary artery disease	70 (20)	31 (23)	39 (18)	.063	33 (14)	16 (13)	17 (13)	1.000
Lung disease	200 (57)	55 (41)	145 (67)	.022	170 (69)	76 (62)	94 (77)	.053
Renal disease	105 (30)	40 (30)	65 (30)	.044	64 (26)	31 (25)	33 (27)	.061
Previous stroke	49 (14)	19 (14)	30 (14)	.033	35 (14)	16 (13)	19 (16)	.749
Malignancy	40 (11)	17 (13)	23 (11)	.054	28 (11)	13 (11)	15 (12)	.841
Cardiovascular risk assessment, n (%)								
RCRI ≥ 3	100 (28)	39 (29)	61 (28)	.035	66 (35)	28 (23)	38 (48)	.050
Frailty score >4	76 (22)	33 (24)	43 (20)	.023	59 (24)	28 (23)	31 (25)	1.000
ICI	77 (22)	47 (35)	30 (14)	<.001	30 (12)	15 (12)	15 (12)	1.000
CPET parameters								
AT, mL/min/kg	7 (3)	8 (2)	7 (3)	<.001	8 (2)	8 (3)	7.8 (3)	.557
VO2Max, mL/min/kg	13 (3)	14 (2)	12 (3)	<.001	13 (2)	14 (2)	13 (3)	.010
VO2Max, mL	1070 (323)	1237 (301)	966 (292)	<.001	1117 (308)	1211 (286)	1022 (302)	<.001
Ve/VCO2	37 (9)	35 (6)	39 (10)	<.001	37 (9)	35 (6)	39 (10)	<.001
Biochemical profile								
Hb, g/L	133 (18)	135 (16)	130 (19)	.036	135 (17)	135 (16)	133 (20)	.568
Creatinine, μmoL/L	102 (44)	98 (35)	106 (53)	.197	103 (43)	100 (36)	110 (56)	.164
eGFR, mL/min/1.73 m^2	62 (17)	64 (18)	61 (16)	.190	61 (17)	62 (17)	60 (17)	.392

AAA, Abdominal aortic aneurysm; *AT*, anaerobic threshold; *BMI*, body mass index; *CIA*, common iliac artery; *CPET*, cardiopulmonary exercise testing; *eGFR*, estimated glomerular filtration rate; *EVAR*, endovascular aneurysm repair; *Hb*, hemoglobin; *ICI*, inducible cardiac ischemia; *RCRI*, revised cardiovascular risk index; *Ve/VCO2*, minute ventilation carbon dioxide ratio; *VO2Max*, maximal oxygen uptake.
Adverse anatomy included significant neck calcification and/or thrombus lining, significant neck angulation, conical neck and significant iliac tortuosity.
[a]Data are presented as mean (standard deviation) or number (%).
[b]*P* value calculated from the independent samples *t*-test for continuous variables or Pearson's χ^2 test for categorical variables.

health benefit of 1.6 QALYs at an incremental cost of £12,840 (US$18,636) yielding an ICER of £8023 (US$11,644). The sensitivity analysis showed that even when using more pessimistic estimates of effectiveness from our data, the ICER increased to £12,689 (US$18,417), which remained highly cost-effective compared with the £30,000 (US$43,541) threshold quoted in the NICE model for cost-effectiveness.

