

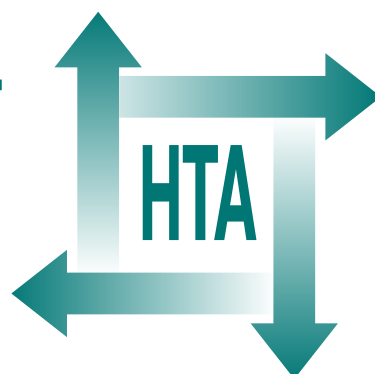
Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model

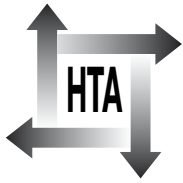
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N Woolacott



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Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model

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Abstract

Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model

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Objective: To determine the clinical effectiveness and cost-effectiveness of endovascular aneurysm repair (EVAR) of infrarenal abdominal aortic aneurysms (AAAs) in patients at varying levels of risk.

Data sources: The following bibliographic databases were searched (2005–February 2007): BIOSIS Previews,[®] CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, ISI Proceedings, MEDLINE,[®] MEDLINE[®] In-Process & Other Non-Indexed Citations, Science Citation Index and Zetoc Conferences.

Review methods: A systematic review of the clinical effectiveness of EVAR was performed using standard methods. Meta-analysis was employed to estimate a summary measure of treatment effect on relevant outcomes based on intention to treat analyses. A second systematic review was undertaken to identify existing cost-effectiveness analyses of EVAR compared with open surgery and non-surgical interventions. Two new decision models were developed to inform the review.

Results: Six RCTs were included in the clinical effectiveness review. Thirty-four studies evaluated the role of patients' baseline characteristics in predicting risks of particular outcomes after EVAR. The majority were based on data relating to devices in current use from the EUROSTAR registry. Compared with open repair EVAR reduces operative mortality (odds ratio 0.35, 95% CI 0.19 to 0.63) and medium-term aneurysm-related mortality (hazard ratio 0.49, 95% CI 0.29 to 0.83) but offers no significant difference in all-cause mortality. EVAR is associated with increased rates of complications and reinterventions, which are not offset by any increase in health-related quality of life. EVAR trial 2 comparing EVAR with non-surgical management in patients unfit for open repair found no differences in mortality between groups; however, substantial numbers of patients randomised to non-

surgical management crossed over to receive surgical repair of their aneurysm. The cost-effectiveness systematic review identified six published decision models. Both models considered relevant for the decision in the UK concluded that EVAR was not cost-effective on average compared with open repair at a threshold of £20,000 per quality-adjusted life-year (QALY). Another model concluded that EVAR would be on average more cost-effective than no surgical intervention in unfit patients at this threshold. The Medtronic model concluded that EVAR was more cost-effective than open repair for fit patients at this threshold. The York economic evaluations found that EVAR is not cost-effective compared with open repair on average at a threshold of £30,000 per QALY, with the results very sensitive to model assumptions and the baseline risk of operative mortality. Exploratory analysis to evaluate management options in patients unsuitable for open surgery suggested that the cost-effectiveness of EVAR may be sensitive to aneurysm size and patient's age at operation. Indicative modelling suggests that EVAR may be cost-effective for small aneurysms in some patient groups. Ongoing RCTs will provide further evidence relating to these patients.

Conclusion: Open repair is more likely to be cost-effective than EVAR on average in patients considered fit for open surgery. EVAR is likely to be more cost-effective than open repair for a subgroup of patients at higher risk of operative mortality. These results are based on extrapolation of mid-term results of clinical trials. Evidence does not currently support EVAR for the treatment of ruptured aneurysms. Further follow-up of the existing UK trials should be undertaken and the relative costs of procedures and devices should be investigated further.

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*Due to the extensive nature of the appendices, these are available only in electronic format. The PDF file of the full report is available at www.hta.ac.uk/1678. It will also be available on *HTA on CD* (see the inside front cover for full details).



Glossary and list of abbreviations

Glossary

Adverse effects and complications Includes aneurysm-related outcomes such as rupture and events specific to endovascular repair, major morbidity (e.g. cardiac events) and reintervention including conversion from endovascular repair to open procedure and secondary intervention.

Aneurysm-related mortality Death from aneurysm-related causes such as rupture. It includes operative mortality and can, but does not always, include postoperative mortality.

Chi-squared (χ^2) test A statistical test used to assess heterogeneity by testing the null hypothesis that the true treatment effects are the same in each study.

Comorbidity The presence of one or more disorders (or diseases) in addition to a primary disease or disorder.

Complications See adverse effects and complications.

Confidence interval (CI) The range of uncertainty about an estimate of a treatment effect. It is the range of values above and below the point estimate that is likely to include the true value of the treatment effect. The 95% CI indicates that there is a 95% probability that the CI calculated from a particular study includes the true value of a treatment effect.

Cost-effectiveness acceptability curve A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for the health system's cost-effectiveness threshold.

Cost-effectiveness analysis The estimation of the costs and health benefits of mutually exclusive treatment strategies in which the consequences are measured in natural units such as years of life gained.

Cox proportional hazards analysis Analysis of one or more risk factors over time on an end point such as death.

Device migration Migration can occur post implantation when there is any movement or displacement of the stent graft in relation to the native aorta or renal arteries. The risk of migration increases with time and can result in the loss of device fixation. To maximise iliac fixation length, the stent graft is placed at the origin of the hypogastric arteries. Device migration may not require further treatment and can be monitored or it can result in aneurysm rupture or endoleak, requiring secondary intervention.

Disutility The reduction in health-related quality of life (measured using utilities) compared with a reference such as the general population.

Endoleak Persistence of blood flow outside the endovascular stent graft but within the aneurysm sac or adjacent vessels in which the graft is deployed. Type I is perigraft or graft related (proximal anastomosis, distal anastomosis, occluder). Blood flow into the aneurysm sac occurs because of an incomplete seal or ineffective seal at the end of the graft. This type of endoleak usually occurs in the early course of treatment, but may also occur later. Type II is retrograde or collateral (mesenteric, lumbar, renal accessory). Blood flow into the aneurysm sac occurs because of opposing blood flow from collateral vessels. In some circumstances, when there are two or more patent vessels, a situation of inflow and outflow develops creating an active blood flow within the channel created within the aneurysm sac. Type III occurs midgraft (fabric tear, graft dislocation, graft disintegration). Blood flow into the aneurysm sac occurs because of inadequate or ineffective sealing of overlapping graft joints or rupture of the graft fabric. Again, this endoleak usually occurs early

continued

after treatment, because of technical problems, or later, because of device breakdown. Type IV is due to the porosity of the graft fabric, causing blood to pass through from the graft and into the aneurysm sac.

Endovascular repair A technique that involves placing a stent graft prosthesis at the site of the aneurysm. The stent graft is inserted through a small incision in the femoral artery in the groin and then carried to the site of the aneurysm using catheters and guidewires and placed in position under radiographic guidance.

EUROSTAR registry A multicentre European database of the outcome of endovascular repair of infrarenal aortic aneurysms.

Fixed-effects model A statistical model that assumes only within-study variation as influencing the uncertainty of results (as reflected in the confidence interval) of a meta-analysis. Variation between the estimates of effect from each study (heterogeneity) does not affect the confidence interval in a fixed-effects model.

Hazard ratio The degree of increased or decreased risk of death or other clinical outcome over a period of time.

Heterogeneity The differences/variability between the individual studies in the estimates of effects.

Homogeneity The degree to which the results of studies are similar.

I^2 statistic A measure to estimate how much of the total variation between the treatment estimates can be attributed to statistical heterogeneity rather than chance. It gives the proportion of the total variation that is due to heterogeneity between study results.

Infrarenal abdominal aortic aneurysm Weakening of the wall of the aorta can lead to a dilatation of the vessel, or aneurysm, in the lower infrarenal part of the abdominal aorta.

Kaplan–Meier survival analysis A method of analysis that enables calculation of survival time for any given proportion of the sample, the probability of survival and the comparison of

the difference in proportions surviving in two groups.

Karnofsky functional autonomy score Allows patients to be classified according to their functional impairment. This can be used to compare the effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Meta-analysis A method of combining studies to produce an overall summary of the treatment effect across studies (see also fixed-effects model and random-effects model).

Multiple regression A method for estimating the relationship between a dependent variable such as mortality (i.e. outcome) and more than one independent explanatory variable such as age or gender. Also referred to as multivariable regression.

Multivariate analysis Method for estimating jointly the relationship between several dependent variables (outcomes) and several independent explanatory variables.

Neck angulation Significant aortic neck angulation may predispose to suboptimal outcome after endovascular abdominal aortic aneurysm repair. Defined as severe ($\geq 60^\circ$), moderate ($40\text{--}59^\circ$) and mild ($< 40^\circ$) aortic neck angulation between the infrarenal aortic neck and the longitudinal axis of the aneurysm.

Odds ratio A way of comparing whether the odds, or likelihood, of a certain event is the same for two groups; the odds refers to the ratio of the number of people having an event to the number not having an event.

Perioperative Generally refers to the three phases of surgery – preoperative, intraoperative and postoperative – and includes, for example, ward admission, anaesthesia, surgery and recovery.

Quality of life (health-related quality of life) A concept incorporating all of the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors that might affect their physical, mental and social well-being.

Quality-adjusted life-year (QALY) Index of health gain in which survival duration is weighted or adjusted by the patient's (health-related) quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Random-effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-study variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Reintervention *See* adverse effects and complications.

Sensitivity analysis A mathematical method that examines uncertainty associated with parameters estimated in the analysis to test the robustness of the analysis findings. In one-way sensitivity analysis each parameter is varied individually; in multiway analysis two or more parameters are varied at the same time; threshold analysis identifies the critical values above or below which the results of a study vary; and analysis of extremes is used to examine the most pessimistic and the most optimistic scenarios. Finally, probabilistic sensitivity analysis attributes distributions of probabilities to uncertain variables that are incorporated within a model.

Short Form-36 (SF-36) The SF-36 is a multipurpose, short-form health survey. It produces an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary

measures and a preference-based health utility index. It is a generic measure as opposed to one that targets a specific age, disease or treatment group.

Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS) model Risk stratification model that includes three levels of risk: level I [age 75–85 years; stable angina with mild angiographic coronary artery disease (CAD) or normal perfusion scan; ejection fraction 30–50%; chronic obstructive pulmonary disease (COPD) with normal activities of daily living; serum creatinine < 2 mg/dl; estimated mortality from open surgical repair 3–5%]; level II (age 85–90 years; stable angina with moderate angiographic CAD or mild to moderate abnormal perfusion scan; ejection fraction 20–30%; COPD with moderate to severe pulmonary dysfunction; serum creatinine 2–3.5 mg/dl; estimated mortality 6–8%); level III (age > 90 years; class II–III angina with significant myocardium at risk based on coronary angiography or perfusion scan; ejection fraction < 20%; COPD requiring home oxygen; serum creatinine > 3.5 mg/dl or on chronic dialysis; estimated mortality 8–13%).

Utility A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life. Negative values of utility are feasible.

Weibull model A specific parametric survival function modelling the relationship between the rate of an event (e.g. death) and time.

List of abbreviations

AAA	abdominal aortic aneurysm	MeSH	Medical Subject Headings in the MEDLINE thesaurus
ASA	American Society of Anesthesiologists	MRC	Medical Research Council
CAD/MI	coronary artery (heart) disease/ myocardial infarction	MRI	magnetic resonance imaging
CAESAR	Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair trial	NExT ERA	National Expertise Based Trial of Elective Repair of Abdominal Aortic Aneurysms
CCI	Charlson Comorbidity Index	NICE	National Institute for Health and Clinical Excellence
CE	Conformité Européenne	NLH	National Library for Health
CHF	congestive heart failure	NVD	National Vascular Database (currently covering open repair of aneurysms)
CI	confidence interval	OR	odds ratio
CIc	commercial-in-confidence	OVER	Open Surgery Versus Endovascular Repair trial
CINAHL	Cumulative Index to Nursing and Allied Health Literature	QALY	quality-adjusted life-year
COPD	chronic obstructive pulmonary disease	QoL	quality of life
CPI	Customized Probability Index	RCT	randomised controlled trial
CT	computed tomography	RETA	Registry of Endovascular Treatment of Abdominal Aortic Aneurysms
DARE	Database of Abstract of Reviews of Effects	ROC	receiver operating characteristic
EQ-5D	EuroQoL 5 dimensions	SD	standard deviation
EVAR	endovascular aneurysm repair	SE	standard error
GAS	Glasgow Aneurysm Score	SF-36	Short Form-36
HR	hazard ratio	SVS/ISCVS	Society for Vascular Surgery/ International Society for Cardiovascular Surgery
HRQoL	health-related quality of life	TRIP	Turning Research Into Practice
HTA	Health Technology Assessment	UKSAT	UK Small Aneurysm Trial
ICER	incremental cost-effectiveness ratio		
IQR	interquartile range		
ITT	intention to treat		
MASS	Multicentre Aneurysm Screening Study		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of information that was deemed commercial-in-confidence or academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence or academic-in-confidence information removed and replaced by the statement 'commercial-in-

confidence information removed' or 'academic-in-confidence information removed' is available on the NICE website (www.nice.org.uk).

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.



Executive summary

Background

Abdominal aortic aneurysms (AAAs) carry a high risk of rupture, which is associated with a mortality rate of about 80%. AAAs can be treated by surgical repair to prevent rupture. However, open repair involves significant risks and approximately 25% of patients with an AAA requiring surgery are considered unfit for open surgery. Endovascular aneurysm repair (EVAR) is a minimally invasive technique that has been used to treat patients with appropriate aneurysm morphology who are classified as either fit for open repair or unfit. EVAR is used both as an elective procedure and to treat symptomatic and ruptured aneurysms.

Objective

The management options available after diagnosis of AAA can be classified as immediate elective surgery with open repair; immediate elective surgery with EVAR; surveillance with an option to defer surgery; or a decision to rule out surgery entirely. The objective of this assessment is to determine the clinical effectiveness and cost-effectiveness of EVAR for repair of infrarenal AAAs in patients at varying levels of risk, including those who are appropriate for open repair and those who are not.

Methods

A systematic review of the clinical effectiveness of EVAR was performed. Recent systematic reviews were used to identify randomised controlled trials (RCTs) and other clinical studies. Additional searches (2005–February 2008) were conducted to search for recent RCTs, publications relating to named registries [Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA) and the European Collaborators on Stent–Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) for EVAR, and the National Vascular Database (NVD) for open surgery] and studies on the relationship between patients' baseline risks and outcomes. The following bibliographic databases were searched: BIOSIS Previews,[®]

Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials, EMBASE, ISI Proceedings, MEDLINE,[®] MEDLINE[®] In-Process & Other Non-Indexed Citations, Science Citation Index and Zetoc Conferences. Searches were not restricted by language or study design and studies written in any language were eligible for inclusion in the review. Studies of EVAR in patients with asymptomatic or symptomatic and ruptured or unruptured infrarenal AAAs were included. Conventional open repair, non-surgical treatment for AAA (sometimes referred to as 'best medical treatment') or surveillance (sometimes referred to as 'watchful waiting') were the appropriate comparators. Only studies reporting at least one of the following outcomes were included: 30-day mortality rate; aneurysm-related mortality; all-cause mortality; health-related quality of life (HRQoL); adverse effects and complications; and reintervention rates including conversion from EVAR to open procedure and secondary intervention. When appropriate, meta-analysis was employed to estimate a summary measure of treatment effect on relevant outcomes based on intention to treat analyses.

A second systematic review was undertaken to identify and compare existing cost-effectiveness analyses of EVAR compared with open surgery and non-surgical interventions. This review included submissions of economic analyses made by EVAR device manufacturers.

Two new decision models were also developed to inform the review. The first compared the cost-effectiveness of EVAR versus open repair in patients with a large aneurysm (≥ 5.5 cm) for whom the decision to operate has been taken. The second decision model, complementary to the first, compared options of early surgery (with EVAR or open repair), watchful waiting and no surgical intervention. Both models investigated the cost-effectiveness of the strategies in patients of varying age, aneurysm size and level of operative fitness. Four fitness levels were defined in the analysis, given a patient's age and aneurysm size: good, moderate, poor and very poor.

Results

Clinical effectiveness

Six RCTs were included in the review. Four compared EVAR and open surgery in patients with unruptured AAAs who were fit for open repair. One RCT compared EVAR with non-surgical management of patients deemed unfit for open repair. A small RCT compared EVAR and open repair in patients with ruptured AAAs. There are five ongoing trials from which results are currently unavailable. The limited data reported by the NVD and RETA registries, and the 'older' devices used and non-current data reported by RETA, highlight the importance of the EUROSTAR data and findings. Thirty-four studies evaluated the role of patients' baseline characteristics in predicting the risks of particular outcomes after EVAR. Three studies evaluated existing scoring systems and one study evaluated the development of a model for assessing risks. However, the majority of the risk modelling studies investigated specific risk factors using multiple regression analysis. The majority of these studies were based on data from the EUROSTAR registry with likely overlap of patients.

Compared with open repair, EVAR reduces operative mortality (odds ratio 0.35, 95% CI 0.19 to 0.63) and aneurysm-related mortality over the medium term (hazard ratio 0.49, 95% CI 0.29 to 0.83) but offers no significant difference in all-cause mortality at mid-term follow-up. EVAR was associated with increased rates of complications and reinterventions and these are not offset by any increase in HRQoL.

There is limited RCT evidence comparing EVAR with non-surgical management in patients unfit for open repair. EVAR trial 2 found no differences in mortality outcomes between groups but this finding cannot be taken as definitive because substantial numbers of patients randomised to non-surgical management crossed over to receive surgical repair of their aneurysm. This may indicate that the benefits of EVAR over no intervention may require more than 4 years of follow-up to become apparent.

The results from these trials are complemented by data from registries, in particular the EUROSTAR registry data relating to devices in current use.

Cost-effectiveness

The systematic review of the economic evidence identified six published decision models. Of the five models comparing EVAR and open repair, two were constructed after the operative mortality

results of the good-quality RCTs were published and are considered to be relevant for the decision in the UK. Both concluded that EVAR was not cost-effective on average at a threshold of £20,000 per quality-adjusted life-year (QALY). One model compared EVAR with no surgical intervention. This model was constructed before the results of the EVAR trial 2 were published. The model concluded that EVAR would be on average more cost-effective than no surgical intervention in unfit patients at a threshold of £20,000 per QALY. One model was submitted by a manufacturer (Medtronic). This model concluded that EVAR was more cost-effective than open repair for fit patients at a threshold of £20,000 per QALY.

The main findings of the York economic evaluations (base-case models at a threshold of £20,000 per QALY) are:

- EVAR is not cost-effective compared with open repair on average given base-case assumptions at a threshold of £30,000 per QALY.
- Results are very sensitive to model assumptions. EVAR may be more cost-effective than open repair if the relative costs of the procedure have fallen, reinterventions are relatively less frequent and follow-up surveillance is currently less intensive compared with the base-case assumptions.
- Results are sensitive to the baseline risk of operative mortality. A subgroup analysis found that EVAR was likely to be cost-effective compared with open repair in patients with poor operative risk and unlikely to be cost-effective in patients with good operative risk. A validated and accepted fitness score is needed to distinguish individual patients by operative risk.
- An exploratory analysis was undertaken to evaluate management options in patients who would not be considered suitable for open surgery, that is, in patients of very poor fitness. This model was based on uncertain data about the natural history of untreated aneurysm. This suggested that the cost-effectiveness of EVAR may be sensitive to aneurysm size and patient's age at operation. Further research in these areas would be important to inform future modelling work.
- Indicative modelling results suggest that EVAR may be cost-effective for small aneurysms (< 5.5 cm) in some patient groups. Ongoing RCTs will provide further evidence relating to these patients. A review of the current guideline that aneurysms should not be

operated on if less than 5.5 cm should then be considered.

Conclusions

Implications for service provision

Based on the results of this assessment of clinical and cost-effectiveness, and using a set of base-case assumptions, open repair is likely to be considered cost-effective compared with EVAR on average in patients considered fit for open surgery. Cost-effectiveness may vary with fitness. EVAR is likely to be more cost-effective than open repair for patients at higher risk of operative mortality. There is considerable uncertainty in this analysis, in particular concerning the relative cost of procedures and rate of reinterventions. An exploratory study suggested that EVAR may be more cost-effective than medical treatment or watchful waiting for some groups of patients unfit for open repair, depending on age and aneurysm size. Evidence does not currently support EVAR for the treatment of ruptured aneurysms.

Suggested research priorities

- Further follow-up of the existing UK trials (EVAR trial 1, EVAR trial 2) should be undertaken.
- The relative procedure costs and device costs should be investigated further.
- Opportunities for individual patient meta-analysis of all RCTs relating to EVAR should be sought.
- Further research is needed on the rates of late complications, reinterventions and aneurysm-related mortality after EVAR, in particular those associated with the most recent generation of devices.
- The optimal surveillance policy following EVAR should be investigated.
- The extent to which the relative treatment effect of EVAR on operative mortality can be assumed constant across subgroups of patients should be further investigated.
- Research is required into how to implement the best available risk scoring systems for the management of AAA into decision-making in routine clinical practice.
- Research is required into the natural history of untreated AAA to determine more reliably when surgical intervention is optimal. The analysis should investigate the impact of different levels and determinants of patient fitness as well as aneurysm size and anatomy.
- A well-defined and well-conducted RCT of EVAR versus watchful waiting, reflecting current clinical practice, is warranted. However, given the difficulties of conducting RCTs in the management of AAA it is probably advisable that the collection of data through the existing, established registries in the UK, particularly RETA (for EVAR) and NVD (for open repair), should be continued.

Chapter 1

Background

Description of health problem

Aortic aneurysms develop when weakening of the vessel wall, often due to atherosclerosis, causes it to bulge, forming a balloon-like projection. This in turn leads to further stretching of the vessel wall and an increase in tension. Eventually, the vessel wall may rupture, leading to massive internal bleeding.

Most aneurysms occur in the abdominal section of the aorta. An abdominal aortic aneurysm (AAA) is defined as an enlargement of the aorta to 1.5 times or more of its normal diameter or of greater than 3 cm. Most AAAs occur in the lower (infrarenal) part of the abdominal aorta.

Symptoms that may occur as an aneurysm enlarges include a pulsating sensation in the abdomen, back pain and abdominal pain, which may spread to the back. Symptomatic AAAs require rapid medical attention. Rupture of an AAA is associated with a mortality rate of about 80%; even when patients undergo emergency surgery, only about half survive beyond 30 days.¹ The risk of rupture increases with the size of the aneurysm. For example, in the UK Small Aneurysm Trial (UKSAT) and associated monitoring study,² the number of ruptures per 100 patient-years was 0.3, 1.5 and 6.5 for patients with AAAs of diameter ≤ 3.9 cm, 4.0–4.9 cm and 5.0–5.9 cm respectively. The rate of rupture may be up to 25% annually for aneurysms with diameters > 6 cm, and a number of studies indicate that without surgery the 5-year survival rate for patients with aneurysms > 5 cm is about 20%.³

The main risk factors for AAAs include age, high blood pressure, male sex, smoking and family history. Because most AAAs are asymptomatic it is difficult to estimate the prevalence of the condition, but screening studies in the UK have estimated a prevalence of 1.3–12.7% depending on the age group studied and the definition of AAA.³ AAAs are about three times more common in men than in women.¹ The incidence of symptomatic AAA in men is approximately 25 per 100,000 at age 50 years, increasing to 78 per 100,000 in those older than 70 years. The overall incidence

of AAAs has increased in recent years and is likely to increase further in line with the ageing of the general population.

Most AAAs are detected by chance during clinical examination or investigation (e.g. ultrasound or radiography) for other conditions. Ultrasound screening of the population for early detection of AAAs has been extensively evaluated. In the UK the large Multicentre Aneurysm Screening Study RCT found that screening men aged 65–74 reduced the risk of aneurysm-related death by 42% over 4 years.⁴ Screening was marginally cost-effective over 4 years and cost-effectiveness was expected to improve substantially over a longer period.⁵ National screening programmes are under consideration by the four UK health departments at the time of writing.

Current service provision

AAAs can be treated by surgical repair to prevent rupture. Conventional ('open') surgical repair involves making a large incision in the abdomen and inserting a prosthetic graft to replace the damaged section of the aorta. Open repair of AAA carries substantial risk of mortality and morbidity, particularly because many patients with an AAA have significant comorbidities (e.g. heart or kidney disease) that reduce their fitness for surgery. Open repair can also be performed laparoscopically, either by hand-assisted laparoscopic surgery or by totally laparoscopic surgery (TLS). Guidance issued by the National Institute for Health and Clinical Excellence (NICE)⁶ states that, although there is adequate evidence of the safety and efficacy of these laparoscopic techniques, the technical demands are such that such procedures should not be used without special arrangements for consent and for audit or research.

In current UK clinical practice, elective surgery is generally recommended for aneurysms > 5.5 cm in diameter, as well as for those of diameter > 4.5 cm with an increase in size of > 0.5 cm in the last 6 months. The UKSAT⁷ and ADAM⁸ trials indicated that there was no mortality advantage of immediate (open) surgical repair over imaging surveillance

in patients with aneurysms of < 5.5 cm diameter. Current guidelines recommend that patients with asymptomatic aneurysms < 4.5 cm are followed up with ultrasonography every 6 months, whereas aneurysms of 4.5–5.5 cm are followed up every 3 or 6 months.

Approximately 25% of patients with an AAA requiring surgery are considered unfit for open surgery.⁹ Such patients will be kept under surveillance with an option to defer surgery or a decision to rule out surgery entirely. As age, fitness and the untreated risk of rupture are evolving over time, the option to defer makes the decision complex and dynamic.^{10,11} It is unclear what the optimum management policy should be in patients considered unfit for open surgery. It may be that a policy whose aim is to try and improve patient fitness might be effective and patients may be offered medical therapy to reduce risk factors, for example smoking cessation and blood pressure reduction therapy, but such a policy has not yet been evaluated.

Description of technology under assessment

Endovascular aneurysm repair (EVAR) is a minimally invasive technique that involves placing a stent graft prosthesis at the site of the aneurysm.¹² The stent graft is inserted through a small incision in the femoral artery in the groin, carried to the site of the aneurysm using catheters and guidewires and placed in position under radiographic guidance. Once in position the stent graft is deployed and anchored to the wall of the aorta using a variety of fixing mechanisms. The graft is stronger than the weakened aorta and allows blood to pass through it without creating pressure on the aneurysm. The main types of endovascular stent grafts are aortic tube grafts (no longer used in the UK), aorto-uni-iliac grafts and aorto-bi-iliac (bifurcated) grafts, with most procedures in the UK using bi-iliac stents. EVAR is carried out under general, regional or local anaesthesia.

EVAR has been used to treat patients both classified as fit for open repair and classified as unfit. It is used both as an elective procedure and to treat symptomatic and ruptured aneurysms. However, it must be emphasised that EVAR is not suitable for all patients. Patient suitability for EVAR depends on the morphology of the aneurysm. This is assessed by diagnostic imaging, usually computed tomography (CT) scanning and occasionally angiography or magnetic resonance imaging

(MRI). In an unselected population of patients with AAA only 55% did not have an absolute morphological contraindication to EVAR.¹³

Potential advantages of EVAR over open repair include reduced time under general anaesthesia, elimination of the pain and trauma associated with major abdominal surgery, reduced length of stay in the hospital and intensive care unit, and reduced blood loss.¹⁴ Potential disadvantages include the development of endoleaks, which occur when blood continues to flow through the aneurysm because the graft does not seal completely or because of backfilling of the aneurysm from other small vessels arising from the aneurysm wall. Thus, although open repair does not require any special follow-up, patients who have undergone EVAR require regular CT scans to check for the presence of late endoleaks.¹⁴ In addition, if the EVAR procedure is unsuccessful or complications arise during the procedure, conversion to open repair may be necessary in patients initially considered unfit for open surgery.¹⁴

Prices of endovascular stent grafts

Endovascular stents are not homogeneous products. There are a number of different endovascular stent devices made by different companies, each with different costs. This is further complicated by the fact that different patients who may be fitted with the same company's device may require different numbers of extensions. The companies who produce these devices also offer different pricing structures (e.g. some charge a price per patient regardless of the number of extensions required whereas others charge based on the parts required). If the price per patient is not fixed then ideally the mean price per case should be calculated based on an assessment of the expected number of extension parts required, which in turn depends on the population case mix. There is also the added complication that individual hospitals often do not actually pay the list price, with manufacturers offering discounts. These considerations make the process of costing a device for the economic evaluation complex.

The NICE *Guide to the Methods of Technology Appraisal*¹⁵ states that: 'Where the actual price paid for a resource may differ from the public list price (for example, pharmaceuticals, medical devices), the public list price should be used'.

Commercial-in-confidence information on the price of different models of stent grafts and academic-in-confidence information on the use

and cost of endovascular devices in EVAR trial 1 has been removed.

Risk score measures for surgical risk

Before any surgical procedure is undertaken the fitness of the patient needs to be assessed. Risk score measures provide numerical scores that have been calculated based on a number of patient factors (e.g. age, gender) that are considered to predict the risk for survival of surgery, with higher scores indicating greater predicted risk. Low risk scores are not the same as no risk.¹⁶ Risk score models vary in complexity and accuracy but enable comparisons of outcomes to be made between groups of patients, institutions and individual surgeons whilst taking into account patient-related factors and comorbidity.¹⁶ Although there are a large number of tools in use to measure operative risk, there is no ideal tool and those in use have many limitations. Measures are used largely to predict risk in various patient groups rather than in individuals, and often the cut-off points between high and low risk are based on costs and the complexity of providing treatment to correct the risk rather than on the risk itself.¹⁷

The main risk scores used in clinical practice, with their roles in predicting risk for EVAR, are outlined below.

American Society of Anesthesiologists

The American Society of Anesthesiologists (ASA) classification system is widely used and, although it was not originally designed to estimate operative risk, many medical professionals use it as a means of preoperative risk assessment and some have identified it as a predictor of postoperative morbidity and mortality.¹⁸ ASA classifies preoperative physical status, allocating patients to one of five categories based on general medical history and examination and not requiring any specific investigations: class I (normal healthy patient), class II (mild systemic disease), class III (severe systemic disease but not incapacitating), class IV (incapacitating systemic disease that is a threat to life) and class V (moribund, not expected to survive 24 hours with or without operation). Generally, ASA is effective in predicting mortality when used alone or in conjunction with other parameters, as postoperative mortality rates rise steadily with the ASA grade.¹⁹ However, there is the potential for interobserver subjective error

as it remains a semisubjective assessment by the Anesthesiologist based on patient comorbidities.¹⁸

Acute Physiology and Chronic Health Evaluation

The Acute Physiology and Chronic Health Evaluation (APACHE) presents an overall score for physiological variables, age points and chronic health and has been used extensively in the intensive care setting. It aims to classify patients on the basis of the severity of illness to facilitate comparison of outcomes, to facilitate the evaluation of new therapies and as an indicator of daily progress. APACHE II measures are based on 12 physiological and laboratory factors in addition to age and previous health status.

The APACHE-AAA model was developed and internally validated specifically to predict outcome in postoperative AAA patients who are managed in the intensive care unit.²⁰ However, this model cannot be used for preoperative decision-making.²¹

Bayesian risk modelling (Customized Probability Index)

The Customized Probability Index (CPI) accounts for significant clinical risk factors (cardiac and non-cardiac) and current medication use in predicting all-cause perioperative mortality in patients undergoing all types of open vascular surgery. It identifies nine independent predictors of perioperative mortality: type of vascular surgery, ischaemic heart disease, congestive heart failure, previous stroke, hypertension, renal dysfunction and chronic pulmonary disease associated with increased risk, and beta-blocker and statin use associated with lower risk. Risk is calculated using the sum of scores for surgical risk (0–46 points), medical history (0–67 points) and cardioprotective medication (statins –10 points and beta-blockers –15 points).²² The EVAR trial participants²³ were assessed for fitness based on clinicians' decisions using clinical parameters that were integrated into the calculation of the modified CPI.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a weighted index of comorbidity (number and seriousness of comorbid diseases) that provides a total score as follows: 1 = myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes;

2 = hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia and lymphoma; 3 = moderate or severe liver disease; 6 = metastatic solid tumour and AIDS. A study²⁴ looking at survival rates of patients with elective open AAA repair reported the CCI as a significant independent predictor of lower survival.

Comorbidity Severity Score

The Comorbidity Severity Score (CSS) was developed specifically for EVAR risk stratification and includes a comorbidity severity score and an anatomic factor severity score, which includes cardiac disease, pulmonary disease, renal disease, hypertension and age. The Modified Comorbidity Severity Score (M-CSS) has been found to be valid for predicting risk in open repair.²⁵ When risk scores for open repair were applied to EVAR patients, observed mortality was different, but this was only statistically significant for the highest risk scores.

Glasgow Aneurysm Score

The Glasgow Aneurysm Score (GAS) estimates preoperative risk profiles that predict perioperative outcomes after open repair and more recently has been shown to predict perioperative and long-term mortality after EVAR.²⁶ GAS is calculated using the formula: risk score = (age in years) + (7 points for myocardial disease) + (10 points for cerebrovascular disease) + (14 points for renal disease) + (17 points for shock) (not necessarily applicable when elective surgery patients). The GAS separates patients into low- or high-risk groups, with high-risk patients receiving a risk score of ≥ 79 points and potentially being considered unsuitable for surgery.²⁷

Goldman Cardiac Risk Index

The revised Goldman Cardiac Risk Index (CRI; Detsky Index) includes six independent variables. An evaluation of cardiac risk indices for patients undergoing non-cardiac surgery carried out by Gilbert *et al.*²⁸ compared the Detsky Index with the Goldman Index and two other indices. Each index was found to provide a statistically significant degree of stratification ($p < 0.001$) and areas under the receiver operating characteristic (ROC) curves were similar. The models were significantly better than chance for predicting myocardial infarction and death. However, although, generally, the indices were useful in providing clinical information about risk, the accuracy of the measures was limited.²⁸

Hardman scoring systems

The Hardman Prognostic Index includes five risk factors: age > 76 years, history of loss of consciousness, electrocardiogram evidence of ischaemia, haemoglobin < 9 g/dl and serum creatinine > 0.19 mmol/l. A small study²⁹ compared the predictive value of the Hardman Index in patients undergoing EVAR and open repair and found that mortality rates increased with rising Hardman scores for both open and EVAR patients.

Leiden score/modified Leiden score

The Leiden score is based on age, gender, presence of myocardial infarction, ST-segment depression, congestive heart failure, renal disease and pulmonary disease, and centre-specific average surgical mortality. The modified Leiden score (M-LS) is based on the same variables but ST-segment depression and centre-specific average surgical mortality are not included and more points are given for severe renal disease. Both the Leiden score and M-LS predicted postoperative mortality, although their accuracy in predicting postoperative complications is somewhat lower.³⁰

POSSUM/V-POSSUM

POSSUM (Physiological and Severity Score for the Enumeration of Mortality and Morbidity) has been widely used for assessing outcomes by risk-adjusted analysis in the UK.¹⁹ It includes a physiological assessment and a measure of operative severity. The physiological assessment includes 12 physiological variables, divided into four grades, which are present at the time of surgery: age, cardiac history, respiratory history, blood pressure, pulse rate, Glasgow coma score, haemoglobin, white blood count, serum urea, serum sodium, serum potassium and electrocardiogram. The operative severity section includes six variables, divided into four grades: operative severity, multiple procedure, total blood loss, peritoneal soiling, presence of malignancy and mode of surgery.

POSSUM has shown favourable results for mortality and morbidity risk prediction and comparative surgical audit, but it does have limitations. In particular, this model and the P-POSSUM model overestimate mortality for low-risk procedures.³¹ An assessment of the validity of V-POSSUM (Vascular-POSSUM) and ruptured AAA-POSSUM models concluded that the two scoring systems were not effective predictors of death after ruptured AAA.³²

Vascular-Biochemistry and Haematology Outcome Modelling

The Vascular-Biochemistry and Haematology Outcome Modelling (V-BOHM) uses data obtained before operation to predict outcome, including haemoglobin level, white blood count, urea, sodium, potassium and age on admission. This model was developed to provide accurate risk prediction for both elective and non-elective AAA surgery (open repair), without the problems often experienced with missing data. An evaluation of the efficacy of the V-BOHM in 2718 patients

found that the model, which also included age and gender as risk factors, was effective in predicting surgical mortality after both open elective and non-elective AAA repair.³³

Others

A number of other risk score measures are used in clinical practice, including the British United Provident Association (BUPA) operative grade, Eagle score, Hospital Prognostic Index and Prognostic Nutritional Index.

Chapter 2

Definition of decision problem

Decision problem

For patients who are suitable for aneurysm repair, is EVAR or open repair more effective and cost-effective? More generally, what is the optimum management strategy for patients with a diagnosis of AAA? Immediate elective surgery with open repair, immediate elective surgery with EVAR, surveillance with an option to defer surgery, or a decision to rule out surgery entirely?

Overall aims and objectives of assessment

The objectives of this assessment are to determine the clinical and cost-effectiveness of endovascular stent grafts for repair of infrarenal AAAs in patients at varying levels of risk, including those who are appropriate for open repair and those who are not. The assessment will build on the information already available, including recent systematic reviews.^{12,34–36} A particular objective is to seek evidence to clarify areas of uncertainty, for example about longer-term outcomes, about the variables and risk factors that influence the effectiveness and safety of EVAR and whether there are subgroups of patients for whom EVAR is particularly appropriate. Recommendations for further research will reflect identified gaps in the evidence base.

The specific objectives of the cost-effectiveness analysis are:

- to structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies
- to populate this model using the most appropriate data identified systematically from published literature and routine data sources
- to relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life-years (QALYs)
- to estimate the mean cost-effectiveness of EVAR compared with standard care (open repair or non-surgical management), based on an assessment of long-term NHS and personal social service costs and quality-adjusted survival
- to report the cost-effectiveness of alternative treatments for specific subgroups of patient, consistent with available evidence; this may include cost-effectiveness according to patients' underlying risk of particular clinical events
- to characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision-makers.

Confidential information

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

Recent systematic reviews by Drury *et al.*³⁴ and Lederle *et al.*³⁵ were used to identify randomised controlled trials (RCTs) and other clinical studies. Additional searches were conducted to identify recent RCTs (2005–7), publications relating to named registries and studies investigating baseline risks. Searches were not restricted by language or study design and studies written in any language were eligible for inclusion in the review.

To identify systematic reviews and guidelines the following databases and web pages were searched/scanned: Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, National Library for Health (NLH) National Library of Guidelines, National Guideline Clearinghouse, NICE web pages.

The following bibliographic databases were searched to identify RCTs (2005–February 2007), risk modelling studies and papers based on registry data: BIOSIS Previews,[®] Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials, EMBASE, ISI Proceedings, MEDLINE,[®] MEDLINE[®] In-Process & Other Non-Indexed Citations, Science Citation Index and Zetoc Conferences. Search strategies are given in Appendix 1. Searches to identify any ongoing trials were carried out using Clinicaltrials.gov, Current Controlled Trials and the National Research Register.

Regular current awareness searches were carried out during the review using both Science Direct and Zetoc. Search alerts were set up for a number of topic-specific journals: *Annals of Vascular Surgery*, *Asia Pacific Journal of Thoracic and Cardiovascular Surgery*, *Cardiovascular Surgery*, *European Journal of Vascular Surgery*, *European Journal of Vascular and Endovascular Surgery*, *Interactive Cardiovascular and Thoracic Surgery*, *Italian Journal of Vascular and Endovascular Surgery*, *Journal of Endovascular Therapy*, *Journal of Thoracic and Cardiovascular*

Surgery, *Journal of Vascular Surgery*, *Operative Techniques in Thoracic and Cardiovascular Surgery*, *Perspectives in Vascular Surgery and Endovascular Therapy*, *Seminars in Thoracic and Cardiovascular Surgery*, *Seminars in Vascular Surgery* and *Vascular and Endovascular Surgery*.

In addition, OvidAutoAlerts were created in both the MEDLINE and EMBASE databases to notify the review team of papers with EVAR in the title, original title or abstract. Current awareness searches were continued until February 2008.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Potentially relevant full paper manuscripts were obtained when possible, and the relevance of each study was assessed independently by two reviewers in accordance with the criteria below. Discrepancies were resolved through discussion or by referral to a third reviewer when necessary. Studies that did not fulfil all of the criteria were excluded, with reasons for their exclusion documented.

Population

Patients with asymptomatic or symptomatic, ruptured or unruptured infrarenal AAAs that were anatomically and clinically suitable for endovascular stent graft repair (EVAR) were included. The study authors' definitions of aneurysm status and suitability for EVAR were used. Studies of patients with aneurysms of any size were included.

Interventions

Studies of elective or emergency EVAR of infrarenal AAAs, using uni-iliac or bi-iliac stent grafts, were included. It was recognised that not all devices evaluated in the research literature would have a CE mark and that several devices would have undergone a number of changes. It was also recognised that manufacturers' devices would have varying indications and contraindications for use. Hence, studies of any EVAR device were eligible but, when data allowed, analysis focused on devices commonly used in current UK practice.

Comparators

Studies in which the comparator was one of the following were included:

- For patients in whom conventional open repair was a treatment option (according to study authors' criteria) conventional open repair was the appropriate comparator.
- For patients in whom conventional open repair was not a treatment option (according to study authors' criteria) the appropriate comparator was non-surgical treatment for AAA (sometimes referred to as 'watchful waiting'). Such treatment will vary across studies but will normally represent best medical care and will typically include a range of strategies to manage vascular risk factors, for example smoking cessation, blood pressure reduction and statin therapy.

Outcomes

Only studies reporting at least one of the following outcomes were included:

- 30-day mortality rate
- aneurysm-related mortality
- all-cause mortality
- health-related quality of life (HRQoL)
- adverse effects and complications; this included aneurysm-related outcomes such as rupture and events specific to EVAR, e.g. frequency of endoleaks and device migration; major morbidity, for example cardiac events, was also assessed
- reintervention rates including conversion from EVAR to open procedure and secondary intervention.

Study designs

Estimates of the treatment effect and safety outcomes of EVAR were derived from RCTs and large registries of relevance to UK practice. The registries used were the Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA) and the European Collaborators on Stent Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) for EVAR, and the National Vascular Database (NVD) for open surgery.

To identify criteria for selecting patients appropriate for EVAR, studies that modelled the spectrum of risk were also reviewed. Risk modelling studies were specific to AAA, focused on risk of mortality following EVAR and used appropriate statistical modelling techniques (e.g. Kaplan–Meier survival analysis, multiple linear or logistic

regression or Cox proportional hazards analysis).

Studies were required to be based on a trial, registry or a series of at least 500 patients from developed countries of relevance to UK practice. The review protocol specified a minimum of 1000 patients; this was reduced to 500 during the review process to allow inclusion of some of the most clinically relevant studies.

Data extraction strategy

Data relating to both study design and quality were extracted by one reviewer, using a standardised data extraction form, and checked by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. For studies with multiple publications, that with the greatest number of participants or the longest follow-up or the latest publication presenting the largest amount of outcome data was extracted. For registries this was interpreted to mean the latest report covering all patients in the registry; publications based on an analysis of registry data that were not reports of the registry as a whole were included in the review for completeness but were not data extracted unless they contained unique data on all patients in the registry. Data were extracted on study details (e.g. study identifier/EndNote ID, author, year, country, setting, number of participants and fitness), patient characteristics (e.g. age, gender, causal/risk factors, comorbidities, aneurysm size/anatomy), intervention (type of stent graft), comparison (details of open repair or medical management), study quality (RCTs and risk model studies) and reported outcomes relating to efficacy and safety as specified above. Careful note was made of definitions used by study authors in relation to fitness for surgery and AAA-related mortality.

Quality assessment strategy

The quality of the individual RCTs and risk model studies was assessed by one reviewer and independently checked for agreement by a second reviewer. Any disagreements were resolved by consensus and, when necessary, a third reviewer was consulted. The quality of RCTs was assessed using standard checklists³⁷ that were adapted to incorporate topic-specific quality issues. The quality of risk models was assessed using a checklist adapted by the authors from a checklist used in a previous systematic review of prognostic models.³⁸ The quality of audit/registry data was not assessed because the included registries were chosen for relevance and prespecified in the protocol.

Data analysis

Data extracted from the studies were tabulated and discussed in a narrative review. The results of the quality assessment were tabulated and, when possible, the effects of study quality on effectiveness data and the findings of the review were discussed. When appropriate, meta-analysis was employed to estimate a summary measure of treatment effect on relevant outcomes based on intention to treat (ITT) analyses. Meta-analysis was carried out using fixed-effects models using Review Manager 4.2. A spreadsheet developed by the MRC Clinical Trials Unit, London, was used to estimate hazard ratios where necessary.³⁹ Heterogeneity was explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the chi-squared test for homogeneity and the I^2 statistic. Risk modelling studies that investigated specific risk factors were interpreted with the aid of charts. Each chart represented one variable and one outcome and displayed the studies that had investigated this factor. Using the measure given in the study each study was plotted on the chart as finding the

variable to be an independent risk factor or not. Summary statements were generated from the charts, indicating the likelihood of a given variable being a risk factor for a given outcome.

Results of the review of clinical effectiveness

Quantity and quality of research available

Included RCTs

Figure 1 presents a flow chart of studies through the review process. Six RCTs were included in the review. Four of these (DREAM,^{40,41} EVAR trial 1^{23,42,43} and the studies by Cuypers *et al.*⁴⁴ and Soulez *et al.*⁴⁵) compared EVAR with open surgery in patients with unruptured AAAs who were fit for open repair. One RCT (EVAR trial 2⁴⁶) compared EVAR with non-surgical management of patients deemed unfit for open repair. A small RCT by Hinchliffe *et al.*⁴⁷ compared EVAR with open repair in patients with ruptured AAAs.

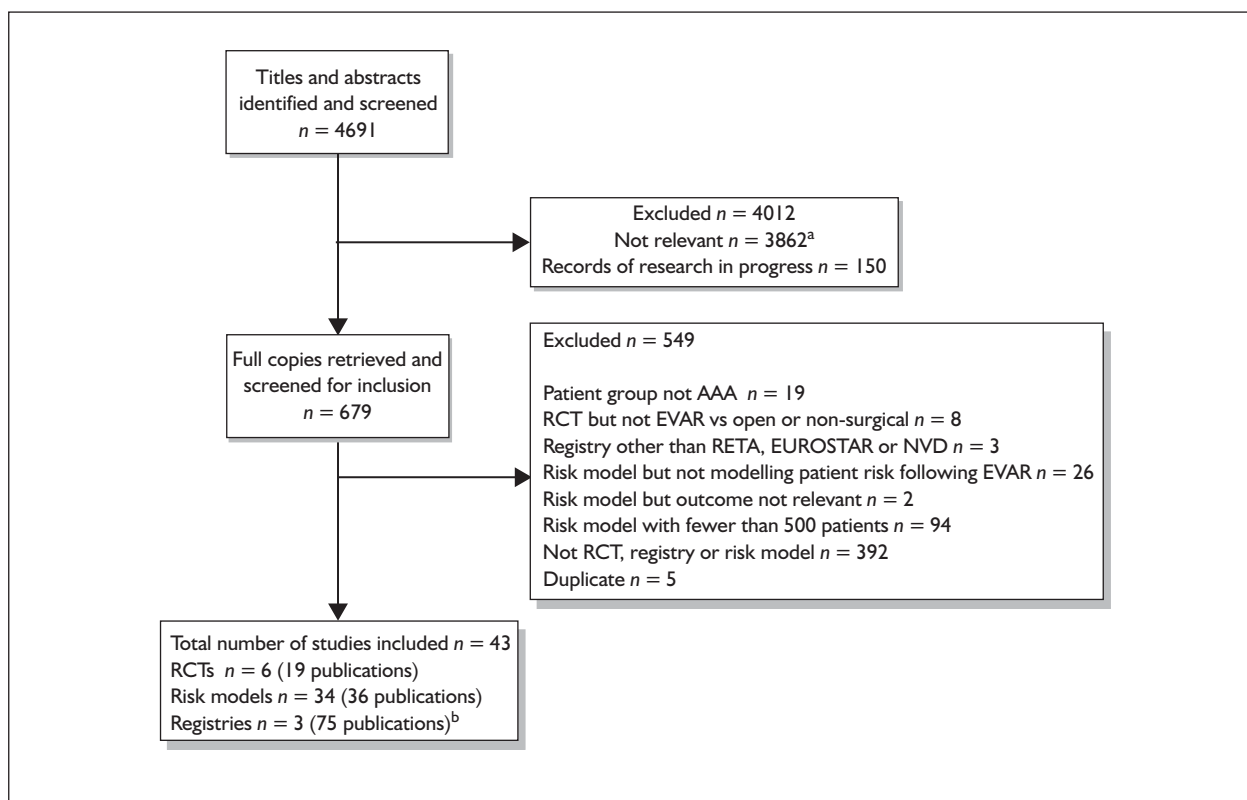


FIGURE 1 Flow chart of studies through the review process. a, Excluded based on title and abstract; b, most registry publications were not data extracted (see Data extraction strategy).

TABLE 1 Quality assessment results for RCTs

Study (main publication)	True randomisation	Adequate concealment of treatment allocation	Outcome assessor blinded	Baseline characteristics comparable between groups	Eligibility criteria reported	Withdrawals or exclusions accounted for	Power calculation reported	Intention to treat analysis
DREAM Blankensteijn 2005 ⁴¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cuypers 2001 ⁴⁴	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
EVAR trial 2 2005 ⁴⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EVAR trial 1 2005 ⁴³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hinchliffe 2006 ⁴⁷	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes
Soulez 2005 ⁴⁵	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Unclear

The results of the quality assessment of the included RCTs are presented in *Table 1*. The main RCTs, DREAM,⁴¹ EVAR trial 1⁴³ and EVAR trial 2,⁴⁶ were all of high quality (positive answers to all quality questions). Some methodological aspects of the remaining RCTs were unclear based on the published reports. The study of EVAR versus open repair for patients with ruptured AAAs⁴⁷ lacked adequate concealment of treatment allocation, perhaps reflecting the ethical and practical problems of conducting an RCT in a setting of emergency surgery. The RCT by Soulez *et al.*⁴⁵ did not report a sample size calculation and probably lacked statistical power to detect differences in mortality and related outcomes.

In addition to methodological quality issues, these RCTs have a number of limitations that may affect their usefulness in assessing the current clinical effectiveness of EVAR relative to open repair and non-surgical management. Of the four RCTs that compared EVAR and open repair in patients with unruptured aneurysms, those of Cuypers *et al.*⁴⁴ and Soulez *et al.*⁴⁵ were small studies and were not designed to assess hard clinical end points such as mortality; furthermore, the study of Cuypers *et al.* was limited to 1 month of follow-up. Hence, the analysis of EVAR versus open repair for unruptured AAAs concentrated on data from the larger RCTs.

The major trials comparing EVAR with open repair, DREAM^{40,41} and EVAR trial 1,^{42,43} randomised patients between November 2000 and December 2003 and between September 1999 and August 2004 respectively. Thus, the devices used and other details of the procedures may not represent current best practice. Published results from the two RCTs represent relatively short periods of follow-up (2 years for DREAM and 4 years for EVAR trial 1). The main analyses of EVAR trial 1 were published in 2004 for 30-day operative mortality⁴² and in 2005 for 4-year follow-up results⁴³ and covered patients randomised up to December 2003. The 4-year results for patients randomised up to August 2004 were included in a publication analysing results by patient fitness.²³ These data were not included in the analyses of mortality outcomes in this review because this was a secondary publication with limited details and because the additional patients were randomised after the official close of recruitment. Finally, the sample size calculation for DREAM was based on a primary end point of short-term mortality and complications, and the trial's power to detect differences in follow-up outcomes is unclear.

The other relevant comparison is between EVAR and continued non-surgical management of patients considered unfit or unsuitable for open repair. The only RCT to have addressed this issue is EVAR trial 2.⁴⁶ Although this was a high-quality RCT in terms of design and methodology, there were problems with its execution. There was a median delay of 57 days between randomisation and procedure in the EVAR arm and 14 patients in this group died before operation (including six from AAA rupture). In total, 47 patients assigned to non-surgical management received surgical aneurysm repair (including 12 who received open repair despite having been classified as unfit for this procedure). These factors complicate the analysis and interpretation of this trial.

The evidence base for EVAR for patients with ruptured AAAs is currently limited to one small pilot trial.⁴⁷ The sample size calculation for this trial was based on recruiting 100 patients, but only 32 patients were randomised, which makes it difficult to draw any firm conclusions from the trial. However, the study showed that it is possible to conduct a randomised trial in this setting. The ongoing Amsterdam Acute Aneurysm Trial, discussed in the following section, should provide further evidence in due course.⁴⁸

Ongoing RCTs

We received information from investigators of five potentially relevant ongoing RCTs who we had contacted to request further details and any data that the investigators were willing to include in our review.

ACE⁴⁹ is a French RCT comparing EVAR and open repair in patients aged 50 years and older with an AAA measuring ≥ 5 cm in diameter (≥ 4 cm if rapidly growing). The primary outcomes are death and major morbidity and the trial enrolled 600 patients. The trial started in January 2003 with an expected completion date of January 2006. The investigators informed us of a possible first publication in January 2008 (V David, Hôpital Henri Mondor, Creteil, France, personal communication, 2008) but further details have not been made available.

The Amsterdam Acute Aneurysm Trial is an RCT comparing EVAR and open repair in patients with a ruptured AAA. A paper describing the background, methods and design of the study has been published.⁴⁸ The primary outcome is a composite of death and severe morbidity assessed in hospital and at 30 days, 3 months and 6 months

postoperatively. Secondary outcomes include HRQoL, length of intensive care stay and cost-effectiveness. The calculated sample size was 40 patients per group. The original scheduled end date for the trial was August 2008, but this has now been extended to October 2010 (www.controlled-trials.com/ISRCTN66212637, accessed 17 August 2009).

OVER (Open surgery Versus Endovascular Repair) is a large US RCT comparing EVAR and open repair in patients aged 50 years and above with an AAA measuring ≥ 5 cm in diameter (≥ 4.5 cm if expanding rapidly).⁵⁰ The primary outcome is all-cause mortality. OVER has an anticipated duration of 9 years and the planned sample size is 900 patients. The expected completion date is October 2011.

NExT ERA (National Expertise Based Trial of Elective Repair of Abdominal Aortic Aneurysms) was a planned pilot study for a national expertise-based RCT comparing EVAR and open repair in Canada.⁵¹ In November 2007 the investigator informed us that the study had been abandoned (T Mastracci, Hamilton Health Sciences, Hamilton, ON, Canada, personal communication).

CAESAR (Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair) is an RCT conducted in Italy comparing EVAR with surveillance (and eventual treatment) in patients with AAAs of diameter 4.1–5.4 cm suitable for EVAR. The design of the study has been published.⁵² The primary outcome is all-cause mortality. Secondary outcomes include aneurysm-related mortality, rupture, perioperative or late complications, conversion to open repair, complications associated with late treatment and HRQoL. A cost analysis is also included. Patients assigned to surveillance are considered for surgery if the aneurysm reaches 5.5 cm in diameter, grows rapidly (> 1 cm/year) or becomes symptomatic. The planned sample size is 740 patients. In November 2007 the investigators informed us that 325 patients had been enrolled and results were not expected until the end of 2008 (F Verzini, Ospedale S. Maria Misericordia, Perugia, Italy, personal communication).