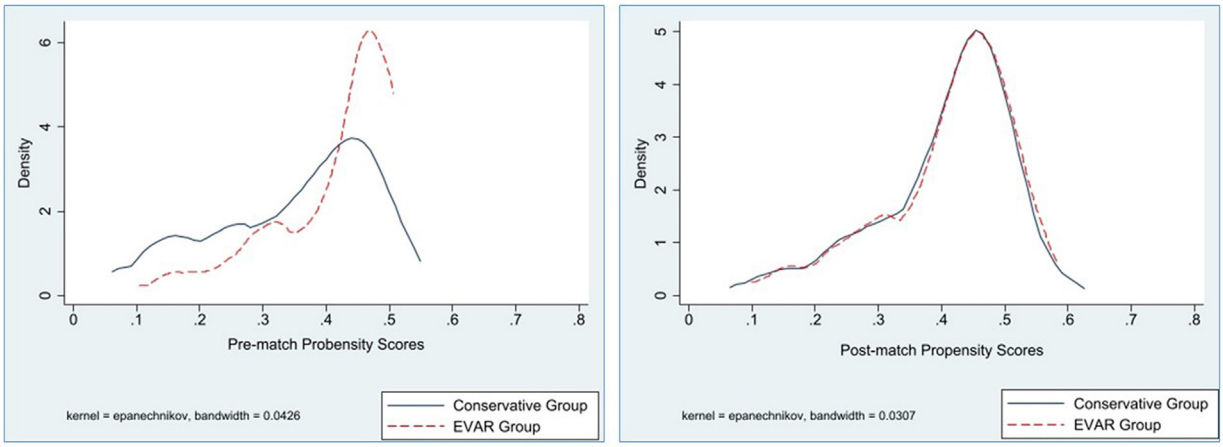

Fig 2. Kernel density estimation plot illustrating pre- and post-matching propensity scores in the endovascular aneurysm repair (*EVAR*) and conservative management groups.

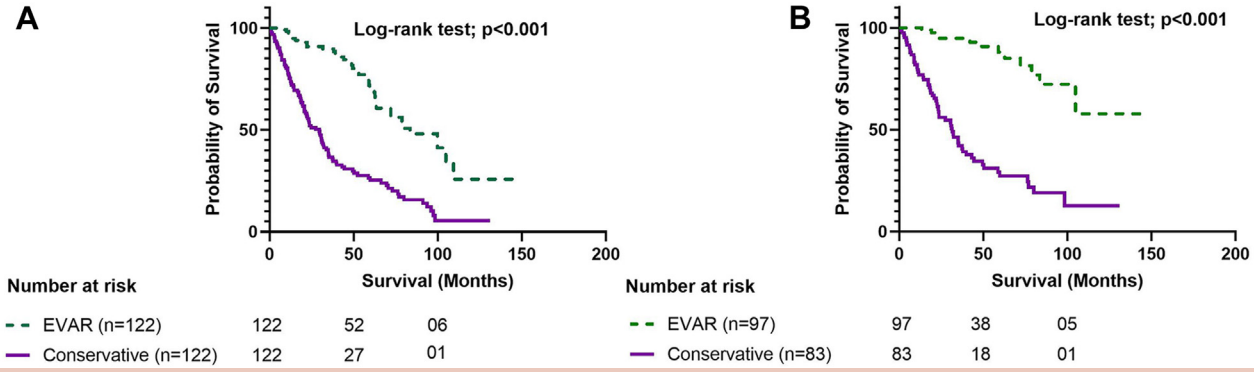

Fig 3. A, Kaplan-Meier survival analysis for all-cause survival from the date of cardiopulmonary exercise test between the endovascular aneurysm repair (*EVAR*) and conservative management groups. **B,** Kaplan-Meier survival analysis for aneurysm-specific survival from the date of cardiopulmonary exercise test between the EVAR and conservative management groups. Numbers at risk for each group are presented below the plot.

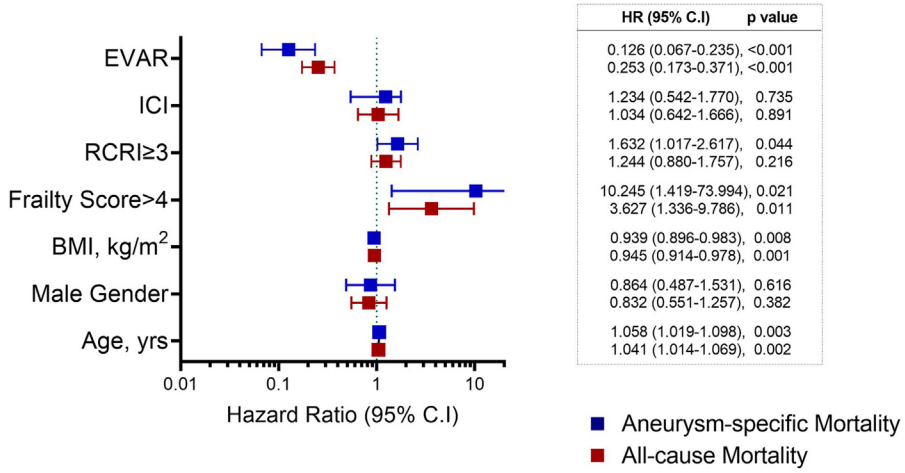

Fig 4. Forest plot depicting the results of univariate Cox proportional hazards regression analysis for all-cause and aneurysm-specific mortality in the whole cohort. The *small squares* represent hazard ratios (*HR*), and the *horizontal lines* represent 95% confidence intervals (*CI*). *BMI,* Body mass index; *EVAR,* endovascular aneurysm repair; *ICI,* inducible cardiac ischemia; *RCRI,* revised cardiovascular risk index.

Table II. Base case cost-effectiveness and sensitivity analysis

	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
NICE NG156					
No intervention	£1050 (US$1524)	2.335			
EVAR	£14,063 (US$20,411)	2.365	£13,012 (US$18,885)	0.030	£430,602 (US$624,967)
Sheffield base case					
No intervention	£923 (US$1340)	1.677			
EVAR	£13,763 (US$19,975)	3.277	£12,840 (US$18,636)	1.600	£8023 (US$11,644)
Sheffield sensitivity analysis					
No intervention	£923 (US$1340)	1.677			
EVAR	£13,544 (US$19,657)	2.672	£12,621 (US$18,318)	0.995	£12,689 (US$18,417)

EVAR, Endovascular aneurysm repair; *ICER*, incremental cost-effectiveness ratio; *NG156*, NICE guideline 156; *NICE*, National Institute for Health and Care Excellence; *QALY*, quality-adjusted life year.

DISCUSSION

To our knowledge, this is the largest recent study to demonstrate that EVAR offers a survival advantage in patients physiologically unfit for open repair compared with conservative management or no intervention. We have demonstrated that EVAR is associated with lower 1-, 3-, and 5-year mortality and longer survival compared with conservative management in patients unfit for open AAA repair over a long period of follow-up (12.5 years).

Our study contradicts previously published data from the EVAR-2 trial,[2] which suggested that EVAR is not associated with longer overall survival compared with no intervention in a cohort of patients considered unfit for OSR but in agreement that aneurysm-related mortality was significantly reduced compared with no intervention. The data presented in our study are based on the prospective objective preoperative physiological assessment of patients with AAA in the form of CPET with a long period of follow-up similar to that of the EVAR-2 trial. CPET is considered the gold standard method for risk and fitness assessment for patients undergoing major intra-abdominal surgery.[8,12-15] Patients fitness in the EVAR-2 trial was decided based on a "traffic light" system including cardiac, respiratory, and renal risk assessments.[2,16,17] Our study, however, is in agreement with another smaller study[18] that compared 37 patients with AAA unfit for OSR who underwent EVAR with 32 patients who were managed nonsurgically and found that EVAR was associated with longer all-cause and aneurysm-specific survivals. Although there was no significant difference between the groups in terms of AT and AAA size, patients in the nonsurgical management group were significantly older, which might have introduced selection bias into the study in addition to the small number of patients. Selection bias was also noted in a study that compared EVAR, OSR, and best medical treatment in high-risk AAA patients classified based on the American Society of Anesthesiologists physical status classification system.[19] Patients offered best medical treatment were older and had larger aneurysm size and comorbidity score compared with EVAR and OSR. In comparison, our study is based on propensity-matched groups with no significant difference in terms of AT, AAA size, age, or gender, including a larger number and more physiologically unfit patients. CPET offers an objective assessment of cardiopulmonary fitness and is widely adopted as the gold standard method for risk assessment in patients planned for elective AAA repair;[8-10,12] however, CPET results in our study were not considered binary and were discussed in the MDT in the context of each individual patient with a decision made after clinical assessment and patient counseling.

Concerns regarding increasing reintervention rate in the EVAR group have been highlighted in the EVAR-2 trial.[2] However, our data did not show an increased reintervention rate in the EVAR group with only 17% requiring reintervention over a follow-up period of 12.5 years with more recent studies reporting similar reintervention rates ranging from 9%[20] to 17%[21] compared with a higher reintervention rate in the EVAR-2 trial at 27%. Looking into the EVAR-2 trial reinterventions in detail, 50% of those were for life-threatening problems and 50% were reinterventions for serious events,[11] which compare favorably to our dataset where all reinterventions were considered serious and none were life threatening. This again reflects evolving EVAR practices since the older EVAR-1 and -2 trials with more advanced technologies. Some secondary EVAR reinterventions can be quite costly, for example, Onyx type 2 embolizations,[22,23] and any future studies will need to carefully manage expensive costly reinterventions.