Included registries

Because of the limited data available from RCTs, and the need for long-term data on safety and efficacy for larger numbers of patients, registry databases were also included in the review. Unlike RCTs, which are not powered to allow ad hoc

comparisons between subgroups, registries provide the opportunity for various types of secondary analysis to be carried out on a large number of patients. They may also report more realistic results than RCTs as registry data are obtained from a range of clinical institutions with varying levels of experience and expertise. Indeed, there is evidence to support the validity of registry data, and that such data provide a true representation of a cross-section of patients, methods and hospitals.⁵³

The three prespecified registries included in the review were described in six reports. Two were of EVAR procedures (EUROSTAR^{54,55} and RETA^{56–58}) and one was of open repair (NVD¹⁶).

Results from RETA were included in two papers; one reported short-term (30-day) outcome⁵⁸ and the other presented mid-term results to 5 years.⁵⁶ Data were also presented in an unpublished report⁵⁷ prepared on behalf of the Vascular Surgical Society of Great Britain and Ireland and the British Society of Interventional Radiology. Data for the NVD registry were reported in the *Fourth National Vascular Database Report*,¹⁶ published on behalf of the Audit and Research Committee of the Vascular Society of Great Britain and Ireland. EUROSTAR data were identified through the progress report for endografts in current use, prepared by the EUROSTAR Data Registry Centre,⁵⁴ and the registry's unpublished protocol paper.

Risk modelling studies

A total of 34 studies^{23,59–91} evaluated the effect of baseline characteristics on the risks of particular outcomes after EVAR (*Table 2*).

The majority of the studies were based on data from the EUROSTAR registry. These studies often investigated a range of potential risk variables such as age and gender and often focused on the investigation of one particular risk factor such as diabetes. However, as there is likely to be overlap of patients between these studies, the number of studies reporting the significance of a factor is not always useful as a guide to the robustness of the evidence. Seven studies^{61,62,78,79,85,86,90} are US based and need to be interpreted within the context of differences in clinical practice between the USA and UK settings. One study was based on an Australian national audit⁶⁰ and one study analysed data from the UK EVAR trials 1 and 2.²³

A further caveat concerns the follow-up period of the studies included in this section. Generally the studies cover a period of 5–10 years, although

TABLE 2 Overview of risk modelling studies

Study details	Data source	Study dates	Type of study		
			Development of a risk assessment algorithm	Investigation of specific risk factors	Evaluation/validation of existing risk assessment algorithm
Biancari 2006 ⁵⁹	EUROSTAR	October 1996–March 2005			✓
Boult 2007 ^{60,92}	Australian national audit	1 November 1999–16 May 2001	✓	✓	
Brewster 2006 ⁶¹	MGH ^a	7 January 1994–31 December 2005		✓	
Brown (EVAR trial participants) 2007 ²³	EVAR trial 1 and EVAR trial 2	September 1999–August 2004		✓	✓
Bush 2007 ⁶²	NSQIP ^b	1 May 2001–31 December 2004		✓	
Buth 2000 ⁶³	EUROSTAR	January 1994–July 1999		✓	
Buth 2000 ⁶⁴	EUROSTAR	January 1994–March 1999		✓	
Buth 2002 ⁶⁵	EUROSTAR	June 1996–March 2001		✓	
Buth 2003 ⁶⁶	EUROSTAR	Not reported		✓	
Cuypers 2000 ⁶⁷	EUROSTAR	January 1994–July 1999		✓	
Diehm 2007 ⁶⁸	EUROSTAR	December 1996–November 2005		✓	
Diehm 2007 ⁹¹	EUROSTAR	March 1994–November 2006		✓	
Hobo 2006 ⁶⁹	EUROSTAR	December 1999–December 2004		✓	
Hobo 2007 ⁷⁰	EUROSTAR	October 1996–January 2006		✓	
Lange 2005 ⁷¹	EUROSTAR	1996–2004		✓	
Leurs 2007 ⁷²	EUROSTAR	Patients registered post 1999 included		✓	
Leurs 2004 ⁷³	EUROSTAR	6-year period to April 2004		✓	
Leurs 2006 ⁷⁴	EUROSTAR	Recruitment began October 1996		✓	
Leurs 2005 ⁷⁵	EUROSTAR	May 1994–December 2003		✓	

continued

TABLE 2 Overview of risk modelling studies (continued)

Study details	Data source	Study dates	Type of study		
			Development of a risk assessment algorithm	Investigation of specific risk factors	Evaluation/validation of existing risk assessment algorithm
Leurs 2005 ⁷⁶	EUROSTAR	1994–2004		✓	
Leurs 2006 ⁷⁷	EUROSTAR	Enrolled 1 December 1996		✓	
Lifeline Registry of Endovascular Aneurysm Repair 2002 ⁷⁸	US Lifeline Registry	Not reported		✓	
Lifeline Registry of Endovascular Aneurysm Repair 2005 ⁷⁹	US Lifeline Registry	5-year data from trials of four EVAR devices: Ancure, AneuRx, Excluder and Powerlink		✓	
Lottman 2004 ⁸⁰	EUROSTAR	January 1994–July 2001		✓	
Mohan 2001 ⁸¹	EUROSTAR	January 1994–January 2000		✓	
Peppelenbosch 2004 ⁸²	EUROSTAR	Over 6 years up to June 2002		✓	
Riambau 2001 ⁸³	EUROSTAR	January 1994–August 1998		✓	
Ruppert 2006 ⁸⁴	EUROSTAR	July 1997–August 2004		✓	
Sampram 2003 ⁸⁵	Cleveland Clinic, OH, USA	1996–2002		✓	
Timaran 2007 ⁸⁶	NIS ^c	2001–4		✓	✓
Torella 2004 ⁸⁷	EUROSTAR	May 1994–June 2002		✓	
van Eps 2007 ⁸⁸	EUROSTAR	December 1996–January 2005		✓	
van Marrewijk 2004 ⁸⁹	EUROSTAR	1996–June 2002		✓	
Zarins 2006 ⁹⁰	AneuRx stent graft trial (40 centres)	1998–9		✓	

a Massachusetts General Hospital, MA, USA.
 b National Surgical Quality Improvement Program.
 c The Nationwide Inpatient Sample from the Healthcare Cost and Utilisation Project.

follow-up of individual patients is generally shorter. Patients are perhaps more ‘typical’ of those in routine clinical practice. However, many of the studies begin in the mid-1990s and this raises issues of older devices and less experience with EVAR.

A final caveat is that the majority of the studies in this section undertook to investigate specific risk factors using multiple regression analysis. As such, statistically significant results can reflect the covariates used in the model, which often were not clear from the published reports. Furthermore,

these studies highlight risk factors but, for example, do not necessarily quantify the effect of older age on risk of aneurysm-related mortality. More useful in this regard were the studies that aimed to develop a risk algorithm⁶⁰ or to evaluate an existing algorithm^{23,59,86} to aid clinical decision-making. These studies were few in number and are discussed later in this chapter (see Assessment of risk factors for adverse outcomes following EVAR). Studies that both develop or validate an algorithm and discuss individual risk factors are discussed within each relevant section.

Table 3 details the quality of the risk model studies. Collectively the studies described the samples in sufficient detail (study characteristics are detailed later in this chapter; see Assessment of risk factors for adverse outcomes following EVAR, especially Tables 28 and 31). Just over half of the studies provided a clear definition of the risk variables under investigation, for example the measurements for a 'large' aneurysm or the definition of 'old age'. The weaknesses of the studies were in reporting details of multivariable modelling, particularly outlining the covariates considered to build the model and how these were chosen. Details of any investigations of interactions between variables were rarely provided. Appropriateness of analysis could not always be ascertained as it was not always clear how continuous variables were handled or whether there was a sufficient number of events to warrant the number of variables under investigation in a study. Finally, nine studies did not present confidence intervals or other measures of uncertainty, making it difficult to assess the precision of any effect measures reported. Overall, no studies clearly met all quality criteria, 12 met five or six of the seven criteria and the remainder met fewer than five criteria.

Assessment of effectiveness from RCTs

EVAR versus open repair (unruptured) Study characteristics

The characteristics of the included RCTs are summarised in Tables 4–7.

Patients

Four RCTs compared EVAR with open repair in patients with unruptured AAAs: DREAM^{40,41} ($n = 351$), EVAR trial 1^{42,43} ($n = 1082$) and the small RCTs of Cuypers *et al.*⁴⁴ ($n = 76$) and Soulez *et al.*⁴⁵ ($n = 40$) (Table 4). It should be noted that a later publication of EVAR trial 1²³ reported a larger sample size ($n = 1252$) because patient recruitment

had continued until August 2004. However, patient details were not provided and therefore data from this later analysis have not been used in the main analyses in this report nor in Table 4.

Patients were predominantly male in all RCTs, the percentage of men ranging from 91% to 98%, reflecting the disease profile. The average age of patients ranged from the late 60s to the mid-70s. The four RCTs were relatively homogeneous in terms of average aneurysm diameter: 6.5 cm in EVAR trial 1, 6.0 cm in DREAM, 5.4 cm in Cuypers *et al.* and 5.2 cm in Soulez *et al.*

The RCTs varied in their reporting of comorbidities and patient fitness. In all four RCTs the majority of patients were current or ex-smokers. Across the four trials the prevalence of diabetes was 10–16% and of heart disease was 43–68%. Other comorbidities were reported for two or three RCTs (Table 5).

Patient fitness scores were reported for all four RCTs but different scoring systems were used. The DREAM investigators⁴⁰ and Cuypers *et al.*⁴⁴ used the ASA classification system; the majority (about two-thirds) of patients in these studies were classified as ASA II. EVAR trial 1 did not report an overall measure of patient fitness in the main publications.^{42,43} In a later analysis,²³ patients were classified as having good, moderate or poor fitness based on modified CPI scores. Of 1252 patients randomised (including some randomised too late for the main analysis), 579 (46.2%) were classified as having 'good', 331 (26.4%) as having 'moderate' and 338 (27.0%) as having 'poor' fitness.

Intervention

Patients receiving EVAR in these four RCTs were recruited between September 1996⁴⁴ and August 2004 (Table 6), although patients recruited to EVAR trial 1 after December 2003 were not included in the main analysis.⁴³ They are included in the analysis by fitness.²³ EVAR trial 1 had the latest closing date for recruitment but DREAM had the most recent start (November 2000). The time period covered by the Cuypers *et al.* trial (1996–9) limits its relevance to current clinical practice. Delay between randomisation and procedure was similar for the two larger RCTs (median 39 days in DREAM and 43 days in EVAR trial 1), although waiting time ranged up to 183 days in DREAM. A wide range of different devices was used within and between trials. In EVAR trial 1 and DREAM, the most commonly used devices were the Zenith (Cook) and Talent (Medtronic) stent grafts.

TABLE 3 Risk model studies quality assessment

Author	Study sample adequately described	Included risk variables clearly defined	Covariates considered to build the multivariate model	Interactions between variables explored	Continuous variables handled appropriately	More than 10 events per included variable	Confidence intervals or other measures of uncertainty presented
Biancari 2006 ⁵⁹	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Boult 2007 ⁶⁰	Yes	Yes	Yes	Not reported	Unclear	No	No
Brewster 2006 ⁶¹	Yes	No	Not reported	Unclear	Unclear	No	No
Brown 2007 ²³	Yes	Yes	Yes	Not reported	Yes	Yes	Yes
Bush 2007 ⁶²	Yes	Yes	Not reported	Unclear	Yes	Yes	Yes
Buth 2000 ⁶³	Yes	No	Not reported	Unclear	Unclear	Unclear	No
Buth 2000 ⁶⁴	Yes	Yes	Yes	Not reported	Unclear	Unclear	Yes
Buth 2002 ⁶⁵	Yes	Yes	Not reported	Unclear	Yes	Yes	Yes
Buth 2003 ⁶⁶	No	No	Not reported	Unclear	Unclear	Yes	Yes
Cuypers 2000 ⁶⁷	Yes	Yes	Yes	Unclear	Yes	No	Yes
Diehm 2007 ⁶⁸	Yes	Yes	Yes	Unclear	Yes	Yes	No
Diehm 2007 ⁹¹	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Hobo 2006 ⁶⁹	Yes	No	Yes	Unclear	Unclear	Yes	No
Hobo 2007 ⁷⁰	Yes	Yes	Not reported	Unclear	Yes	Yes	Yes
Lange 2005 ⁷¹	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Leurs 2007 ⁷²	Yes	No	Not reported	Unclear	Unclear	Unclear	Yes
Leurs 2004 ⁷³	Yes	No	Yes	Unclear	Unclear	No	Yes
Leurs 2006 ⁷⁴	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Leurs 2005 ⁷⁵	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Leurs 2005 ⁷⁶	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes

Author	Study sample adequately described	Included risk variables clearly defined	Covariates considered to build the multivariate model	Interactions between variables explored	Continuous variables handled appropriately	More than 10 events per included variable	Confidence intervals or other measures of uncertainty presented
Leurs 2006 ⁷⁷	Yes	No	Not reported	Unclear	Unclear	Unclear	Yes
Lifeline Registry of Endovascular Aneurysm Repair 2002 ⁷⁸	Yes	No	Not reported	Limited details	No	Unclear	No
Lifeline Registry of Endovascular Aneurysm Repair 2005 ⁷⁹	Yes	No	Yes	Not reported	Yes	Unclear	Yes
Lottman 2004 ⁸⁰	Yes	Yes	Yes	Not reported	No	Yes	No
Mohan 2001 ⁸¹	Yes	Yes	Yes	Unclear	No	Unclear	Yes
Peppelenbosch 2004 ⁸²	Yes	No	Yes	Not reported	Unclear	Unclear	Yes
Riambau 2001 ⁸³	Yes	Yes	Not reported	Unclear	Yes	Yes	Yes
Ruppert 2006 ⁸⁴	No	No	Yes	Unclear	Unclear	Yes	No
Sampram 2003 ⁸⁵	Yes	No	Not reported	Unclear	Yes	Yes	Yes
Timaran 2007 ⁸⁶	Yes	Yes	Yes	Not reported	No	Unclear	Yes
Torella 2004 ⁸⁷	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
van Eps 2007 ⁸⁸	Yes	No	Yes	Unclear	Unclear	No	Yes
van Marrewijk 2004 ⁸⁹	Yes	Yes	Yes	Not reported	Unclear	Yes	Yes
Zarins 2006 ⁹⁰	Yes	Yes	Yes	Not reported	No	Yes	No

TABLE 4 Basic characteristics of RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Country where study was performed	Number of patients randomised			Age of population	Gender	Aneurysm diameter
		Total	EVAR	Comparator			
DREAM Blankensteijn 2005 ⁴¹	Multinational; the Netherlands and Belgium	351	173	178	Mean (SD) 70.1 years [EVAR 70.7 (6.6), open repair 69.6 (6.8)]	Percentage male (total population) 91.7% (EVAR 93.1%, open 90.4%)	Mean (SD) 6 cm [EVAR 6 (0.9), open repair 6 (0.85)]
EVAR trial I EVAR trial participants 2005 ⁴³	UK	1082	543	539	Mean (SD) 74 (6) years [EVAR 74.2 (6.0), open repair 74.0 (6.1)]	Percentage male (total population) 91% [EVAR 494 (91%), open repair 489 (91%)]	Mean (SD) 6.5 cm [EVAR 6.5 (0.9), open repair 6.5 (1.0)]. Measurement tool used spiral CT scan or conventional CT combined with conventional angiography
Cuypers 2001 ⁴⁴	Netherlands	76	57	19	Mean 68.5 years (EVAR 69, open repair 68). Range: EVAR 52–82, open repair 52–81	Percentage male (total population) 92% [EVAR 54/57 (95%), open repair 16/19 (84%)]	Mean 5.4 cm (EVAR 5.6, open repair 5.2). Range: EVAR 5.2–8.4 cm, open repair 4.0–6.1 cm
Soulez 2005 ⁴⁵	Canada	40	20	20	Mean (SD) 70.5 years [EVAR 70.3 (6.4), open repair 71.2 (7.6)]	Percentage male (total population) 39 patients (98%) [EVAR 19/20 (95%), open repair 20/20 (100%)]	Mean (SD) 5.2 cm [EVAR 5.31 (0.48), open repair 5.09 (1.61)]. Measurement tool used spiral CT

CT, computed tomography.

Information on the effects of device brand on outcomes in RCTs is presented later in this chapter (see Analysis by device type). The majority of patients received bi-iliac stent grafts under general anaesthesia, although in DREAM a substantial minority (40%) received regional anaesthesia.^{40,41} The type of anaesthesia used was not reported in the main publications of the EVAR trial I.^{42,43}

Comparator

The comparator intervention in these four RCTs was open repair performed under general anaesthesia according to the centre's standard procedures. The median time between randomisation and procedure was similar for open repair and EVAR in EVAR trial I and the DREAM trial but the DREAM trial recorded a high maximum waiting time (260 days; Table 7).

Results by outcome

30-day mortality

All four RCTs comparing EVAR with open repair in patients with unruptured AAAs (DREAM,⁴¹ EVAR trial I⁴² and the studies by Cuypers *et al.*⁴⁴ and Soulez *et al.*⁴⁵) reported 30-day operative mortality (Figure 2). Results from a later analysis of EVAR trial I based on a larger sample size gave an odds ratio (OR) of 0.38 (95% CI 0.18 to 0.80).²³ The pooled estimate of effect suggested a significantly lower rate of 30-day mortality in the EVAR group: pooled OR 0.35 (95% CI 0.19 to 0.63).

The small Soulez *et al.* trial⁴⁵ did not contribute to this analysis and exclusion of the less relevant data from the Cuypers *et al.* trial⁴⁴ (i.e. a pooled analysis including only the DREAM and EVAR trial I) produced an almost identical measure of effect: pooled OR 0.35 (95% CI 0.19 to 0.64) (Figure 3).

TABLE 5 Patient characteristics in RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Smoking history	Diabetes	Heart disease	Hypertension	Renal disease	Respiratory disease	Fitness scores	Body mass index (BMI)
DREAM Blankensteijn 2005 ⁴¹	Current smokers 209 (59.6%) [EVAR 111 (64.2%), open repair 98 (55.1%)]	35 (10%) [EVAR 18 (10.4%), open repair 17 (9.6%)]	154 (43.8%) [EVAR 71 (41%), open repair 83 (46.6%)]	198 (56.4%) [EVAR 101 (58.4%), open repair 97 (54.5%)]	28 (8%) [EVAR 13 (7.5%), open repair 15 (8.4%)]	81 (23%) [EVAR 48 (27.7%), open repair 33 (18.5%)]	ASA I: 81 (23%) [EVAR 37 (21.4%), open repair 44 (24.7%)]; ASA II: 232 (66%) [EVAR 122 (70.5%), open repair 110 (61.8%)]; ASA III: 38 (10.8%) [EVAR 14 (8.1%), open repair 24 (13.5%)]; ASA IV: 0	Mean (SD) 26.5 kg/m ² [EVAR 26.3 (3.4), open repair 26.6 (4.1)]
EVAR trial I EVAR trial participants 2005 ⁴³	Current smokers 232 (21%) [EVAR 115 (21%), open repair 117 (22%)]]; past smokers 747 (69%) [EVAR 367 (68%), open repair 380 (70%)]]; never smoked 102 (9%) [EVAR 61 (11%), open repair 41 (8%)]	111 (10%) [EVAR 49 (9%), open repair 62 (12%)]	463 (43%) [EVAR 234 (44%), open repair 229 (43%)]	Not reported	Not reported	Not reported	Other; reported in reference 23. Analysis by fitness groups was based on 626 patients randomised to EVAR and 626 randomised to open repair up to 31 August 2004. Patients were classified as having good, moderate or poor fitness based on modified Customized Probability Index scores. Good fitness 579 (EVAR 301, open repair 278), moderate fitness 331 (EVAR 160, open repair 171), poor fitness 338 (EVAR 164, open repair 174), missing fitness 4 (EVAR 1, open repair 3)	Mean (SD) 26.4 kg/m ² [EVAR 26.4 (4.6), open repair 26.4 (4.4)]
Cuypers 2001 ⁴⁴	Current smokers 31 (41%) [EVAR 26 (46%), open repair 5 (26%)]	16% [EVAR 8 (14%), open repair 4 (21%)]	46% [EVAR history of coronary artery disease 25 (44%), open repair history of coronary artery disease 10 (53%)]	56% [EVAR 31 (54%), open repair 12 (63%)]	Not reported	28% [EVAR 17 (30%) COPD, open repair 4 (21%) COPD]	ASA II: 64% [EVAR 34 (60%), open repair 15 (79%)]; ASA III: 36% [EVAR 23 (40%), open repair 4 (21%)]	Not reported
Soulez 2005 ⁴⁵	Current smokers 8 (20%) [EVAR 5 (25%), open repair 3 (15%)]]; past smokers 27 (68%) [EVAR 14 (70%), open repair 13 (65%)]]; never smoked 5 (12%) [EVAR 1 (5%), open repair 4 (20%)]	6 (15%) [EVAR 1 (5%), open repair 5 (25%)]	27 (68%) [EVAR 13 (65%), open repair 14 (70%)]	18 (45%) [EVAR 8 (40%), open repair 10 (50%)]	CrCl < 50 ml/min: 6 (15%) [EVAR 1 (5%), open repair 5 (25%)]	9 (22%) [EVAR 6 (30%), open repair 3 (15%)]	Cardiac status NYHA class I: 18 (45%) [EVAR 10 (50%), open repair 8 (40%)]]; cardiac status NYHA class 2: 22 (55%) [EVAR 10 (50%), open repair 12 (60%)]	BMI > 30 kg/m ² 17 (42%) [EVAR 8 (40%), open repair 9 (45%)]

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; NYHA, New York Heart Association.

TABLE 6 Intervention characteristics in RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Type of device (EVAR)	Graft type (EVAR)	Anaesthesia
DREAM Blankensteijn 2005 ⁴¹	November 2000–December 2003	Median 39 days, range 1–183 days	Elective 173 (100%); emergency 0	Zenith 57 (33.3%); Talent 46 (26.9%); Excluder 37 (21.6%); other 30 (17.5%)	Uni-iliac 6 (3.5%); bi-iliac 160 (94%); other (endovascular tube graft) 1 (0.6%)	Local 9 (5.3%); regional 68 (39.8%); general 94 (54.9%)
EVAR trial I EVAR trial participants 2005 ⁴³	September 1999–1 July 2004 for main analysis. Additional patients recruited up to 31 August 2004 included in some analyses	Median 43 days (IQR 28–69), range 28–70 days	Elective 512 (94% of randomised patients); emergency 0 (0%)	Zenith 261 (51%) (based on $n = 512$; $n = 318$ in later analysis based on patients randomised up to August 2004); Talent 167 (33%) (based on $n = 512$; $n = 187$ in later analysis based on patients randomised up to August 2004); Excluder 36 (7%) (based on $n = 512$; $n = 37$ in later analysis based on patients randomised up to August 2004); other (Quantum or Teramed 10) (2%) (based on $n = 512$)	Uni-iliac 51 (10%) (based on $n = 512$); bi-iliac 461 (90%) (based on $n = 512$)	Not reported
Cuypers 2001 ⁴⁴	September 1996–October 1999	Not reported	Not reported; probably elective, no mention of emergency	Stentor 3 (5%); Vanguard 22 (39%); AneurRx 30 (52%); Lifepath 1 (2%); 1 (2%) had open repair	Bi-iliac 57 (100%)	General 57 (100%)
Soulez 2005 ⁴⁵	September 1998–July 2002	Not reported	Not reported; probably elective	Talent 20 (100%)	Bi-iliac 20 (100%) EVAR patients	Local 1 (5%) EVAR; regional 1 (5%) EVAR; general 18 (90%) EVAR

IQR, interquartile range.

TABLE 7 Comparator characteristics in RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Open repair or non-surgical procedure	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Anaesthesia
DREAM Blankensteijn 2005 ⁴¹	Open repair. Particular open technique used was at the discretion of the surgeon	November 2000–December 2003	Median 39 days, range 4–260 days	Elective 178 (100%)	Local 1 (0.6%) (crossover to EVAR); regional 2 (1.1%) (crossovers to EVAR); general 171 (98.3%) (all patients except 3 crossovers)
EVAR trial I EVAR trial participants 2005 ⁴³	Open repair	September 1999–1 July 2004 for main analysis. Additional patients recruited up to 31 August 2004 included in some analyses	Median 35 days (IQR 19–55), range 20–59 days	Elective 496 (92.0% of randomised patients); emergency unclear [possibly 3 (<1%)]	Not reported
Cuypers 2001 ⁴⁴	Open repair	September 1996–October 1999	Not reported	Not reported; 1 emergency open repair, but analysed as EVAR	General 19 (100%)
Soulez 2005 ⁴⁵	Open repair	September 1998–July 2002	Not reported	Elective	General 20 (100%)

IQR, interquartile range.

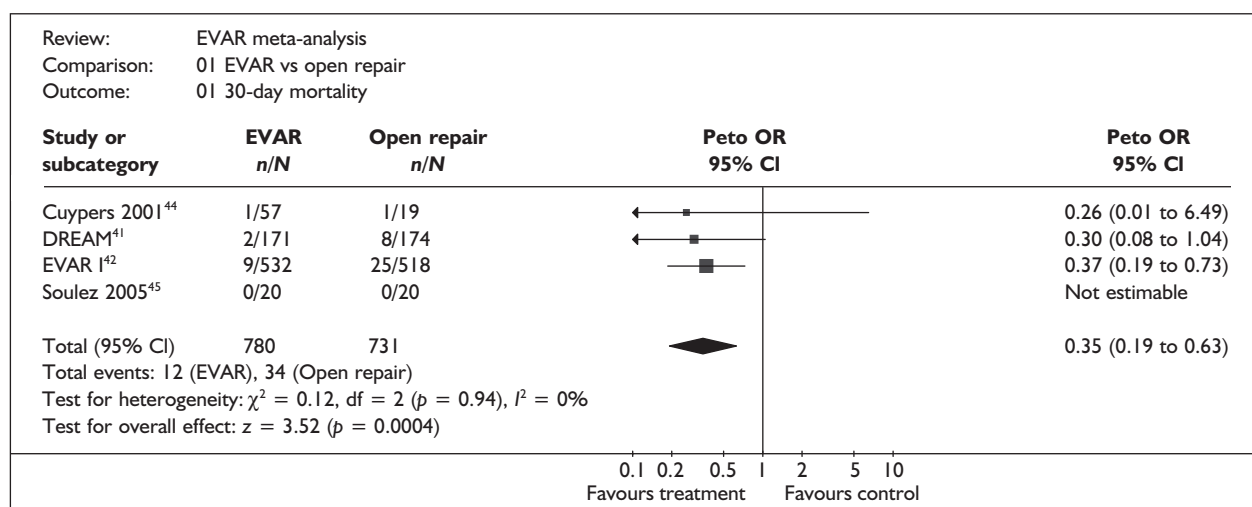


FIGURE 2 EVAR vs open repair: meta-analysis of RCTs for 30-day mortality.

Abdominal aortic aneurysm-related mortality

The two small RCTs failed to provide information on AAA-related mortality at mid-term follow-up. The DREAM trial and EVAR trial 1 had similar definitions of AAA-related mortality, i.e. death within 30 days of the original procedure or a reintervention. DREAM was originally designed to detect differences in a primary end point of short-term mortality and complications and so its power to detect differences at longer-term follow-up is unclear. The mean duration of medium-term follow-up was about 22 months in DREAM compared with a median of about 35 months (2.9 years) in EVAR trial 1. Maximum follow-up in DREAM was 42 months whereas 24% of patients in EVAR trial 1 were followed up for 4 years or more. Longer-term data for AAA-related mortality were not available.

Both RCTs reported lower rates of AAA-related mortality in patients treated with EVAR than in

those undergoing open repair. In DREAM, 3/173 patients in the EVAR group (2.1%) and 9/178 in the open repair group (5.7%) died of aneurysm-related causes. The estimated hazard ratio (HR) was 0.27 (95% CI 0.07 to 1.00, $p = 0.05$). In EVAR trial 1 there were 19/543 and 34/539 deaths in the EVAR and open repair groups respectively. The unadjusted HR was 0.55 (95% CI 0.31 to 0.96, $p = 0.04$); HRs adjusted for primary and secondary covariates were similar. Results from a later analysis of EVAR trial 1 based on a larger sample size gave an HR of 0.60 (95% CI 0.35 to 1.02).²³

The pooled estimate for the HR across the two trials was 0.49 (95% CI 0.29 to 0.83, $p = 0.007$), confirming a statistically significant benefit of EVAR over open repair for this outcome (Figure 4).

In a post hoc analysis, follow-up was divided into the first 6 months after randomisation and the period beyond 6 months. The HR for the

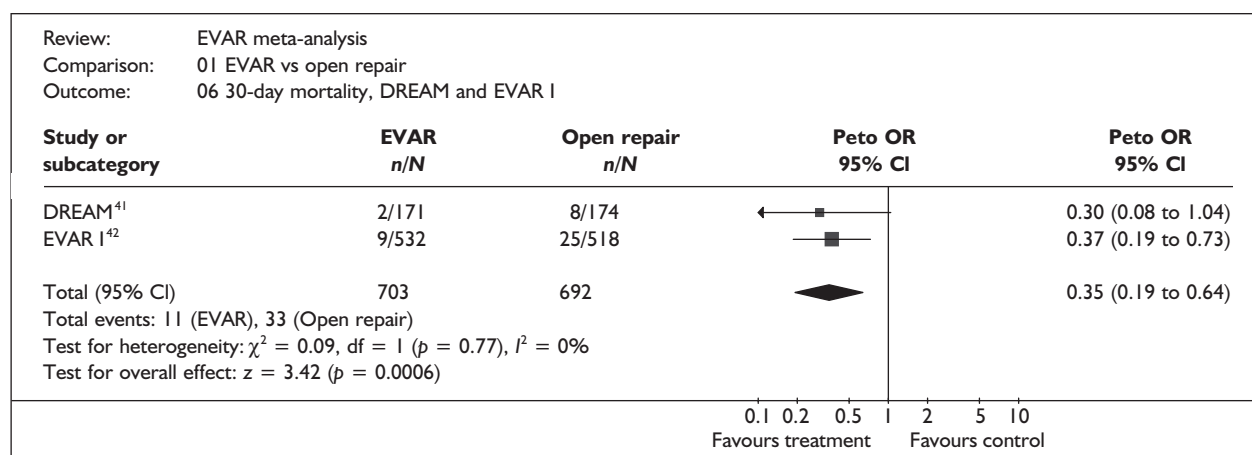


FIGURE 3 EVAR vs open repair: meta-analysis of the DREAM and EVAR trial 1 RCTs for 30-day mortality.

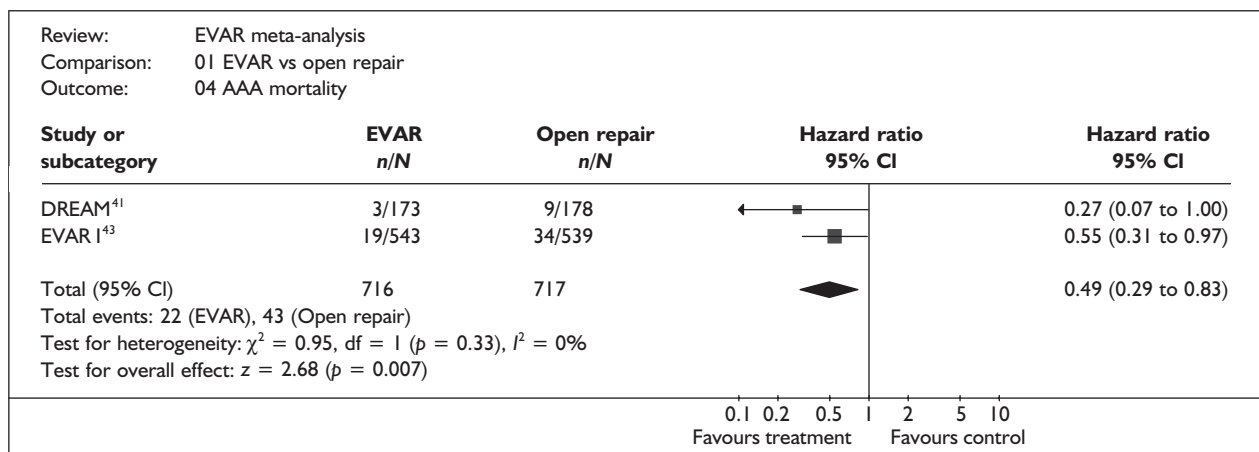


FIGURE 4 EVAR vs open repair: meta-analysis of RCTs for abdominal aortic aneurysm-related mortality at follow-up.

first 6 months was 0.42 (95% CI 0.21 to 0.82), a statistically significant difference favouring the EVAR group. For the later period the HR was 1.15 (95% CI 0.39 to 3.41), i.e. there was no significant difference between groups; the wide confidence interval reflected the small number of AAA-related deaths during this period.

All-cause mortality

Of the four relevant RCTs, only DREAM and EVAR trial 1 provided useful information on all-cause mortality at follow-up (2 years in DREAM and 4 years in EVAR trial 1). The trial by Soulez *et al.*⁴⁵ reported only one death during a mean follow-up of 29 months for the EVAR group and 27 months for the open repair group. In the trial by Cuypers *et al.*⁴⁴ patients were only followed up for 30 days.

The two main RCTs reported no significant differences in medium-term (35 and 42 months, respectively) mortality in patients treated with EVAR compared with those treated with open repair. In DREAM, 20/173 patients in the EVAR group and 18/178 in the open repair group died of any cause. The estimated unadjusted HR was 0.94 (95% CI 0.50 to 1.79, $p = 0.86$). In EVAR trial 1 there were 100/543 and 109/539 deaths in the EVAR and open repair groups respectively. The unadjusted HR was 0.90 (95% CI 0.69 to 1.18, $p = 0.46$); HRs adjusted for primary and secondary covariates were similar. Results from a later analysis of EVAR trial 1 based on a larger sample size gave an HR of 0.93 (95% CI 0.74 to 1.18).²³

In a post hoc analysis, follow-up was divided into the first 6 months after randomisation and the period beyond 6 months. The HR for the first 6 months was 0.55 (95% CI 0.33 to 0.93), a statistically significant difference favouring the

EVAR group. For the later period the HR was 1.10 (95% CI 0.80 to 1.52), i.e. there was no significant difference between groups.

A pooled analysis of the two trials confirmed that there was no statistically significant difference between EVAR and open repair for all-cause mortality at medium-term follow-up (Figure 5).

Rupture

The four included RCTs provided limited information on rupture as a separate outcome. The DREAM study^{40,41} reported that there were no documented postoperative ruptures but that there were two sudden deaths following EVAR in which the possibility of rupture was considered but not proved. There were no aneurysm ruptures in either group in the small short-term study by Cuypers *et al.*⁴⁴ In the small study by Soulez *et al.*⁴⁵ there was one rupture in a patient treated with EVAR. In EVAR trial 1⁴³ three patients randomised to EVAR and seven randomised to open repair had a rupture before surgery. There were two fatal ruptures in the EVAR group and one in the open repair group within 30 days of surgery. After the 30-day point there were six deaths from rupture in the EVAR group and one in the open repair group. At follow-up, nine patients in the EVAR group were reported with graft rupture as a complication, compared with none in the open repair group.

These limited data suggest that rupture may be more of an issue following EVAR than following open repair.

Endoleak

Across the included RCTs endoleaks occurred at varying frequencies (up to approximately 20%) following EVAR in those trials reporting this

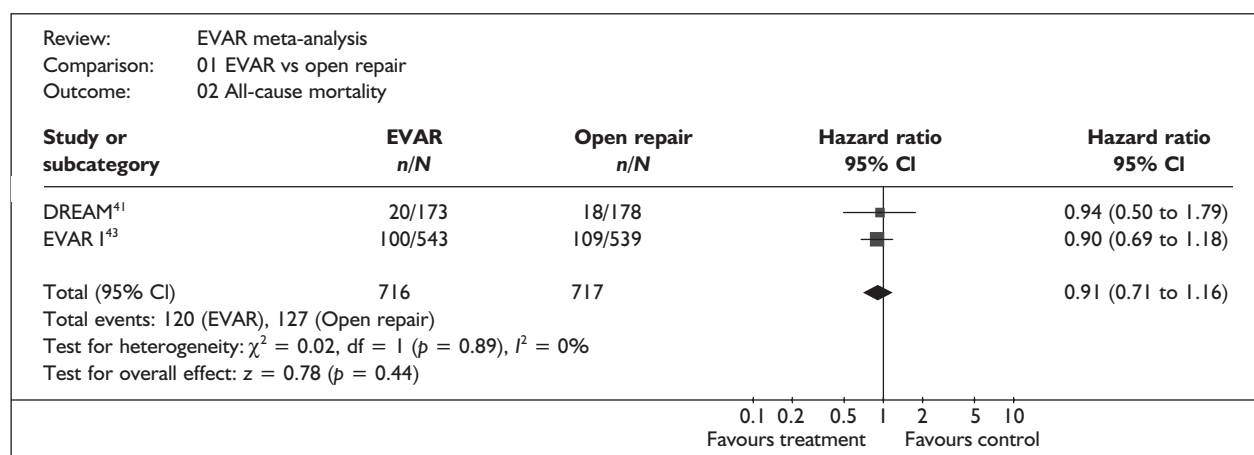


FIGURE 5 EVAR vs open repair: meta-analysis of RCTs for all-cause mortality at follow-up. (Academic-in-confidence information on EVAR trial 1 has been omitted.)

FIGURE 6 Six-year survival curves for all-cause mortality in EVAR trial 1. (Academic-in-confidence information has been removed.)

outcome (Table 8). Type II endoleaks were most common, followed by type I. The Cuypers *et al.* study⁴⁴ did not report data on endoleaks and the DREAM study only reported endoleaks requiring reintervention in the perioperative period [two (1.2%), of which one was regarded as a severe complication].⁴⁰

Device migration

Only the EVAR trial 1⁴³ reported on device migration after EVAR. In this trial, 12/529 patients with a completed EVAR (2.3%) experienced device migration during follow-up, of which seven required reintervention.

Reinterventions

The DREAM and EVAR trial 1 studies compared overall reintervention rates between patients

treated with EVAR and those treated with open repair. In DREAM,⁴¹ the risk of reintervention was significantly higher in the EVAR group for the first 9 months (HR 2.9, 95% CI 1.1 to 6.2, $p = 0.03$) but the groups were not significantly different thereafter (HR 1.1, 95% CI 0.1 to 9.3, $p = 0.95$). Across the medium-term follow-up in EVAR trial 1,⁴³ the HR for reintervention was 2.7 (95% CI 1.8 to 4.1), indicating a significantly higher risk in the EVAR group. The 4-year point estimates for reintervention were 20% for the EVAR group compared with 6% for the open repair group.⁴³

Specific reinterventions of interest are shown in Table 9. When reported (EVAR trial 1 and Soulez *et al.*), rates of short-term EVAR-specific reinterventions were similar to rates of re-exploration of open repair. Conversion of EVAR

TABLE 8 Occurrence of endoleaks in RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Endoleak		
	Type I	Type II	Type III
DREAM	Not reported	Not reported	Not reported
Blankensteijn 2005 ⁴¹			
EVAR trial 1	27 (17 with reintervention) at follow-up (of 529 EVAR patients with repair completed). Unspecified endoleak reported in 4 patients (4 with reintervention)	79 (17 with reintervention) at follow-up (of 529 EVAR patients with repair completed)	8 (4 with reintervention) at follow-up (of 529 EVAR patients with repair completed)
EVAR trial participants 2005 ⁴³			
Cuypers 2001 ⁴⁴	Not reported	Not reported	Not reported
Soulez 2005 ⁴⁵	2 (10%) EVAR	3 (15%) EVAR	Not reported

to open repair within 30 days occurred in 10/531 patients (1.9%) in EVAR trial 1.^{42,43} Cuypers *et al.*⁴⁴ reported no conversions after EVAR, and the other two trials did not report this outcome.

Short-term adverse events

Our analysis of major short-term adverse events concentrated on cardiac and cerebrovascular events within 30 days of surgery. The DREAM,^{40,41} EVAR trial 1^{42,43} and Soulez *et al.*⁴⁵ RCTs did not report this information. DREAM reported complications rather than specific events.

Of the trials comparing EVAR and open repair in patients with unruptured AAA, only Cuypers *et al.*⁴⁴ reported on cardiac events: three (5%) in the EVAR group and two (11%) in the open repair group.

Health-related quality of life

All four RCTs reported some details on HRQoL. All used the Medical Outcomes Study Short Form-36 (SF-36) questionnaire, but different components were reported, making it difficult to synthesise scores across studies. Cuypers *et al.* and EVAR trial 1 also used the EuroQoL 5 dimension (EQ-5D)

TABLE 9 Reinterventions in RCTs of EVAR vs open repair (unruptured aneurysms)

Study (main publication)	Conversion to open repair (EVAR group only)	Correction of endoleak (EVAR group only)	Re-exploration of open repair (open group only)	Other (specify)	Cumulative rate from Kaplan–Meier curve	Hazard ratio
DREAM Blankensteijn 2005 ⁴¹	Not reported	2 (1.2%), of which 1 was classed as severe (0.6%)	Not reported	Not reported	Not reported	9 months: 2.9 (95% CI 1.1 to 6.2, $p = 0.03$) favouring open repair; > 9 months: 1.1 (95% CI 0.1 to 9.3, $p = 0.95$)
EVAR trial 1 EVAR trial participants 2005 ⁴³	10/531 at 30 days (intention to treat)	18/531 at 30 days (intention to treat)	15/516 at 30 days (intention to treat) (16/519 patients with open repair completed at follow-up)	Not reported	EVAR 20%, open repair 6% (4-year point estimates)	2.7 (95% CI 1.8 to 4.1)
Cuypers 2001 ⁴⁴	One patient randomised to EVAR received an urgent open AAA repair because of aneurysm rupture before receiving EVAR. There were no other conversions to open repair	Not reported	Not reported	Not reported	Not reported	Not reported
Soulez 2005 ⁴⁵	Not reported	4 patients	1 patient – operative treatment on an emergency basis with graft limb thrombosis, 7 months after surgery	Not reported	Not reported	Not reported

measure. This summary concentrates on intergroup differences.

The DREAM⁹³ and Cuypers *et al.*⁹⁴ RCTs reported results for all eight SF-36 domains and EQ-5D. In DREAM, full results for all time points were not reported. The groups had similar quality of life (QoL) scores at baseline. Three weeks after surgery the open repair group had significantly lower scores for physical function, social functioning and physical role limitations than the EVAR group. The physical role limitations score in the open repair group was still significantly lower than that of the EVAR group at 6 weeks. However, at 12 months the open repair group scored significantly higher than the EVAR group for physical function, social functioning, emotional role limitations, bodily pain and general health. EQ-5D scores did not differ between the groups until 6 months but at 6 and 12 months the open repair group had significantly higher scores than the EVAR group.⁹³ Cuypers *et al.*⁹⁴ assessed QoL at baseline and after 1 and 3 months. Groups were similar at baseline. At 1 month the EVAR group had significantly higher scores for physical function, physical role limitations, vitality and bodily pain, and for the usual activities element of EQ-5D. All these differences were no longer present at 3 months. Soulez *et al.*⁴⁵ assessed QoL using the SF-36

questionnaire at baseline and at 1, 3, 6, 12, 18 and 24 months. Results for the eight SF-36 domains were presented graphically. The authors reported that there were no significant differences between the groups at any time point.

The EVAR trial 1 RCT⁴³ reported EQ-5D weighted index scores and SF-36 physical and mental component summary scores for baseline, 0–3 months, 3–12 months and 12–24 months (*Table 10*). The groups were similar at baseline. The EVAR group had higher EQ-5D and physical component summary scores at 0–3 months but differences between groups were not significant at later time points. The mental component summary score did not differ between groups at any time point. The number of patients evaluated differed between time points (*Table 10*).

Overall, these data suggest that there may be a short-term QoL advantage for patients treated with EVAR relative to those who receive an open repair. Longer-term QoL data, by contrast, tend to favour open repair. These findings probably reflect the less invasive nature of the intervention in EVAR compared with open repair but also the need for continuing surveillance and the higher rates of complications and reinterventions following EVAR.

TABLE 10 Summary of health-related quality of life data from the EVAR trial 1 RCT

Study (main publication)	HRQoL measure used	Baseline scores, mean (SD)		Mean difference between populations at follow-up
		EVAR population	Comparator population	
EVAR trial 1 EVAR trial participants 2005 ⁴³	EQ-5D	0.75 (0.22) (541 patients)	0.74 (0.23) (531 patients)	0–3 months: crude 0.06 (SE 0.02), adjusted for baseline score 0.05 (SE 0.02) (482 patients); 3–12 months: crude –0.01 (SE 0.02), adjusted for baseline score –0.01 (SE 0.01) (885 patients); 12–24 months: crude –0.01 (SE 0.02), adjusted for baseline score –0.02 (SE 0.02) (764 patients)
	SF-36 physical component summary	39.92 (5.92) (533 patients)	39.83 (5.90) (534 patients)	0–3 months: crude 1.68 (SE 0.53), adjusted for baseline score 1.66 (SE 0.50) (462 patients); 3–12 months: crude –0.05 (SE 0.40), adjusted for baseline score 0.04 (SE 0.37) (849 patients); 12–24 months: crude –0.16 (SE 0.44), adjusted for baseline score –0.15 (SE 0.40) (692 patients)
	SF-36 mental component summary	43.59 (6.79) (533 patients)	43.95 (6.73) (534 patients)	0–3 months: crude –0.18 (SE 0.66), adjusted for baseline score –0.05 (SE 0.66) (462 patients); 3–12 months: crude 0.46 (SE 0.46), adjusted for baseline score 0.41 (SE 0.45) (849 patients); 12–24 months: crude –0.22 (SE 0.50), adjusted for baseline score –0.29 (SE 0.49) (692 patients)

EVAR versus open repair (ruptured aneurysms)

Study characteristics

One RCT⁴⁷ compared EVAR and open repair in patients with ruptured AAAs. Only 32 patients were randomised compared with a planned sample size of 100 and so it is difficult to draw firm conclusions from the trial. Compared with RCTs of elective EVAR, the patients were similar in age but had larger aneurysms and the proportion of women was slightly higher. Non-commercial stent grafts were used in patients receiving EVAR. Other study characteristics are shown in *Tables 11–14*.

Results

30-day mortality

Of the 15 patients randomised to EVAR, one died before receiving surgery, one was converted to open repair and subsequently died and six died in the perioperative period following EVAR. Thus, on an ITT basis the mortality rate was 8/15 (53%). Of 17 patients randomised to open repair, three died before surgery, two died on the operating table and four died in the perioperative period, giving an ITT mortality rate of 9/17 (53%). Other longer-term mortality data were not reported.

Adverse events

In total, 5/11 EVAR patients (45%) and 7/12 open repair patients (58%) who survived the procedure experienced cardiac events. All events were classified as moderate except for one severe event in the open repair group. One patient in the EVAR group suffered severe cerebrovascular complications, compared with none in the open repair group.⁴⁷

EVAR versus non-surgical management (patients with unruptured aneurysms considered unfit for open repair)

Study characteristics

EVAR trial 2⁴⁶ is the only published RCT in this patient group. This UK RCT compared EVAR ($n = 166$) with non-surgical management ($n = 172$) in patients judged to be unfit for open repair. The trial met all quality criteria. The primary end point was all-cause mortality and secondary end points were aneurysm-related mortality, HRQoL, postoperative complications and hospital costs. A total of 14 patients randomised to EVAR died before operation (including six from AAA rupture), and 47 patients assigned to non-surgical management received surgical aneurysm repair (including 12 who received open repair despite having been classified as unfit for this procedure). These factors complicate the analysis and interpretation of the trial. *Tables 15–18* give details of patient, intervention and comparator characteristics.

Results

30-day mortality

Short-term mortality is not a meaningful outcome for comparing between EVAR and no surgical intervention. In the EVAR group of EVAR trial 2,⁴⁶ 13/150 patients who had the procedure (9%) died within 30 days. Of the 47 patients randomised to non-surgical treatment who crossed over to receive EVAR or open surgery, one (2%) died within 30 days.

AAA-related mortality

In the EVAR trial 2 RCT there was no significant difference in AAA-related mortality between

TABLE 11 Basic characteristics of the RCT for EVAR vs open repair in ruptured aneurysm

Study (main publication)	Country	Number of patients randomised			Age of population	Gender	Aneurysm diameter
		Total	EVAR	Comparator			
Hinchliffe 2006 ⁴⁷	UK, University Hospital Nottingham	32	15	17	Median: EVAR 74 years (IQR 68.8–79.5); open repair 80 years (IQR 73.8– 83.8)	Male (total population) 75% (24/32)	Median 8.5 cm (IQR 8.0–10.0) in patients who had EVAR. Measurement tool used CT scan

CT, computed tomography; IQR, interquartile range.

TABLE 12 Patient characteristics in the RCT for EVAR vs open repair in ruptured aneurysm

Study (main publication)	Smoking history	Diabetes	Heart disease	Hypertension	Renal disease	Respiratory disease	Fitness scores	Body mass index (BMI)
Hinchliffe 2006 ⁴⁷	Current smokers 10/32 (31%), past smokers 11/32 (34%), never smoked 11/32 (34%)	Not reported	8/32 (25%)	13/32 (41%); measurement tool not reported	3/32 (9%)	3/32 (9%) with chronic obstructive airways disease	Not reported; not applicable to this patient population	Not reported

TABLE 13 Intervention characteristics in the RCT for EVAR vs open repair in ruptured aneurysm

Study (main publication)	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Type of device (EVAR)	Graft type (EVAR)	Anaesthesia
Hinchliffe 2006 ⁴⁷	1 September 2002–31 December 2004	Median time from clinical diagnosis to operation: 75 minutes (IQR 64–126)	Emergency 13 (100%) (13/15 randomised patients underwent EVAR)	All patients received a two-piece aorto-uni-iliac stent graft made with Gianturco stents with an uncovered suprarenal component	Uni-iliac 11 (100%) (of 13 patients who underwent EVAR, 1 was converted to open repair and 1 to axillofemoral graft)	General 13 (100%)
IQR, interquartile range.						

TABLE 14 Comparator characteristics in the RCT for EVAR vs open repair in ruptured aneurysm

Study (main publication)	Open repair or non-surgical procedure	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Anaesthesia
Hinchliffe 2006 ⁴⁷	Open repair	1 September 2002–31 December 2004	Median time from clinical diagnosis to operation: 100 minutes (IQR 46–138)	Emergency 15 (100%) (14/17 randomised patients underwent open repair and one patient crossed over from the EVAR group)	General 15 (100%)
IQR, interquartile range.					

TABLE 15 Basic characteristics of the EVAR trial 2 RCT

Study (main publication)	Country	Number of patients randomised		Age of population	Gender	Aneurysm diameter
		Total	Comparator			
EVAR trial 2	UK	338	172	Mean (SD) 76.4 (6.45) years (based on n = 338); EVAR 76.8 (6.2), non-surgical treatment 76.0 (6.7); based on n = 143; Zenith device 77.3 (6.8), Talent 75.4 (6.1)	Percentage male (total population) 288 (85%) (based on n = 339); EVAR 141 (85%), non-surgical treatment 147 (85%); based on n = 143; Zenith device 98/109 (89.9%), Talent 28/34 (82.4%)	Median: EVAR 6.4 cm, non-surgical treatment 6.3 cm; range: EVAR 6.0–7.4 cm, non-surgical treatment 6.0–7.0 cm. Measurement tool used CT scan
CT, computed tomography.						

TABLE 16 Patient characteristics in EVAR trial 2

Study (main publication)	Smoking history	Diabetes	Heart disease	Hypertension	Renal disease	Respiratory disease	Fitness scores	Body mass index (BMI)
EVAR trial 2	Current smokers: 57 (17%); EVAR 29 (17%), non-surgical treatment 28 (16%) Past smokers: 259 (77%); EVAR 127 (77%), non-surgical treatment 132 (77%) Never smoked: 22 (6%); EVAR 10 (6%), non-surgical treatment 12 (7%)	47 (14%)	233 (69%)	Not reported	Not reported	Not reported	Other; reported in reference 23. Fitness scores were assigned to patients randomised up to August 2004 (c.f. EVAR trial 1). Mean CPI fitness score 10.0 (SD 11.3) for 404 patients (197 EVAR and 207 no intervention). Little difference between randomised groups (details not reported). Comparison of fitness – 179 patients underwent elective AAA repair in EVAR group and 60 patients in no intervention group: Student's t-test: EVAR 10.5 (SD 11.8); no intervention 6.3 (9.6); p = 0.014	Mean (SD) 26.35 kg/m ² (based on n = 339); EVAR 26.4 (SD 4.9), non-surgical treatment 26.3 (SD 4.4); based on n = 143: 26.85, Zenith 26.9 (SD 5.0), Talent 26.8 (SD 4.6)
CPI, Customized Probability Index.								

TABLE 17 Intervention characteristics in EVAR trial 2

Study (main publication)	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Type of device (EVAR)	Graft type (EVAR)	Anaesthesia
EVAR trial 2 EVAR trial participants 2005 ⁴⁶	September 1999–31 December 2003 (August 2004 for extra patients included in some of the analyses)	Median: 57 days (IQR 39–82) 150 patients randomised to EVAR; 163 days (IQR 78–477) 47 patients crossed over from non-surgical treatment group (35 had EVAR, 12 had open repair)	Not reported	Zenith 86 (59%) (based on $n = 150$) ($n = 109$ in later analysis based on patients randomised up to August 2004); Talent 31/150 (21%) ($n = 34$ in later analysis based on patients randomised up to August 2004); Excluder 10/150 (7%); other: 9/150 (6%) AneurX (Medtronic), 5/150 (3%) Quantum (Cordis, Johnson & Johnson, Waterloo, Belgium), 2/150 (1%) Bard device (Bard, New Jersey), 1/150 (< 1%) Anson Aorfix (Lambard Medical, Oxford, UK), 1/150 (< 1%) EVT (Guidant, Indianapolis), 1/150 (< 1%) Edwards Lifepath (Edwards Lifesciences, Switzerland)	Uni-iliac 14 (10%) based on $n = 143$ in later analysis based on patients randomised up to August 2004; 7 using Zenith device and 7 using Talent device. Bi-iliac 131 (87%) based on $n = 150$; 127 (89%) based on $n = 143$ in later analysis based on patients randomised up to August 2004; 102 using Zenith device and 25 using Talent device	Local: not explicitly reported in main publication; 66 (46%) based on $n = 143$ in later analysis based on patients randomised up to August 2004; 49 using Zenith device and 17 using Talent device. General: 83/150 (55%); 73 (51%) based on $n = 143$ in later analysis based on patients randomised up to August 2004; 59 using Zenith device and 14 using Talent device; 27 (16%) (47 crossovers)
IQR, interquartile range.						