The survival advantage observed in the EVAR group in our study is probably related to advancements in stent graft technology with some studies reporting more durability and less reintervention rates associated with new compared with old endografts.[24-26] Furthermore, adherence to IFU has been shown to reduce reintervention rates mainly secondary to endoleaks in several

studies.[27-29] Other contributing factors would include advancements in disease understanding and an increase in operator skill in graft implantation.[30,31] In particular, our department has pioneered percutaneous access for EVAR, and a large number of patients in this study benefited from this technique, leading to earlier ambulation and quicker discharge from hospital, with a mean length of stay of only 2 days. These percutaneous endovascular techniques have also been shown to be safe in the long term for patients.[32]

Cost-effectiveness analysis. After cost-effectiveness analysis using NICE NG156 modeling techniques, our study shows that EVAR has the potential to be highly cost-effective in this patient population; our estimated ICER is £8023 (US$11,644) per QALY gained compared with £430,602 (US$624,967) in the NICE economic model. Our methods, being consistent with those developed by NICE for NG156, draw on a large body of validated evidence in relation to treatment pathways, costs, and quality of life. These are new and important contemporaneous findings that suggest that the recent NICE guidance NG156, which was based solely on UK cost-effectiveness data, may not reflect contemporaneous EVAR practices within the United Kingdom (Michaels et al[33] ICER £110,000, Chambers et al[34] ICER £48,990, and Brown et al[35] ICER £264,900).

However, there are two drawbacks to our analysis, which relate to the underlying evidence base from the Sheffield cohort and the extrapolation of mortality. First, the data on which our reparameterization is based is not a randomized controlled trial. Although propensity score matching has been used to reduce the size of any biases that may be present, doubts may remain over the magnitude of the effect sizes (HR = 0.204 and HR = 0.640 for the first 4.5 years and thereafter, respectively). This is exemplified by the curve fitting undertaken for our modeling, which suggests that the EVAR group has survival prospects in the first 4.5 years that were similar to those of the general population (of similar age and gender mix). To further explore the impact of a smaller effect size associated with EVAR, we undertook a sensitivity analysis that used an HR on the lower 95% CI of effectiveness for the first 4.5 years (HR = 0.338) and assumed no survival benefit beyond that (HR = 1). This analysis produces an increase in the ICER to £12,689 (US$18,417) per QALY gained, which remains comfortably below the NICE threshold of £30,000 (US$43,541).[10]

Secondly, within the health economics analysis for NG156, two approaches to survival modeling were explored: calibration of life tables and parametric curve fitting. The former provided a superior fit to the EVAR-2 data and was used in the NICE base case analysis; consequently, we adopted the same approach. We have not explored the relative merits of parametric curve fitting in our analysis or indeed alternative formulations of the calibration approach; however, we expect that the aforementioned scenario analysis relating to EVAR effectiveness will go at least some way toward exploring the impact of alternative long-term survival estimates.

The limitation of this study should be acknowledged. This study is a retrospective analysis of a prospective registry of CPET in patients with AAA. Retrospective data analysis can sometimes lack exposure control or the reporting on some important variables and introduce selection and misclassification bias; however, selection bias was reduced by performing propensity-matched analysis. The selection of patients to have EVAR involved factors such as expected patient longevity that could not be included in the propensity matching that might have introduced selection bias in our study compared with a randomized controlled trial. Further variables were considered for the propensity score model to account for other clinical factors that could influence treatment and/or outcome. For example, severe lung disease is potentially important as that has been shown to influence mortality; however, our data relate to lung disease regardless of severity. In addition, cardiovascular risk and frailty were considered to be relevant; however, the available cardiovascular risk and frailty measures within our dataset were the RCRI[36-38] and the Rockwood clinical frailty scale.[39] RCRI is not a predictor of limited life expectancy but a predictor of the likelihood of a cardiac event after intervention. Such limitations are inherent in the use of retrospective data and point toward the need for a prospective randomized study that balances patient groups across observed and unobserved prognostic factors.