TABLE 18 Comparator characteristics in EVAR trial 2

Study (main publication)	Open repair or non-surgical procedure	Dates of procedure	Time lapse between randomisation and procedure	Elective or emergency procedure	Anaesthesia
EVAR trial 2 EVAR trial participants 2005 ⁴⁶	Non-surgical procedure	September 1999–31 December 2003 (August 2004 for extra patients included in some analyses)	Not applicable	Not applicable	Not applicable

FIGURE 7 Six-year survival curves for all-cause mortality EVAR trial 2. (Academic-in-confidence information has been removed.)

patients randomised to EVAR and those randomised to non-surgical management. On an ITT basis, 20/166 patients in the EVAR group and 22/172 in the non-surgical management group died of AAA-related causes by 4 years after randomisation, giving a crude HR of 1.01 (95% CI 0.55 to 1.84, $p = 0.98$); HRs adjusted for primary and secondary covariates were similar.⁴⁶

All-cause mortality

There was no significant difference in all-cause mortality between patients randomised to EVAR and those randomised to non-surgical management. Four years after randomisation, overall mortality was 64%. On an ITT basis, 74/166 patients in the EVAR group and 68/172 in the non-surgical management group died, giving a crude HR of 1.21 (95% CI 0.87 to 1.69, $p = 0.25$); HRs adjusted for primary and secondary covariates were similar.⁴⁶

(Academic-in-confidence information has been removed.)

Rupture

In EVAR trial 2,⁴⁶ nine patients randomised to EVAR had a rupture of their AAA before receiving elective treatment. Of those who received EVAR (178 including patients crossing over from the non-surgical management group), one had a graft rupture following successful treatment. There were 23 ruptures in the non-surgical management group, representing 13.4% of the 172 patients originally randomised to this group. The crude rupture rate was nine per 100 person-years. The authors noted that this rupture rate was considerably lower than that reported in other prospective studies monitoring large aneurysm rupture.

Endoleak

Details of endoleaks in patients who received EVAR in the EVAR trial 2 RCT are shown in *Table 19*.

These figures refer to all patients treated, including those who crossed over from the non-surgical management group.

Device migration

The number of patients with device migration in EVAR trial 2 was 2/178 patients who received EVAR (including crossovers) (1.1%). This was not an ITT analysis.

Reinterventions

EVAR trial 2 reported that 14/178 patients (7.9%) who received EVAR (including crossovers) required reintervention for endoleak, and 8/178 (4.5%) required 'other surgery' (unspecified).⁴⁶ The overall reintervention rate during follow-up was 11.5 per 100 person-years for EVAR and 1.8 per 100 person-years for non-surgical management. By 4 years the estimated reintervention rates were 26% and 4% respectively (HR 5.8, 95% CI 2.4 to 14.0, $p < 0.0001$).⁴⁶ This was an ITT analysis and so the reinterventions in the comparator group may represent patients who crossed over to surgical treatment.

The authors noted that the rate of reinterventions in the EVAR group of EVAR trial 2 seemed higher than that observed in the EVAR group of EVAR trial 1 (11.5 vs 6.9 per 100 person-years) but the difference was not statistically significant (HR 1.4, 95% CI 0.9 to 2.1, $p = 0.1$).⁴⁶

Short-term adverse events

EVAR trial 2 did not report on cardiac and cerebrovascular events within 30 days of surgery.⁴⁶

Health-related quality of life

EVAR trial 2⁴⁶ reported the same QoL outcomes as EVAR trial 1. The only statistically significant difference between groups ($p = 0.04$), for the SF-36 physical component summary score at 0–3 months, favoured the non-surgical management group (*Table 20*).

TABLE 19 Occurrence of endoleaks in the EVAR trial 2 RCT

Study (main publication)	Endoleak		
	Type I	Type II	Type III
EVAR trial 2 EVAR trial participants 2005 ⁴⁶	11/178 patients who received EVAR – not ITT (10 complications after EVAR)	23/178 patients who received EVAR – not ITT (17 complications after EVAR)	6/178 patients who received EVAR – not ITT (5 complications after EVAR)
ITT, intention to treat.			

TABLE 20 Summary of health-related quality of life (HRQoL) data from the EVAR trial 2 RCT

Study (main publication)	HRQoL measure used	Baseline scores, mean (SD)		Mean difference between populations at follow-up
		EVAR population	Comparator population	
EVAR trial 2 EVAR trial participants 2005 ⁴⁶	EQ-5D weighted index score	0.58 (0.31) (164 patients)	0.63 (0.28) (171 patients)	0–3 months: crude 0.01 (SE 0.05), adjusted for baseline score 0.03 (SE 0.05) (139 patients); 3–12 months: crude 0.04 (0.03), adjusted for baseline score 0.06 (0.03) (241 patients); 12–24 months: crude 0.05 (0.04), adjusted for baseline score 0.04 (0.04) (156 patients)
	SF-36 physical component summary	35.47 (6.63) (160 patients)	35.12 (6.23) (171 patients)	0–3 months: crude –1.64 (1.00), adjusted for baseline score –1.86 (0.88) (134 patients); 3–12 months: crude –0.78 (0.83), adjusted for baseline score –1.11 (0.77) (224 patients); 12–24 months: crude –1.47 (1.12), adjusted for baseline score –0.64 (1.04) (130 patients)
	SF-36 mental component summary	45.13 (7.92) (160 patients)	46.31 (6.97) (171 patients)	0–3 months: crude 1.73 (1.47), adjusted for baseline score 2.30 (1.38) (134 patients); 3–12 months: crude –0.08 (1.00), adjusted for baseline score 0.94 (0.95) (224 patients); 12–24 months: crude –0.70 (1.32), adjusted for baseline score 0.50 (1.29) (130 patients)

Analysis by device type

A secondary publication from the EVAR trial participants⁹⁵ reported an analysis by device type of data from the EVAR trial 1 and EVAR trial 2 RCTs. This analysis compared rates of reintervention, aneurysm-related mortality and all-cause mortality in patients who received the Zenith and Talent stent grafts.

In EVAR trial 1 the number of reinterventions per 100 person-years was 6.4 for Zenith ($n = 318$) and 8.6 for Talent ($n = 187$); there were 0.8 aneurysm-related deaths per 100 person-years for Zenith and 1.0 per 100 person-years for Talent; and deaths from all causes were 5.9 per 100 person-years for Zenith and 8.6 per 100 person-years for Talent. Statistically there were no significant differences between outcomes with the Zenith and Talent devices. Adjusted HRs were 0.79 (95% CI 0.51 to 1.21) for reintervention, 0.88 (95% CI 0.29 to 2.65) for aneurysm-related mortality and 0.79 (95% CI 0.53 to 1.19) for all-cause mortality.

In EVAR trial 2 the number of reinterventions per 100 person-years was 9.6 for Zenith ($n = 109$) and 15.1 for Talent ($n = 34$); there were 2.8 aneurysm-related deaths per 100 person-years for Zenith and 4.0 per 100 person-years for Talent; and deaths from all causes were 18.5 per 100 person-years for Zenith and 23.9 per 100 person-years for Talent. Statistically there were no significant differences between outcomes with the Zenith and Talent

devices. Adjusted HRs were 0.69 (95% CI 0.29 to 1.62) for reintervention, 0.94 (95% CI 0.21 to 4.27) for aneurysm-related mortality and 0.85 (95% CI 0.45 to 1.60) for all-cause mortality.

The DREAM⁴¹ and Cuypers *et al.*⁴⁴ studies did not report an analysis by device type, and in the Hincliffe *et al.*⁴⁷ and Soulez *et al.*⁴⁵ studies all EVAR procedures involved the same type of device.

Analysis by neck angulation

None of the included RCTs reported data allowing an analysis of outcomes by neck angulation.

Assessment of effectiveness from registries

Study characteristics

The study characteristics are summarised in Tables 21–24. NVD and RETA included fewer centres and cases than EUROSTAR (4545 cases from 59 centres for NVD, 1000 cases from 41 centres for RETA, and 8345 from 177 centres for EUROSTAR; Table 21) and only involved centres from the UK.

Clinical expertise

NVD and RETA did not specify entry requirements for centres to be eligible for inclusion in the registries. It is therefore unclear what level of expertise the surgical teams had with performing EVAR and open repair, which makes it difficult to compare patient outcomes for the different

TABLE 21 Overview of included registries

Study	Registry name	Centre entry criteria	Patient entry criteria	Number of patients treated	Dates of procedure	Type of device
Ashley 2005 ¹⁶ Open repair	NVD	Not reported	Suitable for open repair	Open infrarenal aortic aneurysm surgery: 4545 cases from 59 centres	Registered 1999–31 March 2004	Not applicable
EUROSTAR collaborators 2006 ⁵⁴ EVAR	EUROSTAR	Sufficient expertise in centre (involvement in a series of at least 10 stent graft procedures for AAA). Throughput of at least 10 patients per year and patients managed by collaborating vascular surgeons and international radiologists	Minimum age 21 years. Patients with aortic aneurysms < 3 cm with iliac aneurysms, pseudoaneurysms or previous (conventional/endovascular) grafts were excluded. Aortic aneurysms measuring 3–4 cm included if they were associated with iliac aneurysms. Anatomic configuration suitable for stented tube or bifurcated prosthesis: infrarenal neck length ≥ 1.5 cm and width < 2.5 cm; iliac artery angulation < 90 degrees (or correctable angulation); common iliac artery < 1.2 cm in diameter and non-stenotic (> 0.6 cm diameter after balloon dilatation, if necessary). Elective AAA operation, without symptoms of rupture or expansion	8345 cases from 177 European centres	Not reported. Data collected prospectively up to June 2006. Data relating to 'older' devices excluded from the report	Zenith 3290/8304 (39.6%); Talent 2349/8304 (28.3%); Excluder I 155/8304 (13.9%); other: AneurRx 984/8304 (11.8%), Endologix 161/8304 (1.9%), Lifepath 134/8304 (1.6%), Fortron 92/8304 (1.1%), EVT 73/8304 (0.9%), Anaconda 66/8304 (0.8%)
Thomas 2005; ⁵⁶ additional data from undated Vascular Surgical Society report ⁵⁷ and Thomas 2001 ⁵⁸ EVAR	RETA	Not reported. UK members of the Vascular Surgical Society and British Society of Interventional Radiology registered cases on a voluntary basis	Age limitations not reported. Aneurysm size not reported. Suitable for open repair; patients classified as fit or unfit for open repair were included. Suitable for EVAR; no criteria specified for elective repair, but majority of cases were asymptomatic (83.2%) or symptomatic (13.5%) AAA. No criteria specified for emergency repair, but small numbers of cases were repair of acute non-ruptured (1.6%) or stable ruptured (1.4%)	1000 cases from 41 centres	January 1996–March 2000	Zenith 144 (14.4%); Talent 117 (11.7%); Excluder 19 (1.9%); other: Ancure 60 (6%), AneurRx 254 (25.4%), Bard device 11 (1.1%), Baxter device 1 (0.1%), Gianturco-Dacron 123 (12.3%), Hol Gianturco-PTFE 17 (1.7%), Hol B Endostent 1 (0.1%), Ivanchev-Malmo 2 (0.2%), Palmaz/PTFE 64 (6.4%), Stenford 2 (0.2%), Vanguard 174 (17.4%), missing 11 (1.1%)

registries and to ascertain whether there may be an association between surgical experience and outcomes. Because procedures carried out by specialist teams with a high level of experience in EVAR result in lower mortality rates and fewer adverse events that lead to secondary interventions,⁵³ EUROSTAR specifies that centres must have a throughput of at least 10 patients undergoing stent graft procedures for AAA per year if they are to be included in the registry.

Data collection

EUROSTAR data were collected using a case record form, which included an informed consent form for signing by the patient. Only surgeons from participating centres who had sufficient expertise (i.e. involvement in a series of at least 10 stent graft procedures for AAA) submitted data to the registry.

Submission of data to the NVD was on a voluntary basis, with almost half of the members of the Vascular Society contributing to the database at the time of the report. However, to gain a true picture of the outcomes of vascular surgery (e.g. AAA repair) throughout Great Britain and Ireland, inclusion of all surgeons performing such operations is needed, but at the time of the report external validation to ensure accuracy and completeness of data had not been undertaken.¹⁶

Data collection for RETA was also on a voluntary basis and the UK centres submitted cases as they were performed. However, the majority of endovascular repairs in the UK at the time were performed as part of the EVAR trials and cases submitted to RETA at the time of their report were cases performed outside the trial (usually early on in a centre's experience to allow entry into the EVAR trials), and as such the full RETA data set of all cases submitted was less representative of UK practice at the time of the report.

It is unclear whether all participants undergoing EVAR or open repair were included in the registry, but as only certain surgeons were submitting cases, potential sample bias cannot be ruled out.

Dates of procedures

Patients were registered and treated between 1999 and 31 March 2004 for NVD, up to June 2006 for EUROSTAR, and between January 1996 and March 2000 for RETA. Data from the RETA registry are therefore very out of date, which suggests that the results may not be relevant to current practice. This highlights the importance of the data provided by the EUROSTAR registry.

The relevance of the data is also reflected in the use of 'older' types of devices by the RETA registry. The latest report from the EUROSTAR registry explicitly excluded any data relating to 'older' devices and included only those patients treated with the newer generation of endografts in current use.

Procedure details

The report from the EUROSTAR registry identified nine devices, with the Zenith, Talent and Excluder devices being the main ones in use (39.6%, 28.3% and 13.9%, respectively), all of which are still in current use. By comparison, the RETA data includes 14 devices (four of which were 'home made'), the main ones in use being AneuRx, Zenith and Gianturco-Dacron (home made) (25.4%, 14.4% and 12.3%, respectively). However, as mentioned above and in Chapter 1 (see Description of technology under assessment), many of the devices included in RETA are no longer in current use. 'In-house' (homemade) uni-iliac stents were once the most often used type of graft but have now been superseded by commercially available and CE-marked devices,⁵⁶ such as those included in the EUROSTAR registry.

Bi-iliac grafts were the most prevalent form of graft type used by EUROSTAR and RETA (89.8% and 70.4%, respectively). This reflects the increasing use of bi-iliac grafts for EVAR, which appear to be superseding other types of graft such as the aortic tube, the use of which fell because of the number of distal endoleaks associated with this type of device.⁵⁶ This again highlights the importance of the EUROSTAR data and its greater relevance to current practice as the RETA registry includes the use of aortic tube grafts and a smaller percentage of patients received bi-iliac grafts compared with patients in the EUROSTAR registry.

General anaesthesia was reported to be used most often by all three registries (*Table 22*).

Patient characteristics

Full details of patient characteristics are given in *Tables 23* and *24*.

To be eligible for inclusion in the EUROSTAR registry, patients were required to meet specific entry criteria: age greater than 21 years and presenting for elective AAA operation without symptoms of rupture or expansion. Patients were excluded if their aneurysms measured < 3 cm, and patients with aneurysms measuring 3–4 cm were only included if they were associated with

TABLE 22 Procedure details for included registries

Study	Graft type ^a	Anaesthesia ^a
Ashley 2005 ¹⁶ NVD	Not applicable	Local 1 (0.02%); regional: epidural 34 (0.7%); general 2461 (54.1%); general + epidural 1503 (33.1%); total 3964 (87.2%); unspecified 546 (12%)
EUROSTAR collaborators 2006 ⁵⁴	Bi-iliac 7497/8345 (89.8%); other: straight 156/8345 (1.9%), tapered 561/8345 (6.7%), unknown 131/8345 (1.6%)	Local 515/8345 (6.2%); regional 2091/8345 (25.1%); general 5739/8345 (68.8%)
Thomas 2005 ⁵⁶ RETA	Uni-iliac 263 (26.4%); bi-iliac 702 (70.4%); other: aortic tube 32 (3.2%), missing data 3	Regional 52/993 (5.2%); general: general alone 908/993 (91.4%), general and regional 32/993 (3.2%)

a Number of patients (%).

iliac aneurysms. The mean aneurysm diameter for patients included in the registry was 5.84 cm, ranging between 3 and 17.2 cm. The majority of patients were male (93.2%) and the mean age was 72.5 years, ranging between 34 and 100 years. Approximately half of the patients had a history of smoking (51.1%), and a high proportion reported a history of heart disease (78.8%) and hypertension (65.5%). Almost half had a history of pulmonary disease (42.3%), a quarter were classed as unfit for open repair and a quarter were considered obese (Table 24).

In the RETA data, details for gender were available for only 51.4% of patients; however, 90% of this population was male. The median age reported was 73 years, ranging between 44 and 93 years. The health status of patients was unclear from the registry data as no details were provided for comorbidities. However, almost half of patients presented with aneurysms > 6 cm and fitness scores indicated that almost a quarter of patients (22.7%) were classified as unfit for open repair. Incomplete reporting of details was one of the shortcomings of this registry as it is difficult to then make comparisons.

In the NVD the majority of patients were male (84.4%), although this figure is almost 10% less than the corresponding figure in the EUROSTAR population. Mean age was 72.5 years, which was comparable to that in the EUROSTAR population. The mean aneurysm diameter was not reported but sizes ranged from < 5 cm to > 9.9 cm and there was a 1-cm difference between the majority of ruptured and the majority of unruptured AAAs. Only one patient characteristic of interest was reported, which indicated that almost half the population (44.2%) had a history of heart disease.

Mortality outcomes

Mortality data from the three registries are summarised in Table 25. From the study characteristics it can be seen that EUROSTAR provides the most up-to-date and complete source of data on EVAR.

EUROSTAR⁵⁴

EUROSTAR presented outcomes for short-term (30-day) and long-term (96 months/8 years) mortality, with 190 (2.3%) deaths occurring within 30 days and 789 (9.5%) during the follow-up period. It is unclear from the report whether patients died from aneurysm-related or other causes. Kaplan–Meier survival analysis reported the cumulative number of deaths as 979 and a mortality rate of 39%. It should be noted, however, that for the 30-day outcome 4543 patients were observed out of 5515 expected; 90 patients were observed out of 326 expected for 84 months' follow-up; and only 20 patients were observed out of 77 for 96 months' follow-up. In total, 111 patients (1.3%) were lost to follow-up, but this will have been included as censored data and accounted for by the Kaplan–Meier survival analysis.

RETA⁵⁶

RETA reported outcomes for short-term (30-day) mortality,⁵⁸ aneurysm-related mortality at follow-up and all-cause mortality at follow-up (5 years/60 months)⁵⁶ (return rates for follow-up data are reported in Table 25). In total, 58 patients (5.8%) died within 30 days and 9 patients were reported to have died from fatal rupture (aneurysm-related mortality) at follow-up [6 (0.8%) at 1 year and 3 (0.8%) at 2 years]. A cumulative rate of all-cause mortality was not reported, although figures were presented for each year of follow-up: 11.9%

TABLE 23 Patient characteristics for included registries

Study	Age of population ^a	Gender (% male)	Aneurysm diameter ^b	Criteria assessing fitness for surgery/EVAR/open repair
Ashley 2005 ¹⁶ NVD	Mean 72.5 (SE 0.12) years	3756/4449 (84.4%)	Range: majority of unruptured AAAs 5.0–7.9 cm; majority of ruptured AAAs 6.0–8.9 cm <5 cm: 88 patients; 5–5.9 cm: 775; 6–6.9 cm: 1113; 7–7.9 cm: 588; 8–8.9 cm: 404; 9–9.9 cm: 136; > 9.9 cm: 109; unspecified: 1251	Not reported
EUROSTAR collaborators 2006 ⁵⁴	Mean 72.5 (SD 7.8) years; range 34–100 years	93.2%	Mean transverse diameter 5.84 (SD 1.16) cm; range 3.0–17.2 cm	Not reported
Thomas 2005 ⁵⁶ RETA	Median 73 years; range 44–93 years	90% (based on 514 cases) ⁵⁷	Median 6 cm; 42% classified as large aneurysms (> 6 cm); range 2.5–15 cm	Fitness for EVAR based on aneurysm morphology but no specific details reported Fitness for open repair: fit: patients in ASA grades I–III; unfit: patients in ASA grades IV or V specified as unfit for open repair because of comorbidity, also those classified as ‘fit’ by ASA grade but with other features making them high risk (unsuitable) for open repair

ASA, American Society of Anesthesiologists.

a Mean age (SD) unless otherwise stated.

b Mean diameter (cm) unless otherwise stated.

TABLE 24 Patient characteristics for included registries (continued)

Study	Smoking history	Diabetes	Heart disease	Hypertension	Renal dysfunction	Respiratory disease	Fitness scores	BMI
Ashley 2005 ¹⁶ NVD	Not reported	Not reported	2011 patients (44.2%) ^a	Not reported	Not reported	Not reported	Not reported	Not reported
EUROSTAR collaborators 2006 ⁵⁴	Current smokers 1885/8107 (23.3%) (SVS/ISCVS risk score 2–3) Past smokers 2252/8107 (27.8%) (SVS/ISCVS risk score 1) (none current, but smoked in last 10 years) Never smoked 3970/8107 (49%) (SVS/ISCVS risk score 0) (no tobacco use or none for last 10 years)	1045/8126 (12.9%)	Cardiac: 4957/8141 (60.9%) (SVS/ISCVS risk score 1–3); carotid: 1436/8038 (17.9%) (SVS/ISCVS risk score 1–3)	5337/8142 (65.5%) (SVS/ISCVS risk score 1–3)	1155/8066 (14.3%) ^b 252/8066 (3.1%) ^c 131/8066 (1.6%) ^d	Pulmonary: 3419/8079 (42.3%) (SVS/ISCVS risk score 1–3)	ASA I 635/8288 (7.7%); ASA II 3467/8288 (41.8%); ASA III 3643/8288 (44%); ASA IV 543/8288 (7%) ^e 2037/8345 (24.4%) ^f	2186/8248 (26.5%) considered obese
Thomas 2005 ⁵⁶ RETA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported: 226/997 (22.7%) classified as unfit for open repair; 699/997 classified as fit for open repair (ASA I–II).	Not reported

ASA, American Society of Anesthesiologists; SVS/ISCVS, Society for Vascular Surgery/International Society for Cardiovascular Surgery.

a Cardiac history [myocardial infarction (MI) ≤ 6 months ago; MI > 6 months ago; heart failure ≤ 1 month ago; heart failure > 1 month ago; orthopnoea; angina – controlled/on exertion; angina – uncontrolled/at rest].

b Creatinine 1.5–3.0 mg/dl, creatinine clearance 30–50 ml/min (SVS/ISCVS risk score 1).

c Creatinine 3.0–6.0 mg/dl, creatinine clearance 15–30 ml/min (SVS/ISCVS risk score 2).

d Creatinine > 6.0 mg/dl, creatinine clearance < 15 ml/min or on dialysis or with transplant.

e ASA IV indicating that a patient is too frail to justify open repair.

f Unfit for open repair when factors other than ASA (e.g. obesity, previous laparotomies) were considered.

TABLE 25 Follow-up and mortality outcomes in included registries

Study	Follow-up	30-day mortality	Aneurysm-related mortality at follow-up	All-cause mortality at follow-up
Ashley 2005 ¹⁶ NVD	Not reported	Crude mortality: unruptured 6.8% (95% CI 5.9 to 7.8%); ruptured 41% (95% CI 37.7 to 44.3%); total 14.8% (95% CI 13.7 to 16.0%)	Not reported	Not reported
EUROSTAR collaborators 2006 ⁵⁴	Minimum follow-up 30 days; maximum follow-up 96 months (8 years)	190/8345 (2.3%)	Not reported	789/8345 (9.5%). Cumulative rate from Kaplan–Meier curve: number of deaths (cumulative) 979, proportion deaths 0.390, proportion surviving 0.610, survival SE 0.036
Thomas 2005 ⁵⁶ RETA	Minimum follow-up 30 days; maximum follow-up 5 years. Return rates for requested follow-up data: 87% at 1 year, 77% at 2 years, 65% at 3 years, 52% at 4 years, 51% at 5 years. Median follow-up 3.1 years	58/992 (5.8%)	Fatal rupture at 1 year 6 (0.8%); fatal rupture at 2 years 3 (0.8%)	At 1 year: 86/721 (11.9%), missing 7, at risk 728; ^a 1–2 years: 37/369 (10%), missing 1, at risk 372; 2–3 years: 13/162 (8%), at risk 161; 3–4 years: 5/63 (7.9%), at risk 65 Published paper reports 11% mortality in year 1 and rates of 10%, 7%, 10% and 8% at 2, 3, 4 and 5 years post procedure respectively ⁵⁶

^a At end of follow-up period.⁵⁷

TABLE 26 Complications in included registries

Study	Rupture	Endoleak	Device migration	Reinterventions	Major adverse events (30-day period)
Ashley 2005 ¹⁶ NVD	Not reported	Not applicable	Not applicable	Not reported	Not reported
EUROSTAR collaborators 2006 ⁵⁴	30 days: 4; follow-up: 37; total: 41 Cumulative rate from Kaplan–Meier curve at 84 months: proportion of ruptures: 0.031; proportion rupture free: 0.969 (SE 0.011)	Not applicable Cumulative rate from Kaplan–Meier curve, 30 days: 496; follow-up: 827; total: 1323 Proportion endoleaks: 0.325; proportion endoleak free: 0.675 (SE 0.021)	30 days: 6; follow-up: 148; total: 154	Conversion to open repair: 30-day conversion: 75 patients (0.9%); follow-up conversion: 102 patients (1.2%); total: 177 patients (2.1%) Cumulative rate from Kaplan–Meier curve: total number of reinterventions at 84 months: 749; proportion of secondary interventions: 0.18; proportion of secondary intervention free: 0.82; secondary intervention free SE: 0.013; total number of reinterventions at 96 months: 1606; proportion of death and secondary interventions: 0.48; proportion of secondary intervention free survival: 0.52 (SE 0.022)	Cardiac events: 272; stroke: cerebral: 57 Systemic complications from operation to discharge: pulmonary: 174; renal: 181; total systemic complications: 928
Thomas 2005 ⁵⁶ RETA	Rupture during deployment: 3 (0.3%) ⁵⁷ Cumulative rate from Kaplan–Meier curve: 2% at 5-year follow- up ⁵⁶	At 30 days: ⁵⁶ type I: proximal 54, distal 19; type II: 44; type III: 15 Cumulative rate from Kaplan–Meier curve. Freedom from endoleak: 88% at 1 year, 80% at 2 years, 76% at 3 years, 71% at 4 years, 68% at 5 years ⁵⁶	9 (0.9%) with device migration requiring conversion to open repair (immediate outcome) New cases at 1-year follow-up 3/631; new cases at 2-year follow-up 9/331; new cases at 3-year follow-up 0/148; new cases at 4-year follow-up 2/56 ⁵⁷	Conversion to open repair: immediate outcome: 33/996 (3.3%). Correction of endoleak: some included under 'conversion to open repair'; totals not clearly reported Cumulative rate from Kaplan–Meier curve. Freedom from reintervention: 87% at 1 year, 77% at 2 years, 70% at 3 years, 65% at 4 years, 62% at 5 years ⁵⁶	Cardiac events: 42 (4.2%) (myocardial infarction/arrhythmia/left ventricular failure ⁵⁷); stroke: 15 (1.5%) (cerebrovascular accident/confusion/ paraplegia ⁵⁷) Cumulative rate from Kaplan–Meier curve: 30-day rates: ⁵⁶ any complication 272/976 (27.8%), technical complication 55/976 (5.6%), wound complications 78/976 (8%), renal failure 40/976 (4.1%), colonic ischaemia 6/976 (0.6%), other medical complication 147/976 (15.1%)

mortality in year 1 and 10%, 8% and 7.9% at 2, 3, and 4 years post procedure respectively.

NVD¹⁶

Mortality rates following open repair were reported for the 30-day period only, with an overall crude mortality rate of 14.8% (95% CI 13.7 to 16.0%). Crude mortality rates for ruptured and unruptured AAAs were 41% (95% CI 37.7 to 44.3%) and 6.8% (95% CI 5.9 to 7.8%) respectively (Table 25).

Complications (Table 26)

EUROSTAR⁵⁴

Some form of major adverse event was experienced by 11.1% of patients, with cardiac, pulmonary and renal events being the most significant. By the end of 96 months' follow-up only a very small proportion of patients (0.5%) experienced rupture and device migration (1.8%), whereas 15.9% of patients experienced endoleak. In total, 9% of patients required some form of reintervention at 84 months, increasing to 19.2% at 96 months.

RETA⁵⁶

RETA reported a very small percentage of ruptures during stent deployment (0.35%)⁵⁷ and a cumulative rate of 2% at 5 years' follow-up.⁵⁶ A total of 132 cases of endoleak (13.2%) were reported at 30 days,⁵⁶ with a cumulative rate of 68% free from endoleak at 5 years' follow-up.⁵⁶ A small number of device migrations were reported: 9 (0.9%) at 30 days (requiring conversion to open repair) and 14 over the 4-year follow-up.⁵⁷

Conversion to open repair within 30 days occurred in 3.3% of cases. Kaplan–Meier totals for cumulative rates of reintervention were not clearly reported; however, the rate at 5 years' follow-up was reported as 62%.⁵⁶ This 5-year figure reflects a much higher reintervention rate than that reported by EUROSTAR at 8 years' follow-up (19.2%). Only small numbers of cardiac events and stroke were reported at 30 days (4.2% and 1.5%, respectively⁵⁷), but overall 27.8% were reported as having experienced some form of complication (including technical complications and renal failure⁵⁶).

NVD¹⁶

No data were reported in the NVD registry for occurrence of endoleak and device migration as these complications cannot occur with open repair. No data were presented for rupture rates, reintervention rates or major adverse events, which limits analysis of the data and prevents comparison with the EVAR registries.

Resource use

Duration of surgery for open repair (NVD) ranged from < 30 minutes to > 359 minutes (approximately 6 hours); for EUROSTAR patients the duration of surgery was between 25 and 720 minutes (12 hours) and for RETA patients the duration of surgery was from 30 to 540 minutes (9 hours). The majority of surgical procedures lasted between 120 and 149 minutes (21.8%) for NVD patients. By comparison, the mean duration for EUROSTAR patients was 130 minutes and the median duration for RETA patients was 150 minutes (Table 27).

The mean length of stay for NVD cases was 13 days for unruptured AAAs and 15.2 days for ruptured AAAs. By comparison, EUROSTAR reported a mean of 5.9 days⁵⁴ (less than half that of NVD cases), and RETA reported a median of 6 days.⁵⁷ The number of days in hospital ranged from 3 to > 30 for RETA, compared with 0–183 for EUROSTAR (Table 27).

HRQoL measures and costs and length of stay for reinterventions were not reported by the registries.

Assessment of risk factors for adverse outcomes following EVAR **Studies evaluating/validating existing risk assessment algorithms**

The Leiden score was investigated in one study³⁰ but this study had fewer than 500 patients so could not be included in the review. The Hardman score was also investigated in one risk model study²⁹ but again fewer than 500 patients were included. Three studies^{23,59,86} investigated existing risk assessment algorithms and included more than 500 patients. Biancari *et al.*⁵⁹ investigated the Glasgow Aneurysm Score (GAS). The GAS was calculated from data entered prospectively according to the formula:

$$\text{Risk score} = (\text{age in years}) + (7 \text{ points for myocardial disease}) + (10 \text{ points for cerebrovascular disease}) + (14 \text{ points for renal disease})$$

The EVAR trial participants²³ used a modified Customized Probability Index (CPI) score. The range of possible scores was –25 (best) to +57 (worst) and points were allotted for ischaemic heart disease (+13), uncontrolled congestive heart failure (+14), receiving treatment for hypertension (+7), respiratory dysfunction (+7), renal dysfunction (+16), beta-blocker use (–15) and statin use (–10).

TABLE 27 Resource use in included registries

Study	Length of hospital and ICU stay ^a	Duration of surgery
Ashley 2005 ¹⁶ NVD	Unruptured: 13 (SE 0.21); ruptured: 15.2 (SE 0.55)	< 30 minutes: 9/2326 (0.4%); 30–59 minutes: 28 (1.2%); 60–89 minutes: 145 (6.2%); 90–119 minutes: 356 (15.3%); 120–149 minutes: 506 (21.8%); 150–179 minutes: 456 (19.6%); 180–209 minutes: 363 (15.6%); 210–239 minutes: 154 (6.6%); 240–269 minutes: 136 (5.8%); 270–299 minutes: 65 (2.8%); 300–329 minutes: 41 (1.8%); 330–359 minutes: 22 (1%); > 359 minutes: 45 (1.9%); unspecified: 2219
EUROSTAR collaborators 2006 ⁵⁴	5.9 (SD 8.1) 8169 patients (98 patients with hospital stay < 1 day) Range 0–183 days	8065 patients; mean duration 130 (SD 58) minutes; range 25–720 minutes
Thomas 2005 ⁵⁶ RETA	Median 6 (range 3 to > 30) ⁵⁷	Median 150 minutes (range 30–540 minutes) ⁵⁷
a Mean number of days unless otherwise stated.		

The GAS and unmodified CPI score are similar and have been shown to be good predictors of immediate postoperative death following elective open repair of AAA.

Timaran *et al.*⁸⁶ investigated the Charlson Comorbidity Index (CCI). The CCI is a validated measure for use with administrative data that correlates with in-hospital mortality after surgical procedures, including AAA repair. The authors first validated the CCI as an independent predictor of in-hospital mortality following EVAR; the CCI was then used to define four surgical risk groups, with a CCI score of 0 corresponding to the lowest risk and 3 to the highest risk.

All three studies assessed the relationship between risk score and 30-day operative mortality; the GAS⁵⁹ and the CPI²³ were also investigated for their ability to predict longer-term all-cause mortality. Only the CPI was tested for aneurysm-related mortality at follow-up.

Sample sizes of the three studies ranged from 1200 to over 65,500 and the data sources used were the EUROSTAR registry, the EVAR trial 1 RCT and a large US administrative database (Table 28). The EVAR trial participants²³ did not report details of the patients studied; the sample included some patients randomised too late for inclusion in the main EVAR 1 trial reports^{42,43} but patient characteristics were presumably similar to those reported there. Timaran *et al.*⁸⁶ did not report a mean age for their population, although an age

distribution was reported. Aneurysm diameter was not reported in this study, which makes it difficult to assess whether the population included patients with AAAs smaller than those generally treated in UK practice.

Study results

Details of the risk scores used in the three studies and the results are summarised in Tables 28 and 29. One study also assessed other risk factors and results for these factors are discussed later in this chapter (see Studies investigating specific risk factors).

30-day operative mortality

GAS was found to be an independent predictor of postoperative death. The 30-day mortality rates were 1.1% for patients with a GAS < 74.4, 2.1% for GAS 74.4–83.6 and 5.3% for those with a score > 83.6. The best cut-off value was a GAS of 86.6; 30-day mortality was 1.6% in patients with a score below this value and 6.4% in those with a higher score.⁵⁹ CCI score was also found to be an independent predictor of in-hospital mortality.⁸⁶ Mortality increased as CCI score increased (OR per point increase 1.12, 95% CI 1.06 to 1.20) and similar results were found in a stratified analysis that included only elective EVAR cases (Table 29).

Fitness level (good, moderate or poor) as determined from the modified CPI score did not significantly affect the OR for EVAR relative to open repair for 30-day operative mortality.²³

TABLE 28 Characteristics of risk modelling studies evaluating/validating existing risk algorithms

Study	Data source	Number of patients	Age of population	Gender	Aneurysm diameter
Biancari 2006 ⁵⁹	Registry – dates enrolled and/or treated: October 1996–March 2005 Registry – other characteristics: EUROSTAR	5498 patients: 59.5% co-existing myocardial disease; 5.7% cerebrovascular disease; 18.2% renal disease 1833 GAS < 74.4; 1832 GAS 74.4–83.6; 1833 GAS > 83.6	Median 72.7 years (IQR 67.3–77.7 years)	Percentage male (total population) 94.1%	Median aortic diameter 5.6 cm (IQR 5.1–6.3 cm). Measurement tool used CT scan and intra-arterial digital subtraction angiography
Brown (EVAR trial participants) 2007 ²³	Trial – dates: patients randomised September 1999–August 2004 Trial – name of trial: EVAR trial 1 and EVAR trial 2 Trial – RCT	EVAR trial 1: 1252 (626 randomised to EVAR and 626 to open repair); EVAR trial 2: 404	Not reported	Not reported	Not reported
Timaran 2007 ⁸⁶	Registry – dates enrolled and/or treated: 2001–4 Registry – other characteristics: the data were from the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project. This is the largest all-payer inpatient database in the USA. It represents a 20% stratified sample of inpatient admissions to US academic, community and acute care hospitals nationwide (approximately 1000 hospitals in 35 states)	65,502 patients	Not reported 4.6% aged 50–59 years; 24.8% aged 60–69; 45.9% aged 70–79; 24.7% aged 80 or over	Percentage male (total population) 82.9%	Not reported

IQR, interquartile range.

TABLE 29 Results of risk modelling studies evaluating/validating existing algorithms

Study	Risk factor(s) used in model and definitions	30-day mortality	Aneurysm-related mortality at follow-up	All-cause mortality at follow-up
Glasgow Aneurysm Score (GAS) Biancari 2006 ⁵⁹	GAS: Risk score = (age in years) + (7 points for myocardial disease) + (10 points for cerebrovascular disease) + (14 points for renal disease). Myocardial disease refers to previously documented myocardial infarction and/or ongoing angina pectoris. Cerebrovascular disease refers to all grades of stroke and includes transient ischaemic attack. Renal disease refers to a history of acute or chronic renal failure and/or a creatinine level above 133 µmol/l and/or creatinine clearance below 50 ml/min (Society for Vascular Surgery/International Society of Cardiovascular Surgery risk score of 1 or more)	Multivariate analysis showed that GAS independently predicted postoperative death ($p < 0.001$). ROC curve showed GAS with area under curve of 0.70 (95% CI 0.66 to 0.74, $p < 0.001$) for predicting postoperative death. Best cut-off value 86.6 (sensitivity 56.1%, specificity 76.2%, accuracy 75.6%, positive predictive value 6.4%, negative predictive value 98.4%)	No risk factors investigated	Multivariate analysis showed that overall survival differed significantly among GAS tertiles (i.e. < 74.4, 74.4–83.6, > 83.6) ($p < 0.001$); 5-year overall survival rate for patients with GAS > 83.6 = 65.2%
Customized Probability Index (CPI) Brown (EVAR trial participants) 2007 ²³	Patients were classified as having good, moderate or poor fitness based on a modified CPI score (based on cardiovascular disease, respiratory dysfunction, renal dysfunction and medication status). The modification was the exclusion of cerebrovascular disease and the weighting of severe aortic stenosis and arrhythmia as risk factors similar to ischaemic heart disease	No significant effect of CPI fitness group on benefit of EVAR over open repair in EVAR trial 1 Good fitness adjusted OR 0.23 (95% CI 0.06 to 0.84, $p = 0.027$); moderate fitness adjusted OR 0.70 (95% CI 0.19 to 2.56, $p = 0.586$); poor fitness adjusted OR 0.29 (95% CI 0.07 to 1.17, $p = 0.082$) p -value for test of interaction for adjusted model = 0.363	Mortality rates were 0.9/100 person-years for good fitness, 1.2/100 person-years for moderate fitness and 1.6/100 person-years for poor fitness There was no significant effect of fitness group on benefit of EVAR over open repair in EVAR trial 1 (no interaction between fitness score and randomised group) Crude HRs: good fitness 0.49 (95% CI 0.21 to 1.15, $p = 0.100$); moderate fitness 0.91 (95% CI 0.31 to 2.70, $p = 0.862$); poor fitness 0.60 (95% CI 0.25 to 1.44, $p = 0.254$) Adjusted HRs: good fitness 0.49 (95% CI 0.21 to 1.16, $p = 0.106$); moderate fitness 1.00 (95% CI 0.33 to 3.00, $p = 0.999$); poor fitness 0.50 (95% CI 0.21 to 1.23, $p = 0.131$) p -value for test of interaction for adjusted model = 0.371	Mortality rates were 5.3/100 person-years for good fitness, 7.7/100 person-years for moderate fitness and 9.9/100 person-years for poor fitness There was no significant effect of fitness group on benefit of EVAR over open repair in EVAR trial 1 (no interaction between fitness score and randomised group) Crude HRs: good fitness 0.76 (95% CI 0.52 to 1.11, $p = 0.151$); moderate fitness 1.11 (95% CI 0.71 to 1.75, $p = 0.643$); poor fitness 1.02 (95% CI 0.68 to 1.51, $p = 0.941$) Adjusted HRs: good fitness 0.76 (95% CI 0.52 to 1.11, $p = 0.151$); moderate fitness 1.13 (95% CI 0.72 to 1.79, $p = 0.595$); poor fitness 0.97 (95% CI 0.65 to 1.45, $p = 0.873$) p -value for test of interaction for adjusted model = 0.281

continued

TABLE 29 Results of risk modelling studies evaluating/validating existing algorithms (continued)

Study	Risk factor(s) used in model and definitions	30-day mortality	Aneurysm-related mortality at follow-up	All-cause mortality at follow-up
<p>Charlson Comorbidity Index (CCI) Timaran 2007⁸⁶</p>	<p>The score is a validated measure for use with administrative data that correlates with in-hospital morbidity and mortality after surgical procedures (including elective AAA repairs). Each of the indicated diagnoses is assigned a weight and summed to provide a patient's total score [from 0 (low risk) to > 3 (high risk)]</p>	<p>From multivariate regression model OR 1.12 (95% CI 1.06 to 1.20, $p < 0.001$) A higher CCI score was associated with early death: CCI 0: 1.8%; CCI 1: 2.0% CCI 2: 2.2%; CCI \geq 3: 3.7%; $p < 0.001$ Stratified analysis that included only elective EVAR found the per point CCI score to be an independent predictor of in-hospital mortality (OR 1.38, 95% CI 1.29 to 1.47)</p>	<p>No risk factors investigated</p>	<p>No risk factors investigated</p>
<p>ROC, receiver operating characteristic.</p>				

Aneurysm-related and all-cause mortality

In the study assessing GAS, median follow-up was 18 months and overall survival differed significantly between the lowest, middle and high GAS groups. The overall 5-year survival rate was 76.7%; patients with a GAS above 83.6 had an overall survival rate of 65.2%.⁵⁹ The EVAR trial found that, although aneurysm-related and all-cause mortality rates increased with decreasing fitness, the benefit of EVAR relative to open repair did not differ between fitness groups for either outcome.²³ This suggests that the modified CPI score used in this study would not be helpful in identifying patients likely to benefit specifically from EVAR or open repair.

Summary statement

There is evidence from single studies that the GAS and CCI score can independently predict short-term (in-hospital or 30-day) mortality following EVAR. These measures have previously been validated for prediction of mortality risk following open AAA repair. The GAS may also be able to predict the longer-term mortality risk following EVAR (based on one study). Based on one study there is no evidence that fitness rating based on a modified CPI score predicts benefit from EVAR compared with open repair.

Studies investigating the development of a risk algorithm

One study, described in three papers,^{21,60,92} focused on the development of an algorithm to assess baseline risks after EVAR. This Australian national audit investigated the role of ASA score, age, AAA diameter and morphology, gender, comorbidities, suitability for open repair, sac size change (preoperative and postoperative), modified 'White's grading system' (aortic neck length < 1.5 cm and angulation > 45°, thrombus present, aortic sac angulation > 60°, severe iliac artery tortuosity, severe iliac artery calcification), device name and type, patient type (private or public) and smoking status in a group of 961 patients. Patients who underwent elective or semi-urgent (non-ruptured aneurysms) EVAR between 1 November 1999 and 16 May 2001 were enrolled. No risk factors for 30-day mortality were investigated.

Boult *et al.*⁹² included the modified White's grading system to determine whether this variable had a predictive effect on the number of reinterventions and endoleaks reported after EVAR. At mid-term follow-up (i.e. 3 years) no significant effects were reported. Similarly, no significant effect was reported for infrarenal neck diameter as a predictive variable for aneurysm-related death.

Four factors were identified as having a significant impact on survival rates: ASA score, maximum aneurysm diameter, age and serum creatinine ($p < 0.001$ for each factor). These variables were combined to estimate predicted 3-year and 5-year survival probabilities (ASA II, III or IV; maximum diameter 5, 5.8 or 7.4 cm; age 70, 77 or 83 years; and serum creatinine 85 or 125 $\mu\text{mol/l}$) (Table 30).

Table 30 indicates that the greatest predicted survival rate would be expected in younger patients (70 years) with lower ASA scores and creatinine levels (85 $\mu\text{mol/l}$) and smaller aneurysm size (5 cm). Boult *et al.*⁶⁰ predicted a 91% survival rate for this group of patients at 3 years' follow-up and a 85% survival rate at 5 years. By contrast, patients expected to have lower survival rates were identified as being older (83 years) with a higher ASA score (i.e. IV), higher creatinine levels (125 $\mu\text{mol/l}$) and a larger aneurysm size (7.4 cm). Survival rates for this group of patients were 44% at 3 years' follow-up and 25% at 5 years, indicating a difference of 47% for 3-year survival and 60% at 5 years between the two groups, that is, 15% expected mortality at 5 years for the low-risk group and 75% for the high-risk group. However, as the authors state, the data presented for patients in the high-risk group were unreliable because of the small sample sizes and should be interpreted with caution.

This study was extended²¹ to develop and internally validate an interactive model to evaluate expected outcomes for a particular patient undergoing EVAR. Key predictor variables were identified and their relationship with 17 success measures was ascertained. Predictor variables were preoperative aneurysm size, age at operation, ASA rating, gender, creatinine, aortic neck angle, infrarenal neck diameter and infrarenal neck length. Success measures included technical and initial clinical success, 3- and 5-year survival, aneurysm-related death and early death (30 days), absence from reinterventions (initial and mid-term), graft complications (initial and mid-term), migration, conversion to open repair, rupture and endoleak. Stepwise forward regression using Akaike's information criterion was used to select which of the preoperative variables should be included in each of the success measure models. Initially regressions only included patients who had all preoperative variables. However, after significant variables were chosen, the regression model was performed again using as many data as possible. The authors assessed the goodness of fit of each of the 17 outcome models. For each of the final

TABLE 30 Survival at 3 and 5 years after EVAR predicted by ASA score, age and aneurysm size

		Additional details							
				Age (years)					
				70		77		83	
				Creatinine ($\mu\text{mol/l}$)					
ASA	Max. diameter (cm)	85	125	85	125	85	125	85	125
Predicted survival at 3 years	ASA II	5	91%	88%	87%	84%	83%	79%	
		5.8	89%	87%	86%	82%	81%	77%	
		7.4	87%	83%	82%	77%	77%	71%	
	ASA III	5	86%	82%	81%	76%	75%	69%	
		5.8	84%	80%	78%	73%	72%	66%	
		7.4	80%	75%	73%	67%	66%	59%	
	ASA IV	5	79%	74%	72%	65%	64%	56%	
		5.8	76%	71%	69%	62%	60%	52%	
		7.4	71%	64%	62%	54%	53%	44%	
Predicted survival at 5 years	ASA II	5	85%	81%	79%	74%	74%	68%	
		5.8	83%	79%	77%	72%	71%	54%	
		7.4	79%	74%	72%	65%	64%	57%	
	ASA III	5	77%	72%	70%	63%	62%	54%	
		5.8	75%	69%	67%	60%	58%	50%	
		7.4	69%	62%	60%	52%	50%	41%	
	ASA IV	5	67%	60%	57%	49%	48%	39%	
		5.8	64%	56%	53%	45%	43%	34%	
		7.4	56%	48%	45%	36%	34%	25%	

Shading indicates estimates with low certainty. Sample sizes < 10 in these regions.
Reprinted from Boulton *et al.*,⁶⁰ with permission from the European Society for Endovascular Surgery.

logistic regression models bootstrapping was used to assess the internal model validity.

All outcome models had a reasonable fit with the exception of the outcome model for conversion to open repair. In terms of validation, survival, aneurysm-related deaths, migrations and conversions to open repair performed best in predictive discrimination. Models for survival, migrations and conversions to open repair performed best in terms of bias-corrected R-squared index. The models with the smallest calibration error were 3- and 5-year survival, early deaths and mid-term type 1 endoleaks. The interactive model is available from www.surgeons.org/asernip-s/audit.htm. Users can enter up to eight preoperative variables and review the predicted success rate and confidence intervals. The model can be used at an initial consultation

where, for example, information is known about age, ASA score, aneurysm diameter, gender and serum creatinine. Following CT scanning, measurements could be added on aortic neck angle, infrarenal neck length and infrarenal neck diameter.

Studies investigating specific risk factors

In total, 32 studies investigated specific risk factors after EVAR.⁶⁰⁻⁹¹ One study⁶⁰ has already been discussed above as its main aim was to develop a risk algorithm. However, specific risk factors were also discussed and are reported here. Of the three studies discussed in the section on validation of existing algorithms,^{23,59,86} one⁸⁶ also presents further data on specific risk factors and is mentioned in this section. The remaining 30 studies focused exclusively on the evaluation of one or more risk factors after EVAR. *Table 31* details

the characteristics of patients in all of the studies included in this section.

Sample size ranged from 676 to 65,502. Six studies^{60,61,73,85,90,91} had fewer than 1000 participants, 25^{62–72,74–84,87–89} had between 1000 and 6500 participants and one US study had over 65,000 participants.⁸⁶ The mean or median age of between 70 and 75 years of age reflected the fact that AAA is predominantly a disease of old age. Equally, the higher prevalence of AAAs in men was reflected in the studies with percentages of men ranging from 81.4% to 99.3% when reported. When reported, mean aneurysm size tended to be between 5.5 cm and 5.9 cm. However, not all studies reported the range of aneurysm size and it is likely that some studies contained participants receiving EVAR who would not normally be considered given their aneurysm size under UK current practice.

Across the studies the following risk variables were investigated: age, gender, smoking status, ASA status, pre-existing conditions, renal function, fitness for open procedure, aneurysm size, aortic neck and aneurysm angle, aortic neck length and graft configuration and device type. Each risk variable will be discussed in its own section and each of the five outcomes of 30-day mortality, aneurysm-related mortality, all-cause mortality, reintervention and endoleak will be discussed by variable. All studies contributing relevant data to each section will be discussed as appropriate.

Some studies presented ORs or HRs whereas others reported a variable as significant or not

significant. Details of any numerical data provided can be found for each individual study in Appendix 4. Included in each section on a given risk variable is a graphical representation of the evidence. The height of the bars represents sample size and the data source is indicated by the shading of the bars. From this it can be determined which variables from which studies and for which outcomes have been found in multivariable regression to be significant or non-significant. It should, however, be noted that studies may be missing on the non-significant sides of the charts. This is due to the fact that they were not reported or were not included in multivariable analysis as they had been found in univariate analyses not to be significant. We are reliant on the reporting of each individual study.

Within the constraints outlined above, an attempt has been made at the end of the risk model section to summarise and interpret the evidence for risk factors and adverse outcomes after EVAR.

Age

In total, 24 studies^{60,61,63–67,69,71–74,77–79,81,82,84,86–91} investigated the role of age in relation to adverse outcomes after EVAR (*Figures 8–12*). Age was either treated as a continuous variable or dichotomised, for example into under 80 years and octogenarians.⁷¹

The evidence showed age to be a risk factor for 30-day mortality (*Figure 8*). For the outcome of aneurysm-related mortality evidence was mixed (*Figure 9*). For all-cause mortality all nine studies in this group correctly identified increasing age

TABLE 31 Patient characteristics of risk modelling studies

Study	Number of patients	Age of population ^a	Gender (% male)	Aneurysm diameter ^b
Boult 2007, ⁶⁰ Boult 2006 ⁹²	961	75.0 (SD 6.9) years	86%	Men 5.8 (SD 1.05) cm; women 5.5 (SD 0.9) cm
Brewster 2006 ⁶¹	873	75.7 (SD 7.6) years; range 49–99 years	81.4%	5.68 (SD 1.06) cm
Bush 2007 ⁶²	2368	72.2 years	99.3%	Not reported
Buth 2000 ⁶³	1892	70 years; range 37–90 years	91%	Median 5.6 cm; range 2.8–15 cm
Buth 2000 ⁶⁴	1554	70 years; range 37–90 years	91.4%	Median 5.6 cm; range 2.8–15 cm
Buth 2002 ⁶⁵	3075	71.7 years	92.7%	5.66 cm
Buth 2003 ⁶⁶	3595	Not reported	Not reported	Not reported
Cuyper 2000 ⁶⁷	1871	69.7 years	91.8%	5.6 cm
Diehm 2007 ⁶⁸	6383	72.4 (SD 7.6) years	93.8%	5.87 cm (calculated)

continued

TABLE 31 Patient characteristics of risk modelling studies (continued)

Study	Number of patients	Age of population ^a	Gender (% male)	Aneurysm diameter ^b
Diehm 2007 ⁹¹	711	No anaemia 74.6 (SD 7.5) years; anaemia 78.5 (SD 7.5) years	90.9%	No anaemia 5.7 (SD 0.97) cm; anaemia 6.08 (SD 1.22) cm
Hobo 2006 ⁶⁹	2846	72.0 (SD 7.5) years	94%	5.8 cm
Hobo 2007 ⁷⁰	5183	72.6 years; range 43–100 years	93.8%	5.9 cm
Lange 2005 ⁷¹	4433	Patients < 80 years: 70.3 (SD 6.5) years; octogenarians 83.4 (SD 2.9) years Range: patients < 80 years: 43–79 years; octogenarians: 80–100 years	Patients < 80 years: 94.8%; octogenarians: 90.2% ($p < 0.0001$)	Patients < 80 years: 5.76 (SD 1.04) cm; octogenarians 6.2 (1.22) cm ($p < 0.0001$)
Leurs 2007 ⁷²	1033	DREAM: 70.6 (SD 6.51) years; EUROSTAR: 71.6 (SD 7.67) years	92.7%	DREAM: 6.06 (SD 0.89) cm; EUROSTAR: 6.04 (SD 1.02) cm
Leurs 2004 ⁷³	676	72.1 years (calculated); range 43–96 years	93%	5.67 cm
Leurs 2006 ⁷⁴	3499	73.2 years	94.0%	6.1 cm
Leurs 2005 ⁷⁵	6017	71.8 years; range 28–100 years	93.5%	Max AAA diameter > 6 cm: 28.5%
Leurs 2005 ⁷⁶	4233	Not reported; range 37–101 years	93.7%	5.8 cm; range 4.0–11.0 cm
Leurs 2006 ⁷⁷	5892	72.3 years	94.1%	5.86 cm
Lifeline ^c 2002 ⁷⁸	1646	73.1 (SD 7.9) years	88.6%	5.57 cm (SD not reported)
Lifeline ^c 2005 ⁷⁹	2664	73.1 (SD 7.8) years; range 45–96 years	88.6%	5.58 (SD 1.02) cm; range 2.1–12.0 cm
Lottman 2004 ⁸⁰	3270	Not reported	93%	44% aneurysm diameter < 5.5 cm; 56% aneurysm diameter 5.5 cm
Mohan 2001 ⁸¹	2146	Median 70 years; range 37–92 years	92%	2.1–15.0 (median 5.6) cm
Peppelenbosch 2004 ⁸²	4392	Not reported; range 43–109 years	93.2%	57.2 cm (SD not reported); range 4.0–14.5 cm
Riambau 2001 ⁸³	2862	Not reported	92.2%	5.62 cm
Ruppert 2006 ⁸⁴	5557	72 years; range 41–100 years	Not reported	5.85 cm; range 4–14.5 cm
Sampram 2003 ⁸⁵	703	75 (SD 8.1) years; range 48–100 years	86%	5.4 (SD 1.0) cm in minor dimension and 5.8 (SD 1.1) cm in major dimension
Timaran 2007 ⁸⁶	65,502	Not reported	82.9%	Not reported
Torella 2004 ⁸⁷	3992	70–72 years	93%	Current devices 5.7 (SD 10.8) cm; withdrawn devices 5.6 (SD 10.5) cm
van Eps 2007 ⁸⁸	5167	72 years; range 43–100	94.3%	Patients with normal renal function 5.81 (SD 1.08) cm; patients with renal dysfunction 5.96 (SD 1.17) cm ($p < 0.001$); Range 4–17.2 cm
van Marrewijk 2004 ⁸⁹	3595	71.2 (calculated); range 37–100 years	94%	5.7 cm (SD not reported)
Zarins 2006 ⁹⁰	923	71.3–74.6 years across groups	88–90% across groups	5.7 (SD 1.5) cm

a Mean age unless stated otherwise.

b Mean cm unless stated otherwise.

c Lifeline Registry of Endovascular Aneurysm Repair.

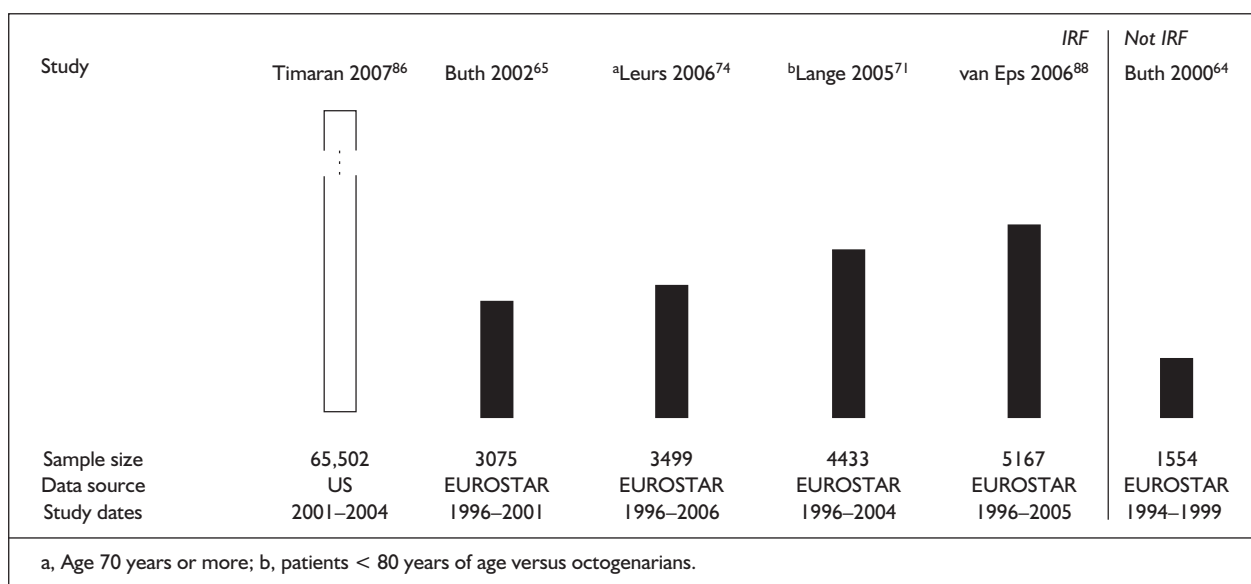


FIGURE 8 Age and 30-day mortality. Studies to the left of the vertical line found age to be an independent risk factor (IRF), whereas those to the right did not.

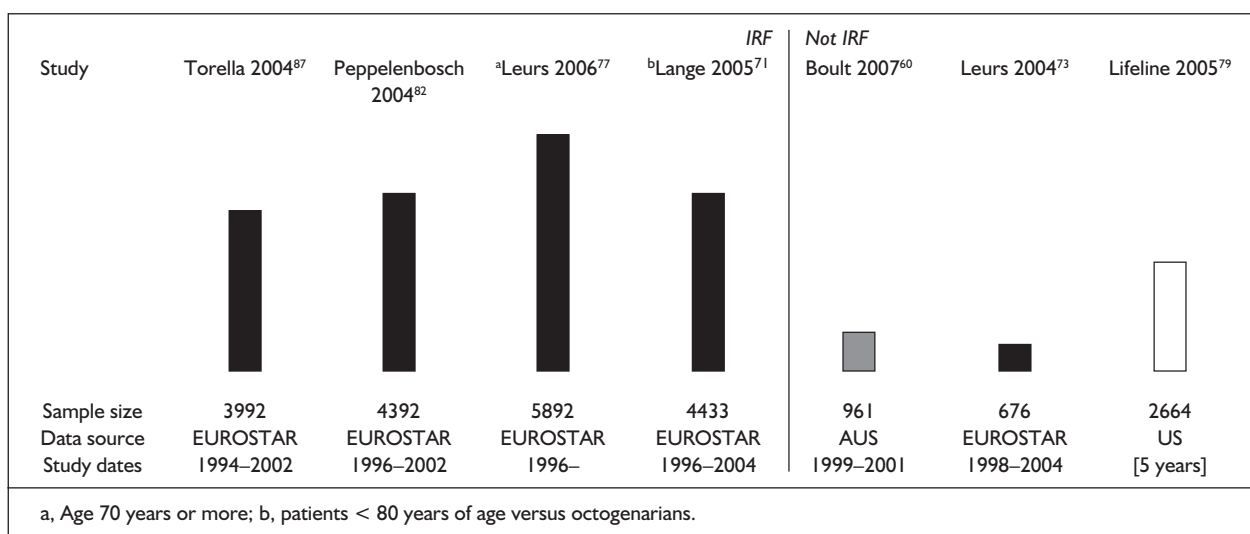


FIGURE 9 Age and aneurysm-related mortality. Studies to the left of the vertical line found age to be an independent risk factor (IRF), whereas those to the right did not.

as an independent risk factor (Figure 10). Results for reintervention were almost all analyses of EUROSTAR data and most, but not all, studies concluded that age was not a risk factor (Figure 11). On balance the mainly EUROSTAR-based evidence indicates that age is an independent risk factor for type II endoleak or all types of endoleak (Figure 12).

Varying interpretations of old age and the way that data were handled may affect findings and may

explain some of the inconsistency in the results in this section.

Gender

A total of 11 studies^{60,61,63,64,69,79,81,82,86,87,89} investigated the role of gender in relation to adverse outcomes after EVAR (Figures 13–17).

The results of the very large recent US-based study and the smaller, older EUROSTAR study provide contradictory results regarding the association

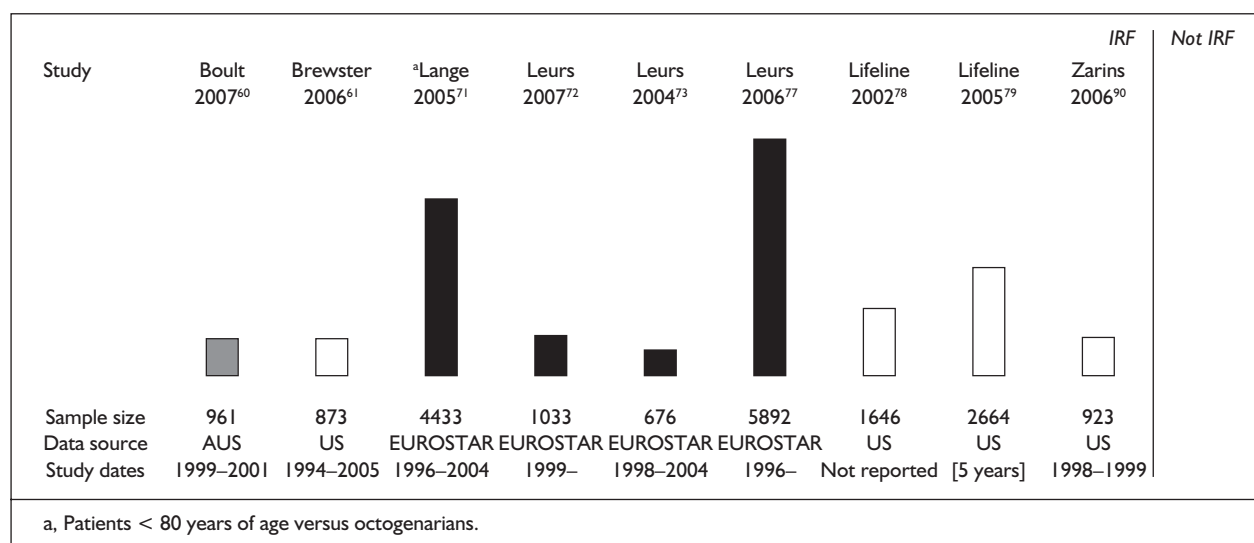


FIGURE 10 Age and all-cause mortality. Studies to the left of the vertical line found age to be an independent risk factor (IRF), whereas those to the right did not.

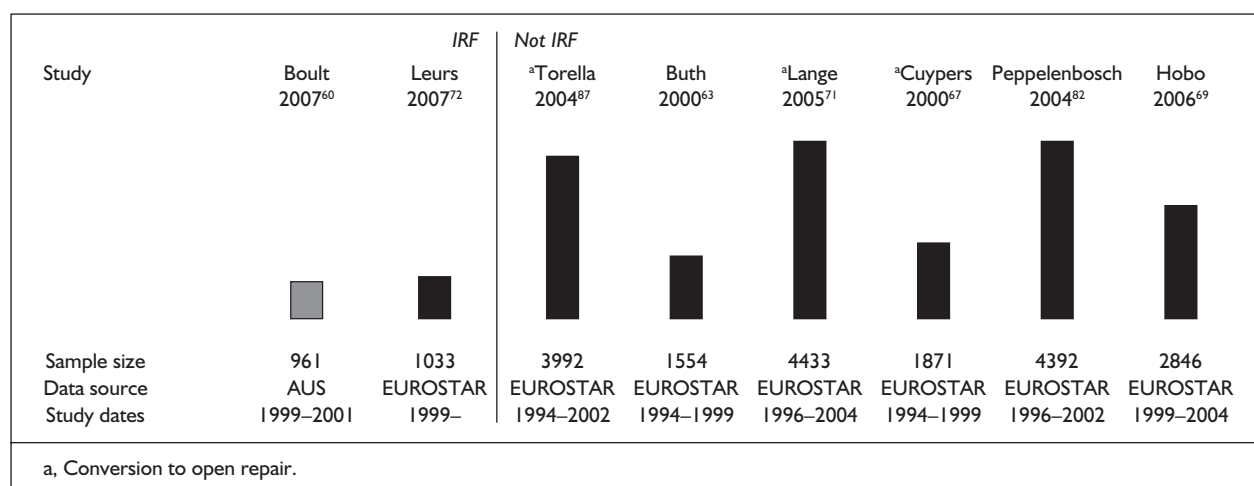


FIGURE 11 Age and reintervention. Studies to the left of the vertical line found age to be an independent risk factor (IRF), whereas those to the right did not.

between female gender and 30-day mortality (Figure 13). However, given the small number of female patients in most series the very large study is likely to be more reliable. Therefore, there may be a link between female gender and 30-day mortality. There is no indication of any link between female gender and aneurysm-related or all-cause mortality (Figures 14 and 15). The evidence suggests that gender is not an independent risk factor for reintervention (Figure 16). There is contradictory evidence regarding association with endoleak (Figure 17).

Pre-existing conditions

In total, 19 studies^{60,64,65,68,69,72–76,78,79,81–83,88–91} investigated the role of pre-existing conditions in relation to adverse outcomes after EVAR. The studies assessed the role of a range of pre-existing conditions such as pulmonary insufficiency, diabetes, chronic heart failure, obesity, anaemia and hypertension (Figures 18–22).

The available analyses of EUROSTAR data indicate that cardiac status, high blood pressure and obesity are not independent risk factors for 30-

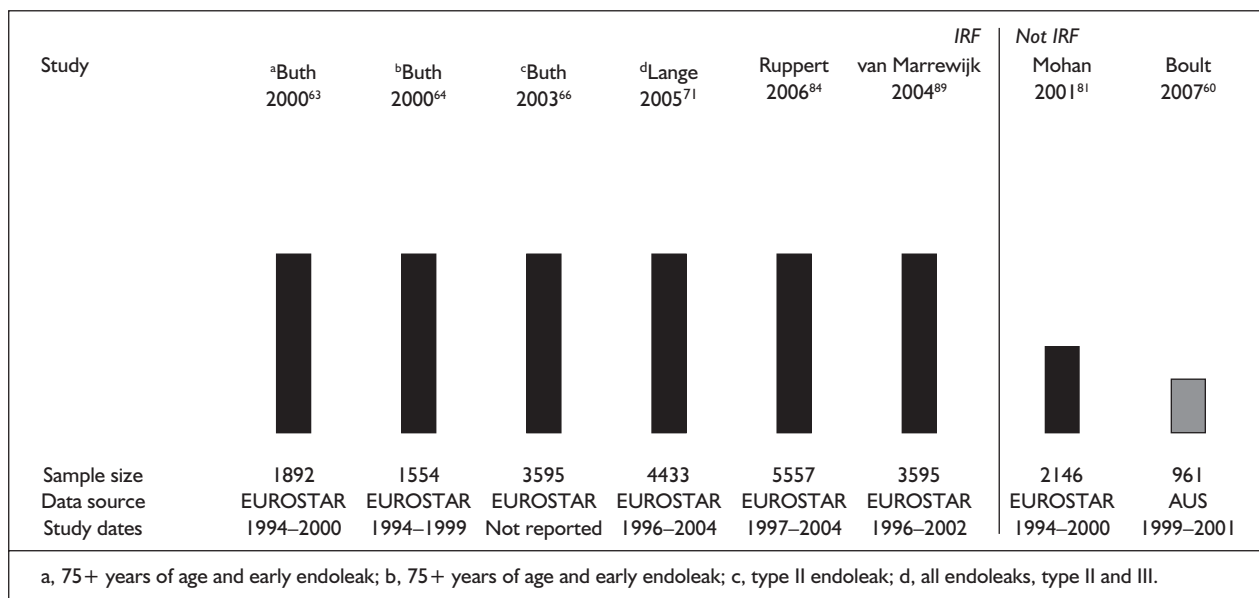


FIGURE 12 Age and endoleak. Studies to the left of the vertical line found age to be an independent risk factor (IRF), whereas those to the right did not.

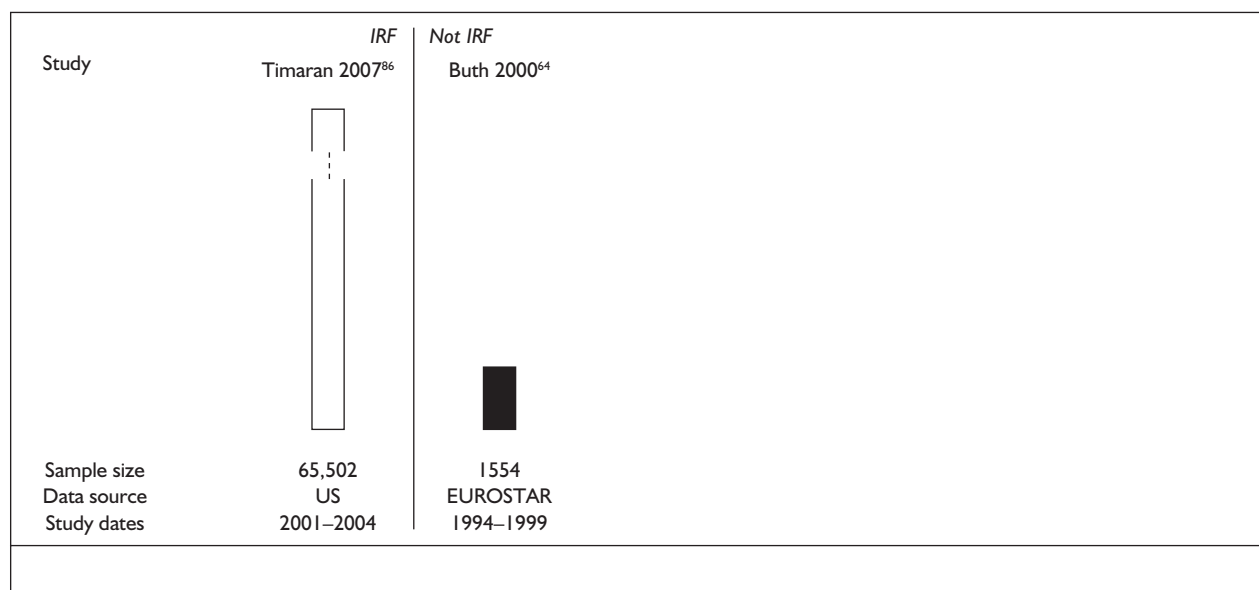


FIGURE 13 Female gender and 30-day mortality. Studies to the left of the vertical line found gender to be an independent risk factor (IRF), whereas those to the right did not.

day mortality. The results regarding diabetes and pulmonary impairment as predictors of 30-day mortality are inconsistent (*Figure 18*).

The analyses for aneurysm-related mortality showed inconsistent results for pulmonary status. However, the evidence suggested that diabetes is not a risk factor for aneurysm-related mortality and based on one US study hypertension was not found

to be a risk factor for aneurysm-related mortality. Evidence on other pre-existing conditions was lacking for this outcome (*Figure 19*).

There were inconsistent results regarding cardiac disease and all-cause mortality after EVAR. The majority of studies found that pulmonary status/chronic obstructive pulmonary disease (COPD) was an independent risk factor for all-cause mortality

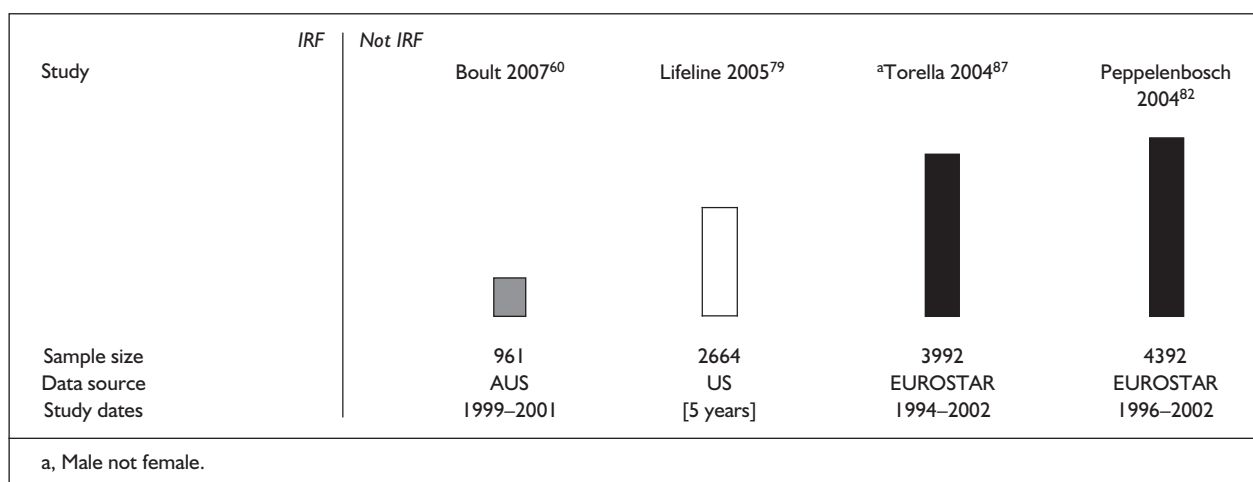


FIGURE 14 Female gender and aneurysm-related mortality. Studies to the left of the vertical line found gender to be an independent risk factor (IRF), whereas those to the right did not.

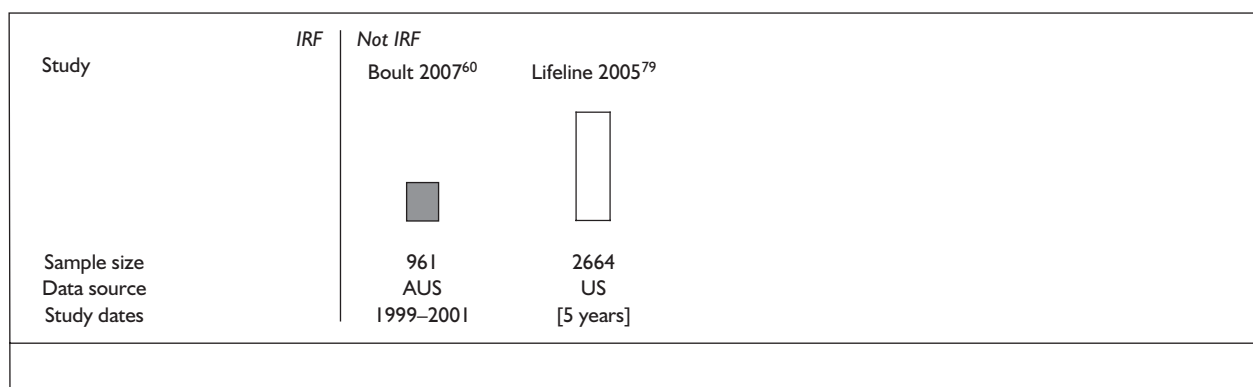


FIGURE 15 Female gender and all-cause mortality. Studies to the left of the vertical line found gender to be an independent risk factor (IRF), whereas those to the right did not.

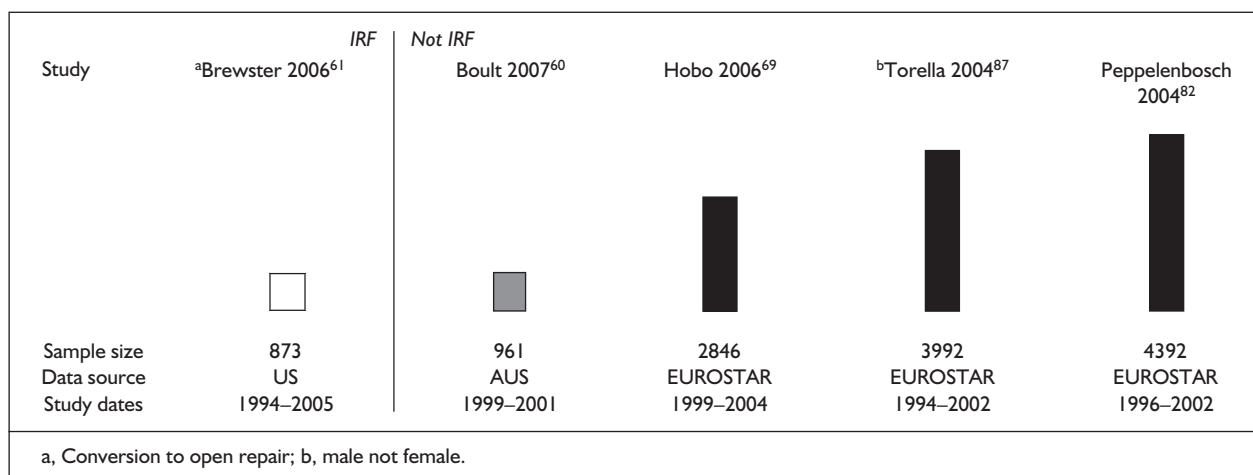


FIGURE 16 Female gender and reintervention. Studies to the left of the vertical line found gender to be an independent risk factor (IRF), whereas those to the right did not.

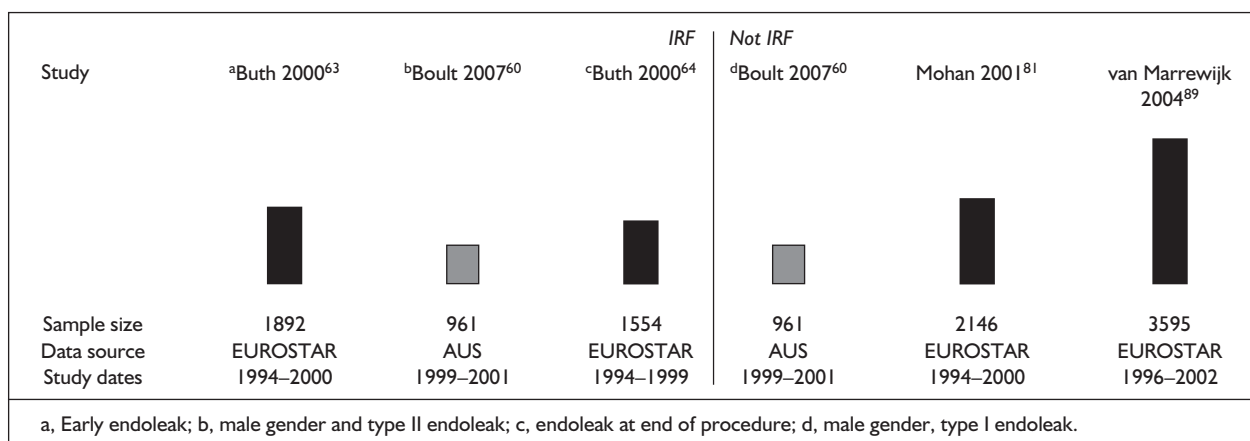


FIGURE 17 Female gender and endoleak. Studies to the left of the vertical line found gender to be an independent risk factor (IRF), whereas those to the right did not.

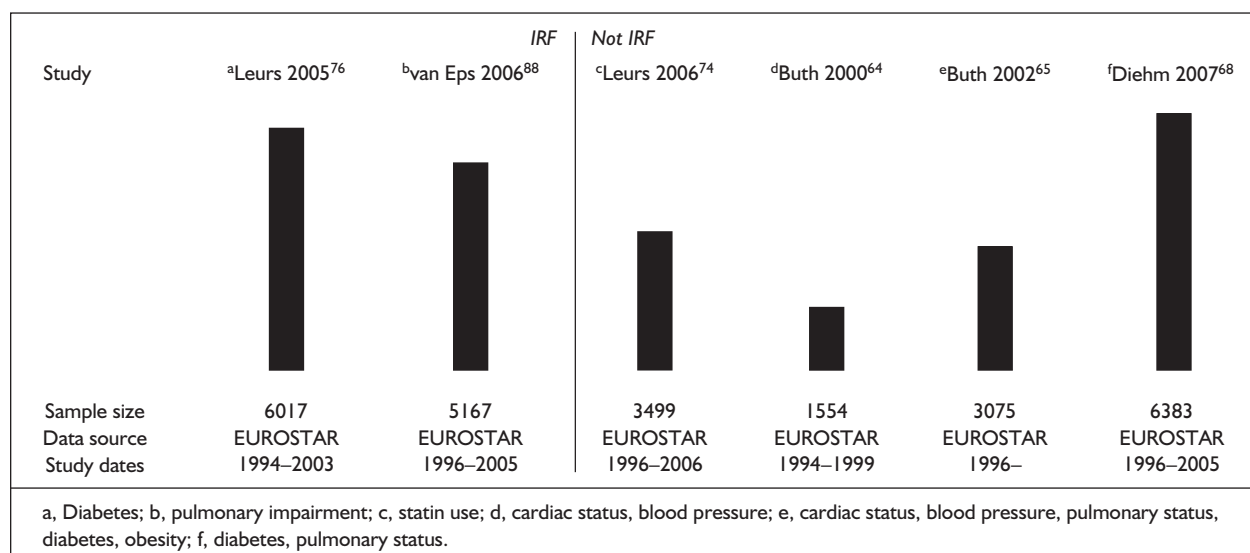


FIGURE 18 Pre-existing conditions and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

after EVAR in both the EUROSTAR and the US populations. The findings for diabetes as a risk factor for all-cause mortality were inconsistent. In one EUROSTAR and one US study hypertension was not found to be a risk factor for all-cause mortality. Evidence was lacking on other risk factors (Figure 20).

The available analyses suggest that diabetes is not a risk factor for reintervention/conversion to open repair. One Australian study concluded that the higher the number of pre-existing conditions the greater the rates of reintervention whereas all EUROSTAR studies found that pre-existing

conditions did not tend to predict reintervention (Figure 21).

The studies consistently found that pre-existing conditions were not risk factors for endoleak (Figure 22).

Renal function

A total of 11 studies^{60,61,65,73,78,79,82,83,88,89,91} investigated renal function/renal impairment as a potential risk factor for adverse outcomes in multivariable modelling (Figures 23–27). Although all outcomes were considered, the outcome of reintervention was only investigated in one study.

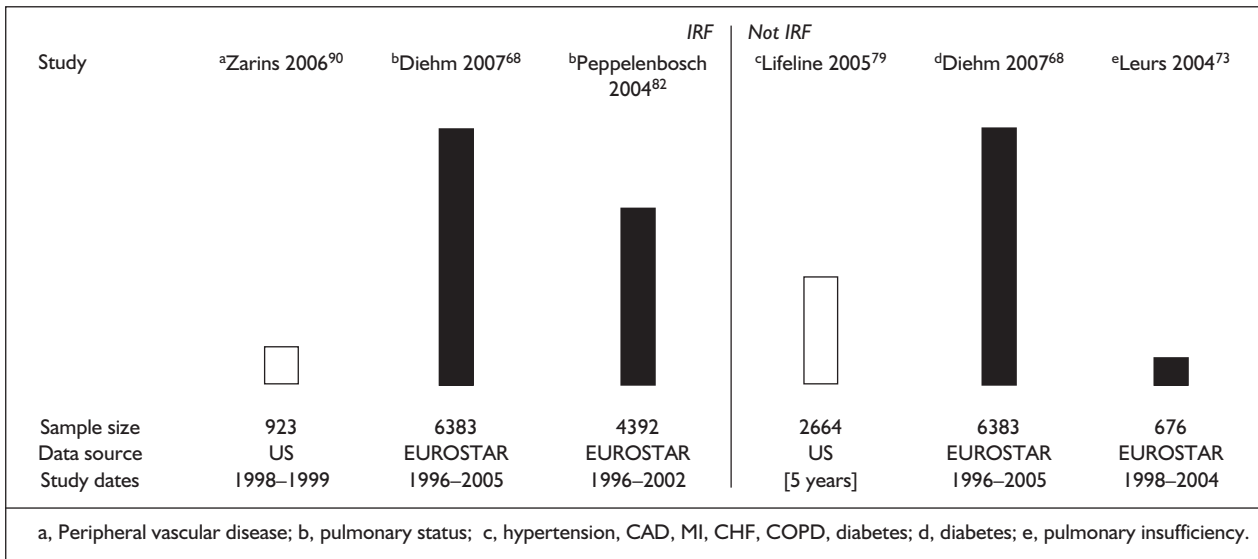


FIGURE 19 Pre-existing conditions and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

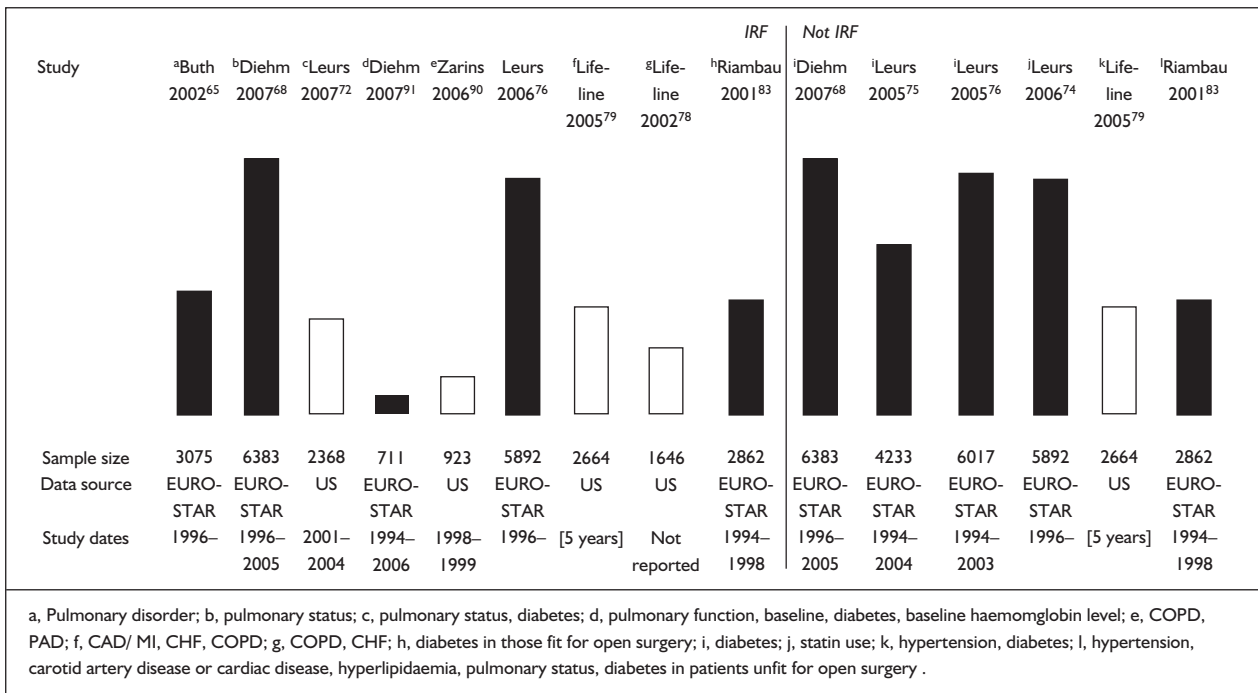


FIGURE 20 Pre-existing conditions and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

There was consistent evidence from a small number of studies that renal impairment affects 30-day mortality after EVAR (Figure 23) but inconsistent evidence of its effects on aneurysm-related mortality (Figure 24). The balance of evidence suggests that renal impairment is an independent risk factor for all-cause mortality (Figure 25).

Analyses of EUROSTAR data indicate no link between renal dysfunction and reintervention (Figure 26) or endoleak (Figure 27) after EVAR.

Fitness for open procedure

Six studies investigated whether patients' fitness for open procedure determined adverse outcomes

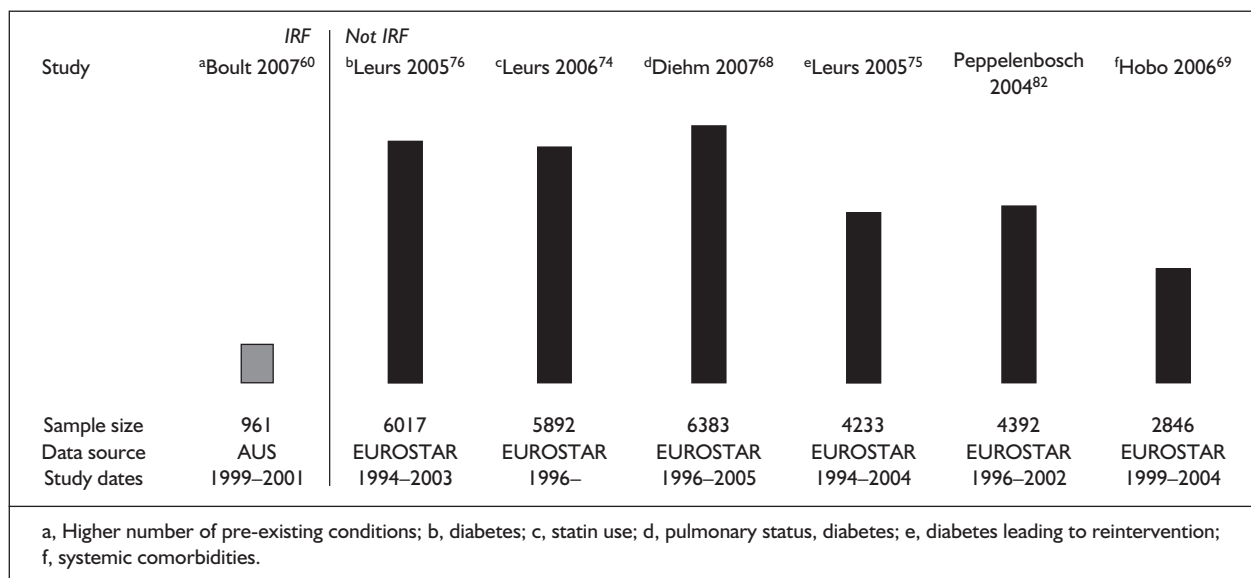


FIGURE 21 Pre-existing conditions and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

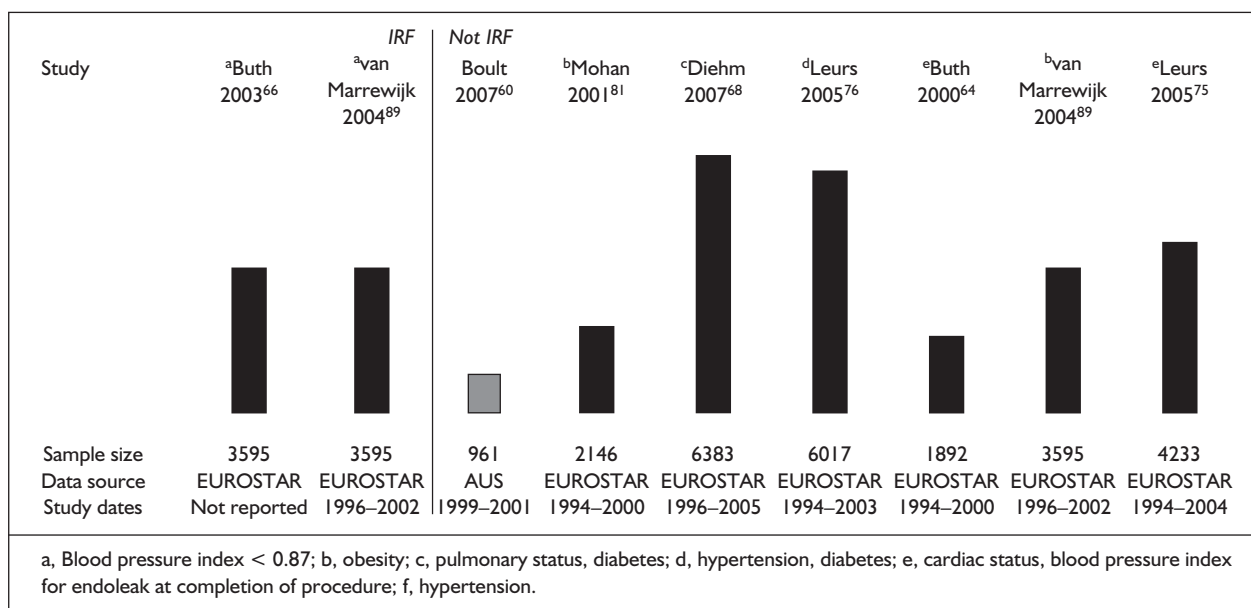


FIGURE 22 Pre-existing conditions and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

after EVAR (Figures 28–32). Five of these were based on EUROSTAR data^{64,65,73,82,87} whereas one was based on a national Australian audit.⁶⁰

There was inconsistent evidence linking fitness and 30-day mortality but the more recent analysis with a larger cohort suggested there might be an association (Figure 28). On balance, analyses indicate that fitness for open procedure is linked to

aneurysm-related mortality (Figure 29). Evidence was lacking to link fitness for open procedure and all-cause mortality (Figure 30), and, on balance, fitness was not an independent risk factor for reintervention (Figure 31) or endoleak (Figure 32).

ASA status

In total, 12 studies^{60,62–65,69,77,81,82,88–90} investigated the role of patients' ASA status in relation to adverse

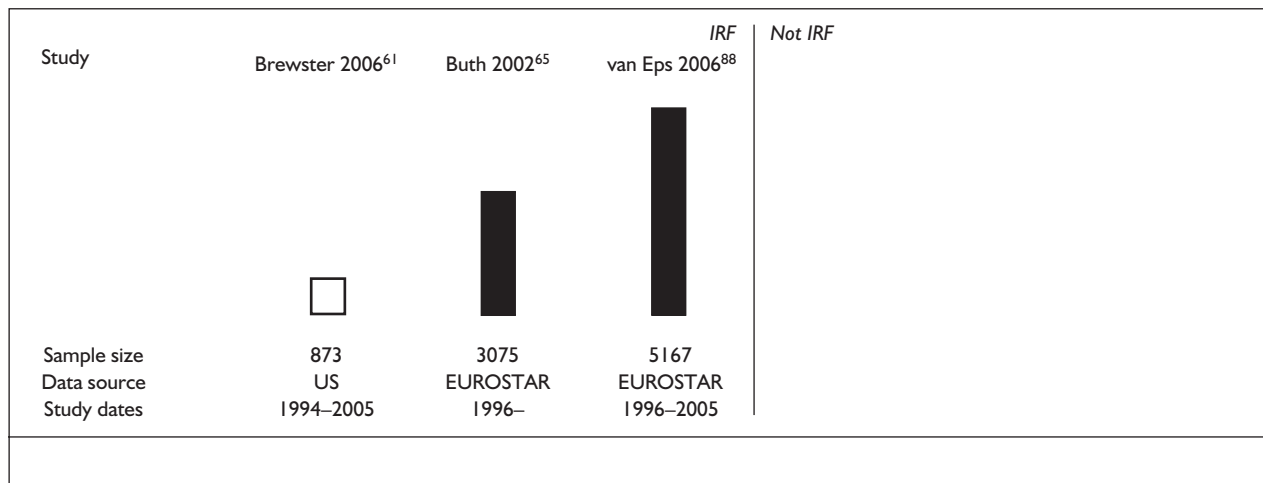


FIGURE 23 Renal function and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

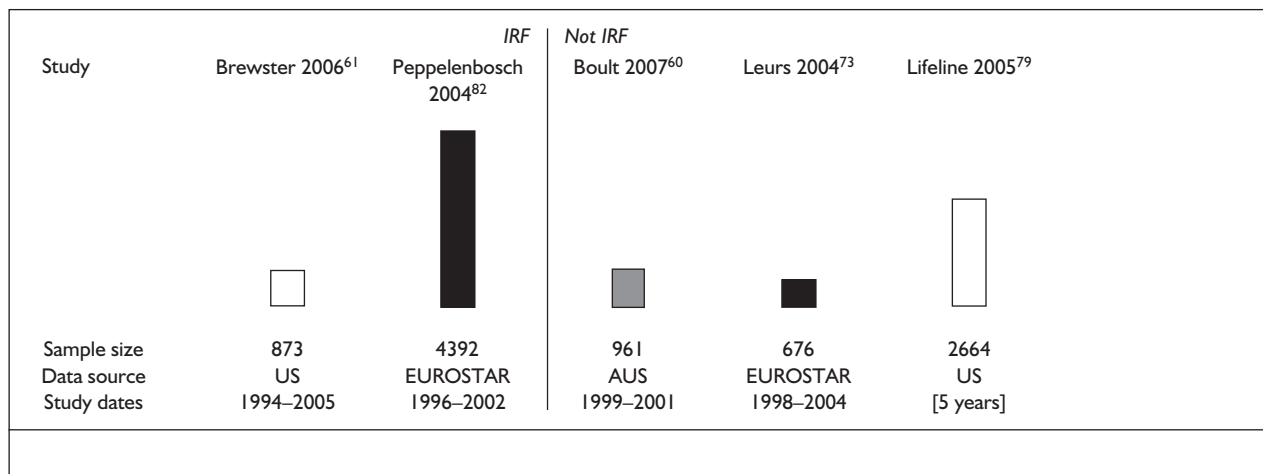


FIGURE 24 Renal function and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

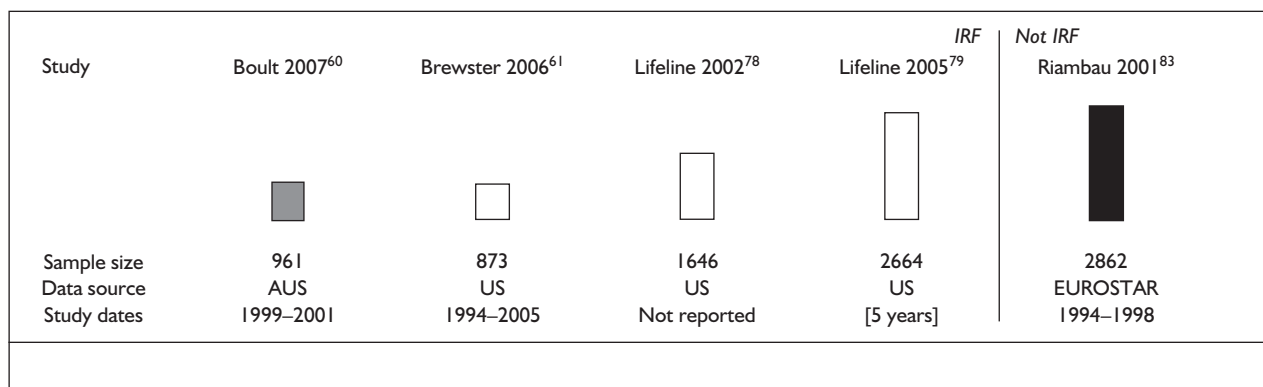


FIGURE 25 Renal function and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

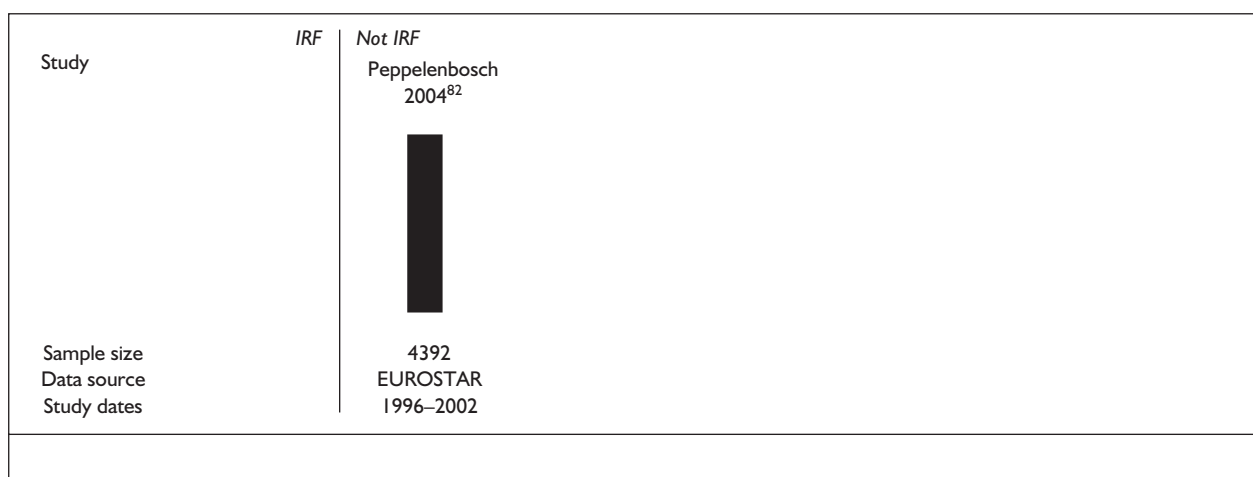


FIGURE 26 Renal function and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

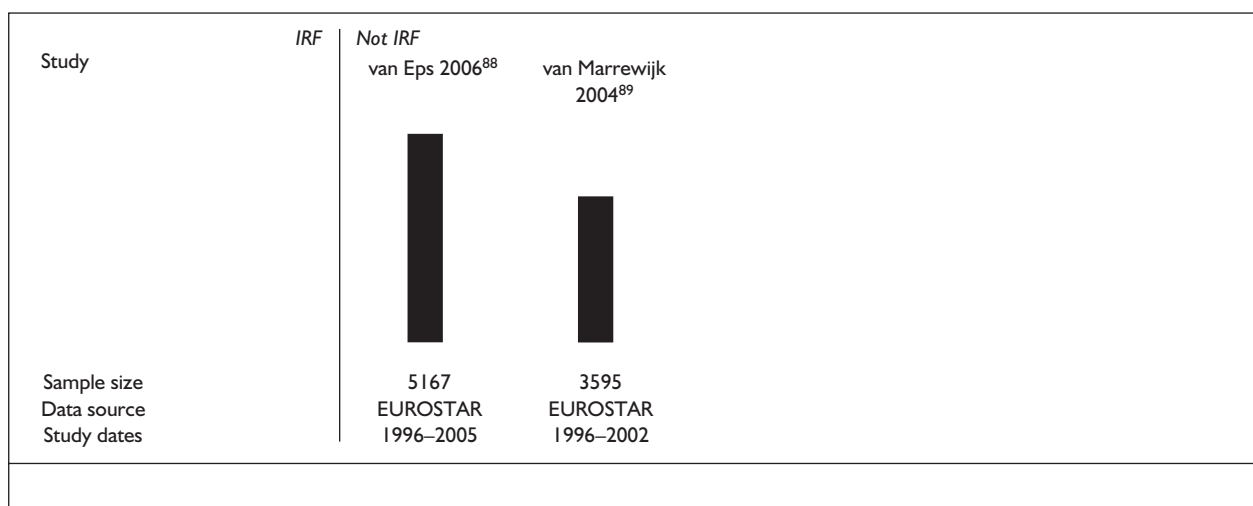


FIGURE 27 Renal function and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

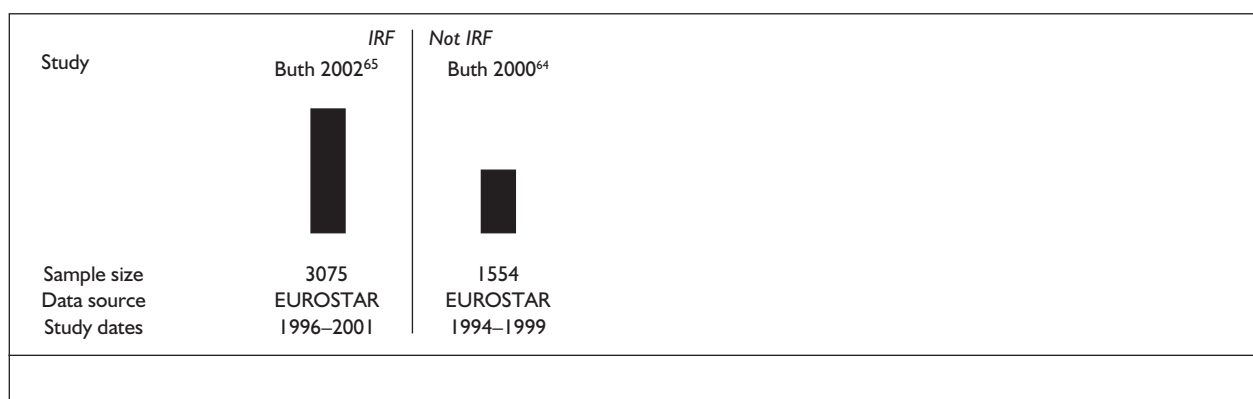


FIGURE 28 Fitness for open procedure and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

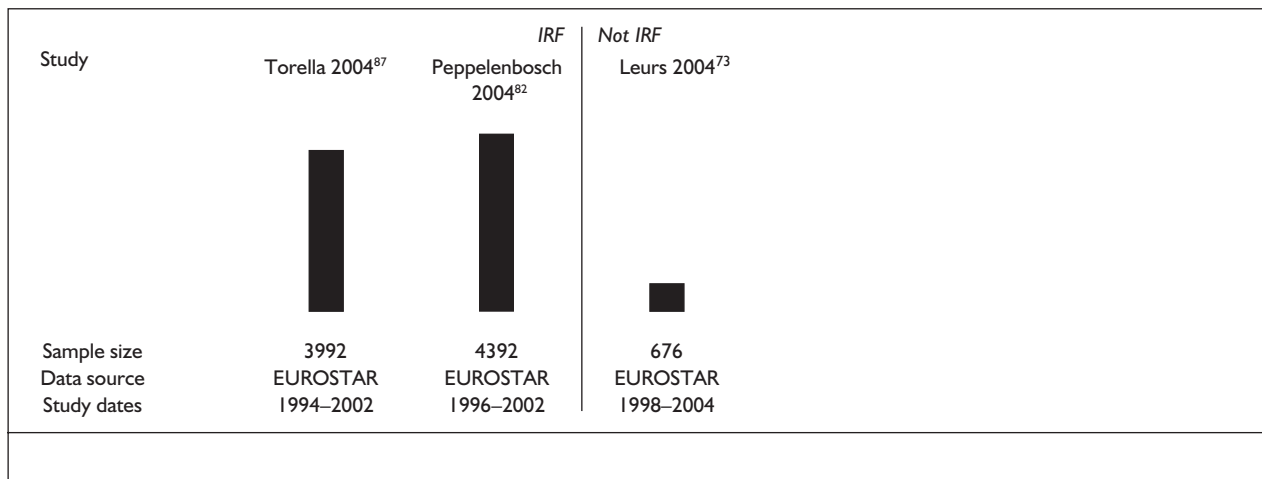


FIGURE 29 Fitness for open procedure and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

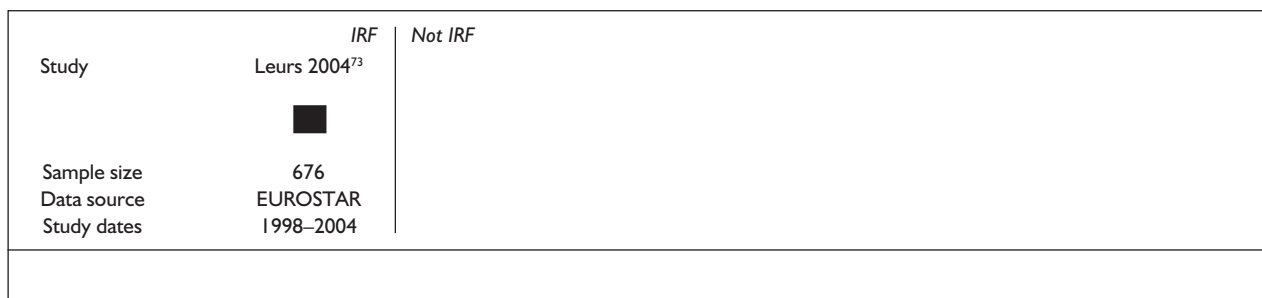


FIGURE 30 Fitness for open procedure and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

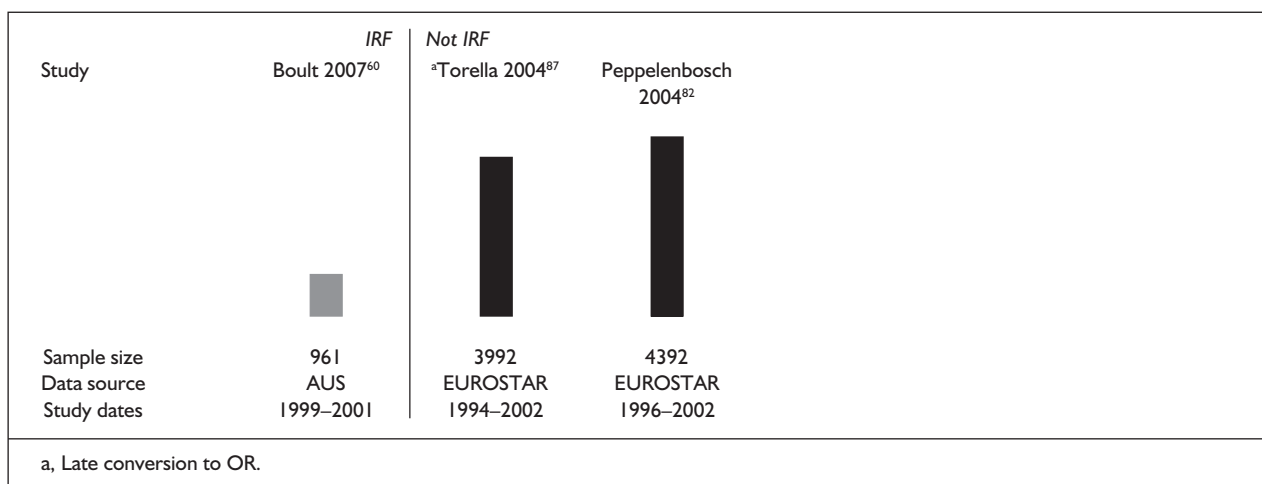


FIGURE 31 Fitness for open procedure and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

Study	IRF	Not IRF		
		Mohan 2001 ⁸¹	Buth 2000 ⁶⁴	Boult 2007 ⁶⁰
Sample size		2146	1554	961
Data source		EUROSTAR	EUROSTAR	AUS
Study dates		1994–2000	1994–1999	1999–2001

FIGURE 32 Fitness for open procedure and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

outcomes after EVAR (Figures 33–37). The majority of the studies were based on EUROSTAR data.