To conclude, EVAR is associated with all-cause and aneurysm-related survival advantage compared with no intervention in selected patients unfit for open AAA repair in the long term. In contrast to the recent NICE guidance NG156, our study also shows that EVAR has the potential to be highly cost-effective in this patient population, with an estimated ICER of £8023 (US$11,644) per QALY gained.

We propose that this new study highlights the need for a new randomized controlled trial to further assess the efficacy of contemporary EVAR in patients unfit for open AAA repair and then a further review of the NICE guidance NG156 in light of any new trial results.

The authors would like to thank NICE and in particular Joshua Pink for providing the cost analysis model for the EVAR-2 trial. Although the model was made available by NICE, this does not imply that it endorses the analyses undertaken, nor any associated conclusions. The views expressed in this publication are those of the authors and not necessarily those of NICE.

AUTHOR CONTRIBUTIONS

Conception and design: YS, SD, KK, TC, SG
Analysis and interpretation: YS, SD, TC, SG
Data collection: YS, KK, SG
Writing the article: YS, SD, TC, SG
Critical revision of the article: YS, SD, KK, TC, SG
Final approval of the article: YS, SD, KK, TC, SG
Statistical analysis: YS, SD
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Overall responsibility: YS

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APPENDIX (online only).

Details of the model changes

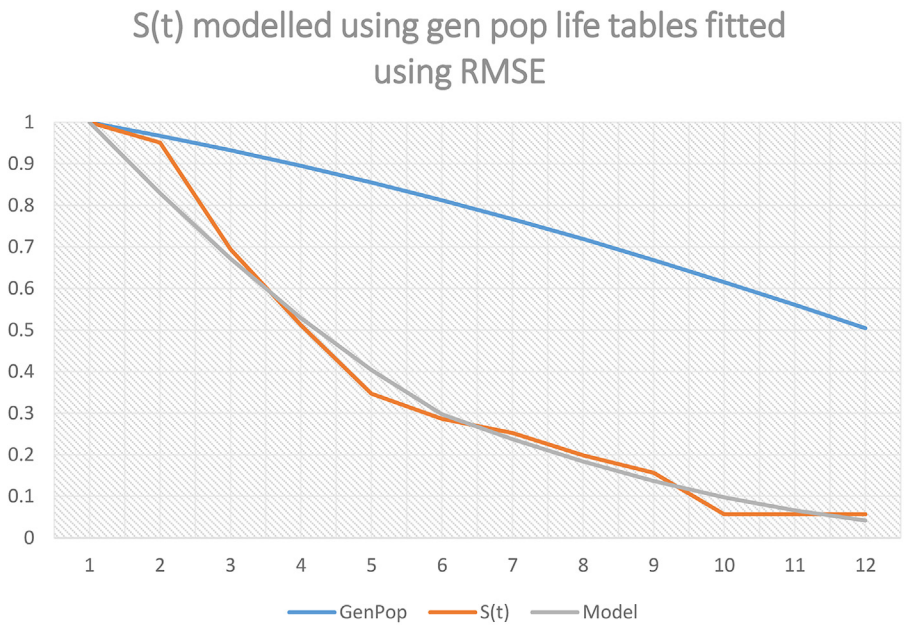
Calibration of no intervention to UK life tables

Calibration was undertaken in line with the modeling undertaken for the NICE guideline as described in the Health Economics Appendix (https://www.nice.org.uk/guidance/ng156/documents/supporting-documentation-2). The only deviation from the NICE methods was that the most recent life tables were used in preference to those matching the dates of EVAR-2 recruitment.

In short, standard UK life tables were adjusted using two hazard ratios (<4.5 years and >4.5 years), which were selected using Solver in Microsoft Excel to minimize the weighted root mean square error (wRMSE) of the points fitted to the annual survival estimates from the Kaplan-Meier curve. The general population curve for a cohort of 76-year-old people, 78% of whom were male, is shown in Supplementary Fig A1, (online only) together with the cohort data (S(t)) and the modeled data.