According to EUROSTAR data, ASA classes III and IV are predictive of statistically significantly worse 30-day mortality (Figure 33). Evidence for aneurysm-related mortality was inconsistent (Figure 34). With the exception of a large US study, all analyses found ASA to be an independent risk factor for all-cause mortality (Figure 35). On balance, ASA status was not found to be a significant independent risk factor for reintervention (Figure 36) or endoleak (Figure 37).

Smoking status

Seven studies^{60,64,66,76,80,81,89} investigated smoking status as a risk factor for adverse outcomes after EVAR.

The evidence suggests that smoking status is not associated with adverse outcomes after EVAR (Figures 38–42). However, the evidence investigating smoking and mortality after EVAR is very limited.

Aneurysm size

In total, 19 studies^{60,61,63,64,67,69,72,73,76,78,79,81,82,84,85,87–90} investigated aneurysm size as a potential risk factor for adverse outcomes in multivariable modelling (Figures 43–47).

More recent and larger cohort analysis demonstrates that aneurysm size is an independent risk factor for 30-day mortality (Figure 43). Evidence also suggests that it is an independent risk factor for aneurysm-related mortality (Figure 44) and all-cause mortality (Figure 45). Evidence for aneurysm size as an independent risk factor for reintervention (Figure 46) and endoleaks (Figure 47) is inconsistent.

Aortic neck and aneurysm angle

Eight studies^{60,64,70,74,76,81,82,87} investigated aortic neck and aneurysm angle as potential risk factors for adverse outcomes in multivariable modelling (Figures 48–52). With the exception of one Australian study⁶⁰ all were based on EUROSTAR populations.

The balance of evidence suggests no effect of aortic neck and aneurysm angle on 30-day mortality (Figure 48), aneurysm-related mortality (Figure 49) or all-cause mortality (Figure 50). Evidence with regard to reintervention (Figure 51) and endoleak (Figure 52) was mixed allowing no firm conclusions to be drawn.

Aortic neck length

Nine studies^{60,66,67,74,76,81,82,87,89} investigated aortic neck length as a potential risk factor for adverse outcomes in multivariable modelling (Figures 53–57). With the exception of one Australian study⁶⁰ all were based on EUROSTAR populations.

There was limited evidence available for 30-day mortality (Figure 53). Evidence with regard to aneurysm-related mortality was inconsistent but none of the EUROSTAR analyses found it to be an independent risk factor (Figure 54). Evidence for all-cause mortality was limited but suggestive of no effect (Figure 55). Evidence regarding reintervention rates was mixed (Figure 56) as was the evidence for endoleak (Figure 57) with possible differences with type of endoleak.

Graft configuration and device type

In total, 10 studies^{60,61,64,67,69,81,82,84,87,89} investigated the roles of graft configuration and device type in adverse outcomes after EVAR (Figures 58–62).

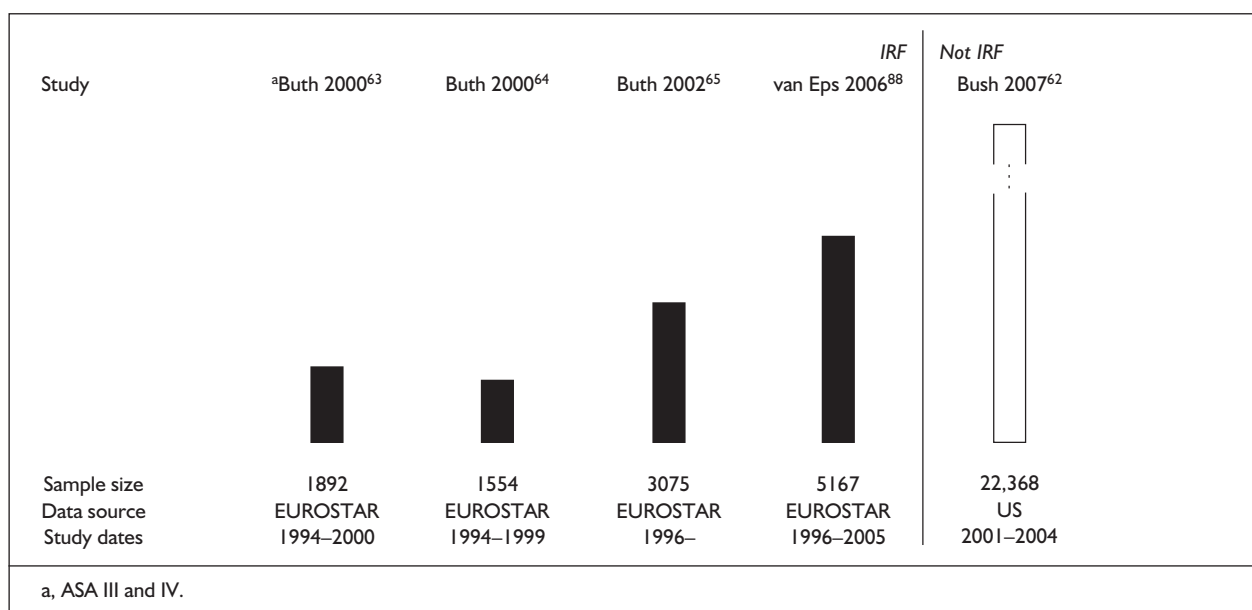


FIGURE 33 ASA class and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

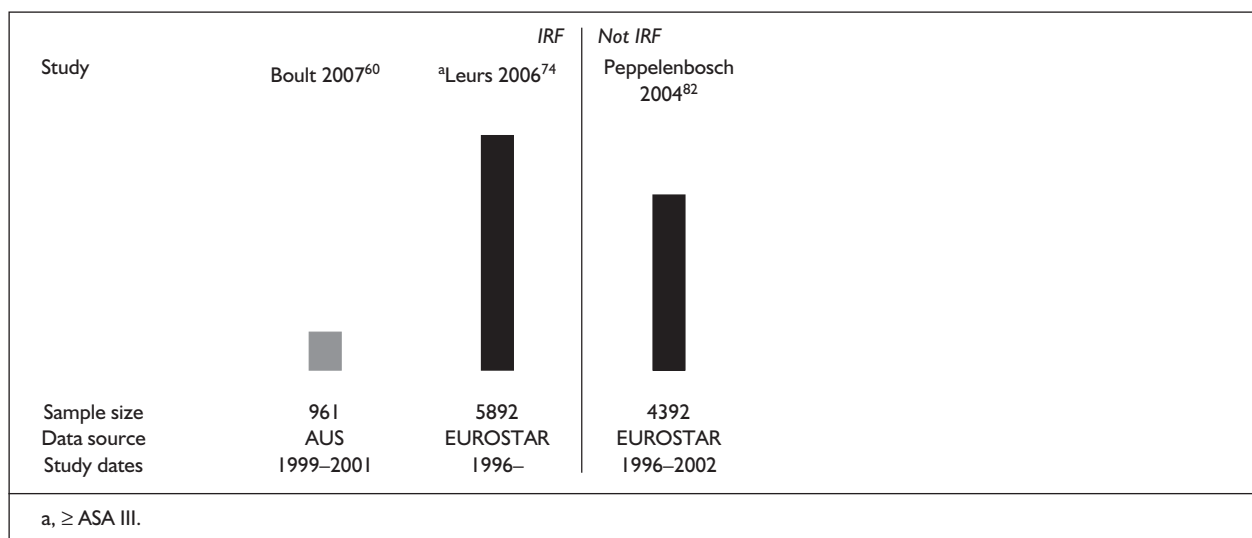


FIGURE 34 ASA class and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

The evidence regarding graft configuration/device type and 30-day mortality (Figure 58) and all-cause mortality (Figure 60) was too limited to draw conclusions. The balance of evidence suggests that there might be a link between device type and aneurysm-related mortality (Figure 59). Evidence regarding graft configuration/device type and

reintervention (Figure 61) and endoleak (Figure 62) was inconsistent.

Summary statements

A large number of studies have modelled the risk of mortality and other adverse outcomes after EVAR. We do not have definitive evidence on all of

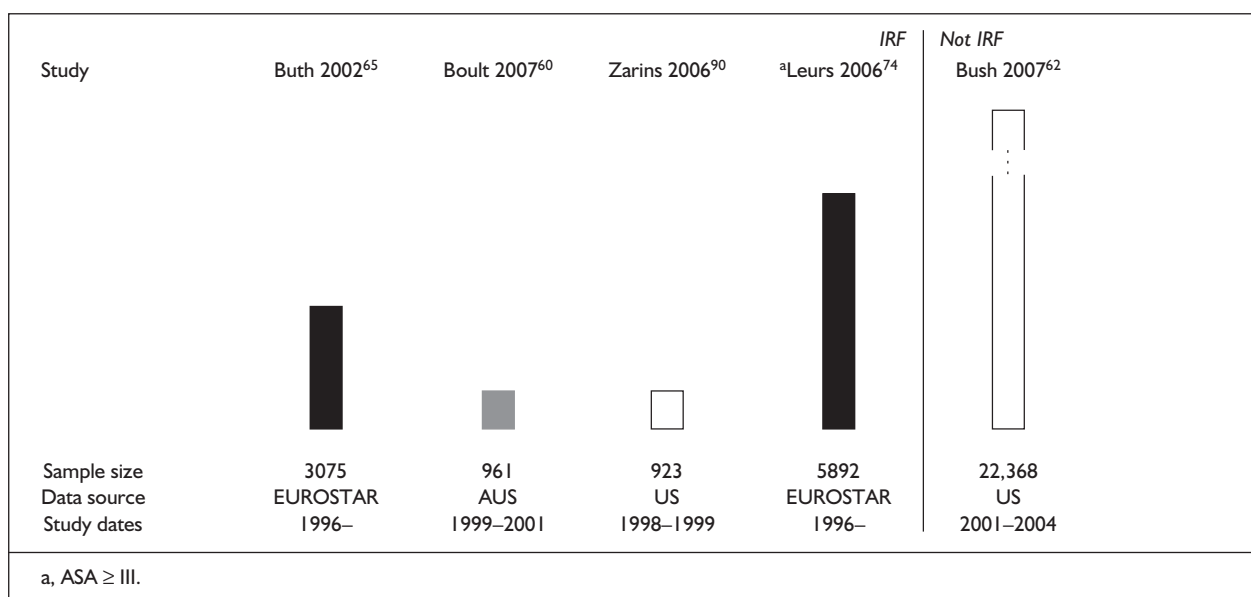


FIGURE 35 ASA class and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

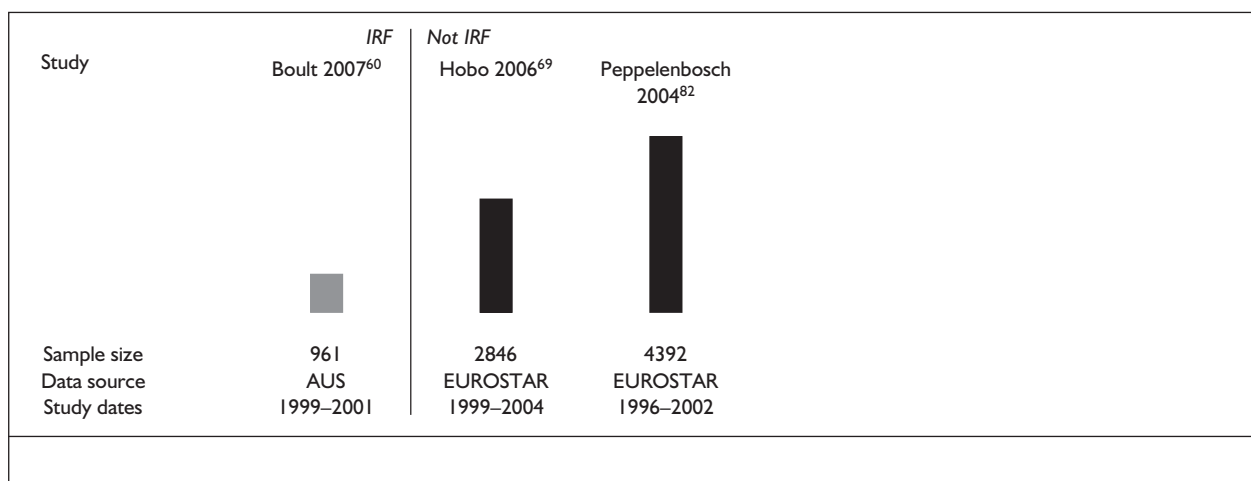


FIGURE 36 ASA class and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

the risk factors and outcomes explored. The firmest evidence supports the following conclusions.

30-day mortality

Increasing age is a risk factor for 30-day mortality and the results of a very large recent US-based study suggest that there may be a link between female gender and this outcome. Cardiac status, high blood pressure and obesity were not found to be independent risk factors for 30-day mortality but there was consistent evidence from a small number of studies that renal impairment

affects this outcome. There was a suggestion of a link between fitness and 30-day mortality and, according to EUROSTAR data, ASA classes III and IV are predictive of statistically significantly worse 30-day mortality. Aneurysm size is likely to be an independent risk factor for 30-day mortality but the balance of evidence suggests no independent effect of aortic neck and aneurysm angle. The evidence regarding graft configuration/device type and 30-day mortality was too limited to draw conclusions.

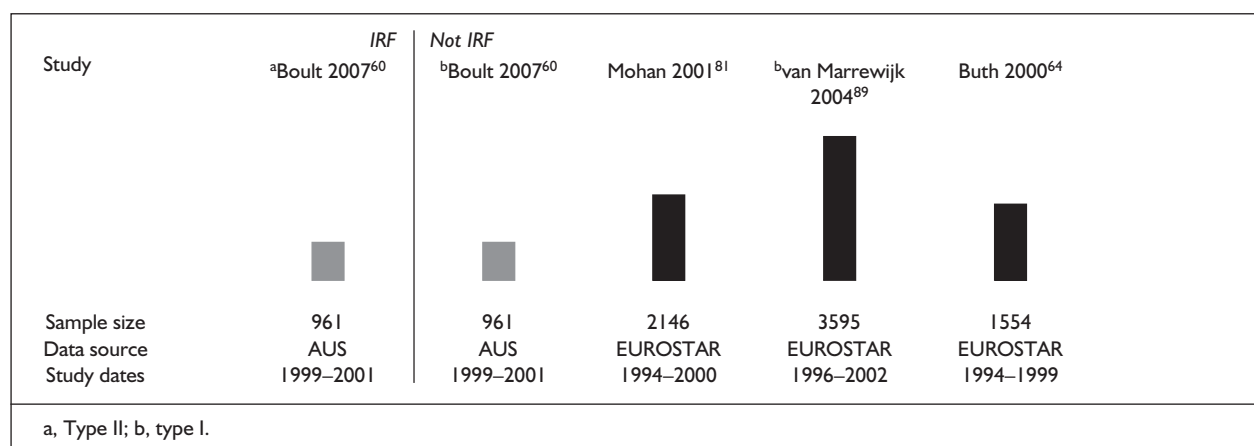


FIGURE 37 ASA class and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

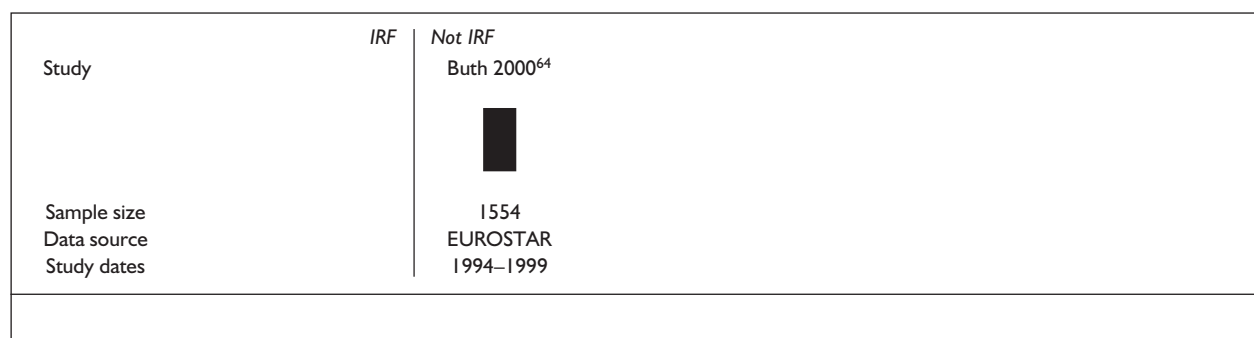


FIGURE 38 Smoking status and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

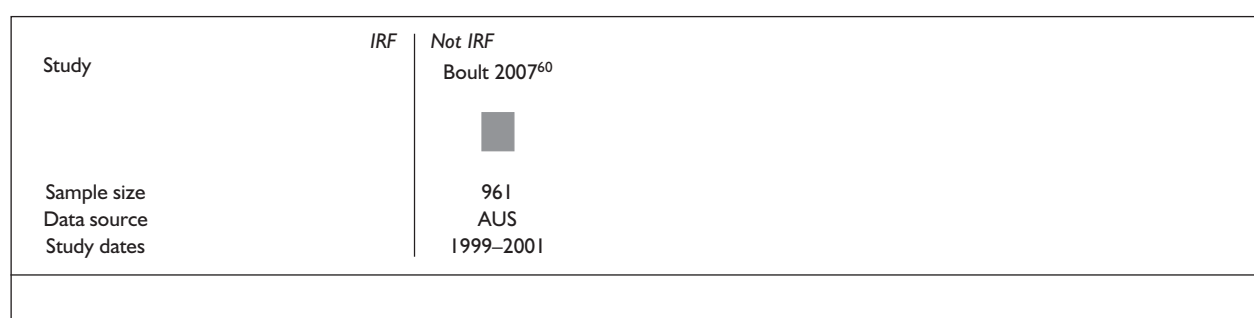


FIGURE 39 Smoking status and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

Aneurysm-related mortality

There is no indication of a link between female gender and aneurysm-related mortality. The evidence suggested that diabetes and (based on one US study) hypertension were not risk factors for this outcome. Evidence on other pre-existing conditions was lacking. On balance, analyses

indicate that fitness for open procedure is linked to aneurysm-related mortality. Aneurysm size is also likely to be an independent risk factor for this outcome. The balance of evidence suggests no effect of aortic neck and aneurysm angle on this outcome but a possible link between device type and aneurysm-related mortality.

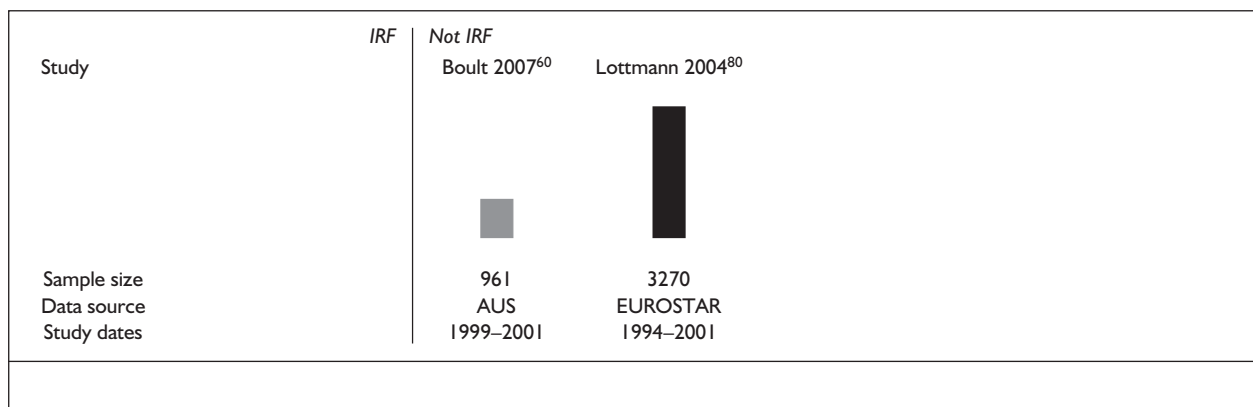


FIGURE 40 Smoking status and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

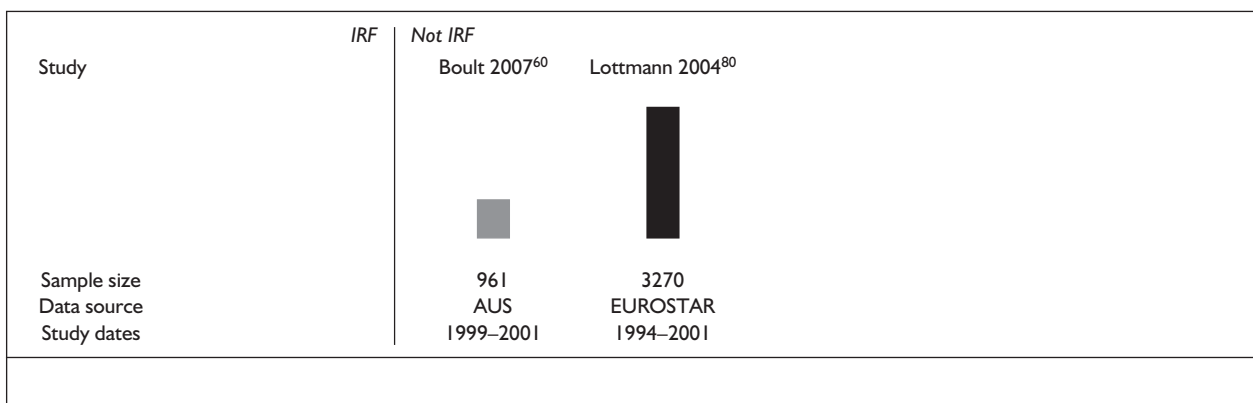


FIGURE 41 Smoking status and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

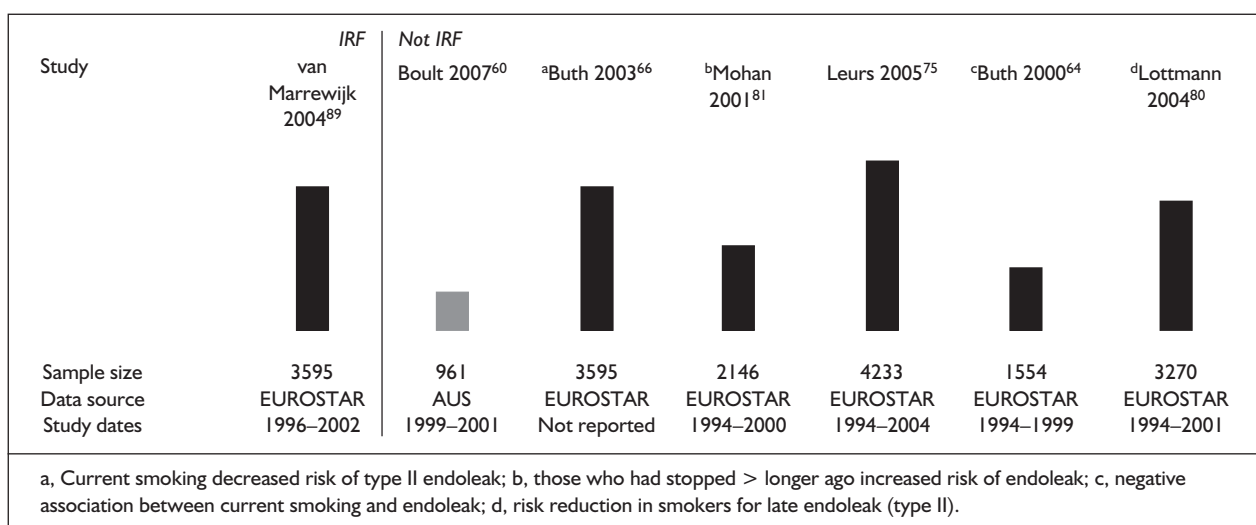


FIGURE 42 Smoking status and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

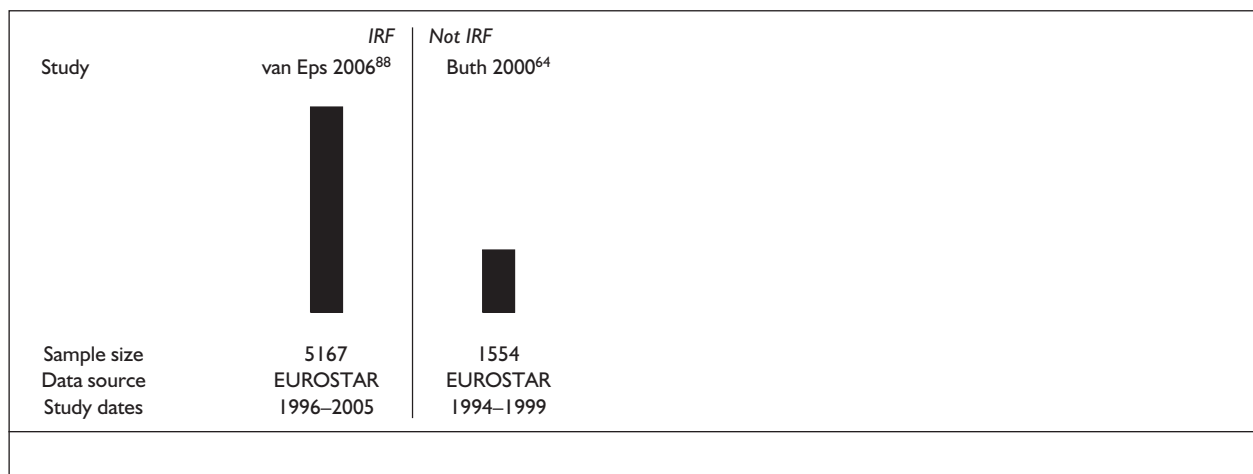


FIGURE 43 Aneurysm size and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

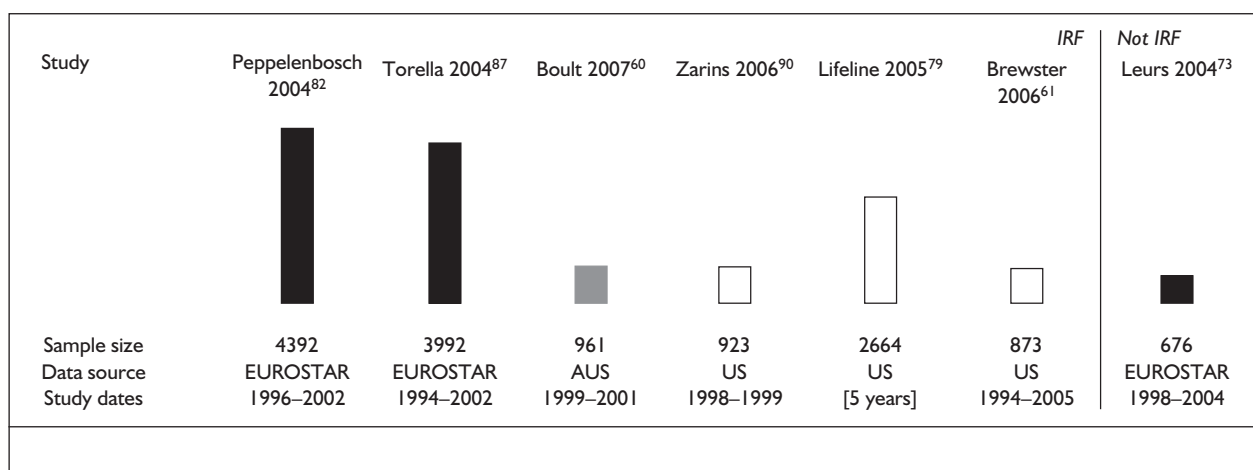


FIGURE 44 Aneurysm size and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

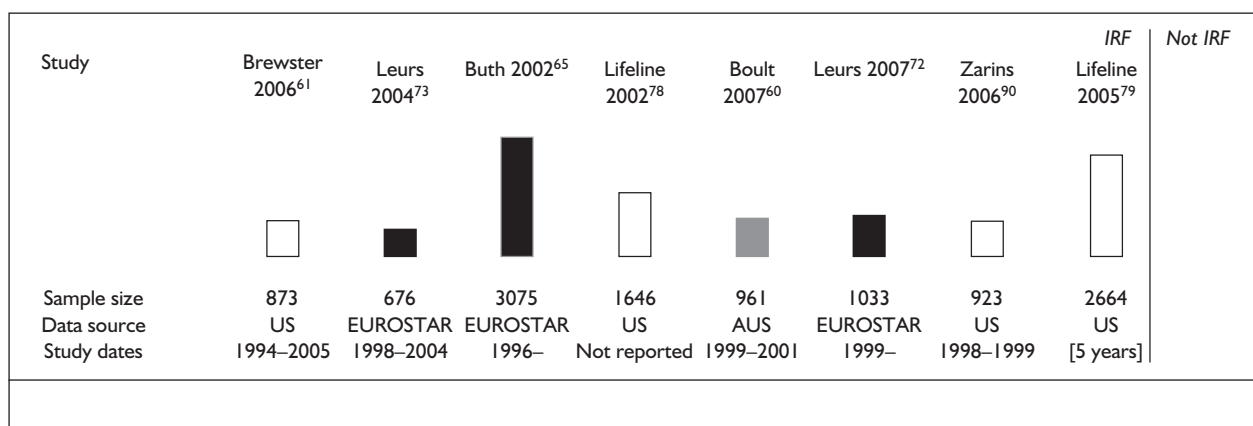


FIGURE 45 Aneurysm size and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

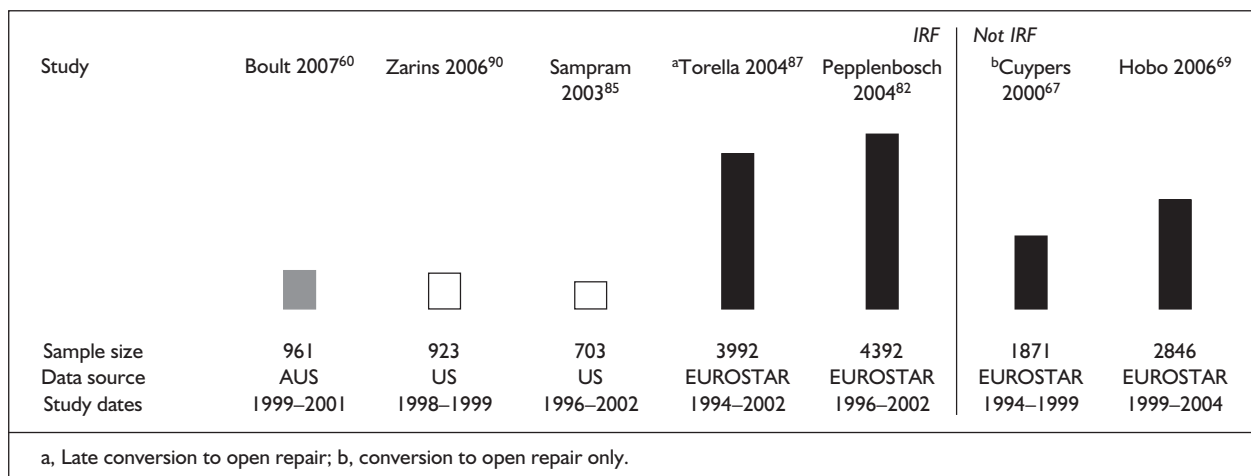


FIGURE 46 Aneurysm size and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

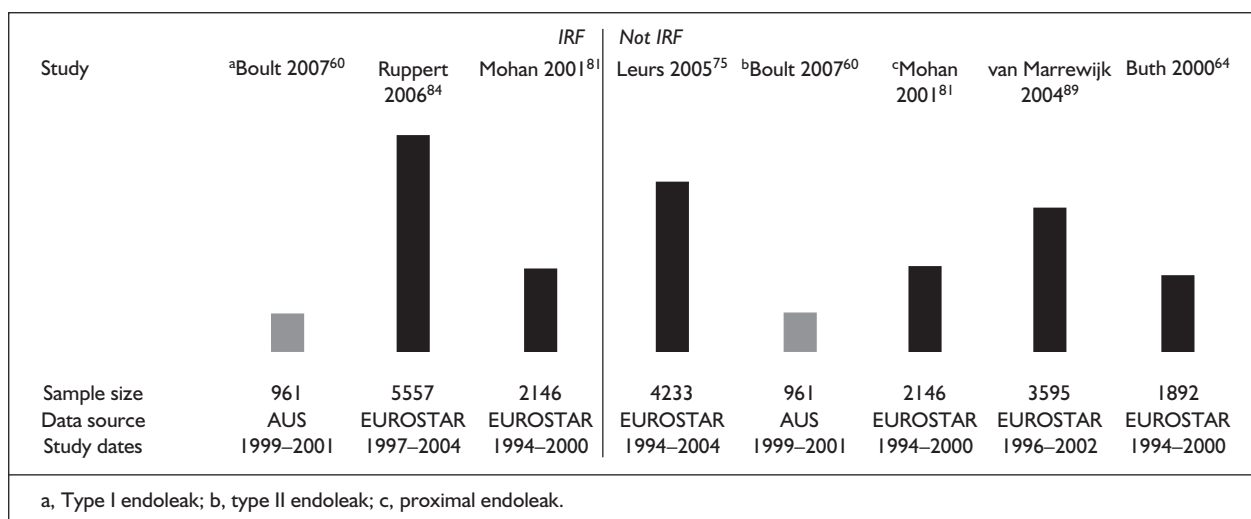


FIGURE 47 Aneurysm size and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

All-cause mortality

Increasing age had a self-evident role in all-cause mortality, but there is no indication of any link between female gender and this outcome. The majority of studies found that pulmonary status/COPD was an independent risk factor for all-cause mortality after EVAR but evidence was lacking or inconsistent on other comorbidities. The balance of evidence did suggest that renal impairment is an independent risk factor for all-cause mortality. With the exception of a large US study, all analyses found ASA status to be an independent risk factor for all-cause mortality. The very limited evidence

suggests that smoking status is not associated with adverse outcomes after EVAR. Aneurysm size is likely to be an independent risk factor for all-cause mortality but the balance of evidence suggests no effect of aortic neck and aneurysm angle. The evidence regarding graft configuration/device type and all-cause mortality was too limited to draw conclusions.

Reintervention

The evidence suggests that age and gender were not risk factors for reintervention. The available analyses also suggest that diabetes is not a risk

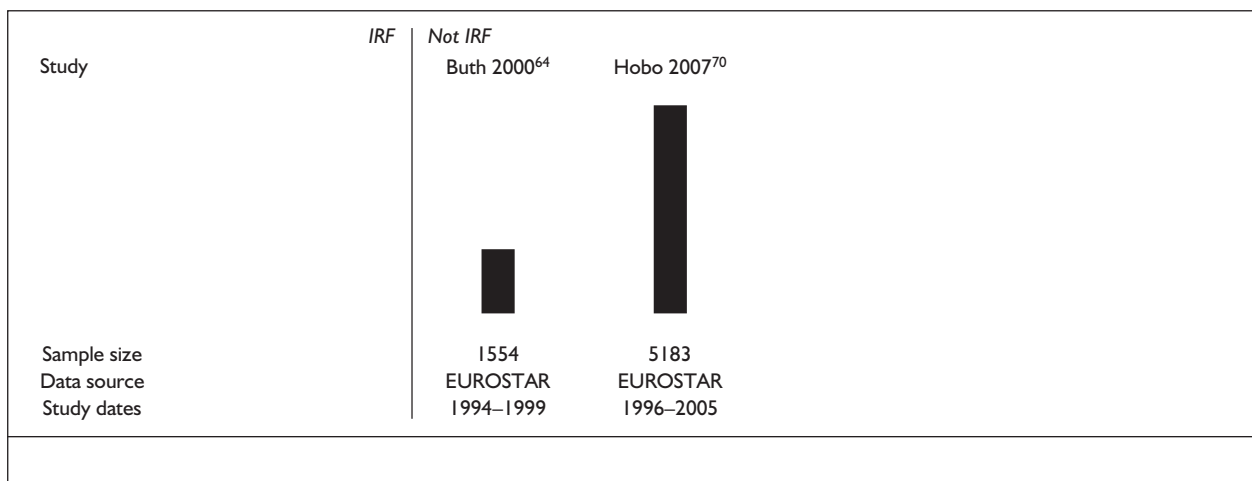


FIGURE 48 Aortic neck/aneurysm angle and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

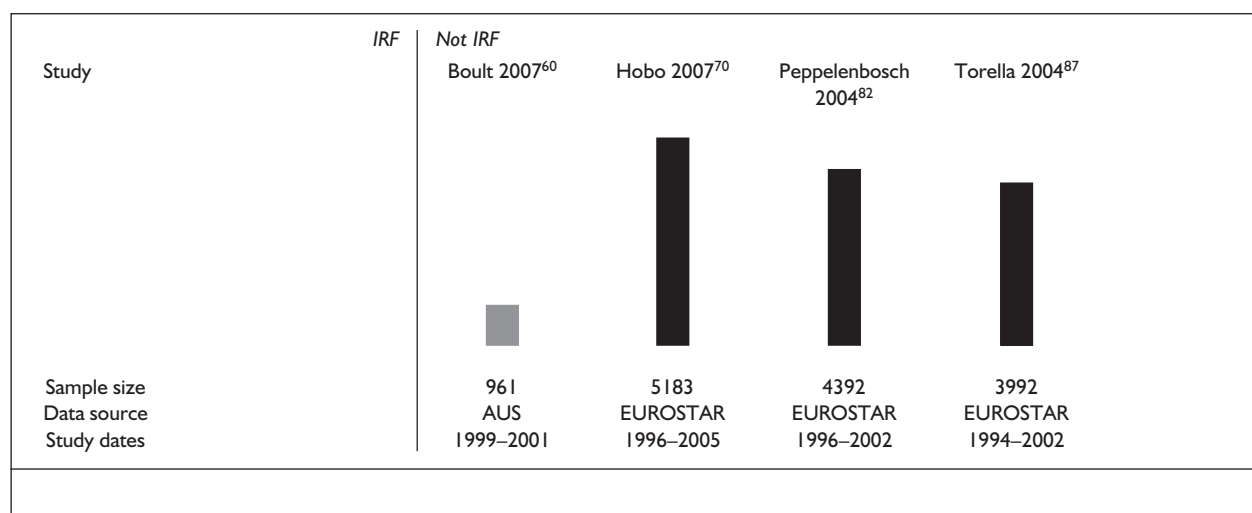


FIGURE 49 Aortic neck/aneurysm angle and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

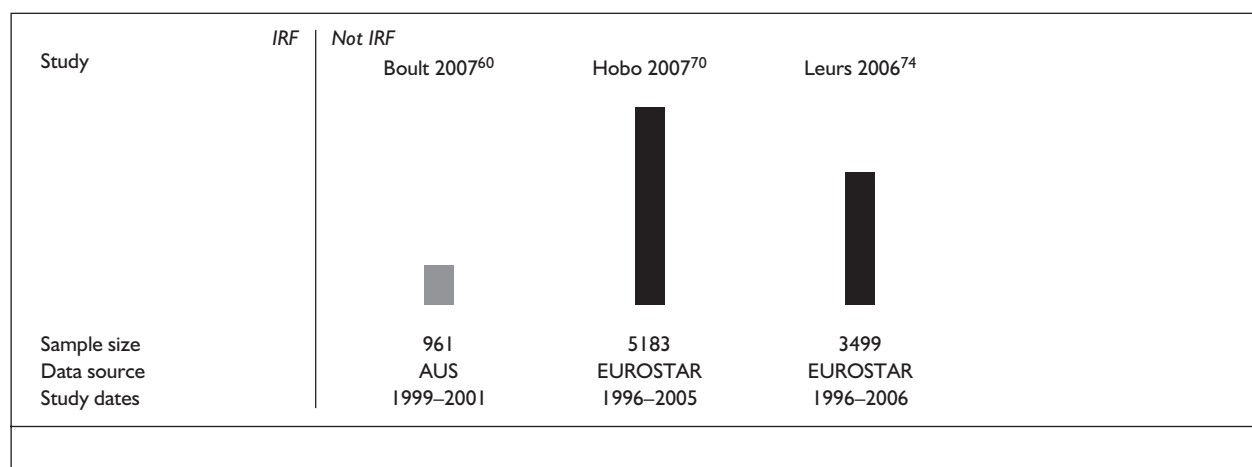


FIGURE 50 Aortic neck/aneurysm angle and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

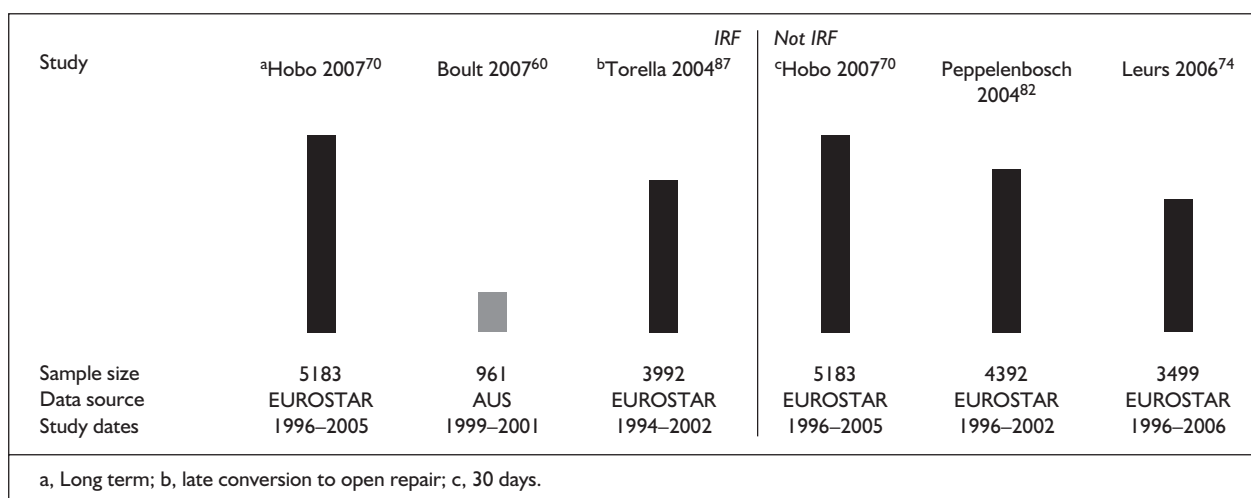


FIGURE 51 Aortic neck/aneurysm angle and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

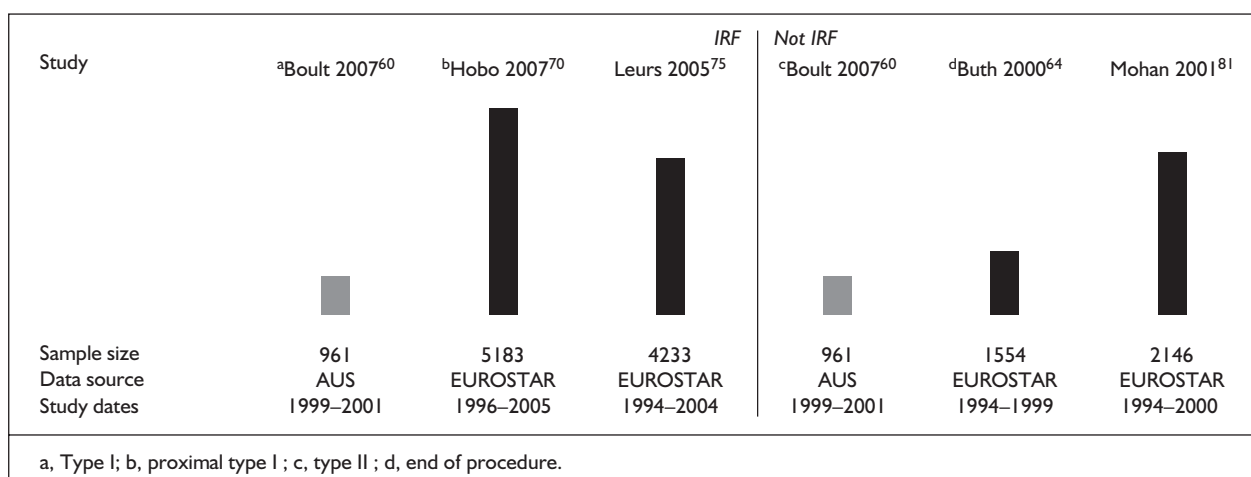


FIGURE 52 Aortic neck/aneurysm angle and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

factor for reintervention/conversion to open repair. One Australian study concluded that the higher the number of pre-existing conditions the greater the rate of reintervention whereas all EUROSTAR studies found that pre-existing conditions did not tend to predict reintervention. Single analyses of EUROSTAR data indicate no link between renal dysfunction and reintervention after EVAR. On balance, fitness and ASA status were not independent risk factors for this outcome.

Endoleak

On balance, the evidence indicates that age is an independent risk factor for type II endoleak or all types of endoleak. However, the studies consistently found that pre-existing conditions were not risk factors for endoleak. Single analyses of EUROSTAR data indicate no link between renal dysfunction and endoleak. On balance, fitness and ASA status were not independent risk factors for this outcome.

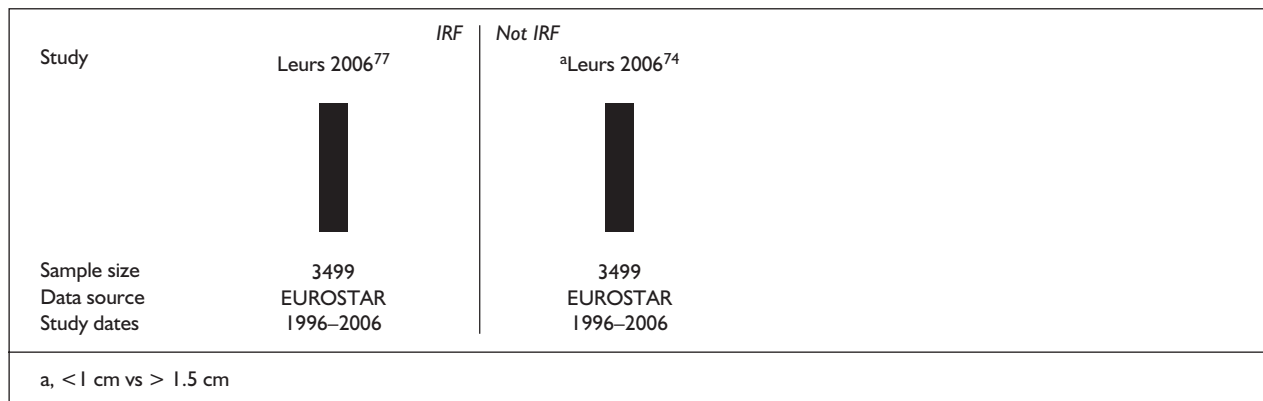


FIGURE 53 Aortic neck length and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

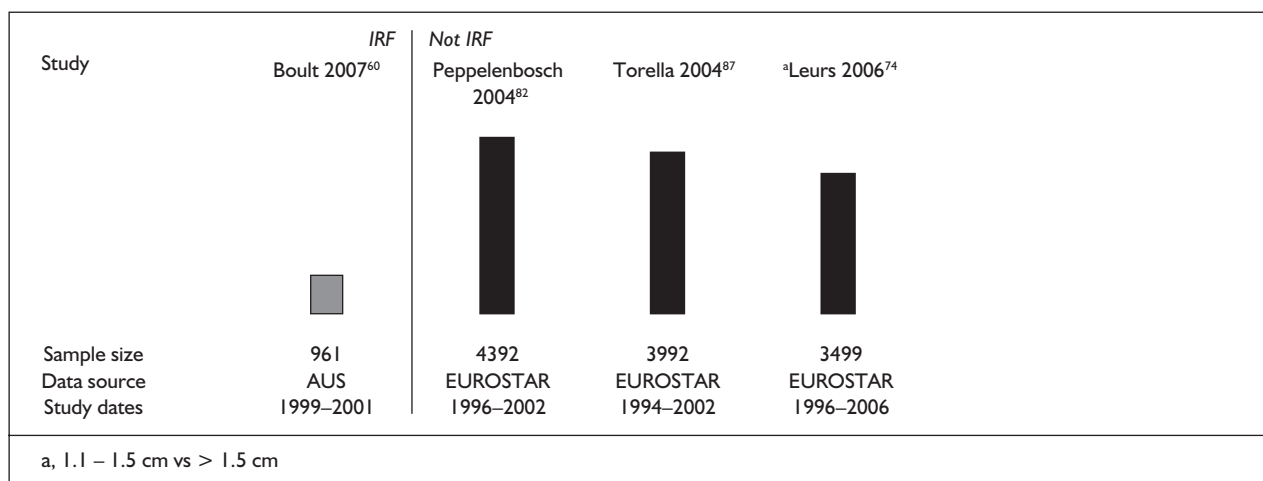


FIGURE 54 Aortic neck length and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

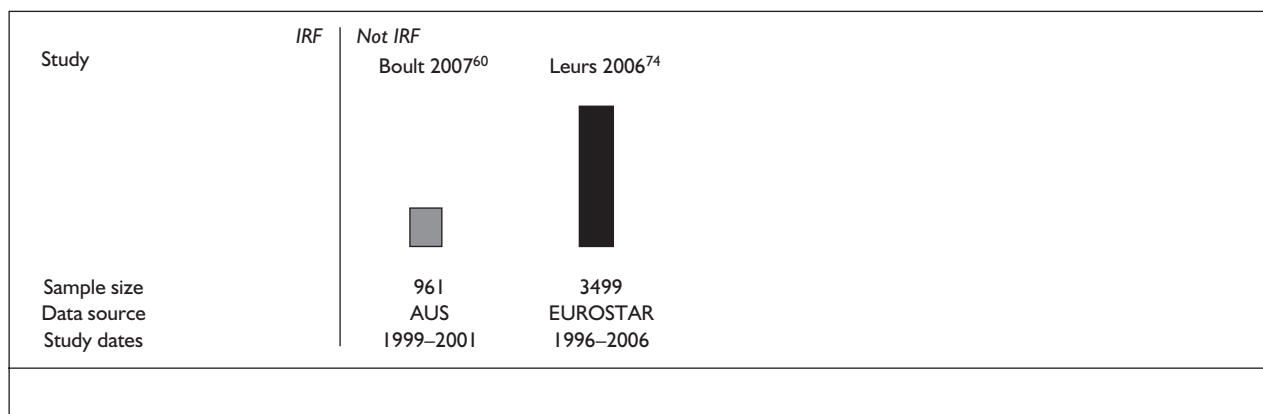


FIGURE 55 Aortic neck length and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

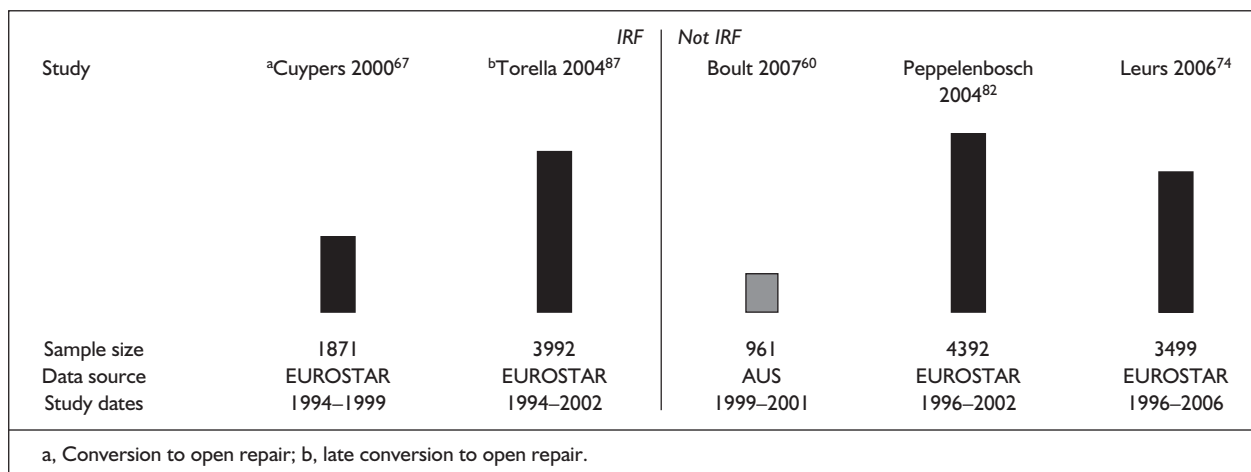


FIGURE 56 Aortic neck length and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

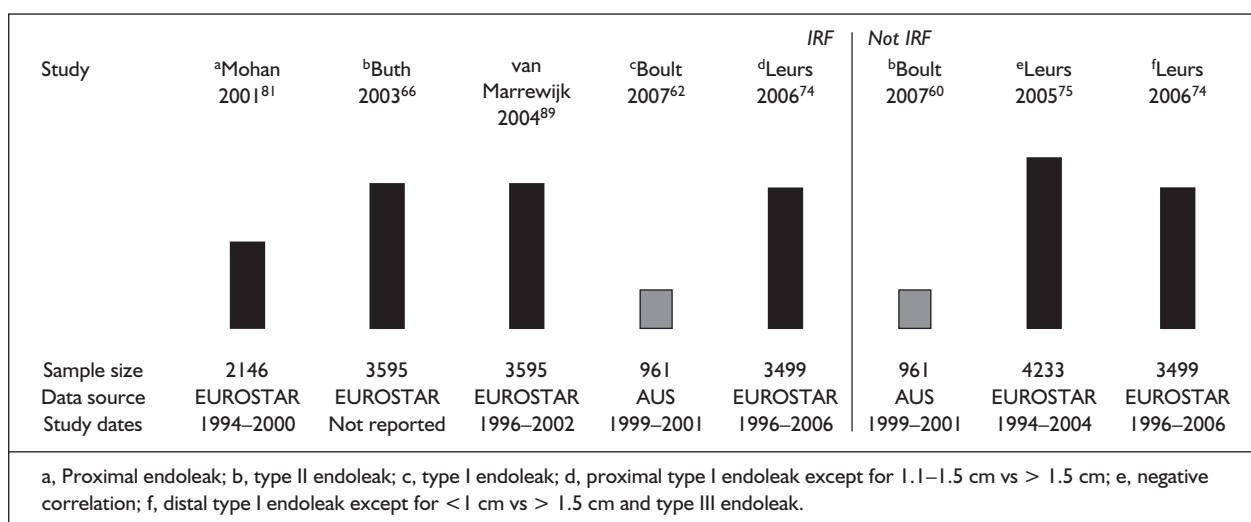


FIGURE 57 Aortic neck length and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

Discussion of assessment of clinical effectiveness

Currently, the EVAR trial 1,^{42,43} EVAR trial 2⁴⁶ and DREAM^{40,41} studies represent the best randomised evidence for evaluating EVAR. EVAR trial 1 and DREAM provide evidence that EVAR reduces operative mortality compared with open repair in patients considered to be fit for both procedures. EVAR is associated with a reduction in aneurysm-related mortality over the medium term (up to 4 years after randomisation in EVAR trial 1 and 2 years in DREAM) but there is no significant

difference in all-cause mortality between EVAR and open repair at mid-term follow-up. The reason for the failure of the short-term benefit of EVAR over open repair to translate into an advantage in the longer term is unclear. One important factor is that patients requiring surgery for AAA are at a high risk of mortality. Because EVAR is a less traumatic surgical procedure than open repair, fewer people die as an immediate result of the procedure. However, these high-risk patients die within a relatively short time scale and so by 4 years postoperatively the mortality rate in patients treated with EVAR or with open repair is

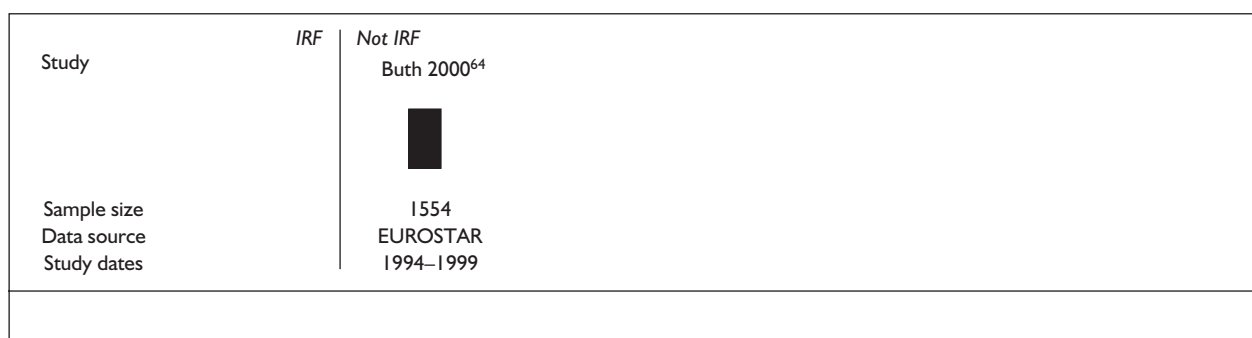


FIGURE 58 Graft configuration/device type and 30-day mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

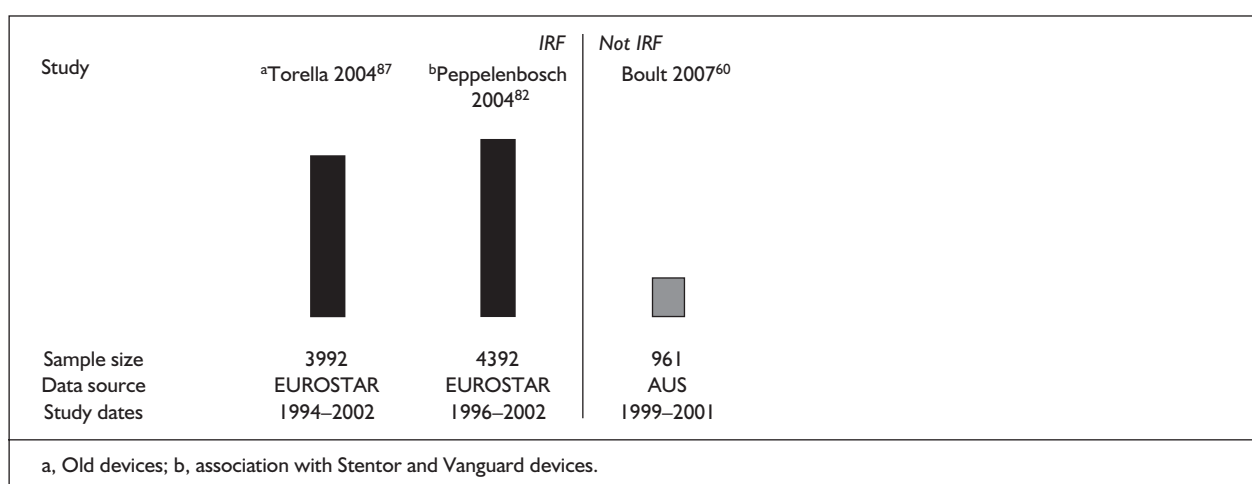


FIGURE 59 Graft configuration/device type and aneurysm-related mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

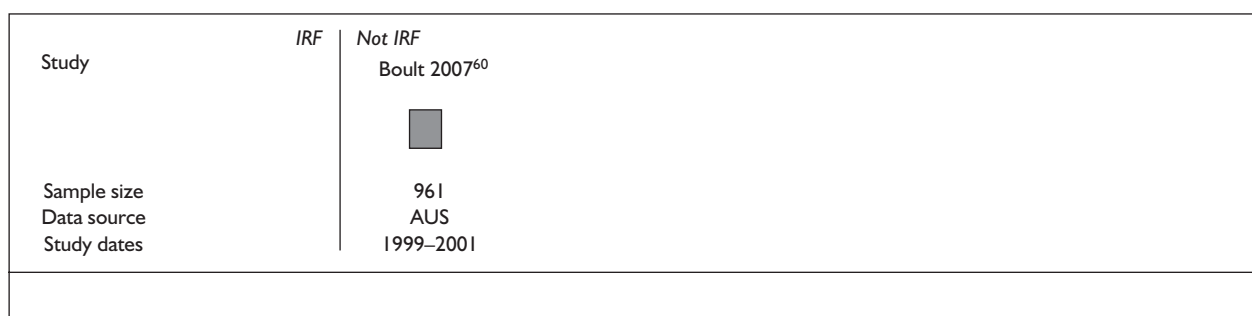


FIGURE 60 Graft configuration/device type and all-cause mortality. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

the same. Other reasons why the mortality rate in the EVAR-treated patients converges with that of the open repair patients include the higher rate of complications and the need for reinterventions in the former group, which are not offset by any increase in HRQoL, possibly because of the

increased level of monitoring required with EVAR because of the risk of complications.

Analysis of the EVAR trial data²³ did not find any evidence that a benefit of EVAR over open repair could be predicted using the CPI score for

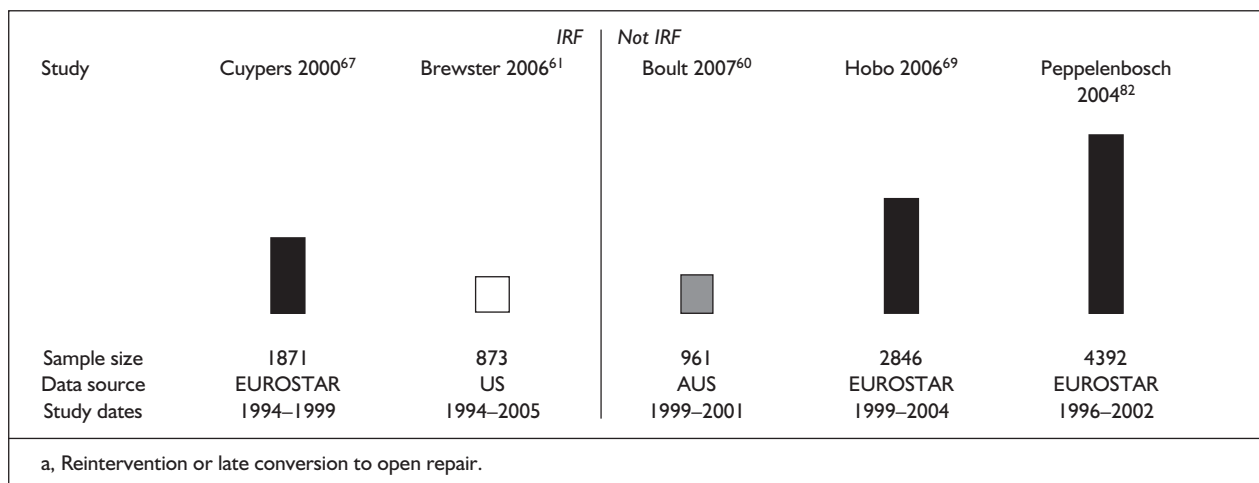


FIGURE 61 Graft configuration/device type and reintervention. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

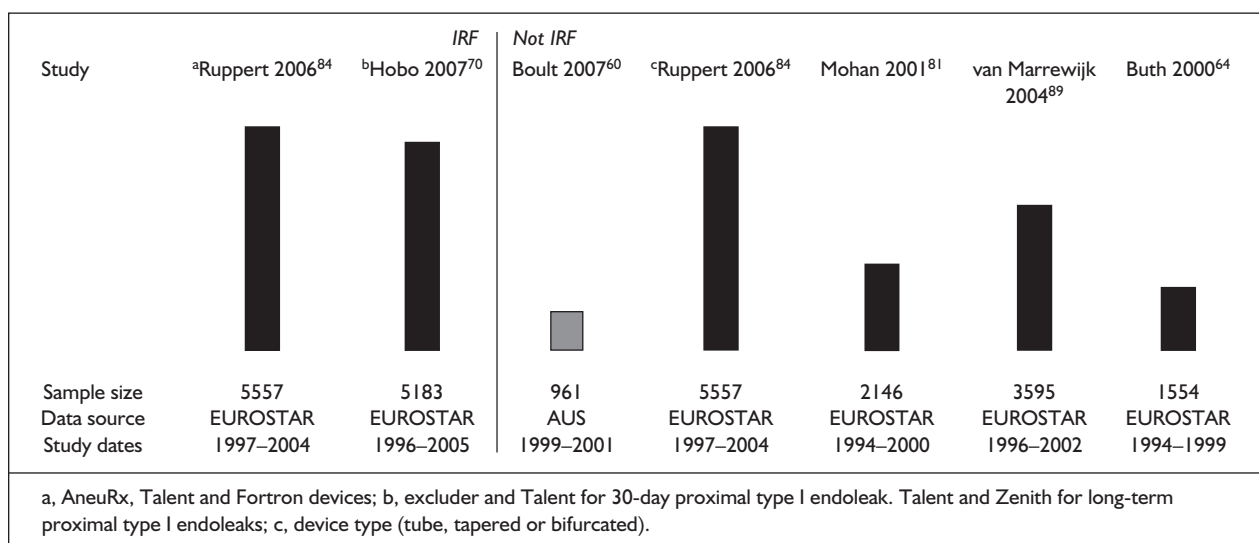


FIGURE 62 Graft configuration/device type and endoleak. Studies to the left of the vertical line found pre-existing conditions to be an independent risk factor (IRF), whereas those to the right did not.

preoperative fitness. A large number of studies have modelled the risk of mortality and other adverse outcomes following EVAR. These do not provide definitive evidence but age, gender, renal impairment, fitness, ASA class and aneurysm size may be predictive of poorer 30-day survival. There may be a link between fitness for open procedure, aneurysm size and device type and aneurysm-related mortality. In terms of all-cause mortality, pulmonary status, renal impairment, ASA class and aneurysm size might adversely affect this outcome. We did not consistently find any risk factors that

were predictive of reintervention. For the outcome of endoleak only age was found to be a possible independent risk factor.

Although measures validated for open repair have been applied to EVAR, and age, aneurysm size, ASA class and the clinician's definition of 'fitness' do appear to be associated with outcomes, there is currently no fully validated risk scoring tool to assist clinical decision-making. One study²¹ has produced an internally validated model for predicting a wide range of short- and long-term

outcomes following EVAR. The model uses eight variables (aneurysm size, age, ASA score, gender, serum creatinine, aortic neck angle, infrarenal neck diameter and infrarenal neck length) to predict risk of perioperative mortality and morbidity, mid-term survival (3 and 5 years) and need for reintervention. Further research into subgroups of patients who may benefit particularly from EVAR is warranted.

There is limited RCT evidence comparing EVAR with non-surgical management in patients unfit for open repair. EVAR trial 2⁴⁶ found no differences in mortality outcomes between groups but this finding cannot be taken as definitive because substantial numbers of patients randomised to non-surgical management crossed over to receive surgical repair of their aneurysm, which would be expected to dilute the difference between the arms. In effect, this trial was a comparison of EVAR with delayed aneurysm repair, except that the rules governing when to intervene were not defined. A trial designed and conducted specifically to address this question would be helpful.

The results from these trials are complemented by data from registries, in particular the EUROSTAR registry data relating to devices in current use.⁵⁴ The 30-day mortality rate of 2.3% in this registry is comparable with the rate of 1.7% in the EVAR arm of the EVAR trial 1 RCT. In the UK NVD¹⁶ the crude operative mortality rate following open repair of unruptured aneurysm was 6.8%, compared with 4.7% in the open repair arm of EVAR trial 1. Overall cumulative survival following EVAR was 61% with follow-up of up to 8 years.

The EUROSTAR registry provides a large sample for assessing complications after EVAR with follow-up of up to 7 years compared with the relatively small sample available from the trials. The cumulative rate of rupture from the EUROSTAR data was 3.1%, that of endoleak 32.5% and reintervention 18%. Few data on rupture were available from the trials. The rate of endoleak from the trials was lower (about 20%) but the cumulative rate of reintervention in EUROSTAR was similar to the 4-year point estimate for the EVAR group in EVAR trial 1 (20%)⁴³ but lower than that from EVAR trial 2 (26%)⁴⁶, probably reflecting the lower fitness of the patient population in this trial.

Several relevant trials are in progress including ACE (EVAR versus open repair),⁴⁹ OVER (large RCT similar to EVAR trial 1 in a US population)⁵⁰ and CAESAR (EVAR versus surveillance for small

aneurysms).⁵² A small RCT in Nottingham⁴⁷ indicated that it is feasible to randomise patients with ruptured AAAs to immediate EVAR or open repair and a further trial addressing this patient group (Amsterdam Acute Aneurysm Trial⁴⁸) is in progress. The overall body of randomised evidence relevant to EVAR is thus expected to increase in the next few years.

Other relevant evidence

Although the clinical review focused on identifying the most rigorous and useful evidence, some study designs were precluded from consideration by the prespecified exclusion criteria. A recent study by Schermerhorn *et al.*⁹⁶ compared outcomes following EVAR and open repair in large matched cohorts of Medicare recipients in the USA. It is discussed here because of its relevance to the economic model (see Chapter 4, York economic assessment).

This study used administrative data to identify Medicare beneficiaries who had undergone elective AAA repair during 2001–4. To control for non-random assignment of patients to procedures they created matched cohorts of patients after constructing logistic regression models that predicted the likelihood of undergoing EVAR (propensity score). Each patient who underwent EVAR was matched with the patient with the closest propensity score who underwent open repair. The 61,598 patients aged 67 years or older who underwent AAA repair were reduced to two matched cohorts with 22,830 patients in each (45,660 patients altogether). The average age of the patients was 76 years and approximately 80% were male. Perioperative (within 30 days) and long-term (during available follow-up) outcomes were evaluated.

The mortality rate within 30 days was 1.2% after EVAR and 4.8% after open repair (relative risk for open repair 4.00, 95% CI 3.51 to 4.56, $p < 0.001$), an absolute difference of 3.6%. The absolute advantage of EVAR over open repair increased with increasing age: from 2.1% absolute risk reduction at 67–69 years to 8.5% at 85 years or older. All major perioperative medical complications were less likely after EVAR than after open repair. Conversion from EVAR to open repair was required in 1.6% of patients. Some vascular and abdominal surgical complications were more common after open repair than after EVAR, as were complications related to laparotomy. The mean length of hospital stay was 3.4 days after EVAR and 9.3 days after open repair ($p < 0.001$).

The early survival benefit from EVAR persisted for about 3 years in the whole population, after which time the survival curves were similar. The benefit lasted less than 18 months in patients aged 67–74 years but for at least 4 years in those aged 85 years and older. Rupture rates were higher in the EVAR group (1.8% versus 0.5% at 4 years, $p < 0.001$), as were AAA-related reinterventions (9.0% versus 1.7% at 4 years, $p < 0.001$). Laparotomy-related complications were more frequent in the open repair group (9.7% versus 4.1% at 4 years, $p < 0.001$).

Important features of this study were that it used a large sample drawn from routine clinical practice, although reflecting practice in the USA rather than in the UK. Patients were followed to the 4-year time point, comparable with published data from the EVAR trial 1 RCT. The finding of an early mortality benefit from EVAR but no difference between groups in the longer term is similar to the findings of the EVAR trial 1 and DREAM studies. The study provides important data on the relationship between age and the benefit of EVAR relative to open repair. It also identified a higher rate of laparotomy-related complications in the open repair group; such complications were not taken into account in previous analyses.⁹⁶ This may suggest that the increased risk of non-AAA-related reinterventions following open repair may offset the increased risk of AAA-related reinterventions following EVAR.

Limitations of the study reflect its non-randomised design and its reliance on administrative data. The use of propensity scoring produced two cohorts closely matched on known prognostic factors but could not rule out differences between groups in unknown or unmeasured factors that might have an influence on prognosis.

Data on aneurysm size were not available in the administrative database and so it is difficult to say whether the populations included patients not meeting UK guidelines for AAA repair. Similarly, anatomic suitability for EVAR could not be determined from the available data and so it is unclear how many patients were assigned to open repair because they were not suitable for EVAR.⁹⁶ Although, as noted above, the study reports on surgical complications and laparotomy-related complications and reinterventions, it does not report on EVAR-specific complications such as endoleak.

In conclusion, this large observational study⁹⁶ provides data on perioperative and follow-up outcomes from large cohorts of patients treated with EVAR and open repair in routine clinical practice. These data supplement and generally support the findings of RCTs in patients with unruptured AAAs who are fit for both procedures (EVAR trial 1 and DREAM). However, the limitations of observational study design and reliance on administrative data should be borne in mind.

Chapter 4

Assessment of cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

Methods

A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials and modelling studies. Only full economic evaluations that compared two or more options and considered both costs and consequences were included.

The following databases were searched for relevant published literature: EconLIT, EMBASE, Health Economic Evaluations Databases (HEED), MEDLINE, IDEAS and NHS Economic Evaluation Database (NHS EED). Full details of the main search strategy for this review are presented in Appendix 1.

One reviewer assessed all obtained titles and abstracts for inclusion. The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and Jefferson.⁹⁷ This information is summarised within the text of the report, alongside a detailed critique of the study and the relevance to the UK NHS. The complete version of the checklist for each study considered is presented in Appendix 2.

Results

The systematic literature search identified seven studies that met the inclusion criteria for the cost-effectiveness review. The cost-effectiveness review also considered the Medtronic submission to NICE. The following sections provide a detailed critique of the cost-effectiveness evidence from the included studies and an assessment of the quality and relevance of the data from the perspective of the UK NHS. A quality assessment checklist is provided for each study.

Cost-effectiveness studies focusing on the EVAR trial I population/level

This section considers economic evaluation studies focusing on a patient population similar to that in EVAR trial I (i.e. patients requiring surgery and considered fit for open repair).

Patel et al. *The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model*¹⁰⁵

Overview

This study was designed to determine whether EVAR is a cost-effective alternative to open surgery in the treatment of AAAs. The base case was defined as 70-year-old men with an AAA of 5 cm in diameter. This study was conducted before the publication of trial results for either EVAR trial I or DREAM.

The authors developed a Markov decision model to compute lifetime QALYs and costs for a hypothetical cohort of patients who underwent either EVAR or open surgery. In the model, once a patient has undergone a procedure, either EVAR or open surgery, the outcomes include a successful repair or any of a number of complications. Effectiveness, resource use and cost data were derived from the literature. *Figure 63* provides a schematic for the Markov model developed by the authors of this study.

Summary of effectiveness data

Effectiveness data were derived from the literature with preference given to data derived from large multicentre studies. For open surgery a large Canadian study was used to derive mortality and morbidity rates. For EVAR, because there were no RCTs at the time that this study was published, mortality rates were taken as an average of those in the three largest trials and the occurrence of long-term morbidity was estimated from other sources. It should be noted that their review found EVAR

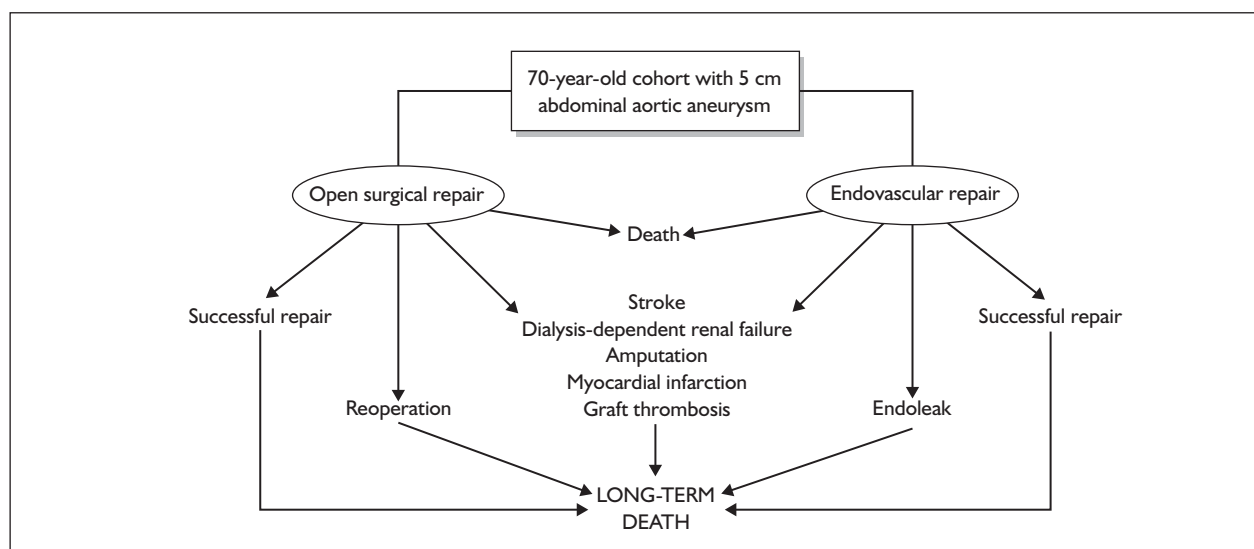


FIGURE 63 Schematic of model from Patel et al.,¹⁰⁵ with permission from Elsevier.

to have lower stroke, myocardial infarction, major amputation and dialysis-dependent renal failure rates than open repair during primary admission. For reinterventions, probabilities for both initial procedures were derived from the literature. The study also considered the immediate and late conversions of EVAR to open surgery.

A quality adjustment factor was assigned for each year of survival of a patient who had a major morbidity, for example a quality adjustment factor of 0.4 was used for a patient who had had a major stroke. Quality adjustment for temporary conditions was achieved through subtracting disutilities from the overall QALY estimate. Although it is not made clear in the study, it would appear that patients who are experiencing no complications are assigned a utility of 1. This would appear inappropriate given the age and general ill health of the patients being considered. QALYs were discounted at a rate of 3% per annum. Table 32 presents some of the key effectiveness parameters used in the model.

Summary of resource utilisation and cost data

The costs were derived from the cost accounting system at New York Presbyterian Hospital, as well as from the literature. For calculating the costs of the open surgery and EVAR procedures, the major resources consumed were identified and the costs calculated based on the average resource use reported in the literature. Fees for surgeons and radiologists were derived from the Medicare reimbursement rates for the appropriate current procedural terminology codes. The immediate and long-term costs of major long-term morbidities, such as stroke, dialysis-dependent renal failure and myocardial infarction, were derived from the literature. For EVAR rigorous postoperative surveillance was also conducted, with CT scanning at 1 week, 3 and 6 months, 1 year and annually thereafter. The study assumed that there was no follow-up surveillance for those patients who underwent open repair. Costs were discounted at a rate of 3% per annum. Table 33 presents values for some of the key cost parameters used in the model.

TABLE 32 Key effectiveness parameters from Patel et al.¹⁰⁵

Key parameters	Value	Source
EVAR operative mortality (%)	1.2	Average of three studies: Blum et al., ⁹⁹ Goldstone et al., ¹⁰⁰ Zarins et al. ¹⁰¹
Open repair operative mortality (%)	4.8	Johnston ¹⁰²
Conversion of EVAR to open repair during primary procedure (%)	2.0	Weighted average of four studies: Blum et al., ⁹⁹ Mialhe et al., ¹⁰³ Jacobowitz et al., ¹⁰⁴ Zarins et al. ¹⁰¹

TABLE 33 Key resource cost parameters from Patel *et al.*¹⁰⁵

Key resources	Cost	Source
Initial hospitalisation for EVAR procedure	US\$20,083	Assumptions and literature
Initial hospitalisation for open repair procedure	US\$16,016	Assumptions and literature

Summary of cost-effectiveness

For a hypothetical cohort of 70-year-old men with an AAA of 5 cm in diameter, EVAR produced more QALYs than open surgery (7.95 versus 7.53, respectively) at a higher lifetime cost (US\$28,901 versus US\$19,314). This yielded an ICER of US\$22,826 per QALY.

A wide range of sensitivity analyses were also undertaken. It was found that the ICER was sensitive to changes in mortality and morbidity rates of open surgery or EVAR, initial hospitalisation costs of EVAR or open surgery, and the conversion rate of EVAR to open repair during primary procedure. For example, it was found that the mortality rate of open surgery had a large effect on the ICER, such that halving the mortality rate of open surgery from 4.8% to 2.4% (and keeping the operative mortality rate of EVAR constant) increased the ICER to US\$43,408 per QALY; similarly, if the mortality rate of the EVAR procedure was doubled from 1.2% to 2.4% (keeping the operative mortality rate of open repair constant) the ICER increased to US\$30,064 per QALY.

Table 34 presents ICERs for the base case and some of the sensitivity analyses performed in the study.

Comments

General

Patel *et al.*¹⁰⁵ have found that under their base-case assumptions EVAR is a cost-effective alternative

to open repair in 70-year-old men with an AAA of 5 cm in diameter.

Internal validity

The largest concern with the Patel *et al.* study is that it is based on non-randomised data (as the study predates the publication of the randomised trials), which raises immediate issues over the accuracy of the parameter estimates because of selection bias.

External validity

There are a number of concerns with the Patel *et al.* study that raise questions over the relevance of the results for the UK setting. First, the study is US based and also dated (it was published in 1999). Second, the study makes a large number of assumptions that are not supported by evidence provided by the subsequent RCTs (of which the results, it should be noted, were not available at the time). For example, the RCTs found no evidence that the occurrence of stroke or myocardial infarction is different between the treatment groups,⁴³ but Patel *et al.* have assumed that it was lower after EVAR, which is one factor causing the results to be in favour of EVAR. Third, the methods used to account for disutility in the immediate aftermath of the initial procedure will bias against open repair when compared with other studies because of the longer relative period of post-intervention disutility assumed in the open repair arm compared with the EVAR arm than in other studies (the study assumes a loss of 47 days of perfect health for open repair, but a loss of only

TABLE 34 Key cost-effectiveness results from Patel *et al.*¹⁰⁵

Scenario	ICER
Base case	US\$22,836 per QALY
Discounted incremental QALYs generated by EVAR compared with open repair	0.42 QALYs
Discounted incremental cost of EVAR compared with open repair	US\$9587
Sensitivity analyses/alternate assumptions	
Open repair mortality rate 2.4% instead of 4.2%	US\$43,408 per QALY
Increase in initial hospitalisation costs of EVAR to US\$30,000	US\$48,046 per QALY
Increase in rate of conversion of EVAR to open repair during primary procedure from 2% to 15%	US\$50,944 per QALY

11 days of perfect health for EVAR). Subsequent studies, which are discussed at length later in this chapter, found that patients in both arms return to full health within 3 months of either EVAR or open repair.^{106,107} There are also concerns about whether the HRQoL scores are comparable to those used in other studies, and whether they are appropriate for the UK.

It should also be noted that Patel *et al.* are evaluating the treatments in a patient population having AAAs of a diameter of 5 cm, which is smaller than that recommended by current guidelines (see Chapter 3).

Bosch et al. Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair¹⁰⁸

Overview

Bosch *et al.*¹⁰⁸ performed a cost-utility analysis comparing lifetime costs and QALYs for treatment with EVAR or treatment with open repair. The aim of the study was to evaluate the cost-effectiveness of EVAR compared with open repair.

The authors developed a Markov decision model comparing lifetime costs and QALYs for EVAR and open repair in a cohort of 70-year-old men with AAAs of between 5 and 6 cm in diameter. The clinical effectiveness data for the study were derived from the published literature, which at the time did not include the two largest RCTs (EVAR trial 1⁴³ and DREAM⁴⁰). The authors focused on studies with large patient series and cases of both EVAR and open surgery. Resource use and cost estimates were derived from various sources, which will be discussed further.

Figure 64 provides a schematic of the model used by the authors.

Summary of effectiveness data

Because of the lack of RCTs a meta-analysis of the short-term results of studies comparing patients who underwent EVAR with matched patients who underwent open surgery was undertaken. The meta-analysis allowed calculation of the operative mortality rates for each procedure as well as the rates of complications in the short term (however, it is unclear from the study what time period is considered the short term). The meta-analysis found that the most commonly reported systemic and remote complications at 30 days

were cardiac, cerebral, renal and pulmonary. It was assumed that these complications had a long-term effect, which resulted in decreased HRQoL and added long-term costs. They estimated that the probability of systemic/remote complications was considerably lower with EVAR than with open surgery (a probability of 0.13 for EVAR versus 0.32 for open repair). Following the initial treatment period no new systemic complications could occur except when a patient underwent emergent surgical repair. In the long term an annual average rupture rate of 0.01 for EVAR was used, with no rupture after open repair; for long-term reintervention a rate of 0.08 per year was used for EVAR and 0.01 per year for open surgery. Long-term life expectancy was calculated based on age- and sex-specific mortality rates from life tables for the US general population; however, this would seem inappropriate given the general ill health of the patient population being considered. For patients with major systemic complications, survival was adjusted with an excess mortality rate.

Quality of life weights before treatment and after recovery from either treatment were set similar to those in the general population. To show the effect that the treatments had in the short term on quality of life, a 10% reduction in the first month following EVAR was assumed, and a 30% reduction for 2 months following open surgery was assumed. Long-term quality of life adjustments were also made for patients with cardiac, cerebral, renal or pulmonary complications. QALYs were discounted at a rate of 3% per annum.

Table 35 presents values for some of the key parameters used by the authors.

Summary of resource utilisation and cost data

The authors included costs for procedures (including patient time productivity costs), morbidity and mortality, and imaging in follow-up. All costs were converted to year 2000 US dollars. Procedure costs included those of the hospital, physician and patient for EVAR, open surgery, percutaneous treatment and emergent surgical repair of rupture. The hospital cost and physician fees were derived from Medicare reimbursement rates by using diagnosis-related groups. Patient costs were determined by multiplying the daily wage rate by the number of days spent in hospital. It should be noted that when considering patient

FIGURE 64 Schematic of model from Bosch et al.¹⁰⁸ (Commercial-in-confidence information has been removed.)

TABLE 35 Key effectiveness parameters from Bosch et al.¹⁰⁸

Key parameters	Value	Source
Mortality of open repair (%)	4.0	Meta-analysis of nine studies ¹⁰⁹⁻¹¹⁷
Mortality of primary EVAR (%)	3.0	Meta-analysis of nine studies ¹⁰⁹⁻¹¹⁷
Probability of immediate conversion after EVAR	3.0	Meta-analysis of nine studies ¹⁰⁹⁻¹¹⁷
Annual rupture risk after EVAR (%)	1.0	Harris et al., ¹¹⁸ Zarins et al. ¹¹⁹
Annual long-term failure rate of EVAR, excluding ruptures, requiring treatment	8.0	Zarins et al. ¹¹⁹
Annual long-term failure rate of open repair requiring treatment	1.0	Hallet et al. ¹²⁰

costs the authors of the study do not appear to have accounted for other sick days that did not involve hospital stays. For costs for morbidity and mortality, if a major systemic/remote complication occurred during surgery then extra costs were added to the procedure costs. Costs of follow-up included physician visit costs, imaging costs and patient costs. In the model, patients who underwent EVAR were imaged at 3, 6 and 12 months, and annually thereafter. All costs were discounted at 3%. Table 36 presents some of the key resource costs used in the model.

Summary of cost-effectiveness

In the base case it was found that EVAR resulted in more QALYs than open repair (6.74 versus 6.52, respectively) and also more costs (US\$39,785 versus US\$37,606, respectively), resulting in an ICER of US\$9905 per QALY. A wide range of sensitivity analyses, including both one- and two-way analyses,

were also performed. These found that the results were highly sensitive to the uncertain parameters in the model, such as the systemic complication rate, long-term failure rate and rupture rate. For example, if the annual rate for procedures in follow-up in the EVAR arm was increased from 8% to 12% then the ICER increased to US\$56,630 per QALY, and if the rate exceeded 12% then the ICER was more than US\$100,000 per QALY. Table 37 presents the ICERs for the base case and for some of the sensitivity analyses performed in the study.

Comments

General

The authors of this study have found that, given typical thresholds, EVAR is likely to be considered cost-effective compared with open repair in 70-year-old men with AAAs of between 5 cm and 6 cm in diameter.

TABLE 36 Key resource cost parameters from Bosch et al.¹⁰⁸

Key resources	Cost	Source
Endovascular repair procedure	US\$19,642	Medicare
Open repair procedure	US\$23,484	Medicare
Follow-up imaging (per visit)	US\$483	Medicare

TABLE 37 Key cost-effectiveness results from Bosch et al.¹⁰⁸

Scenario	ICER
Base case	US\$9905 per QALY
Discounted incremental QALYs generated by EVAR	0.22 QALYs
Overall incremental cost of EVAR arm compared with open repair arm	US\$179
Sensitivity analyses/alternative assumptions	
Annual rate for procedures in follow-up after EVAR increased from 8% to 12%	US\$56,630 per QALY
Annual long-term failure rate after open surgery decreased from 1% to 0.5%	US\$54,233 per QALY

Internal validity

There are a number of issues with the Bosch *et al.* study that may have led to the results produced being inaccurate. First, the fact that the values used for the parameters in the model are not based on RCT evidence (as the study predates the subsequent trials) is clearly a major weakness and raises doubts about their relevance. Second, in the absence of better data, the authors have been forced to make a large number of assumptions (e.g. about recovery time, cost of mortality, quality of life, number and type of additional procedures performed, etc.), thus limiting the robustness of the results. The authors state that the sensitivity analyses conducted test these assumptions and evaluate the influence that any uncertainty in these assumptions may have on the base-case ICER. However, as only one- and two-way sensitivity analyses were conducted and the results were not all presented, the authors are unlikely to have accurately captured the uncertainty in their assumptions.

External validity

There are several issues with the Bosch *et al.* study beyond those described above that may limit the transferability of the results to a UK setting. First, the inclusion of patient costs (productivity costs) may mean that the results of this study are difficult to compare with those of other studies that do not include patient costs in their resource use estimates. Second, it should also be noted that the study includes patients with AAAs of between 5 cm and 5.5 cm in diameter. Such patients would not currently be considered for surgery in the UK, where only patients with AAAs of > 5.5 cm in diameter are considered for surgery. Third, as the results are based on a US population in a US health-care setting, they may not be transferable to the UK because of the differences in the patient population and resource use.

Michaels et al. Cost-effectiveness of endovascular abdominal aortic aneurysm repair¹⁰⁷

Overview

This study evaluated the cost-effectiveness of EVAR compared with open repair in patients fit for surgery (RC1) or with conservative management in those unfit for surgery (RC2) (this section of the study will be discussed later in this chapter; see Cost-effectiveness studies focusing on the EVAR type 2 population). The aim of the study was to determine an optimal strategy for the use of EVAR based on the best available evidence at the time.

Effectiveness and resource use data were based on recent RCTs (EVAR trial 1⁴² and DREAM⁴⁰) as well as on a systematic review of the literature. The study was conducted after the short-term (30-day) operative mortality results were published from these trials but before the mid-term results were available. The authors developed a Markov model and used it to consider two separate 'reference cases', one of which was similar to the EVAR trial 1 population. They considered fit 70-year-old patients with an AAA of 5.5 cm in diameter for which the choice of treatment was between EVAR and open surgery (RC1). The primary outcome measure for the cost-effectiveness analysis was the incremental cost per QALY gained. The authors used a 10-year time horizon. The evaluation was undertaken from the perspective of the NHS.

Figure 65 represents the Markov decision model for RC1.

Summary of effectiveness data

Short-term operative mortality probabilities were taken from the EVAR trial 1⁴² and DREAM trial.⁴⁰ The probabilities of reintervention and complications were derived from a previously conducted systematic review. General mortality was taken from standardised mortality tables for England and Wales (it should be noted that it is not stated whether these have been adjusted for the poorer health of patients with aneurysms). Aneurysm-related mortality was calculated from a previous modelling study.

Utility estimates were based on published figures derived from the EQ-5D tariff values for men aged 65–74 years. To account for the lower HRQoL initially following surgery, a reduction in keeping with that seen after major surgery was applied for the first 4 weeks after open surgery and for the first 2 weeks after EVAR. QALYs were discounted at a rate of 3.5% per annum.

The key effectiveness parameters for the model are reported in Table 38.

Summary of resource utilisation and cost data

Most costs were based on NHS reference costs for 2003–4¹²³ with the mean cost being the point estimate. For the probabilistic sensitivity analysis a normal distribution was assumed with standard deviation based on the assumption that 50% of observations were within the published interquartile range. The additional incremental cost of EVAR was estimated from data collected

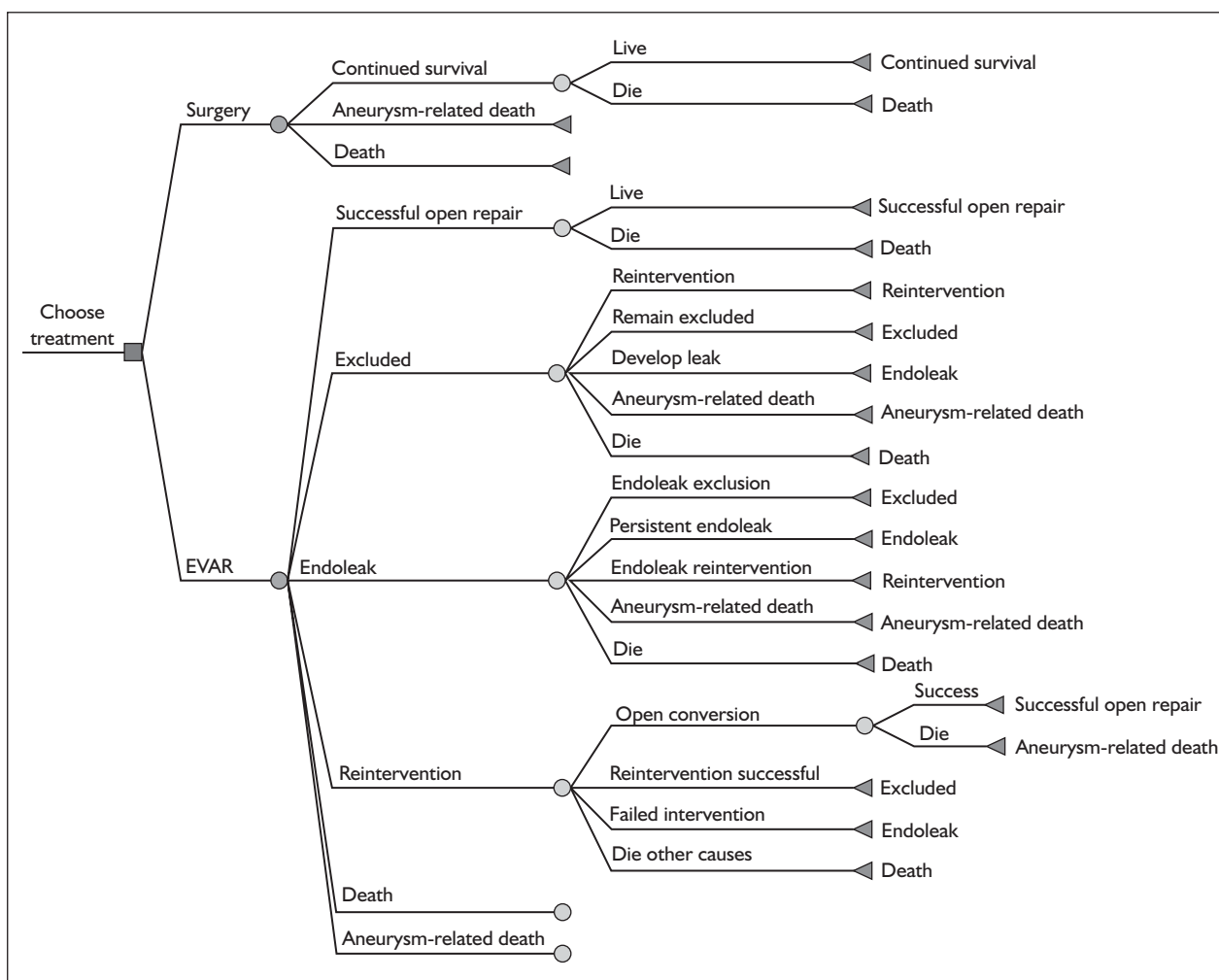


FIGURE 65 Schematic of model from Michaels et al.¹⁰⁷ © British Journal of Surgery Society Ltd. Reproduced with permission, granted by John Wiley & Sons on behalf of the BJSS Ltd.

TABLE 38 Key effectiveness parameters from Michaels et al.¹⁰⁷

Key parameters	Value	Source
Mortality of open repair (%)	5.80	EVAR trial ¹⁴² and DREAM ⁴⁰
Mortality of primary EVAR in initial 1-month period (%)	1.85	EVAR trial ¹⁴² and DREAM ⁴⁰
Probability of conversion of EVAR to open repair during primary procedure (%)	1.90	Drury et al. ¹²¹
Utility for living patient following treatment	0.8	Health Survey for England 1996 ¹²²

at the Sheffield Teaching Hospital NHS Trust. Follow-up costs for EVAR were based on NHS reference costs with the assumption that on average an EVAR patient will have two outpatient visits and two CT scans per year. After open repair the average cost of a reintervention in the EVAR arm

again used NHS reference costs¹²³ but was based on the case mix of reinterventions as recorded in the EUROSTAR registry.¹²⁴ All costs have been discounted at a rate of 3.5% per annum. The key resource cost parameters for the model are reported in Table 39.

TABLE 39 Key resource cost parameters from Michaels *et al.*¹⁰⁷

Key resources	Cost	Source
Cost of open AAA repair	£4269	NHS reference costs ¹²³
Cost of EVAR repair	£8769	Sheffield Teaching Hospital NHS Trust
EVAR follow-up cost per month	£41.50	NHS reference costs ¹²³
Reintervention	£4790	NHS reference costs ¹²³ and EUROSTAR ¹²⁴

Summary of cost-effectiveness

RC1 reference case

The base-case results for RC1 showed that EVAR resulted in increased QALYs (0.1 QALYs) compared with open surgery but also increased costs (£11,449), resulting in an ICER of £110,000 per QALY.

A variety of univariate sensitivity analyses was also undertaken, such as changing the initial incremental cost of the EVAR procedure, altering the discount rate, changing the time horizon, using mortality rates from the systematic review instead of the clinical trials and altering the reintervention rate. The ICER was as low as £53,773 per QALY when the initial incremental cost of EVAR compared with open surgery was reduced to £0 and as high as £144,552 when the time horizon was increased to 15 years. When the mortality rates were taken from the review instead of the trials, EVAR was dominated by open surgery.

Michaels *et al.* also undertook a probabilistic sensitivity analysis. All of the simulations generated an ICER of greater than £30,000 per QALY (i.e. the probability of the ICER being less than £30,000 per QALY was zero).

Table 40 presents the ICERs for the RC1 base case as well as for some of the sensitivity analyses conducted.

TABLE 40 Key cost-effectiveness results from Michaels *et al.* (RC1)¹⁰⁷

Scenario	ICER
Base case	£110,000 per QALY
Discounted incremental QALYs generated by EVAR (RC1)	0.10
Discounted incremental cost of EVAR patient compared with open repair patient (RC1)	£11,449
Sensitivity analyses/alternative assumptions	
Incremental cost of initial EVAR procedure £0	£53,773 per QALY
15-year time horizon	£144,552 per QALY

Comments

General

Michaels *et al.* found that EVAR does not appear to be cost-effective in an EVAR trial 1-type patient (i.e. RC1 in their analysis). This is because of the high incremental cost and low incremental effectiveness of EVAR compared with open surgery.

Internal validity

Short-term operative mortality rates in the Michaels *et al.* study are based on RCT evidence. However, as this study was conducted before mid-term results from the RCTs were available, longer-term probabilities are based on the results of a review of the literature¹²¹ and have not been derived from RCTs. As such they are open to bias and may not accurately reflect those of the patient population being considered.

The study in the base case also only considers a time horizon of 10 years (although this is extended to 15 years in sensitivity analysis). This may not be long enough to capture all of the cost and outcome differences between the two trial arms.

External validity

The study is UK based and has been conducted from the perspective of the NHS. However, as noted above, not all of the parameters have been estimated from RCTs and are thus open to bias.

Epstein et al. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm¹⁰⁶
Overview

The study evaluated the cost-effectiveness of EVAR compared with open surgery in a patient population of 74-year-old men with a diagnosed AAA of diameter ≥ 5.5 cm. It should be noted that several of the authors of this report were authors of this study.

The authors constructed a Markov decision model to estimate the lifetime costs and QALYs of male patients aged 74 years with an AAA of diameter ≥ 5.5 cm. Effectiveness and resource use data used to populate the Markov model were largely drawn from an RCT, EVAR trial 1. The model includes the risks of death from aneurysm and other cardiovascular and non-cardiovascular causes, secondary reinterventions and non-fatal cardiovascular events.

ICERs were reported for the base case as well as for a number of sensitivity analyses (e.g. for different starting ages). The probability that EVAR is cost-effective at a threshold of £20,000 per QALY and £40,000 per QALY was also reported, based on probabilistic sensitivity analyses.

Figure 66 provides a schematic of the model used in the study.

Summary of effectiveness data

The effectiveness data were largely taken from EVAR trial 1 although this has been supplemented by other data sources. Mortality from the initial procedure was calculated from EVAR trial 1. It

was assumed that if an EVAR patient converted to open repair during the primary admission then they would have the same long-term prognosis as an individual who had originally been allocated to EVAR. Mortality rates after the initial admission were estimated as three competing risks: (1) death from an AAA cause, (2) death from a cardiovascular cause other than AAA and (3) death from a non-cardiovascular cause. Patients were also at risk of a non-fatal cardiovascular event or a readmission for a second AAA procedure, all of which were associated with higher costs and lower utilities. The model assumed that the initial operative mortality benefit of EVAR compared with open repair was eroded after 2 years by additional deaths from cardiovascular causes after EVAR, based on the results of EVAR trial 1 and the DREAM trial showing that there was no difference in mid-term survival between the treatments. The model also assumed that there would be a small but persistent difference in late aneurysm-related deaths between the treatments.

It has been assumed that the baseline utility of these patients is the same as that of the age-specific UK general population estimates. There is an initial loss of utility for 1 month post surgery with open repair resulting in a larger loss (a reduction of 0.094 compared with 0.027 for EVAR).⁴³ There is also a 1-month loss of utility for a non-disabling stroke or myocardial infarction, and a permanent utility decrease following a disabling stroke. In the base case all QALYs were discounted at a rate of 3.5% per annum.

Table 41 provides a summary of some of the key effectiveness parameters used in the model.

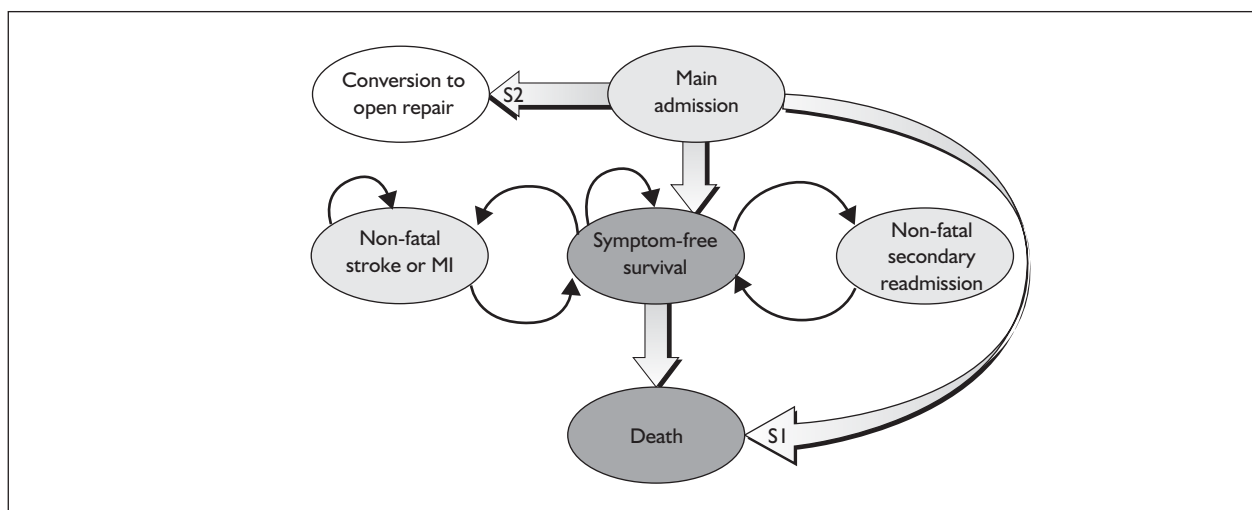


FIGURE 66 Schematic of model from Epstein et al.¹⁰⁶ © British Journal of Surgery Society Ltd. Reproduced with permission, granted by John Wiley & Sons on behalf of the BJSS Ltd.

TABLE 41 Key effectiveness parameters from Epstein *et al.*¹⁰⁶

Key parameters	Value	Source
Probability of operative (30-day) mortality for EVAR (%)	5.0	EVAR trial I ⁴³
Probability of operative (30-day) mortality for open repair (%)	1.6	EVAR trial I ⁴³
Probability of conversion to open repair from EVAR during primary admission (%)	0.8	EVAR trial I ⁴³
Mortality rate from AAA-related causes during follow-up with EVAR	6 per 15,000 patient-months, assumed constant over patient's lifetime	EVAR trial I ⁴³
Mortality rate from AAA-related causes during follow-up with open repair	1 per 15,000 patient-months, assumed constant over patient's lifetime	EVAR trial I ⁴³

Summary of resource utilisation and cost data

Resource utilisation and cost data for the initial EVAR or open repair surgery, a conversion to open repair during primary EVAR, and a secondary readmission for an AAA have all been taken from the EVAR trial. Costs for non-fatal cardiovascular events have been taken from Jones *et al.*¹²⁵

All patients in the EVAR group have been assumed to require hospital outpatient attendances and CT to monitor their aneurysm repair. In the base case it was assumed that two surveillance visits would be required in the first year and then one annually thereafter. The costs for these visits and scans have been taken from NHS reference costs.¹²³ In the base case all costs were discounted at a rate of 3.5% per annum. *Table 42* summarises some of the key cost parameters used by the authors in the model.

Summary of cost-effectiveness

In the base case EVAR was more costly than open repair by £3800 per patient but also produced fewer lifetime QALYs than open repair (mean -0.020 QALYs). Therefore, under the base-case assumptions EVAR was dominated by open repair.

The base-case assumptions were varied in a series of secondary analyses to reflect alternative

evidence and opinions about some of the key parameters in the model. In only one case was the EVAR ICER found to be under £30,000 per QALY. This occurred when the age of the initial cohort was increased from 74 to 82 years (with a greater absolute difference in operative mortality between the treatments) and the lower long-term rate of cardiovascular death after open surgery was replaced with the assumption that there is no difference in the rate of cardiovascular death after open repair or EVAR.

ICERs for the base case and some of the sensitivity analyses conducted are presented in *Table 43*.

Comments

General

Epstein *et al.* found that EVAR was not a cost-effective use of resources in 74-year-old male patients with an AAA of diameter ≥ 5.5 cm. Under their base-case assumptions they found that EVAR was dominated by open repair (i.e. it had higher costs but worse outcomes).

Internal validity

The authors of this study have used RCT evidence to parameterise this model, which is the most preferred form of evidence according to NICE.¹⁵ However, they have still had to make assumptions,

TABLE 42 Key resource cost parameters from Epstein *et al.*¹⁰⁶

Key resources	Cost	Source
EVAR procedure	£10,726	EVAR trial I ⁴³
Open repair procedure	£9578	EVAR trial I ⁴³
Conversion to open repair during primary EVAR	£42,067	EVAR trial I ⁴³

TABLE 43 Key cost-effectiveness results from Epstein et al.¹⁰⁶

Scenario	ICER
Base case	EVAR dominated
Discounted incremental QALYs generated by EVAR	-0.020 QALYs
Discounted incremental cost of EVAR arm compared with open repair arm	£3578
Sensitivity analyses/alternative assumptions	
Age 82 years and no difference in rate of cardiovascular death after open repair or EVAR	£27,000 per QALY
Same hazard of cardiovascular death following each treatment strategy	£42,000 per QALY
No difference between EVAR and open repair in the long-term rate of AAA-related death	£42,000 per QALY

particularly for the rates of cardiovascular deaths and non-fatal events in the medium term. Assumptions were also made about values of parameters after 4 years as this is the maximum length of follow-up that was available from the EVAR trial. If these assumptions do not hold then the accuracy of the results will be questionable.

External validity

Epstein *et al.* have conducted the results from the perspective of the NHS. This is the appropriate perspective for NICE to make decisions. However, as noted in the internal validity section, if any of the assumptions made do not hold then the relevance of the results to the NHS may be in question. Some data from EVAR trial 1, particularly regarding procedure costs and long-term reintervention rates of current devices, may be dated.