The modeled survival is produced with hazard ratios of 4.711 and 4.176 for the pre- and post-4.5-year periods, respectively. Using an unweighted root mean square error produced a more pronounced kink, with HRs of 5.224 and 3.584, respectively.

Although easier to identify with the full Kaplan-Meier curve, it is noted that the point at which S(t) kinks, while being close to 4.5 years, may be at a different point. Also, it is recognized that the calibrated life-table approach, as favored by NICE, may not be superior to the use of parametric survival modeling when applied to the Sheffield data.



Supplementary Fig A1 (online only). General population, Sheffield and modeled survival data. *RMSE*, root mean square error.

Cells used to operationalize the changes

Parameter	Cell	Original value	Revised value	Original ICER	Revised ICER
Perioperative (deaths, total patients)[a]	Parameters !J80, !I80	13, 179	1, 122	£430,602	£71,375
No intervention calibration <4.5 years (HR)	Parameters !F148	3.539	4.711	£430,602	£114,641
No intervention calibration >4.5 years (HR)	Parameters !F149	1.625	4.176	£430,602	£230,727
Peri-postoperative effectiveness <4.5 years (HR)	Parameters!F166	0.742	0.204	£430,602	£13,474
Peri-postoperative effectiveness <4.5 years (HR)	Parameters!F167	1.54	0.640	£430,602	£27,530
Reintervention rate (0-6 months, 0.5-4 years, >4 years)	Parameters !F323, !F324, !F325	0.253, 0.038, 0.038	0.132, 0.020, 0.020	£430,602	£379,515
Reinterventions (% life threatening)[b]	Parameters !F320	50%	0%	£430,602	£430,602

HR, Hazard ratio; *ICER*, incremental cost-effectiveness ratio.
[a]The figures of 13 and 179 in the model generate a 7.9% perioperative mortality rate that is used in the model. However, setting the figure of 7.3% to a zero generates errors due to the use of logarithms in associated calculations. Consequently, the sample size for the no intervention groups in the Sheffield cohort is used (n = 122) and a single event added, hence 1/122, or 0.8%.
[b]Although the NG156 Health Economics Appendix presents evidence of differential costs for life-threatening and serious reinterventions in Table H41 (£12,866 vs £4628, respectively), the base case analysis uses the same unit cost for other types of reintervention in cell parameters !F780 (£8670). Consequently, the ICER does not change when the proportion of life-threatening reinterventions is reduced to 0%; it would be expected to reduce.

Supplementary Table I (online only). Amended parameters for the base case and sensitivity analysis

Model parameter	Source of parameterization	
	EVAR-2	Sheffield
Perioperative mortality, %	7.3	0.8[a]
No intervention calibration (HR; <4.5 years, >4.5 years)	3.539, 1.625	4.711, 4.176
EVAR effectiveness (HR; <4.5 years, >4.5 years)	0.742, 1.454	0.204, 0.640
Reintervention rate per annum (0-6 months, >6 months)	0.253, 0.038	0.132, 0.020
Life threatening intervention, %	50	0
Scenario sensitivity analysis	—	0.338, 1.000
EVAR effectiveness (HR; <4.5 years, >4.5 years)		
All other parameters are Sheffield base case		

EVAR, Endovascular aneurysm repair; *HR*, hazard ratio.
[a]An error message is returned in the model when a zero is entered for this value. Consequently, we assumed a single perioperative death among the Sheffield cohort of 122 patients, which produces a nonzero rate (0.8%) and no error message.

Supplementary Table II (online only). Reinterventions based on time since endovascular aneurysm repair (*EVAR*)

	EVAR (n = 122)
Any reintervention, n (%)	25 (17)
Time of reintervention	
EVAR to 6 months	6
6 months to 4 years	18
4 years to 8 years	1
Beyond 8 years	0
Type of reintervention	
Added stent (graft limb extension)	3
Embolization of type 2 endoleak	12
Thrombectomy of occluded graft limb	1
Angiolpasty of graft limb	2
Aorto-uni-iliac device deployment	1
Femoro-femoral crossover graft angioplasty	1
Full reline of graft	1
Reline of graft limb	2
Nylon wrap for type 1 endoleak	1
Palmaz stent for type 1 endoleak	1