Prinssen et al. Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial¹²⁶

Overview

The authors conducted a cost-effectiveness analysis of a multicentre randomised trial of EVAR compared with open repair in patients with AAAs of ≥ 5 cm in diameter. The analysis is conducted for up to 1 year after the original procedure. All of the

effectiveness and resource use data were taken from the DREAM trial (therefore relevant data from EVAR trial 1 has been excluded).

Summary of effectiveness data

HRQoL was assessed using the EQ-5D questionnaire. Questionnaires were filled in by the trial patients at baseline (upon randomisation) and at 3 and 6 weeks and 3, 6 and 12 months postoperatively. By using linear interpolation for periods between measurements, quality-adjusted survival time was calculated up to 1 year after inclusion. A small and non-significant benefit of open repair compared with EVAR was found. *Table 44* summarises the QALY outcomes from the two trial arms over a 1-year period.

Summary of resource utilisation and cost data

Costs associated with treatment and follow-up until 1 year after inclusion were calculated by multiplying individual patient resource use recorded in the trial by unit costs. All costs were calculated in 2003 euros.

The costs of lost productivity were also calculated. These took account of sick leave and travel, as well as other costs incurred by the patients and their families. *Table 45* summarises the average total cost in each trial arm based on a bootstrap estimate.

TABLE 44 Key effectiveness parameters from Prinssen et al.¹²⁶

Key parameters	Value	Source
QALYs generated by EVAR over 1 year	0.72 QALYs	DREAM ¹²⁶
QALYs generated by open repair over 1 year	0.73 QALYs	DREAM ¹²⁶

TABLE 45 Key resource cost parameters from Prinssen et al.¹²⁶

Key resource	Cost	Source
Average total cost of EVAR patient (from bootstrap)	€18,179	DREAM ¹²⁶
Average total cost of open repair patient (from bootstrap)	€13,886	DREAM ¹²⁶

Summary of cost-effectiveness

The authors found that patients in the EVAR group experienced less QALYs than those in the open repair group (0.72 QALYs versus 0.73, respectively) whilst incurring more costs (€18,179 versus €13,886, respectively). Thus, EVAR was dominated by open repair with a 1-year time horizon.

The authors also conducted a non-parametric bootstrapping approach to evaluate the joint uncertainty in outcomes and costs.

Table 46 presents the key cost-effectiveness results for the study.

Comments

General

The authors of this study have found that, with a 1-year time horizon, EVAR is dominated (it has higher costs and lower effectiveness) by open repair in patients with an AAA of diameter ≥ 5 cm in size. It should be noted that this inclusion criteria is different to that in EVAR trial 1 in which only patients with an AAA of ≥ 5.5 cm in diameter were included.

Internal validity

The approach taken by the authors of this study raises issues about the validity of the results produced. Most importantly, the short time horizon means that any differences between arms post 1 year have not been captured and these may be important when determining cost-effectiveness. For example, given that mortality was higher in

the open repair arm than in the EVAR arm, by not extrapolating results the authors may have biased their results against the EVAR arm by not accounting for the fact that there are more patients still alive at 1 year in this arm and thus more patients who can accrue QALYs over time. They have also ignored differences in complications and mortality that arise after 1 year.

External validity

The study is a Dutch study and as such the results may not be transferable to an NHS setting. The inclusion of patient costs is also not relevant for NICE decision-making; however, if anything this would be expected to bias the results against open repair because of the observed longer recovery time after the initial procedure in this arm.

Medtronic submission. Endovascular aneurysm repair (EVAR) for the treatment of infra-renal abdominal aortic aneurysms (AAA)¹²⁷

Overview

In this study the authors conducted a cost-utility analysis comparing EVAR with open repair. The patient population considered was that of EVAR trial 1, i.e. patients with an unruptured infrarenal AAA of at least 5.5 cm in diameter who are considered fit for open surgery. The average age of the population was 70 years and 90% of patients were men.

The authors developed a two-stage model to estimate the lifetime costs and QALYs of EVAR

TABLE 46 Key cost-effectiveness results from Prinssen et al.¹²⁶

Variable	Estimate
Total average cost of EVAR patient over 1 year	€18,595
Total average cost of EVAR patient over 1 year (bootstrapped)	€18,179
Total average cost of open repair patient over 1 year	€13,627
Total average cost of open repair patient over 1 year (bootstrapped)	€13,886
Average QALYs generated by EVAR patient	0.72 QALYs
Average QALYs generated by open repair patient	0.73 QALYs

and open repair in this patient population: first, a decision tree for the first 30 days post surgery; second, a Markov model from 30 days post surgery until death.

Figure 67 represents the short-term decision tree for the first 30 days post surgery. At the end of the first 30 days patients in the EVAR arm will end up in one of four states: (1) successful EVAR with no complications, (2) EVAR with complications, (3) conversion to open surgery or (4) death. Conversely, those in the open repair arm initially may end up in one of three states: (1) open repair with no complications, (2) open repair with complications or (3) death.

Once patients enter the 30 days post surgery Markov model (Figure 68) then they must be in one

of four health states: (1) no complications requiring secondary intervention, (2) technical complications requiring secondary intervention, (3) systemic complications (split into a first-year phase and then subsequent years phase) or (4) death.

Summary of effectiveness data

The effectiveness data used to parameterise the model were largely drawn from EVAR trial 1⁴³ but were supplemented with data from additional sources.

For the short-term model, mortality estimates and the need for secondary intervention were based on data from EVAR trial 1. However, the risk of conversion from EVAR to open surgery was based on clinical expert opinion rather than on the trial (the authors used a probability of conversion

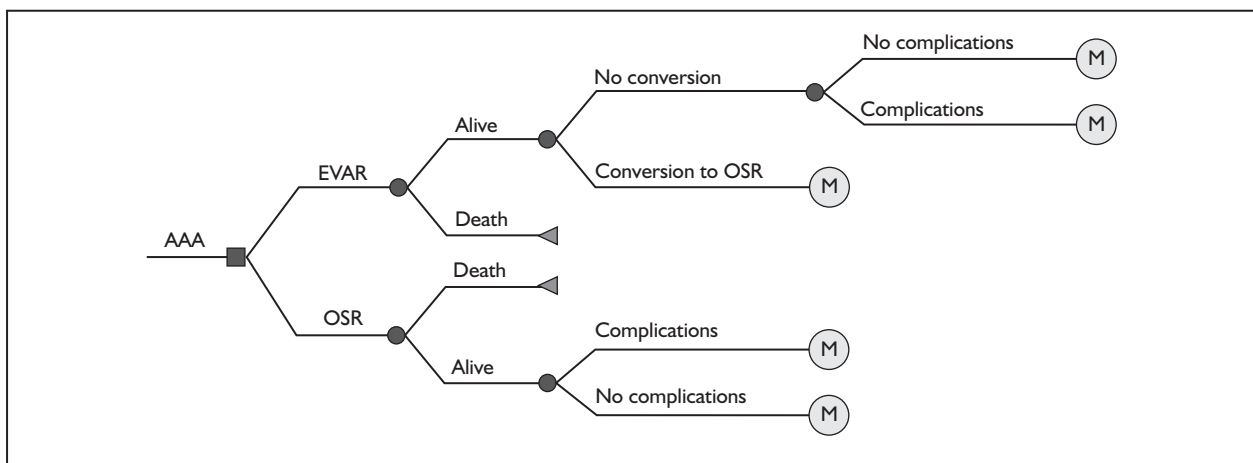


FIGURE 67 Schematic of decision tree from Medtronic submission,¹²⁷ reproduced with permission from Medtronic.

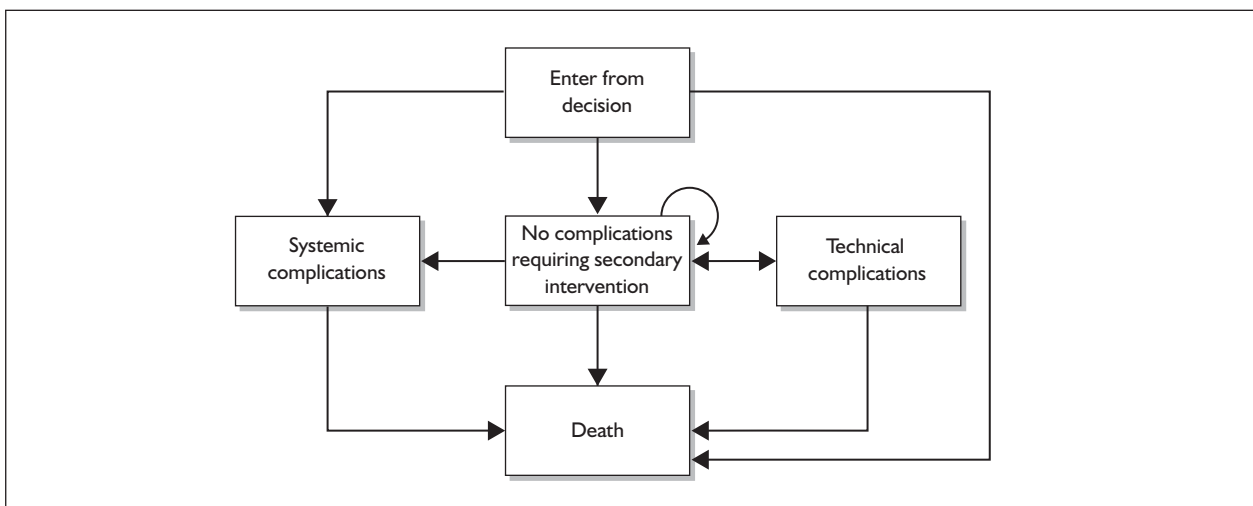


FIGURE 68 Schematic of Markov model from Medtronic submission,¹²⁷ reproduced with permission from Medtronic.

of 0.2%, which is much lower than that used in other studies, e.g. Epstein *et al.*,¹⁰⁶ in which the probability was four times larger at 0.8%, taken from EVAR trial 1⁴³).

The baseline risk of systemic complications (myocardial infarction, temporary and permanent renal failure, and disabling and non-disabling stroke) for EVAR patients in the first 30 days was estimated from the EUROSTAR data set. The relative risk of systemic complications for open surgery versus EVAR was taken from a meta-analysis of observational studies and one RCT (DREAM). The authors have assumed that the incidence rates for systemic complications follow the same pattern as for all-cause mortality, i.e. that open repair patients have a higher incidence in the first 30 days post surgery whereas EVAR patients have a higher incidence from 30 days to 18 months post surgery. Therefore, it has been assumed that over the first 18 months the number of events that occur in the two groups is equal. The authors have achieved this in the model by using the incidence rate of myocardial infarction and stroke in the general UK population for the open repair group from 30 days to 18 months. Then the relative risk for EVAR was calculated such that the number of events was equal at 18 months. However, it should be noted that the numbers of events in each arm were only equal for myocardial infarction and stroke and not for renal failure. This was considered to be closely related to the intervention itself and therefore could only occur in the first 30 days, hence there was a higher prevalence of renal failure in the open repair arm. The authors have then assumed that no new systemic complications occur from 18 months onwards.

Long-term risks of mortality and secondary interventions were also based on data from EVAR trial 1.⁴³ The authors considered two scenarios for estimating the difference in late mortality (after 30 days). First, they considered a relative risk for EVAR compared with open repair for late mortality (for any cause) of 1.055, applied for 4 years. The authors stated that this relative risk was calculated from EVAR trial 1 but it was not clear exactly how this was carried out. In the second scenario the difference in mortality between the two treatments is only due to AAA mortality, and the authors estimate a relative risk of 1.18, again based on EVAR trial 1 results for late aneurysm mortality. It should be noted that EVAR trial 1 reported HRs (EVAR relative to open surgery) for aneurysm-

related mortality of 0.42 (95% CI 0.21 to 0.82) for the first 6 months and 1.15 (95% CI 0.39 to 3.41) from 6 months to 4 years; the corresponding HRs for total mortality in the two periods were 0.55 (95% CI 0.33 to 0.93) and 1.10 (95% CI 0.80 to 1.52) respectively. The authors assumed that from 1 month post surgery until 4 years the patients experience this as a constant relative risk of death. At 4 years it has been assumed that patients in both arms experience a risk of death that is similar to that of the background UK population with adjustments for increased incidence of cardiovascular death in an AAA population after surgery.

The risk of patients requiring a secondary intervention was derived from EVAR trial 1 and then supplemented with data from other sources. The total number of secondary interventions was taken from the EVAR trial; the secondary intervention rate was 1.72% per month from 2 to 6 months post surgery in the EVAR arm and 1.03% in the open repair arm, whereas for post 6 months the rate in the EVAR arm was 0.27% and there were no secondary interventions post 6 months in the open repair arm. The percentages of these secondary interventions that were transabdominal, extra-anatomic or transfemoral has then been derived from other sources, notably EUROSTAR for the EVAR group and expert clinical opinion for the open repair group. Both patient groups have a constant risk of secondary intervention from the operation until 6 months post operation. Post 6 months it is assumed that open repair patients are no longer at risk of secondary interventions and that the rate of reintervention for EVAR patients remains constant over time. The authors have also assumed that patients do not experience disutility from secondary interventions and that they have the same prognosis as other patients after the reintervention.

Utility scores for health states have been taken directly from EVAR trial 1. In the first 3 months post surgery, those in the open repair arm had a lower utility than those in the EVAR arm (0.67 versus 0.73). From 24 months onwards it was assumed that utility was equal in both arms (although it was age dependent). Disutility scores for the systemic complications have been drawn from several sources.

Table 47 presents the values used for some of the key parameters in the model.

TABLE 47 Key effectiveness parameters from Medtronic submission¹²⁷

Key parameters	Value	Source
Mortality of open repair (%)	4.19	Brown <i>et al.</i> ²³
Mortality of primary EVAR (%)	1.62	Brown <i>et al.</i> ²³
Probability of conversion of EVAR to open repair (%)	0.2	Brown <i>et al.</i> ²³ and expert opinion
Mortality all-cause (monthly) – EVAR	0.48%	EVAR trial I ⁴³
Mortality all-cause (monthly) – open repair	0.46%	EVAR trial I ⁴³
Mortality AAA-related (monthly) – EVAR	0.035%	EVAR trial I ⁴³
Mortality AAA-related (monthly) – open repair	0.034%	EVAR trial I ⁴³

Summary of resource utilisation and cost data

(Commercial-in-confidence information has been removed.)

The authors also assumed that 50% of follow-up scans are now duplex ultrasound and 50% are CT, with the same frequency of monitoring as in the EVAR trial 1 protocol. As duplex ultrasound is cheaper than CT this reduced the overall cost of monitoring in the EVAR arm.

The costs for secondary interventions were drawn from NHS reference costs.¹²³ The costs for the same type of intervention (e.g. transabdominal intervention) are assumed to be the same for each treatment arm. However, the percentage of each type of intervention as a proportion of the total number of secondary interventions differs between the two treatments, with open repair having the highest proportion of the most costly procedures, making the average cost per secondary intervention higher in the open repair group. These percentages are not based on trial evidence but instead on the EUROSTAR registry in the case of the EVAR arm and on clinical opinion in the case of the open surgery arm. *Table 48* presents some of the values used for key cost parameters in the model.

Summary of cost-effectiveness

The authors found that in the base case patients treated with EVAR were expected to receive more QALYs than those treated with open surgery but at a higher cost (commercial-in-confidence information has been removed). This resulted in an ICER of £15,681 per QALY for EVAR compared with open repair.

The authors also conducted univariate sensitivity analyses for all of the parameters in the model, using the values for the lower and upper confidence limits of each parameter. They found that the ICER was most sensitive to the short-term relative risk of operative mortality.

Table 49 presents ICERs for the base case and the sensitivity analysis in which the short-term relative risk of mortality was varied.

Comments

General

The authors of this study have found that, under their base-case assumptions, EVAR is a cost-effective use of resources compared with open surgery in the EVAR trial 1 patient population (i.e. patients with an average age of 70 years, 90% of whom are men, and with an AAA of at least 5.5 cm in diameter) assuming a cost-effectiveness threshold of £20,000 per QALY.

TABLE 48 Key resource cost parameters from Medtronic submission¹²⁷

Key resources	Cost	Source
Cost of open AAA repair	(CiC information has been removed)	EVAR trial I ⁴³
Cost of EVAR repair	(CiC information has been removed)	Medtronic ¹²⁷
CiC, commercial-in-confidence.		

TABLE 49 Key cost-effectiveness results from Medtronic submission¹²⁷

Scenario	ICER
Base case	(CiC information has been removed)
Discounted incremental QALYs generated by EVAR	(CiC information has been removed)
Discounted incremental cost of EVAR patient compared with open repair patient	(CiC information has been removed)
Sensitivity analyses/alternative assumptions	
Lower confidence limit for short-term relative risk of mortality [CiC information has been removed]	(CiC information has been removed)
Upper confidence limit for short-term relative risk of mortality [CiC information has been removed]	(CiC information has been removed)
CiC, commercial-in-confidence.	

Internal validity

The first issue relates to assumptions made about the rate of systemic complications (renal, cardiac and cerebrovascular events). In particular, the Medtronic analysis assumed that no new systemic complications occurred after 18 months; that there were no new cases of renal failure after 30 days; and that open repair patients have a higher incidence of all systemic complications before 30 days but EVAR patients have a higher incidence from 1 to 18 months such that they have equal incidence at 18 months. To test whether these assumptions affected the results we conducted an additional sensitivity analysis using the Excel model supplied to us by Medtronic. We set the rates of renal failure and cardiovascular complications in the first 30 days and in the long-term model to be the same after EVAR and open repair (ORs and HRs equal to 1). We found that there was only a small difference (ICER £18,000 per QALY) compared with the Medtronic base case (commercial-in-confidence information has been removed) and we conclude that these assumptions do not affect the overall conclusions of the Medtronic model.

Second, the authors assume that there is no disutility associated with secondary interventions and no risk of perioperative complications. If these assumptions do not hold then they will bias the results in favour of EVAR being cost-effective, as EVAR has a higher rate of secondary interventions.

Third, (commercial-in-confidence information has been removed).

Fourth, Medtronic also assume that a small difference in survival in favour of EVAR is maintained over the patient’s lifetime (commercial-

in-confidence information has been removed). This model assumption is not supported by the results of the EVAR trial 1 and DREAM trials, which both found no difference in survival at 4 years.

External validity

In addition to the key issues discussed above there are other issues that may affect the validity of the results for the UK setting. (Commercial-in-confidence information has been removed.)

Bowen et al. Systematic review and cost-effectiveness analysis of elective endovascular repair compared to open surgical repair of abdominal aortic aneurysms¹²⁸

Overview

The authors developed a decision-analytic model to evaluate the costs and QALYs associated with EVAR and open surgical repair. The model relates to 70-year-old male patients with AAAs of 5.5 cm diameter who are considered medically suitable to undergo either open surgical repair or EVAR over a period of 13 months. The first 30 days are modelled using a decision tree and the following 12 months are modelled using a Markov decision model. The Markov models for the following 12 months for those patients who received EVAR and those patients undergoing open surgical repair were similar, with conversion to open surgical repair and the endoleak states removed.

Summary of effectiveness data

Several sources of data were used to parameterise the model, including data from a non-randomised field evaluation conducted by the authors and results from a systematic literature review. Most of the probabilities used in the model were derived

TABLE 50 Key effectiveness parameters from Bowen et al.¹²⁸

Key parameters	Value	Source
Probability of death immediately following EVAR (%)	2.6	Meta-analysis
Probability of death immediately following open surgical repair (%)	4.3	Meta-analysis
Probability of early conversion from EVAR to open surgical repair (%)	1.2	Meta-analysis
Utility in first 30 days following EVAR	0.70	Field study
Utility in first 30 days following open surgical repair	0.56	Field study
Utility in first 90-day cycle following initial 30 days for EVAR	0.83	Field study
Utility in first 90-day cycle following initial 30 days for open surgical repair	0.67	Field study
Utility in second 90-day cycle following initial 30 days for EVAR	0.85	Field study
Utility in second 90-day cycle following initial 30 days for open surgical repair	0.77	Field study
Utility in fourth 90-day cycle following initial 30 days for EVAR	0.91	Field study
Utility in fourth 90-day cycle following initial 30 days for open surgical repair	0.91	Field study

from the literature review and meta-analyses. These included the EVAR 1 and DREAM trials as well as other non-randomised sources. It should be noted that it is not clear which sources were used for the meta-analysis for probability of death. All-cause mortality was derived from the life tables of Statistics Canada. The utility values assigned to different states in the model were based on adjusted estimates of the EQ-5D scores reported in the field evaluation conducted by the authors.

Table 50 presents some of the key effectiveness parameters from the study.

Summary of resource utilisation and cost data

Data on costs and resource use were derived from a variety of sources. The costs of the initial hospitalisation for each treatment arm were derived from the costs observed in the field study conducted by the authors. This field study was a non-randomised prospective study that aimed to compare EVAR patients at high risk for open surgical repair with patients receiving open surgical repair with either low or high surgical risk. The study prospectively collected clinical outcomes, resource utilisation data and quality of life information.

Costs of major complications during initial hospitalisation (e.g. myocardial infarction, stroke, etc.) were based on mean hospital costs for each condition found in the Ontario Case Costing Initiative database. The 1-year follow-up costs for EVAR and open surgical repair were also derived from the field study. Costs were also derived from the literature.

The values for some key resource cost parameters are reported in Table 51.

Summary of cost-effectiveness

In the base case EVAR was both more costly than open surgical repair (C\$32,079 versus C\$17,503) and more effective (0.863 QALYs versus 0.772 QALYs) over a period of 13 months. As such the incremental cost per QALY was found by the authors to be C\$160,176 (Table 52). Because of concerns that the authors had over some of the non-randomised results used from the systematic review to parameterise the model, particularly with regards to complications, the authors performed a secondary analysis in which complication costs and rates were taken from the field study. Because of the low number of complications observed in the EVAR arm of the field study the ICER was lower than that found in the base case (C\$22,528 per QALY versus C\$160,176 per QALY; Table 52).

TABLE 51 Key resource cost parameters from Bowen et al.¹²⁸

Key resources	Cost	Source
Hospitalisation for open surgical repair – no major complications	C\$13,243	Field study
Hospitalisation for EVAR – no major complications	C\$23,525	Field study

TABLE 52 Key cost-effectiveness results from Bowen et al.¹²⁸

	Value
Base case	C\$160,176 per QALY
Incremental QALYs generated by EVAR	0.091
Incremental cost of EVAR arm compared with open repair arm	C\$14,576
ICER based on field evaluation complication rates and costs	C\$22,528 per QALY

Comments**General**

Bowen *et al.* found that in their base case EVAR did not appear to be a cost-effective use of resources (with an ICER of C\$160,176 per QALY). However, when results from their field study were used in place of results from the literature review EVAR appeared to be cost-effective assuming a threshold of as low as C\$23,000 per QALY.

Internal validity

The use of non-randomised data in this study raises issues about the internal validity of the results for both the primary and secondary analyses. Although RCT data have been used (EVAR trial 1 and DREAM), the authors have synthesised these data with data from non-randomised studies. The authors have also not conducted sensitivity analyses to test the robustness of their results to changes in certain parameters.

External validity

The study is conducted from the perspective of the Canadian health-care system and as such its applicability to the UK NHS is unclear. The use of non-randomised data, which raises issues around the internal validity of results, also affects the external validity of the results.

Bowen et al. Systematic review and cost-effectiveness analysis of elective endovascular repair compared to open surgical repair of abdominal aortic aneurysms¹²⁹

Overview

A cost-effectiveness analysis was performed based upon a field evaluation conducted by the authors of this report. The analysis focused on high-risk patients and had a time horizon of 1 year. As this study only considers data from the authors' non-randomized field study and does not incorporate other evidence (e.g. from the available RCTs), its relevance to the UK is considered to be limited. Therefore, only a brief review of the study is presented here.

Summary of effectiveness data

The authors estimated the life-years gained over 1 year using results from the field study and Kaplan–Meier survival curves. The life-years were then converted into QALYs by combining the survival curves with utility estimates, also derived from the field study, over time.

The authors also conducted sensitivity analysis on the time horizon considered in the study using several assumptions regarding the extrapolation of survival curves (no convergence, convergence after 10 years, convergence after 5 years and convergence after 3 years).

Summary of resource utilisation and cost data

The authors collected resource use in their field study over 1 year and used these data to inform the costs. The authors also calculated the costs due to productivity losses.

Summary of cost-effectiveness

In the analysis over 1 year the authors found that for high-risk patients EVAR was both less costly and more effective than open surgical repair and as such EVAR dominated open surgical repair.

When a longer time horizon was specified EVAR does result in more costs than open surgical repair under all four assumptions regarding the survival curves. However, even when there is convergence after 3 years the incremental cost per QALY is still only \$18,616 and as such EVAR still appears cost-effective.

Comments**General**

The results suggest that EVAR may be a cost-effective use of resources compared with open surgical repair in high-risk patients.

Internal validity

The use of non-randomised field study data raises serious issues over the validity of these results.

External validity

The study is conducted from a Canadian perspective and as such its applicability to the UK NHS is questionable. The study also takes account of productivity losses, which is inappropriate from a UK NHS perspective and which raises further issues about the applicability of the results.

Discussion of EVAR trial 1-type population models

The studies considered in the previous sections have conflicting results, with some finding EVAR to be a cost-effective use of resources^{105,108,127} and others finding it a non-cost-effective use of resources.^{106,107,126} The studies are considered separately in this section in light of the evidence provided by the other studies.

Patel *et al.*¹⁰⁵ found that under their base-case assumptions EVAR is a cost-effective alternative to open repair in 70-year-old men with AAAs of 5 cm in diameter. This contrasts with UK studies (i.e. Epstein *et al.*¹⁰⁶ and Michaels *et al.*¹⁰⁷) which have found that EVAR is not cost-effective compared with open repair in similar, if not identical, patient groups. Other authors (e.g. Prinssen *et al.*¹²⁶) have argued that the key reason for the contradictory results produced by Patel *et al.*¹⁰⁵ is that the combined and lasting mortality and severe morbidity rate used by the authors (1.1% for EVAR versus 9.1% for open repair) was far too optimistic in favour of EVAR and that such a benefit was not shown in EVAR trial 1 or the DREAM trial. As the study is US based, and given the other issues identified, it does not appear possible to draw any conclusions from it about the cost-effectiveness of EVAR with regards to a UK NHS setting.

Bosch *et al.*¹⁰⁸ found that, given typical thresholds, EVAR is likely to be considered cost-effective compared with open repair in 70-year-old men with AAAs of between 5 and 6 cm in diameter. This contrasts with other more recent studies (e.g. Epstein *et al.*¹⁰⁶ and Michaels *et al.*¹⁰⁷) that have found EVAR not to be a cost-effective use of resources in similar patient groups. As the model in Bosch *et al.*¹⁰⁸ has been parameterised based on non-RCT data and the study is US based it does not appear reasonable to transfer its conclusions to a UK NHS setting.

Michaels *et al.*¹⁰⁷ found that EVAR does not appear to be cost-effective in an EVAR trial 1-type patient (i.e. RC1 in their analysis). The high incremental

cost and low incremental effectiveness of EVAR compared with open surgery in patients who are fit for open surgery (RC1) is consistent with the results of the other recent study.¹⁰⁶ However, the study was not able to make use of mid-term results from EVAR trial 1 as they were not available to the authors at the time.

Epstein *et al.*¹⁰⁶ found that EVAR was not a cost-effective use of resources in 74-year-old male patients with AAAs of diameter ≥ 5.5 cm. Under their base-case assumptions they found that EVAR was dominated by open repair (i.e. it had higher costs but worse outcomes). This study was adapted for use in the economic model presented later in this chapter (see York economic assessment).

Prinssen *et al.*¹²⁶ found that, with a 1-year time horizon, EVAR is dominated by open repair (it has higher costs and lower effectiveness) in patients with AAAs of diameter ≥ 5 cm. The approach taken by the authors of this study raises issues about the validity of the results produced. Most importantly, the short time horizon means that any post 1 year differences between arms have not been captured. However, despite there being no extrapolation of results over the patients' lifetimes the conclusions appear to be consistent with those of Epstein *et al.*¹⁰⁶ and Michaels *et al.*¹⁰⁷ These three papers appear to be the most relevant published studies from a UK perspective.

The authors of the unpublished Medtronic study¹²⁷ found that, under their base-case assumptions, EVAR is a cost-effective use of resources compared with open surgery in the EVAR trial 1 patient population. This contradicts the results of both Michaels *et al.*¹⁰⁷ and Epstein *et al.*¹⁰⁶, who found that in the same population EVAR was not a cost-effective use of resources. The York economic assessment presents a decision model comparing EVAR and open repair that investigates the main assumptions made by each of these authors in more detail. *Table 53* summarises the studies and provides the base-case cost-effectiveness results.

Cost-effectiveness studies focusing on the EVAR type 2 population

This section considers economic evaluation studies focusing on a patient population which is similar to that in EVAR trial 2 (i.e. patients considered unfit for open repair).

TABLE 53 Summary of studies considering EVAR trial 1-type populations

Study	Summary	Patient population	QALYs	Costs	ICER
Michaels 2005 ¹⁰⁷ (RC1)	Markov model comparing EVAR with open repair	Fit 70-year-old patients with an AAA of 5.5 cm diameter	0.10	£11,449	£110,000 per QALY
Bosch 2002 ¹⁰⁸	Markov model comparing EVAR with open repair	70-year-old men with an AAA of between 5 and 6 cm in diameter	0.22	US\$179	US\$9905 per QALY
Patel 1999 ¹⁰⁵	Markov model comparing EVAR with open repair	70-year-old men with an AAA of 5 cm in diameter	0.42	US\$9587	US\$22,836 per QALY
Epstein 2008 ¹⁰⁶	Markov model comparing EVAR with open repair	Male patients aged 74 years with an AAA of diameter \geq 5.5 cm	-0.020	£3578	EVAR dominated
Prinssen 2007 ¹²⁶	Within-trial analysis comparing EVAR with open repair	Fit patients with an AAA of \geq 5 cm in diameter	-0.01	€4968	EVAR dominated
Medtronic 2007 ¹²⁷	Markov model comparing EVAR with open repair	Patients with an average age of 70 years, 90% of whom are men, and with an AAA of at least 5.5 cm in diameter	(CiC information has been removed)	(CiC information has been removed)	£15,681 per QALY

CiC, commercial-in-confidence.

Michaels et al. Cost-effectiveness of endovascular abdominal aortic aneurysm repair¹⁰⁷

Overview

This study evaluated the cost-effectiveness of EVAR compared with open repair in patients fit for surgery (RC1) or with conservative management in those unfit for surgery (RC2). The aim of the study was to determine an optimal strategy for the use of EVAR based on the best available evidence at the time. The study was published before the results of the EVAR trial 2 were available.

Effectiveness and resource use data were based on recent RCTs (EVAR and DREAM) as well as on a systematic review of the literature. The authors developed a Markov model and used it to consider two separate 'reference cases', one of which, RC1, was discussed in the previous section. In this section we will consider their modelling of 80-year-old patients with an AAA of 6.5 cm diameter who were considered unfit for open surgery and for whom the choice of treatment was between EVAR and conservative management (RC2). The primary outcome measure for the cost-effectiveness analysis was the incremental cost per QALY gained. The authors used a 10-year time horizon. The evaluation was undertaken from the perspective of the NHS.

The model for RC2 is similar to that of RC1 (*Figure 65*) with the surgery arm being replaced by a conservative management arm. Conservative management in this model excludes the option for elective surgery.

Summary of effectiveness data

Short-term operative mortality probabilities were taken from the EVAR⁴² and DREAM⁴⁰ trials. However, it should be noted that these trials were conducted in patient populations who were considered fit for open repair and thus the mortality probability of EVAR found might not be applicable to the less healthy patient population considered here. The probabilities of reintervention and complications were derived from a previously conducted systematic review. General mortality was taken from standardised mortality tables for England and Wales. Aneurysm-related mortality was calculated from a previous modelling study.

Rupture rates for conservative management were based on three published studies¹³⁰⁻¹³² and are a function of aneurysm size. Expansion rates were also taken from other studies.¹³²⁻¹⁴⁰ It should be noted that these studies are dated (all were published before 1992) and may not accurately

reflect the current natural history of untreated aneurysm.

Utility estimates were based on published figures derived from the EQ-5D tariff values for men aged 65–74 years. To account for the lower HRQoL initially following surgery, a reduction in keeping with that seen after major surgery was applied for the first 2 weeks after EVAR. QALYs were discounted at a rate of 3.5% per annum.

The key effectiveness parameters for the model are reported in *Table 54*.

Summary of resource utilisation and cost data

Most costs were based on NHS reference costs for 2003–4¹²³ with the mean cost being the point estimate. For the probabilistic sensitivity analysis a normal distribution was assumed with standard deviation based on the assumption that 50% of observations were within the published interquartile range. The procedure cost of EVAR was assumed to be the average national NHS reference cost for open surgery plus an additional incremental cost of EVAR estimated from data collected at the Sheffield Teaching Hospital NHS Trust. Follow-up costs for EVAR were based on NHS reference costs with the assumption that on average an EVAR patient will have two outpatient visits and two CT scans per year. It is not clear from the published paper if patients in the no surgery arm received continuing surveillance. The average cost of a reintervention in the EVAR arm again used NHS reference costs but was based on the case mix of reinterventions as recorded in the EUROSTAR

registry.¹²⁴ All costs have been discounted at a rate of 3.5% per annum. *Table 55* summarises the key resource cost parameters from the study.

Summary of cost-effectiveness

RC2 reference case

The base-case results for RC2 showed that EVAR resulted in increased QALYs (1.64 QALYs) compared with conservative management but also extra costs (£14,077), resulting in an ICER of £8579 per QALY.

A variety of sensitivity analyses was also undertaken on the RC2 reference case. The ICERs for the RC2 group ranged from £5215 per QALY (when initial incremental cost of EVAR was reduced to £0) to £19,971 per QALY (when the time horizon was reduced to 5 years).

The authors also undertook a probabilistic sensitivity analysis. All of the simulations generated an ICER of less than £30,000 per QALY (i.e. the probability of the ICER being less than £30,000 per QALY was 1). *Table 56* presents the ICERs for the RC2 base case and for some of the sensitivity analyses conducted.

Comments

General

Michaels *et al.*¹⁰⁷ found that EVAR may be a cost-effective intervention in patients who are unfit for open surgery. With a 10-year time horizon they found that, compared with medical management, EVAR resulted in more QALYs at a higher cost, giving an ICER of £8579 per QALY.

TABLE 54 Key effectiveness parameters from Michaels *et al.*¹⁰⁷

Key parameters	Value	Source
Mortality of primary EVAR for first month post surgery (%)	1.85	EVAR trial 1 ⁴² and DREAM ⁴⁰
Probability of conversion of EVAR to open repair (%)	1.9	Drury <i>et al.</i> ¹²¹
Utility for living patient following treatment	0.8	Health Survey for England 1996 ¹²²

TABLE 55 Key resource cost parameters from Michaels *et al.*¹⁰⁷

Key resources	Cost	Source
Cost of EVAR repair	£8769	Sheffield Teaching Hospital NHS Trust
EVAR follow-up cost per month	£41.50	NHS reference costs ¹²³
Reintervention	£4790	NHS reference costs ¹²³ and EUROSTAR ¹²⁴

TABLE 56 Key cost-effectiveness results from Michaels et al. (RC2)¹⁰⁷

Scenario	Result
Base-case ICER (RC2)	£8579 per QALY
Discounted mean incremental QALYs generated by EVAR compared with no surgery (RC2)	1.64
Discounted mean incremental cost of EVAR compared with no surgery (RC2)	£14,077
Sensitivity analyses/alternative assumptions	
EVAR procedure costs the same as average cost of open repair	£5215 per QALY
5-year time horizon	£19,971 per QALY

Internal validity

This study was conducted before the EVAR trial 2 long-term results were published and has thus relied on other sources to parameterise the model. Some of the parameters have been derived from non-randomised sources and are thus open to bias. The use of the EVAR trial 1 operative mortality rate also appears inappropriate given the differences between the patient group considered in this study (one that is unfit for open surgery) and the EVAR trial 1 population (all of whom were considered fit for open surgery).

External validity

The study is UK based and has been conducted from the perspective of the NHS. However, estimates of aneurysm growth rates and rupture rates in untreated patients from the literature may not reflect rates expected in patients anatomically suitable for EVAR.

EVAR trial participants – Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial⁴⁶

Overview

EVAR trial 2 investigated whether EVAR improved survival compared with no intervention in patients who were considered unfit for open repair. Although it was not explicitly a cost-effectiveness study, we review it in this section because the study reported life expectancy and costs, and there have been no other cost-effectiveness analyses published in the light of the results of this trial. The mean age of patients in the EVAR arm was slightly higher than in the no intervention arm (76.8 years versus 76.0 years, respectively). The mean AAA diameter was also marginally larger in the EVAR arm than in the no intervention arm (6.4 cm versus 6.3 cm, respectively).

In the trial patients were followed up over 4 years and data on mortality, HRQoL (measured by the EQ-5D and the SF-36) and resource use were collected over this period.

Summary of effectiveness data

The EVAR trial 2 found that the 30-day operative mortality rate for the EVAR group was 9%. The no intervention group was found to have a rupture rate of 9.0 per 100 person-years. By the end of the 4 years, overall mortality was around 64% and this did not significantly differ between the two trial arms. The trial also found no significant difference in aneurysm-related mortality between the two trial arms.

HRQoL data was collected from the EVAR arm patients at 1, 3 and 12 months after the operation, whereas for the no intervention arm it was collected from the patients at 2, 4 and 13 months after randomisation (this was based on the assumption that it would take 1 month following randomisation for the EVAR procedure to be performed). No clear and consistent differences in HRQoL between the two trial arms were found.

Summary of resource utilisation and cost data

Resource use and cost estimations were calculated using the same methods as those used in EVAR trial 1 (e.g. data on resource use were collected using case report forms, which were then multiplied by unit costs to calculate total costs). Resources considered included, among others, initial procedure resource use, hospital stay, secondary AAA procedures, outpatient visits and surveillance using CT.

The study found that the EVAR arm had considerably greater mean hospital costs per patient than the no intervention arm (£13,632 versus £4983 respectively).

Summary of cost-effectiveness

The study found that EVAR did not improve HRQoL over the follow-up period, had a high 30-day operative mortality rate, had no 4-year survival benefit and had considerably higher costs than in the no intervention arm. Therefore, in the patient group considered (patients of around 66 years of age with an AAA of approximately 6.5 cm in diameter) it appeared that EVAR may be dominated by the no intervention arm (i.e. EVAR has higher costs and worse outcomes).

Comments

General

EVAR trial 2 investigated whether EVAR improved survival compared with no intervention in patients who were considered unfit for open repair. This study found that EVAR led to no improvement in outcomes but had a higher cost.

Internal and external validity

In Chapter 3 several issues that complicate the analysis of the EVAR trial 2 were discussed. These include the long delay between randomisation and procedure and the fact that a number of individuals in the no intervention arm received EVAR or open repair. This raises issues over the validity of the study in terms of whether it accurately captures the costs and benefits of the two strategies (EVAR or no intervention) it aimed to evaluate.

Summary of studies considering EVAR trial 2-type populations

Table 57 summarises the results of the two studies considering an EVAR trial 2-type population. Michaels *et al.*¹⁰⁷ found EVAR to be a cost-effective use of resources compared with medical management in AAA patients who are considered unfit for open surgery. The results produced for

the RC2 group, however, do not agree with the results from EVAR trial 2,⁴⁶ which found that the EVAR arm was dominated by the medical management/no intervention arm (i.e. EVAR was more costly and with similar survival at 4 years). However, as discussed above there were issues with the EVAR trial 2 which may mean that its results do not accurately reflect the costs and benefits of the intended strategies. An economic model presented later in this chapter aims to add to the evidence from the RCT by bringing together the available evidence on costs and outcomes in treated patients with the limited data on natural history in untreated patients, to compare the strategies of surgery, no surgery or watchful waiting (see Model comparing immediate elective surgery, watchful waiting and no intervention).

York economic assessment

Introduction

The York economic assessment is divided into two complementary parts. The first part will compare the cost-effectiveness of EVAR versus open repair in patients with large aneurysms. This analysis assumes that the decision to operate has already been taken. The second part estimates the cost-effectiveness of policies on when, as well as how, the aneurysm repair should be carried out. As well as EVAR and open repair we consider no surgery and watchful waiting as alternative policies.

We consider that the population of patients with large aneurysms is clinically heterogeneous, which may mean that cost-effectiveness differs between patient groups. We show how the results might be affected by three key patient characteristics: age, fitness (risk of operative mortality) and aneurysm

TABLE 57 Summary of studies for EVAR trial 2-type populations

Study	Summary	Patient population	Incremental QALYs, EVAR	Incremental costs, EVAR	ICER
Michaels 2005 ¹⁰⁷ (RC2)	Markov model comparing EVAR with medical management	80-year-old patients with an AAA of 6.5 cm diameter who were considered unfit for open surgery	1.64	£14,077	£8579 per QALY
EVAR trial participants 2005 ⁴⁶	Within-trial analysis comparing EVAR with no intervention	76-year-old patients with a mean AAA diameter of approximately 6.3 cm who are considered unfit for open repair	Not stated	£8649	EVAR dominated by no intervention arm

size. Each variable affects the parameters of the model in a distinct way. Chapter 3 found age to be a risk factor for operative mortality in most studies, as well as for long-term survival, independent of aneurysm diameter and other factors. Fitness in this model represents pre-existing conditions examined in Chapter 3, such as cardiac, pulmonary or renal insufficiency, which might be predictive of operative mortality.¹⁴¹ However, the large number of combinations of potential risk factors and levels would make the presentation of results cumbersome if stratified in this way. It is more convenient to express fitness according to a single scale. In this analysis we define four levels of operative fitness:

- good fitness, or no pre-existing conditions affecting operative mortality
- moderate fitness, with twice the odds of operative mortality compared with a person of the same age and aneurysm size with good fitness
- poor fitness, with four times the odds of operative mortality compared with a person of the same age and aneurysm size with good fitness
- very poor fitness, with eight times the odds of operative mortality compared with a person of the same age and aneurysm size with good fitness.

From a clinical perspective these relative (un)fitness scores could in principle arise from any combination of factors. For example, Chapter 3 showed the evidence on the use of the GAS to predict early and late mortality in EVAR and open repair.⁵⁹ Unfortunately, no scoring system has achieved widespread acceptance.¹⁴² Furthermore, in practice, clinicians are skilled at subjectively assessing 'fitness' and Chapter 3 showed that these assessments are predictive of both short- and long-term mortality after surgery.^{23,65} Therefore, for this analysis we have used a general 'fitness' score as defined above.

We believe it is important that the model reflects clinical heterogeneity for three reasons. First, if cost-effectiveness differs between patient groups then it may be efficient to limit the use of EVAR to patients in whom it is cost-effective. Second, even if there are practical or ethical reasons that make it difficult to limit EVAR to particular patient groups, the decision model should nevertheless incorporate heterogeneity. Inputs to the model such as operative mortality and late mortality are

correlated as they depend on common clinical risk factors. If the case mix of the target population differs from that of the trial population then these inputs to the model must be adjusted for the appropriate case mix in a consistent manner. Third, if results depend on clinical factors, further research should be directed towards understanding and if possible mitigating those risks.

The following section describes the methods and results of the York model for the comparison of EVAR with open repair. This is followed by a section describing the methods and results of a model for the comparison of surgery with watchful waiting. The chapter concludes with a discussion.

Comparison of EVAR and open repair

Model comparing EVAR and open repair in patients with an AAA of at least 5.5 cm and considered fit for open repair

Overview

The model compares a strategy of open repair with that of EVAR for patients with a diagnosed AAA of at least 5.5 cm in diameter and considered fit for open repair. The perspective of the model is that of the UK NHS. The measure of health benefit is expected QALYs over the patient's lifetime. The price year is 2007 and all costs are measured in UK pounds. Costs and health benefits in future years were discounted at a rate of 3.5% per year.¹⁵ The model is closely based on a previously published model undertaken by some of the assessment team.¹⁰⁶ The main difference is that this model extends the analysis for patients of different ages, fitness levels and aneurysm sizes at the time of the decision to undertake surgery.¹⁴³ The base-case model assumed that these factors influenced baseline risks but that the effect of treatment on operative mortality (OR of EVAR versus open repair) was constant for all patient groups.

The analysis seeks to provide estimates of the cost-effectiveness of management options for all patients in the relevant AAA populations. However, it should be emphasised that most RCT and registry data on EVAR relate to men (see Chapter 3). The cost-effectiveness of EVAR versus open repair in women is explored in a secondary analysis, given the limited data available. Furthermore, untreated rupture rates may differ between men and women and the implications of this are discussed in the model comparing surgery with watchful waiting.

Model structure

The model starts after the decision to operate has been made. The model structure is shown in *Figure 69*. Patients enter the model and have a primary aneurysm repair procedure (i.e. either EVAR or open repair). Following this, patients may die, convert to open repair or survive the procedure. Survivors pass into a Markov cohort model to estimate lifetime costs and QALYs. It has been assumed that patients who convert from EVAR to open repair during the primary admission have the same long-term prognosis as patients initially undergoing open repair. Unlike the model shown in Epstein *et al.*,¹⁰⁶ this model does not estimate the incidence of cardiovascular complications such as stroke and myocardial infarction, as the clinical review (Chapter 3) found no evidence that the incidence of these events differed between treatments in the short or long term.

Parameter estimation

Operative mortality: equation 1

Estimation of odds ratio of the treatment effect The treatment effect for operative mortality was obtained from the synthesis of the RCTs^{41,43,44} reported in Chapter 3. The pooled OR for 30-day mortality from these trials is 0.35 (95% CI 0.19 to 0.63). The base-case analysis considers the OR for treatment effect to be constant (proportional) for all patient groups. This assumption has been investigated in two studies^{23,96} (see Chapter 3). Brown *et al.*²³ examined the impact of varying fitness level (assessed by a modified version of the CPI fitness score) on data from the EVAR trial 1

and found no significant interaction ($p = 0.28$) when fitness was considered a continuous variable. Schermerhorn *et al.*⁹⁶ compared operative mortality in a non-randomised cohort of Medicare beneficiaries, adjusting by a propensity score to try to control for selection bias. They found that the OR for treatment effect was similar across all age groups, although the OR tended to be greatest in the youngest (and therefore the fittest) patients: the OR for EVAR versus open repair for all ages was 0.25 (95% CI 0.22 to 0.28), and for ages 67–69 years was 0.16 (95% CI 0.13 to 0.20).

Estimation of the baseline risk of operative mortality The probability of operative mortality after EVAR was estimated for different patient groups. This represents the baseline risk of death at 30 days. A logistic regression was constructed using individual patient data from patients enrolled in EUROSTAR between 1994 and 2006.⁵⁴ EUROSTAR data were used because, as described in Chapter 3, these are the most relevant to current clinical practice for EVAR. The explanatory variables were selected from those assessed in Chapter 3: age (continuous), gender, smoking status, ASA status III or IV, pre-existing conditions, renal function, fitness for open procedure, aneurysm size (in 0.5-cm increments), aortic neck and aneurysm angle, aortic neck length and graft configuration and device type. To reflect improved outcomes arising from changes in patient selection, devices and procedures, a variable was included to indicate whether the patient was enrolled after 31 December 1999. The results of the regression are shown in *Table 58* for

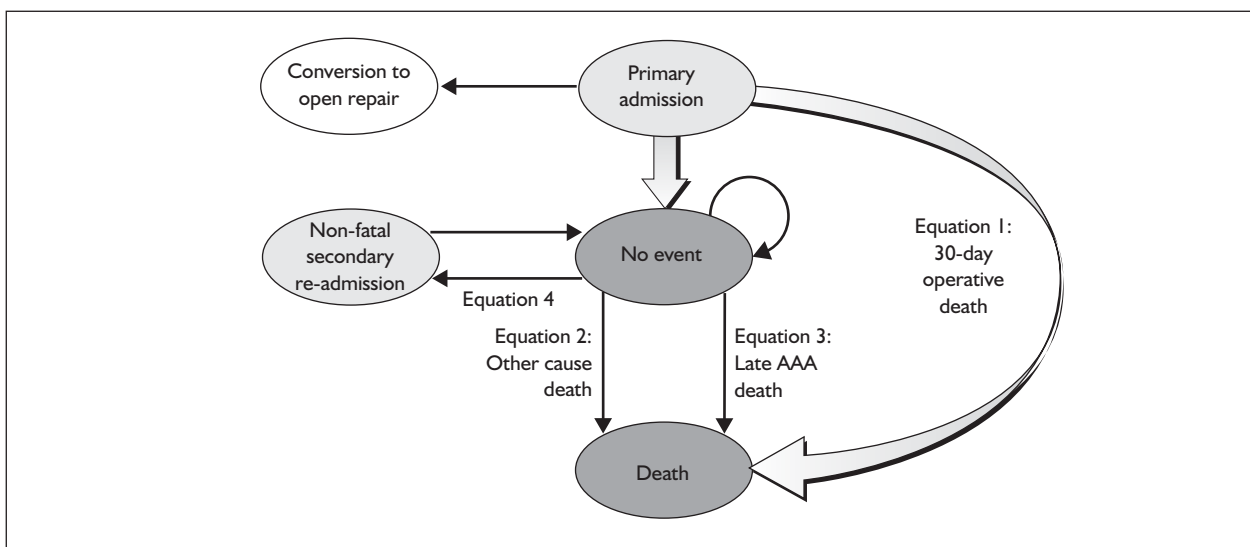


FIGURE 69 Model structure, once a decision to treat has been made.

the statistically significant variables. The predicted probabilities of operative mortality after EVAR and after open repair calculated in the base-case model are shown in *Table 59* for patients of good, moderate and poor fitness at various ages and aneurysm sizes. Fitness is defined in a general way as described in the introduction to the York assessment model, such that a patient with good fitness of a given age and aneurysm size is assumed to have none of the risk factors in *Table 58*, a patient with moderate fitness is assumed to have twice the odds of operative mortality of a patient with good fitness and a patient with poor fitness is assumed to have four times the odds of operative mortality of a patient with good fitness.

Long-term model

Chapter 3 found that the early advantage of EVAR in terms of operative mortality diminished over the medium term, with no statistically significant difference in overall survival after about 2 years based on the results of the EVAR trial⁴³ and DREAM trial.⁴¹ As discussed in Chapter 3 the cause of this erosion of the early survival advantage after EVAR is unclear. One factor may be a greater risk of rupture or aneurysm-related death after EVAR than after open repair. It may also be a consequence of the natural variability in the fitness of the population with large AAAs. It may be that open surgery precipitates operative mortality in patients who were already at high risk from other conditions and who would have died of other causes in the medium term. It is also possible that it is simply a chance finding in both trials.

To reflect this uncertainty in the reasons for the erosion of the early survival advantage after

EVAR, the model was constructed in such a way that different scenarios about patient prognosis following repair of the aneurysm could be explored, based on the available evidence. The overall late mortality rate, $h(t)$, at time t can be written as the sum of two competing risks: death from non-aneurysm-related causes ($h_{\text{Other}}(t)$) (equation 2 in *Figure 69*) and late death from aneurysm-related causes ($h_{\text{AAA}}(t)$) (equation 3 in *Figure 69*):

$$h(t) = h_{\text{Other}}(t) + h_{\text{AAA}}(t)$$

Each of these separate risks is discussed in the following sections.

Estimation of the rate of non-aneurysm-related deaths more than 30 days after aneurysm repair: equation 2

The rate of non-aneurysm-related deaths in the model after more than 30 days, $h_{\text{Other}}(t)$, was in turn constructed from the product of three components: the rate of non-aneurysm-related deaths in the general population, $h_0(t)$, multiplied by the relative risk in patients with a large AAA after aneurysm repair, $HR_{\text{LargeAneurysm}}$, multiplied by the relative risk after an EVAR procedure compared with open repair, HR_{EVAR} . Formally, this can be expressed as:

$$h_{\text{Other}}(t) = h_0(t) \times HR_{\text{LargeAneurysm}} \times HR_{\text{EVAR}}(t)$$

These three components of non-aneurysm-related death after surgery in the model are illustrated in *Figure 70*. Mortality rates in the general population (h_0) were estimated from life tables,¹⁴⁴ adjusting for aneurysm mortality.¹⁴⁵ The parameter $HR_{\text{LargeAneurysm}}$ can be thought of as representing the general prognosis for survival free from non-aneurysm-

TABLE 58 Results of logistic regression of deaths within 30 days of EVAR, from the EUROSTAR data 1994–2006 (equation 1 in *Figure 69*)

Patients included in the model	9667		
Deaths	230		
Log likelihood	–992		
	Coefficient	SE (coefficient)	Odds ratio
Per year of age over or under 74 years	0.07	0.01	1.074
Per cm AAA over or under 5.5 cm	0.30	0.05	1.347
Older device	0.43	0.16	1.537
Unfit for open surgery	0.63	0.14	1.879
Renal condition	0.68	0.14	1.974
ASA III or IV	0.70	0.17	2.023
Constant	–4.89	0.16	

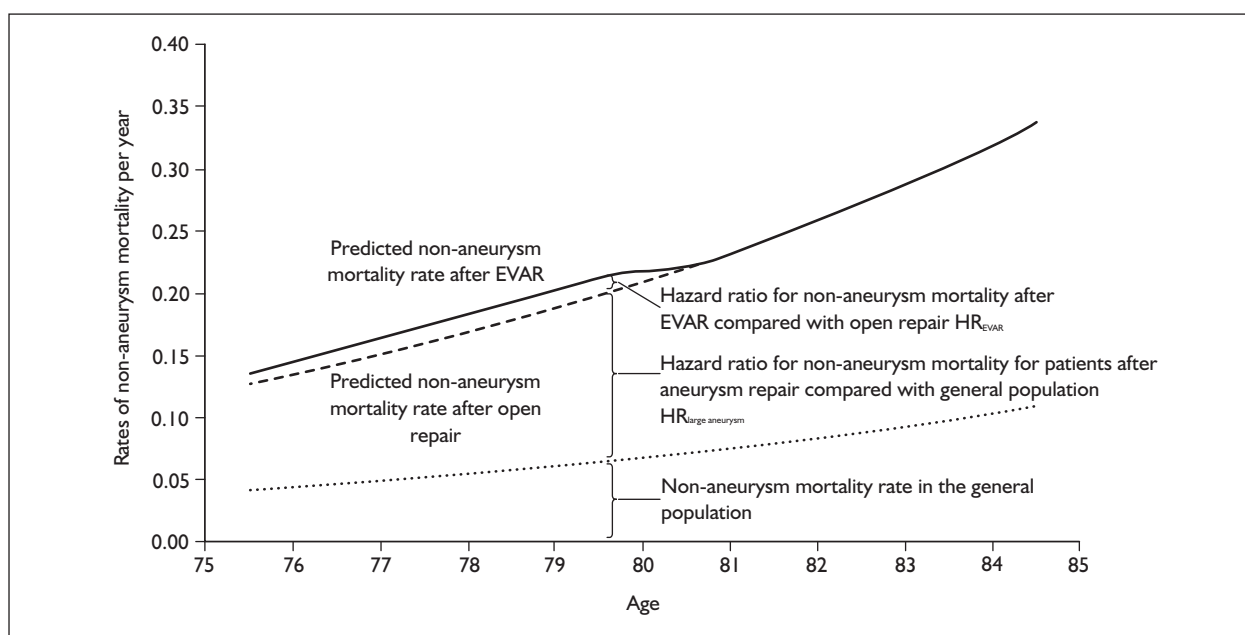
TABLE 59 Predicted probabilities of operative mortality after EVAR and open repair in the base-case model in patients of good, moderate and poor fitness, for different ages and aneurysm diameters

		EVAR			Open repair		
		Age (years)			Age (years)		
		70	75	80	70	75	80
Aneurysm 5.5 cm							
Fitness	Good	0.006	0.008	0.011	0.015	0.021	0.030
	Moderate	0.011	0.016	0.022	0.030	0.042	0.060
	Poor	0.022	0.031	0.044	0.060	0.085	0.122
Aneurysm 6.5 cm							
Fitness	Good	0.008	0.011	0.015	0.020	0.029	0.041
	Moderate	0.015	0.021	0.030	0.040	0.057	0.081
	Poor	0.030	0.042	0.059	0.080	0.115	0.164

Operative mortality after EVAR is estimated from the logistic regression shown in Table 58, and that after open repair assuming that the pooled odds ratio estimated in Chapter 3 applies to all patient groups.

related death after aneurysm repair for a person of that fitness and aneurysm size relative to the general population of that age. The review of risk factors in Chapter 3 found that aneurysm size at the time of the procedure was predictive of the probability of long-term survival after EVAR. This is thought to be primarily cardiovascular risk. Brady *et al.*¹⁴⁶ found a strong association between

aneurysm diameter and the risk of non-aneurysm-related cardiovascular mortality after aneurysm repair in the UK Small Aneurysm Trial and Study: the relative risk of cardiovascular death increased by 31% for each standard deviation increase in aneurysm diameter on a log scale (about 0.8 cm on the natural scale), after adjusting for other risk factors. We estimated the relationship between risk

**FIGURE 70** Rates of mortality from non-aneurysm-related causes after EVAR and open repair used in the base-case model for a patient aged 75 years with an AAA of 5.5 cm and of poor fitness at baseline.

factors and non-aneurysm-related deaths using a Cox survival regression based on the EUROSTAR data set, censoring on AAA deaths. The results of this analysis are shown in *Table 60*.

In the decision model, patients with small (< 5 cm) aneurysms and no other risk factors were assumed to have the same risk of non-aneurysm-related mortality as the general population of the same age and gender. As shown by the HRs in *Table 60*, a patient with a large aneurysm at surgery (5.5 cm) would expect a rate of non-aneurysm-related death 34% greater than that in the general population of the same age; this value would be 76% greater if the aneurysm were ≥ 6.5 cm at surgery.

The clinical review in Chapter 3 found that there were several factors, such as renal insufficiency and ASA class, that were strongly associated with both operative death and long-term survival. The risk modelling shown in *Tables 58* and *60* confirms these findings and furthermore finds that these factors are associated with late non-aneurysm-related deaths. This correlation between factors predictive of operative death and late non-aneurysm-related mortality lends support to the hypothesis that open repair is precipitating deaths in the most risky patients. As described earlier in this chapter (see Introduction), here we aimed to define fitness in a general way, rather than specifying results for every possible risk factor and combination of factors. However, we need to include the correlation between early and late mortality in the model in order to estimate life expectancy for a patient of

a given operative fitness. The best way to estimate this correlation would be to calculate the risk of late non-aneurysm-related mortality associated with each level of a validated and generally accepted operative risk scoring system. As we do not have such a risk scoring system, we illustrate the model for groups with different levels of operative fitness as follows. We consider patients with renal insufficiency to represent a moderate fitness group, with about twice the odds of operative mortality (OR 1.97, *Table 58*) and a 40% greater risk of late non-aneurysm-related mortality (HR 1.39, *Table 60*), and patients with both renal insufficiency and ASA class III or IV to represent a group with poor fitness, with almost four times the odds of operative mortality ($1.97 \times 2.02 = 3.99$, *Table 58*) and almost double the risk of late non-aneurysm-related mortality ($1.39 \times 1.40 = 1.95$, *Table 60*). Further work will be needed to confirm these estimates of the correlation between early and late mortality in different populations using validated risk scoring systems.

Rate of convergence of survival curves for non-aneurysm-related mortality after EVAR and open repair (HR_{EVAR}) Given that the EVAR trial 1 and DREAM trial found that the early survival advantage after EVAR was not maintained over the medium term (Chapter 3) it is necessary to estimate the rate of convergence of the survival curves after the primary admission (parameter HR_{EVAR} , see *Figure 70*). A large US matched-cohort study⁹⁶ (see Chapter 3) found that both the initial difference in operative mortality of EVAR compared with

TABLE 60 Results of Cox survival analysis of the rate of non-aneurysm-related deaths more than 30 days following aneurysm repair, from the EUROSTAR data 1994–2006

	Coefficient	SE (coefficient)	Hazard ratio ^a
Per year of age over 74 years	0.043	0.004	–
Unfit for open surgery	0.396	0.076	1.49
AAA 5.1–5.4 cm	0.185	0.112	1.20
AAA 5.5–5.9 cm	0.290	0.113	1.34
AAA 6–6.4 cm	0.429	0.116	1.54
AAA 6.5+ cm	0.565	0.108	1.76
Older generation	0.141	0.070	1.15
Pulmonary condition	0.250	0.067	1.28
ASA III or IV	0.334	0.070	1.40
Renal condition	0.332	0.076	1.39

a The hazard ratio is the exponential of the coefficient. The hazard ratio for age is not shown because this is included in the Cox analysis only as an adjustment factor. The model calculates relative risks of non-aneurysm-related mortality for patients with relevant risk factors compared with mortality rates in the general population of a given age.

open repair and the time taken for the survival curves to meet strongly depended on age. Younger patients (67–74 years) had an absolute difference in operative mortality of less than 2.5% but the proportion surviving at 18 months was the same after EVAR and open repair. On the other hand, 85-year-olds had an absolute reduction of 8.5% in operative mortality and the difference in survival was maintained between the groups until 4 years (Figure 71). These results suggest that, even though the process causing the survival curves to converge might be unknown, the phenomenon is observed in all patient fitness groups. Furthermore, the benefit of EVAR is prolonged in those patient groups with the greatest difference in operative mortality.

The EVAR trial 1 divided the follow-up into the first 6 months after randomisation and the period from 6 months (to allow for delays between

randomisation and surgery) and calculated all-cause mortality HRs for the two periods to be 0.55 (95% CI 0.33 to 0.93) and 1.10 (95% CI 0.80 to 1.52) respectively (see Chapter 3). However, the HR for 6 months onwards is not directly useable in the model as we need the HR for non-aneurysm-related deaths occurring more than 30 days after the procedure. In the intention to treat analysis the EVAR trial 1 found 81 deaths (seven aneurysm related) occurring more than 30 days after the procedure in patients randomised to EVAR and 71 deaths (two aneurysm related) occurring more than 30 days after the procedure in those randomised to open repair.⁴³ In the base-case model we assume an HR of late non-aneurysm-related death of 1.072 (74 versus 69 deaths) as an estimate of $HR_{EVAR}(t)$, given that the number of patients and mean length of follow-up in the groups were similar. This is assumed to apply to the EVAR group until the non-

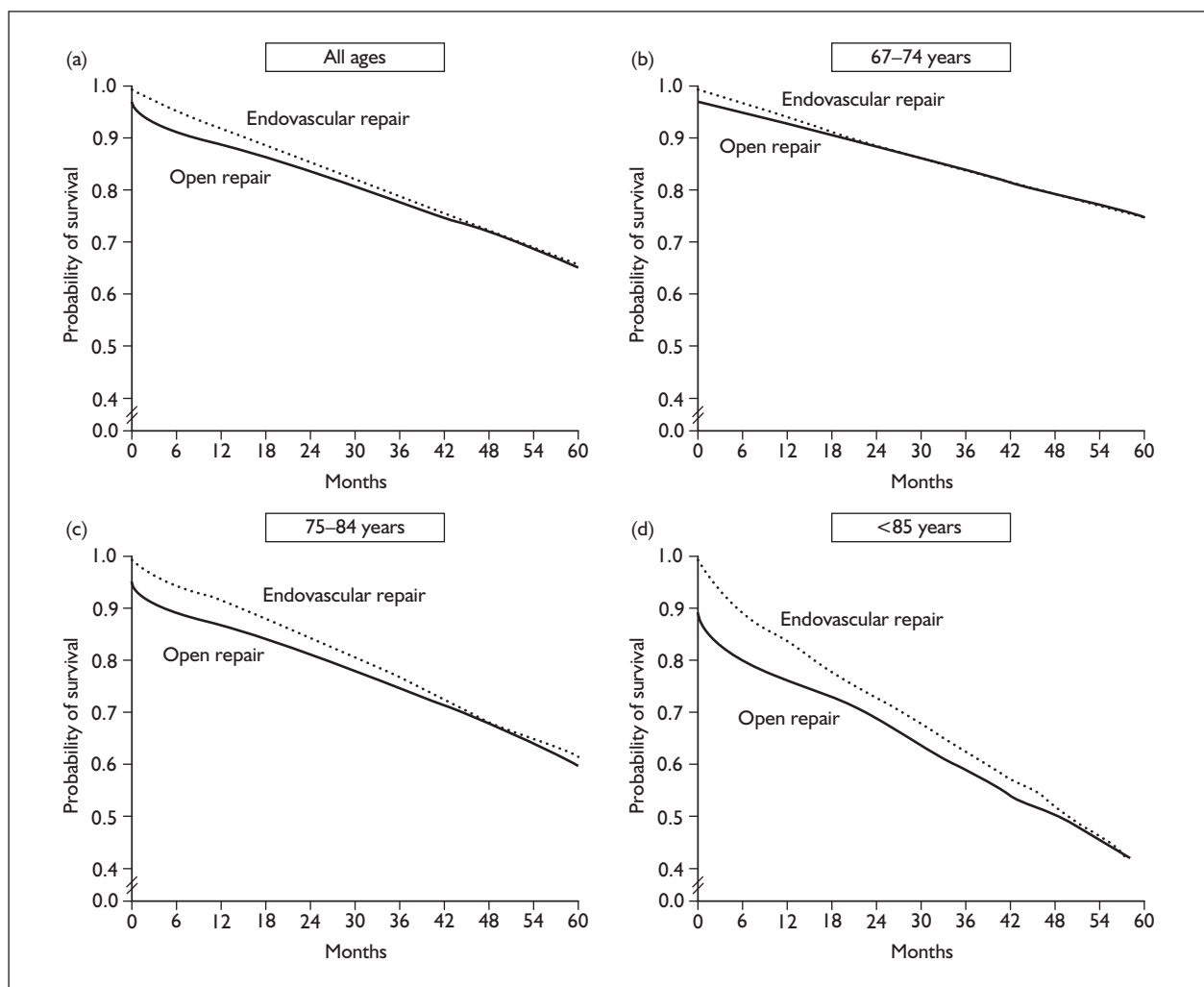


FIGURE 71 Survival of patients undergoing EVAR or open repair of AAA, overall and according to age. From Schermerhorn et al.,⁹⁶ with permission from the Massachusetts Medical Society.

aneurysm-related survival curves converge, and for non-aneurysm-related deaths to be the same in both arms thereafter [$HR_{\text{EVAR}}(t) = 1$]. Sensitivity analysis explored other scenarios.

Estimation of the rate of late aneurysm-related death: equation 3

Hazard ratio for treatment effect for late aneurysm-related deaths Chapter 3 found that the difference in aneurysm-related death between EVAR and open repair is maintained up to 4 years. Even if the rate of late aneurysm death is low, it is important to include it in the model if it is thought that there might be a persistent difference between the rates after EVAR and open repair. The HR (EVAR relative to open repair) for aneurysm-related mortality 6 months or more after randomisation estimated by the EVAR trial 1 was 1.15 (95% CI 0.39 to 3.41),⁴³ with a wide confidence interval because of the few deaths included (see Chapter 3). However, this HR would seem to underestimate the difference in observed aneurysm-related deaths occurring more than 30 days after the primary procedure (seven after EVAR versus two after open repair in about 1250 patient-years of follow-up in each arm), perhaps because some of the deaths occurred in the first 6 months. For the base-case value in the model we estimated the HR (EVAR relative to open repair) from EVAR trial 1 for late aneurysm-related deaths occurring more than 30 days after the primary procedure, censoring on other causes of death. This was estimated to be 2.46 (95% CI 0.48 to 12.7).¹⁰⁶ However, this is not a randomised comparison because of different lengths of time from randomisation to surgery in the two arms. On the basis of clinical opinion we used a HR of 1.5 for the base case. Sensitivity analysis explored other estimates.

Baseline rate of late aneurysm-related deaths occurring more than 30 days after EVAR Chapter 3 found that baseline aneurysm size was associated with

aneurysm-related death after EVAR in most studies. We estimated the baseline rate of aneurysm-related death after EVAR occurring after 30 days using the EUROSTAR data set for patients enrolled between January 1994 and November 2006, censoring on other causes of deaths.⁵⁴ Table 61 shows the data stratified by the date of enrolment and AAA diameter at enrolment. The mean rate of late aneurysm-related death for recent patients was 0.4% per year in patients with large AAA (5.5–6.4 cm) and 1.2% per year in patients with very large AAA (> 6.5 cm). These rates are lower than those found in an earlier published analysis of the EUROSTAR data,⁸² but confirm the earlier finding that rates of late aneurysm-related mortality after EVAR are strongly associated with aneurysm size at the time of the procedure (see Chapter 3). The higher rate in earlier enrolments might indicate improvement in devices and procedures but could also arise because patients were followed up for a longer period, with more time for the aneurysm to expand, or because of more cautious patient selection.

It is uncertain whether, for any given patient, the risk of late aneurysm-related death is constant, increasing or decreasing with time from surgery. Peppelenbosch *et al.*⁸² estimated that the risk of late aneurysm-related death tended to increase with time from surgery, using EUROSTAR data for patients enrolled from 1996 to 2002. For patients with large aneurysm (5.5–6.5 cm) the rate of late aneurysm-related death was 0.3% in the first 3 years rising to 2.1% after 4 years. For patients with very large aneurysm (> 6.5 cm) the rate was 1% in the first 3 years rising to 8% in the fourth year.

This apparent increase in the risk of death with time from EVAR may be confounded by evolution of devices and surgical technique, as those patients with the longest follow-up underwent EVAR with the oldest devices. We tried to adjust for this by

TABLE 61 Late aneurysm-related deaths, excluding operative mortality, in patients undergoing EVAR. EUROSTAR data stratified by enrolment date and baseline AAA diameter

Enrolment date	AAA size	n	Deaths by November 2006	Patient-years at risk	Mean follow-up (years) per patient	Mean rate per year
Before 1 January 2000	< 5.5 cm	1200	24	4753	3.96	0.5%
	5.5–6.4 cm	786	34	2977	3.79	1.1%
	≥ 6.5 cm	435	30	1410	3.24	2.1%
After 1 January 2000	< 5.5 cm	2296	10	4296	1.87	0.2%
	5.5–6.4 cm	2211	16	4116	1.86	0.4%
	≥ 6.5 cm	1340	28	2311	1.73	1.2%

estimating parametric survival models, including a variable representing the year that the device was fitted. *Table 62* shows the results of the parametric survival regression using the EUROSTAR data (1994–2006) for a log-normal, a Weibull and an exponential (constant hazard) distribution. *Figure 72* shows the rate of aneurysm-related death over time predicted by each regression model (for patients aged 74 years with an AAA of 5.5 cm). The Weibull and log-normal models estimate similar rates of aneurysm-related death during the first 5 years, the hazard increasing over time for these patients to a maximum of about 0.4%. The Weibull model then predicts that the hazard continues to gradually increase over time, whereas the log-normal model predicts that the rate after 5 years then gradually decreases over time. The average rate (exponential model) for this patient group was 0.33%.

Hence, there is considerable uncertainty about the relationship between late aneurysm-related death and time from surgery. The base-case model assumed that the rate of late aneurysm-related death was constant from 1 month after surgery (exponential survival model). Sensitivity analyses explored alternative scenarios. An increasing rate might correspond with a belief that the aneurysm continues to expand after EVAR, whereas a

decreasing rate might correspond with a belief that patients at risk will be successfully identified by long-term surveillance and receive appropriate treatment.

Illustration of differences in operative, aneurysm-related and non-aneurysm-related causes of death between EVAR and open repair in the base-case model

Figure 73 illustrates how predicted death rates for each cause differ in the base-case model between EVAR and open repair. The figure shows the differences in the cumulative rates of death between the treatments (in patients at risk up to time t) for all-cause deaths, AAA deaths and non-AAA death. The initial difference in favour of EVAR is due to a benefit in early operative mortality. There is a continuing difference in late aneurysm-related mortality between the treatments. There is also a difference in late non-aneurysm-related deaths because of there being a greater proportion of patients with poor fitness among survivors of EVAR than among survivors of open repair. This higher rate of mortality persists until the survival curves for late non-aneurysm-related death converge, in this case at about 4 years. Although there is a persisting difference in aneurysm-related deaths after the survival curves meet, this has only a small effect on all-cause mortality because of the relatively high competing risk of deaths from other causes (*Figure 74*).

TABLE 62 Results of log-normal, Weibull and exponential survival models of the rate of aneurysm-related deaths occurring more than 30 days following aneurysm repair with EVAR, from the EUROSTAR data (equation 3 in *Figure 69*)

Number of observations	8182					
Number of deaths	142					
Patient-months (patient-years)	228,471 (19,039)					
	Log-normal model		Weibull model		Exponential model (base case)	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Per year of age over 74 years	-0.04	0.01	0.04	0.01	0.04	0.01
AAA size 5.5–5.9 cm	-0.48	0.25	0.52	0.26	0.52	0.26
AAA size 6–6.4 cm	-0.64	0.26	0.69	0.27	0.68	0.27
AAA size 6.5+ cm	-1.35	0.23	1.33	0.22	1.32	0.22
Older generation	-0.85	0.20	0.82	0.18	0.89	0.18
Unfit for open repair	-0.68	0.20	0.64	0.20	0.62	0.19
Intercept	9.16	0.46	-9.00	0.39	-8.53	0.22
Log sigma coefficient	0.81	0.07				
Log shape coefficient			0.12	0.08		
Log likelihood	-731		-728		-729	

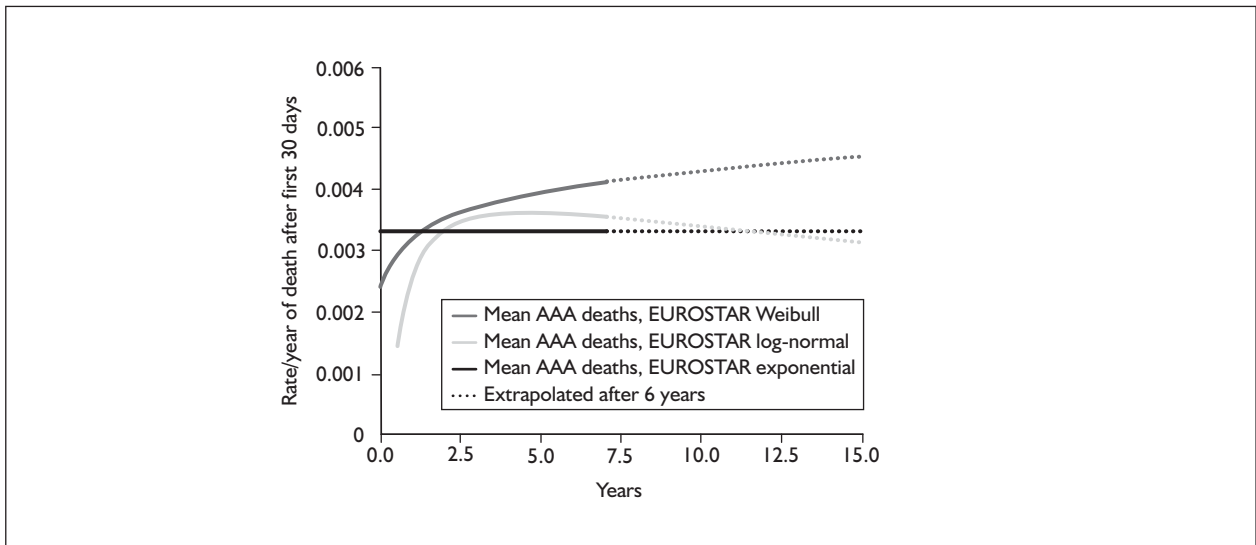


FIGURE 72 Predicted rates of aneurysm-related death occurring more than 30 days following aneurysm repair with EVAR for a patient aged 74 years, with an aneurysm diameter 5.5–5.9 cm, with a recent EVAR device and fit for open surgery. Estimated from EUROSTAR data using an exponential model, a Weibull model and a log-normal model. Dashed lines indicate extrapolation beyond the maximum of 6 years of follow-up between 2000 and 2006.

Rate of late readmission for complications: equation 4

In the model patients are at risk of readmission for a secondary AAA procedure. We estimate readmissions rather than late complications because for the purpose of the model we are primarily interested in this outcome to predict the use of health-care resources. The rate of

readmission to hospital after discharge from the primary admission was estimated from the EVAR trial 1 data using a Weibull model with deaths as censoring variables.¹⁰⁶ The estimated coefficients of the Weibull model are shown in *Table 63*. As in Chapter 3 this regression did not find age and pre-existing conditions to be associated with readmissions, but, unlike Chapter 3, it also did

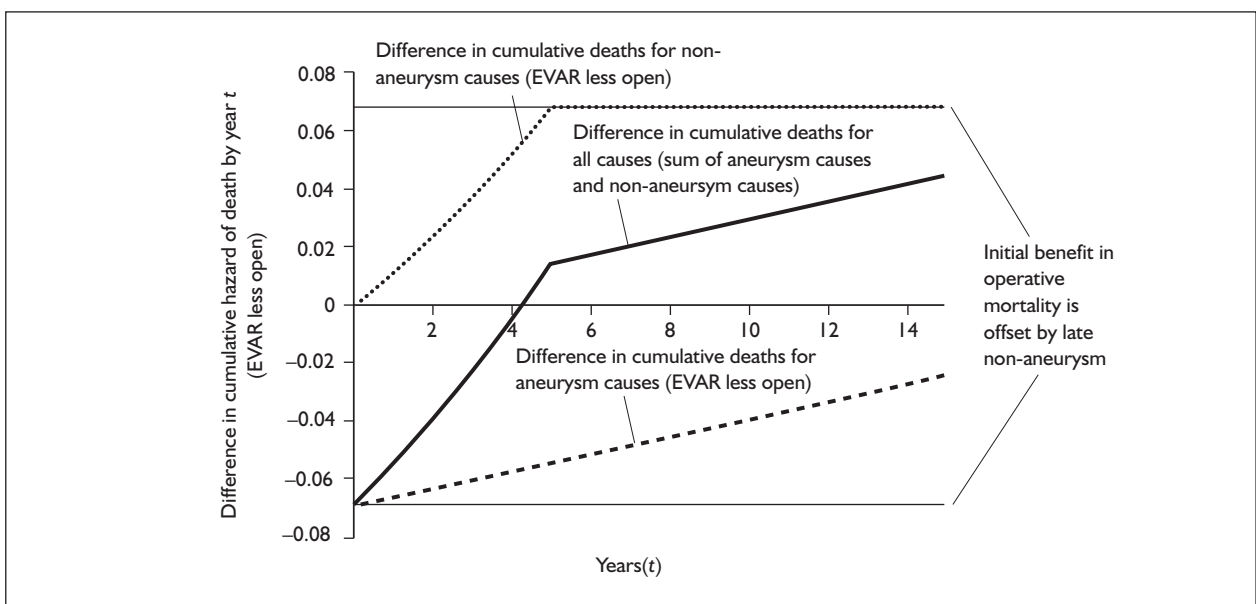


FIGURE 73 Illustration of the difference between the treatments in the cumulative rates of death (from aneurysm-related and non-aneurysm-related causes) estimated in the base-case decision model for a patient aged 75 years with a large AAA (6.5 cm) and poor fitness.

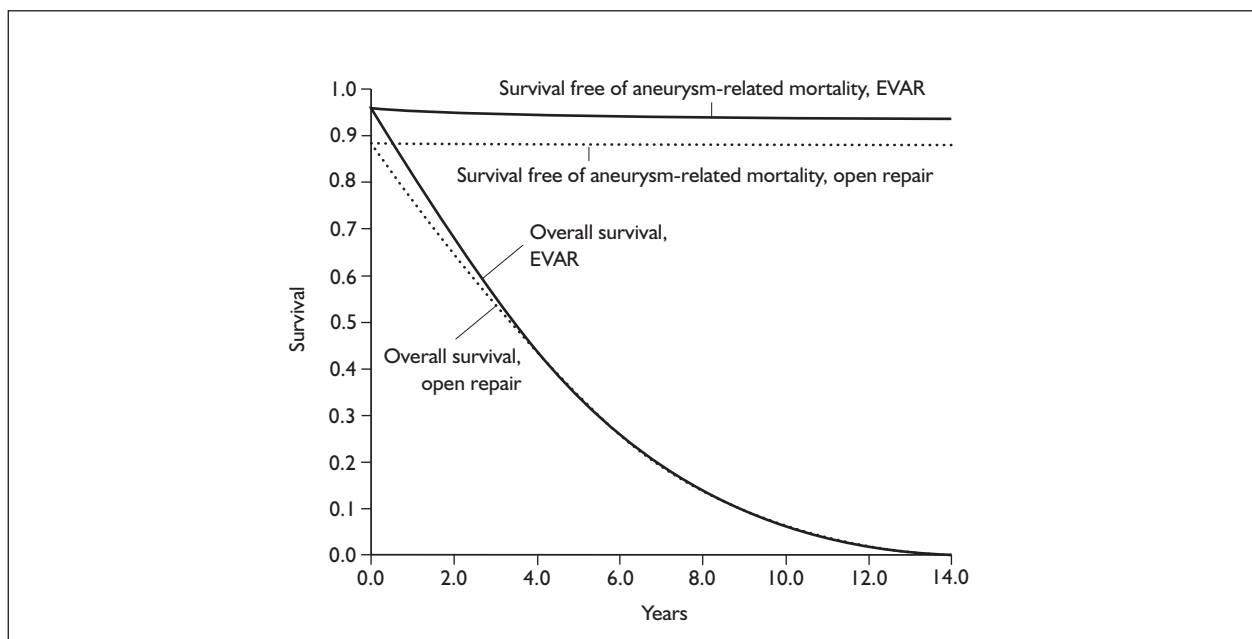


FIGURE 74 Proportions surviving each year free from aneurysm-related death and all-cause death estimated in the decision model for a patient aged 75 years with a large AAA (6.5 cm) and poor fitness.

not find aneurysm size to be a risk factor, perhaps because of the relatively few events. The base-case model used this regression to predict the rate of readmission after EVAR to be about 10% per patient-year in the first 6 months, declining to <2.5% per year by 5 years (Figure 75).

Chapter 3 reported that the treatment effect HR for reinterventions (EVAR relative to open surgery) was 2.7 (95% CI 1.8 to 4.1), but this includes reinterventions in the primary admission,⁴³ the costs of which are included in the average procedure cost. The estimated HR for readmissions after EVAR compared with open repair using an intention to treat analysis was 6.75 (SE 2.56)

(Table 63). This is consistent with the proportion of patients with aneurysm-related reinterventions found by Schermerhorn *et al.*⁹⁶ at 4 years (9.1% after EVAR and 1.7% after open repair). However, this may overestimate the relative risk of EVAR for two reasons. First, EVAR trial 1 did not record late reinterventions for laparotomy. Schermerhorn *et al.*⁹⁶ estimated that 4.7% of patients had laparotomy-related reinterventions 4 years after EVAR and 9.7% after open repair. Second, vascular surgeons may now be less inclined to reintervene for some types of complication, such as type 2 endoleak. The data presented in Chapter 3 indicate that about 35% of interventions after EVAR were for type 2 endoleak. As the EVAR trial 1

TABLE 63 Results of Weibull survival model of the rate of readmission following aneurysm repair, using individual patient data from the EVAR trial 1. Patients are followed up within randomised groups after discharge from the primary procedure (equation 4 in Figure 69)

Number of observations	1050		
Number of readmissions	62		
Patient-months (patient-years)	29,415 (2451)		
	Coefficient	SE	Hazard ratio ^a
EVAR intervention	1.91	0.38	6.75
Constant	-6.12	0.43	
Log (shape parameter)	-0.53	0.001	

a The hazard ratio is the exponential of the coefficient.

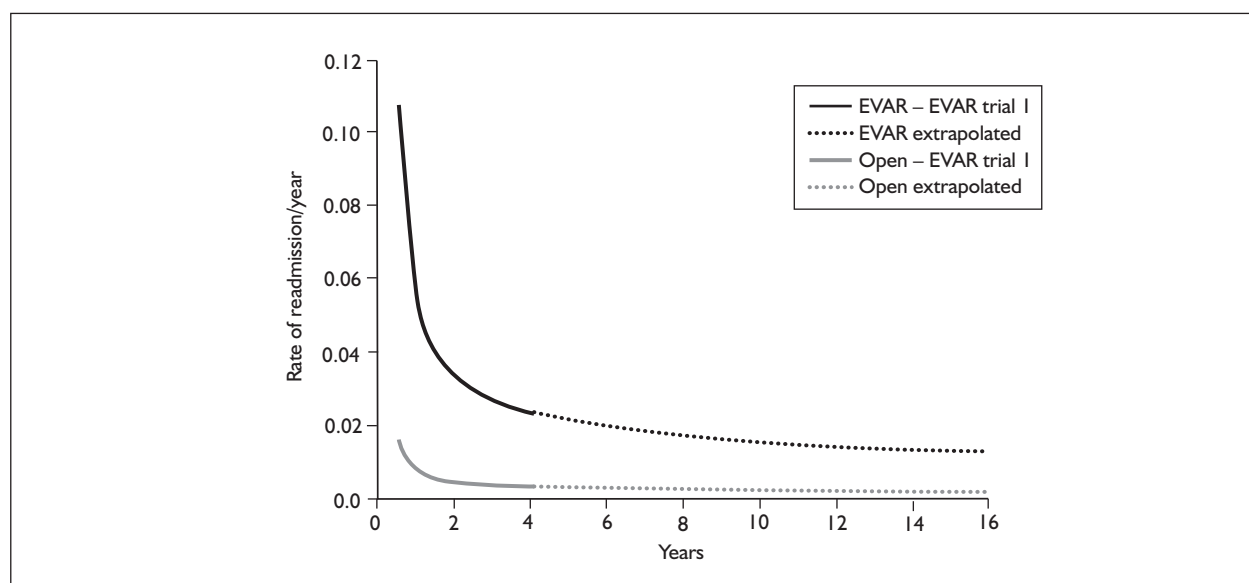


FIGURE 75 Predicted rates of readmission per year over time (Weibull regression, Table 63, EVAR trial 1 data). Dashed lines show the rates of readmission predicted beyond the maximum 4-year follow-up available in EVAR trial 1.

represents our best estimate of recent UK practice, we use an HR of 6.75 as the base case but explore this with sensitivity analyses.

Resource use and costs

Costs are incurred in the model during the primary admission, during surveillance post surgery and if the patient is readmitted to hospital for an aneurysm-related complication.

Costs and resource use during the primary procedures

The costs and resources used in the primary procedure are shown in Table 64 for the base-case model. Expected resource use in both procedures is estimated from intention to treat analysis of the EVAR trial 1.^{43,106} As these data are the mean for all of the patients in the trial they include the expected costs of in-hospital complications and mortality. It is possible that, given the evolution of devices and procedures, these data do not represent current practice compared with the period 1999–2003 when the trial was recruiting. Chapter 3 found that the mean total length of stay reported in the most recent registry data was 13 days after open repair¹⁶ and 6 days after EVAR,⁵⁴ considerably less than in the EVAR arm of the EVAR trial 1.⁴³ However, the EVAR trial 1 data represent the best available randomised comparison of resource use in the UK and so were used for the base case. A postal survey of UK hospitals was conducted in January 2008 to investigate whether length of stay has changed since the EVAR trial 1. The results are presented

in Appendix 3. The survey found that length of stay may be currently lower after both EVAR and open repair than in EVAR trial 1, and that the difference in length of stay in general wards may now be greater than that estimated by EVAR trial 1. This scenario was explored in sensitivity analysis. It is likely that costs will depend on the risk characteristics of the patient, for example EVAR trial 2⁴⁶ found that these high-risk patients used slightly more hospital resources than patients in the EVAR trial 1. However, the base case assumed that the difference in costs between EVAR and open repair was constant for all patient groups. Chapter 1 presents the list prices of each of the EVAR devices included in this review, when known.

Intensive care during the primary procedure

In the base case, resource use and costs are based on the actual use of intensive care and high dependency units as recorded by the EVAR trial 1.⁴³ There is no evidence from the survey in January 2008 that the EVAR trial 1 underestimates the difference between EVAR and open repair in patients' length of stay in intensive care facilities (see Appendix 3). However, mean length of stay may not represent the full opportunity cost of these facilities, because some centres require an intensive care bed to be available before commencing a procedure, in case it is needed. The survey results in Appendix 3 show that 86% of surgical teams would cancel an open repair procedure if an intensive care unit bed was not available compared with 22% who would cancel an EVAR

TABLE 64 Costs and resources used in the primary procedure

	Cost (£)		Resource use		Unit cost (£)	Source
	EVAR	Open repair	EVAR	Open repair		
During the primary procedure						
Theatre time (minutes)	1593	1794	182	205	525	ISD Scotland; theatre services RI42X ¹⁴⁷
Preoperative days	467	541	1.9	2.2	246	NHS reference costs 2006/7; QZ01A ¹⁴⁸
ICU days	947	3247	0.7	2.4	1353	NHS reference costs 2006/7; XCO5ZTHE ¹⁴⁸
HDU days	593	1252	0.9	1.9	659	NHS reference costs 2006/7; XC05ZHDU ¹⁴⁸
Ward days	1697	2263	6.9	9.2	246	NHS reference costs 2006/7; QZ01A ¹⁴⁸
Blood (ml)	105	575	164	896	289	National Blood Service ¹⁴⁹
Contrast (ml)	14	0	195	6	3.5	Medtronic ¹²⁷
Total cost of primary procedure	10,416	9893				
Conversion to open repair during primary procedure					42,067	EVAR trial I, ⁴³ Epstein <i>et al.</i> ¹⁰⁶
Subsequent to primary procedure (EVAR or open repair)						
Readmission					5936	EVAR trial I, ⁴³ Epstein <i>et al.</i> ¹⁰⁶
Outpatient visit					83	NHS reference costs 2006/7; speciality 107 ¹⁴⁸
Computed tomography					108	NHS reference costs 2006/7; RA10Z ¹⁴⁸
HDU, high dependency unit; ICU, intensive care unit.						

procedure. This requirement might be a reason for the longer average waiting time for open repair experienced by patients in EVAR trial I. As well as longer waiting times for aneurysm surgery, this requirement might also affect patients waiting for other surgical procedures as there is a shortage of capacity of intensive care facilities in many surgical centres in the UK.

Surveillance post surgery

All patients undergoing EVAR, whether they experience adverse events or not, are assumed to require regular specialist hospital outpatient attendances and CT scans to monitor their aneurysm repair. In the base case, based on the

results of a survey of UK hospitals participating in the EVAR trials,⁴³ it was assumed that patients require two surveillance visits during the first year and one visit per year thereafter. Patients who have open repair require only one visit in the first year and none thereafter.¹⁰⁶ A survey was undertaken in January 2008 to update this information as part of this review (Appendix 3), which showed that these assumptions are broadly typical of current practice, although the frequency of surveillance tends to diminish with time.

Health-related quality of life

Chapter 3 reported the EVAR trial I results, which showed that HRQoL measured by EQ-5D tended

to decline in the first 3 months after randomisation but by less after EVAR, with a difference in HRQoL in favour of EVAR after 3 months of 0.05 (SE 0.02).⁴³ HRQoL recovered by 3–12 months and there was no significant difference between the groups. Based on these findings the base case assumed that HRQoL declined by 0.077 in the 6-month period following open surgery and by 0.027 following EVAR. Patients without the need for reinterventions were assumed to recover to age- and sex-specific average population values of HRQoL 6 months after the procedure. Other utility values used in the model are shown in *Table 65*.

Cost-effectiveness analysis

Standard decision rules were followed for the cost-effectiveness analysis using expected costs and QALYs.¹⁵¹ When there are two options under comparison, the ICER is calculated if both the cost and the benefits of EVAR exceed those of open repair. If EVAR is more costly but less effective than the alternative then EVAR is dominated and no ICER is calculated.

The same decision rule can be expressed in terms of maximising ‘expected net benefit’.¹⁵² Expected net benefit (NB) for a treatment option is defined as:

$$NB(\lambda) = \lambda \times QALYs - costs$$

where λ is the threshold cost-effectiveness used by the decision-maker. This is the most convenient decision rule when there are three or more mutually exclusive strategies being compared, as is the case in the subsequent section in which we compare open surgery, EVAR and watchful waiting. Results are shown for thresholds of £20,000 and £30,000 per QALY.

The results of the decision model are shown (1) for the aggregate UK population who are considered suitable for aneurysm repair and (2) disaggregated according to age group, aneurysm size and operative fitness. Appendix 6 explains how the mean characteristics of the UK population were determined.

One-way sensitivity analyses were carried out by varying key parameters in the model. A probabilistic sensitivity analysis, based on the uncertainty in all of the parameters of the model, was undertaken to estimate the probability that EVAR is more cost-effective than open repair as a function of the threshold ICER.¹⁵³

Table 66 shows the uncertainty arising from measurement error in the estimates of each of the parameters used in the base-case model comparing EVAR and open repair. Some parameters have been estimated from regression equations (equations 1–4) and therefore there may be correlations between the coefficients of these equations. The Cholesky matrix was estimated for each risk equation and used to calculate the distribution of the linear predictor for these parameters, assuming that the coefficients of these equations follow a joint normal distribution.

Results of York economic assessment: EVAR compared with open repair for patients with a large aneurysm (5.5 cm or more) and assessed as fit for open repair
Results for aggregate population

Table 67 shows the results of the decision model for the average UK population.

In the base-case analysis, the total incremental lifetime cost of EVAR versus open repair is

TABLE 65 Health-related quality of life (HRQoL) values used in the model

	Mean	Source
More than 6 months after successful surgery		
Age ≤ 75 years	0.78	Kind et al. ¹⁵⁰
Age > 75 years	0.75	Kind et al. ¹⁵⁰
Loss of utility for 0–6 months after a procedure		
EVAR procedure	0.027	EVAR trial 1 ⁴³
Open procedure	0.077	EVAR trial 1 ⁴³
After readmission	0.077	Assumption
HRQoL or utility is an index measure of morbidity on a scale of 1 (good health) to 0 (death) with negative utilities feasible.		

TABLE 66 Probability distributions for the parameters used in the probabilistic sensitivity analysis, for a 75-year-old patient with an aneurysm of 6.5 cm and of moderate fitness

Parameter	Value	Mean	SE	Alpha	Beta	Distribution	Risk equation (if applicable)	Source
Operative mortality								
Probability operative mortality EVAR	0.021					Joint normal (Cholesky)	Equation 1	EUROSTAR ⁵⁴
Odds ratio EVAR vs open repair	0.35	-1.05	0.373			Log-normal		Meta-analysis, chapter 3
Conversion to open repair in primary admission	0.008			4	496	Beta		EVAR trial 1 ⁴³
Non-AAA death								
Hazard ratio AAA population vs general population	2.452					Joint normal (Cholesky)	Equation 2	EUROSTAR ⁵⁴
All-cause hazard ratio after EVAR vs open repair	1.072	0.070	0.160			Log-normal		EVAR trial 1 ⁴³
Late AAA death								
Hazard ratio (EVAR vs open repair)	1.5	0.41	0.38			Log-normal		Expert opinion
Late AAA death (deaths/year)	0.009					Joint normal (Cholesky)	Equation 4	EUROSTAR ⁵⁴
Resource use								
Cost difference EVAR less open repair (£)	523	523	230			Normal		EVAR trial 1 ⁴³
Hazard ratio for reinterventions (EVAR vs open repair)	6.753	1.910	0.380			Log-normal		EVAR trial 1 ⁴³

£2002. This can be approximately broken down as the additional cost of the initial procedure (£520), conversions to open repair (£250), late reinterventions (£820) and the additional cost of surveillance (the remainder, about £410). The total difference in lifetime QALYs between EVAR and open repair is estimated to be 0.041. The positive benefit of EVAR is maintained as a cumulative QALY gain of 0.056 up to about 3 years, but is subsequently offset by extra late aneurysm-related deaths and reinterventions in the long term after EVAR. The ICER for the base case is approximately £49,000 per QALY (calculated as 2002/0.041).

The model includes an excess hazard of late non-aneurysm-related death after EVAR until the survival curves converge. If the excess hazard is set such that the survival curves converge at 8 years (with other parameters as the revised base case) then the ICER is approximately £22,000 per QALY.

If the excess hazard is twice that of the base case then the survival curves converge at 2 years and the ICER is approximately £96,000 per QALY.

The revised base case assumes that the hazard of late aneurysm-related death is 1.5 times greater after EVAR than after open repair, for the lifetime of the patient. If there is no difference (HR of 1) then the ICER is £29,000 per QALY. If the HR is 1.2, the ICER is approximately £37,000 per QALY. The HR may be time varying, for example there may be no excess hazard after 4 years. This scenario gives similar results to the revised base case, with an ICER of approximately £49,000 per QALY.

The original base case in the assessment report assumed that the HR of late reintervention was 6.7 for the lifetime of the patient, although the absolute rate of reintervention is declining over

time and is low (about 2% per year) 4 years after EVAR (see *Figure 75*). If there is no difference between treatments (HR of 1) the ICER is approximately £27,000 per QALY. If the HR is 1.5 (corresponding to the relative hazard of reinterventions for any cause in Schermerhorn *et al.*⁹⁶) the ICER is £29,000 per QALY.

The original base case assumed that one follow-up appointment per year with CT was required after EVAR. If the cost per year was half of this then the ICER is £44,000 per QALY. If there are no follow-up visits (with reinterventions and aneurysm deaths remaining unchanged) then the ICER is approximately £39,000 per QALY.

There may be a correlation between follow-up visits, reinterventions and late aneurysm-related deaths. In a favourable scenario, if there are fewer complications after EVAR, with less need for follow-up, fewer reinterventions and fewer aneurysm-related deaths, then the ICER is approximately £24,000 per QALY.

If the OR of operative death is 0.25 rather than 0.35 as used in the base case then the ICER is approximately £22,000 per QALY, with other parameters as in the revised base case. The survival curves take 4.5 years to converge, as the initial benefit from EVAR is larger.

The base case assumed that the EVAR procedure cost £523 more than open repair. We conducted a sensitivity analysis with a lower cost for the EVAR procedure, for example reflecting less use of intensive care than in the EVAR trial 1. If it is assumed that EVAR costs £623 less than open repair, the ICER is approximately £21,000 per QALY. If it is assumed that EVAR costs the same as open repair, the ICER is £36,000 per QALY. In a multivariate sensitivity analysis, if EVAR costs the same as open repair and the costs of intervention and follow-up are lower than in the base case then the ICER is £12,000 per QALY.

We also conducted a probabilistic sensitivity analysis using the distributions shown in *Table 66*. The results are shown in *Table 67*. The probability that EVAR is cost-effective in the base case is 0.261 at £20,000 per QALY or 0.424 at £30,000 per QALY. At a threshold willingness to pay of £20,000 per QALY, EVAR is more likely to be cost-effective than open repair under some scenarios: if the survival curves do not converge; if the HR of reintervention is 1.5 and the annual surveillance cost of follow-up is low; if the OR of operative

mortality is 0.25; or if the EVAR procedure costs less than open repair. It may seem counterintuitive that in some scenarios the ICER (the measure of mean cost-effectiveness) is greater than £20,000 but the probability that EVAR is cost-effective is more than 50% (the measure of median cost-effectiveness) at a threshold of £20,000 per QALY. This occurs because the Markov model is non-linear, and the distribution of net benefits is not symmetrical over all of the simulations of the probabilistic sensitivity analysis.

Base-case results disaggregated by patient subgroup

Table 68 shows the cost-effectiveness results for EVAR compared with open repair by age, aneurysm size and fitness at baseline. The results of the base-case model suggest that EVAR is cost-effective for patients of relatively poor fitness at most ages and aneurysm sizes. For patients with relatively good fitness (i.e. no comorbidity) open repair is more cost-effective. Note that the result for patients with moderate fitness, aged 75 years and with an aneurysm of 6.5 cm corresponds to the average result shown in *Table 67*.

In general, the ICER of EVAR versus open repair is lower for older patients than for younger patients, for patients with a larger aneurysm size than with a smaller aneurysm size, and for patients of poorer fitness than of better fitness (*Table 68*). Older patients and those with larger aneurysms and poorer fitness face increased operative mortality. The model assumes that the relative treatment effect (OR) of operative mortality is constant across risk groups. Therefore, the absolute benefit of EVAR compared with open repair is greater in patients of poorer operative risk. Furthermore, there is a long-term risk of complications and reinterventions after EVAR. Patients with a longer life expectancy face a greater cumulative risk of complications, with additional costs, disutility and risk of late aneurysm-related mortality.

The ICER comparing EVAR and open repair does not decrease in a linear progression with age (*Table 68*). For example, for a patient with moderate fitness and aneurysm size of 6.5 cm, the ICER is £92,000 per QALY at age 70 years, £49,000 per QALY at age 75 years and £33,000 per QALY at age 80 years. This occurs because the ICER is a ratio of the difference in costs to the difference in health benefits and increases rapidly as the difference in the denominator approaches zero. The lifetime difference in costs is similar for all age groups (about £2000) whereas the lifetime

difference in QALYs is only 0.025 in 70-year-olds but 0.052 in 80-year-olds, because the absolute difference in operative mortality is greater for older patients.

There is a non-linear relationship between aneurysm size and operative mortality. The EUROSTAR data predicted that the risk of late aneurysm-related death after EVAR increases with aneurysm size at the time of the procedure (equation 3, *Table 62*), confirming estimates made by studies on earlier EUROSTAR data sets.⁸² The increased risk of late aneurysm-related death causes the ICER of EVAR versus open repair to be greater for patients with an aneurysm size of 6.5 cm than for patients with an aneurysm size of 6 cm (*Table 68*).

Table 68 shows that EVAR might also be cost-effective compared with open repair in older patients (80 years or more) with moderate fitness and very large aneurysms (≥ 7.5 cm). Although we define fitness in this analysis as 'moderate' if patients have few pre-existing conditions relative to other patients of their age, operative mortality would be high in absolute terms for these patients, estimated at 6.7% after EVAR and 17% after open repair. A policy of no surgery or watchful waiting should also be considered for patients with high expected operative mortality, compared with the risk of rupture without surgery. These policies will be evaluated in the model comparing immediate elective surgery, watchful waiting and no intervention.

The cost-effectiveness of EVAR compared with open repair in women

The risk equations (equations 1–4) estimated earlier in this section did not find gender to be a significant explanatory variable, and therefore the base-case model does not distinguish between male and female patients, other than to use life tables for men to estimate non-aneurysm-related mortality in the general population. However, Chapter 3 identified one large study⁸⁶ that found an independent effect of gender on 30-day operative mortality (OR women versus men 1.46, 95% CI 1.26 to 1.68). A secondary analysis explored the cost-effectiveness of EVAR specifically in women, assuming greater 30-day operative mortality after EVAR in women as estimated by Timaran *et al.*⁸⁶, assuming that the average treatment effect (OR) of 30-day mortality of EVAR compared with open repair found by the RCTs in Chapter 3 applies to women and using the age-specific non-aneurysm-related mortality rates (life tables) for the female

general population. Results were very similar to those of the base case.

Comparison of York model with Medtronic model of EVAR versus open repair

The Medtronic model comparing EVAR and open repair was described earlier in this chapter (see Systematic review of existing cost-effectiveness evidence). The main differences between the York base-case model and the Medtronic¹²⁷ base-case model are:

- the difference between EVAR and open repair non-aneurysm-related mortality rates in the medium term
- the difference in late aneurysm-related mortality
- the hospital costs (intensive care and operating theatre time) of the EVAR procedure
- the relative rate of reinterventions.

The assumptions made by Medtronic¹²⁷ are shown as scenario 18 in *Table 67*. In this scenario there is a slower rate of convergence of the survival curves than in the York base case, a lower relative cost of EVAR and no difference in late aneurysm-related deaths between EVAR and open surgery. The Medtronic model presented results for a patient aged 70 years with an aneurysm size of ≥ 5.5 cm. Fitness was unspecified in the Medtronic model (i.e. results were for the average level of fitness of patients in the EVAR trial 1). When these assumptions are used in the York model the ICER is about £15,000 per QALY, consistent with the results reported in the Medtronic report.¹²⁷

Figure 76 illustrates the differences between the assumptions for all-cause mortality made in the York model and in the Medtronic model. The figure shows the difference in cumulative deaths between EVAR and open repair predicted by the models. The York model assumed that the initial survival advantage of EVAR for operative mortality would be entirely offset within 3 years by a relatively higher non-aneurysm-related death rate after EVAR. This scenario is consistent with the results of EVAR trial 1, DREAM and a large US matched-cohort study.⁹⁶ The predicted survival curves are shown in *Figure 77* for a patient aged 70 years with an aneurysm size of 5.5 cm. Furthermore, the York model assumed that there would be a small but persistent difference between the treatments in the rate of late aneurysm-related deaths. This scenario is consistent with the long-term EUROSTAR data.⁸² In contrast, the base-case

TABLE 67 Results for the base-case and sensitivity analyses for the average UK population suitable for EVAR or open surgery

No.	Description of scenario	Parameters	
		Hazard ratio for late aneurysm deaths	Excess non-aneurysm mortality after EVAR
1.	Base case	1.5	1.072
2.	No difference in late non-aneurysm mortality: survival curves do not converge	1.5	1.000
3.	Very small difference in late non-aneurysm mortality: very slow rate of convergence of the survival curves	1.5	1.010
4.	Small difference in late non-aneurysm mortality: slow rate of convergence of the survival curves	1.5	1.030
5.	Larger difference in late non-aneurysm mortality: faster convergence of the survival curves	1.5	1.144
6.	No difference in late aneurysm mortality	1.0	1.072
7.	Lower HR of late aneurysm mortality (HR = 1.2)	1.2	1.072
8.	No difference in aneurysm mortality after 4 years (HR = 2.46 from 30 days to 4 years and HR = 1 thereafter)	Time varying	1.072
9.	Half the yearly cost of follow-up after EVAR	1.5	1.072
10.	No follow-up beyond first year after EVAR or open repair	1.5	1.072
11.	No difference between treatments in late reinterventions	1.5	1.072
12.	Lower HR of late reinterventions	1.5	1.072
13.	Lower cost of follow-up and lower rate of reintervention than in base case	1.5	1.072
14.	Odds ratio of operative mortality is 0.25 not 0.35	1.5	1.072
15.	EVAR procedure costs £1100 less than in base case (e.g. less use of ITU), i.e. £623 less than open repair instead of £523 more than open repair	1.5	1.072
16.	EVAR procedure costs same as open repair	1.5	1.072
17.	EVAR and open repair procedure costs are equal, with lower cost of follow-up and lower rate of reintervention than in base case	1.5	1.072
18.	EVAR procedure costs £623 less than open repair, fewer reinterventions than in base case, lower rate of excess mortality after EVAR (Medtronic model)	^a	1.055

HR, hazard ratio; P(20K)/P(30K), probability that EVAR is cost-effective at £20,000/£30,000 per QALY.
 a In this scenario there is an excess rate of mortality for any cause (HR = 1.055) for 4 years after EVAR. There are no additional late aneurysm deaths. There is no excess mortality after 4 years, and the survival curves do not meet.

model of Medtronic assumed a more optimistic scenario, that the rate of convergence of the survival curves would be slightly slower and that the survival curves would not meet. There would be no further difference in deaths beyond 4 years and, therefore, a slight long-term difference in survival would be maintained in favour of EVAR over the lifetime of the patients (*Figure 76*). The predicted survival curves when the Medtronic assumptions are used in the York model are shown in *Figure 78*.

Comparison of York model with other published economic evaluations

The base-case model found that EVAR was not expected to be cost-effective on average, but was cost-effective for patients with poorer fitness. These

results can be compared with the published models for similar patient groups. The systematic review of existing cost-effectiveness evidence presented earlier in this chapter found that the studies by Michaels *et al.*¹⁰⁷ and Epstein *et al.*¹⁰⁶ were the published economic evaluations most relevant to the current decision in England and Wales. JA Michaels, DM Epstein and MJ Sculpher are authors of one or both of these published papers and also of this report.

Both Michaels *et al.*¹⁰⁷ and Epstein *et al.*¹⁰⁶ concluded that EVAR was not expected to be cost-effective in patients eligible for elective surgery. However, there were differences between these

Cost/year of follow-up visits (£)	Hazard ratio for late reintervention	Model predictions					
		Years to convergence of survival curves	ΔQALY	ΔCost (£)	ICER (£/QALY)	P(20K)	P(30K)
108	6.7	3.0	0.041	2002	48,990	0.261	0.424
108	6.7	Lifetime	0.107	2023	18,873	0.621	0.720
108	6.7	8.0	0.090	2018	22,419	0.533	0.710
108	6.7	5.0	0.067	2011	30,136	0.382	0.572
108	6.7	2.0	0.021	1995	96,085	0.13	0.247
108	6.7	4.0	0.068	1999	29,276	0.338	0.539
108	6.7	3.5	0.055	2001	36,553	0.291	0.477
108	6.7	2.5	0.041	2005	48,567	0.249	0.421
54	6.7	3.0	0.041	1798	43,988	0.296	0.454
0	6.7	3.0	0.041	1593	38,987	0.341	0.513
108	1.0	3.0	0.044	1187	27,184	0.490	0.627
108	1.5	3.0	0.043	1259	29,010	0.437	0.581
54	1.5	3.0	0.043	1052	24,227	0.581	0.686
108	6.7	4.5	0.091	2000	21,922	0.542	0.688
108	6.7	3.0	0.041	868	21,245	0.561	0.688
108	6.7	3.0	0.041	1485	36,326	0.354	0.497
54	1.5	3.0	0.043	534	12,305	0.738	0.813
98	2.7	Lifetime	0.076	1098	14,506	0.654	0.788

published models and the York model in the assumptions used to arrive at this conclusion. Michaels *et al.* found a greater long-term benefit in favour of EVAR than the York model, and a greater difference in costs, but this study was published before the mid-term results of the good-quality RCTs were available. The study by Epstein *et al.* was published after the mid-term results of the RCTs were available, and based on these trial results assumed that the survival curves for EVAR and open repair would meet by 4 years. The published model has been adapted for use in the York economic evaluation. The main difference in the parameter values between the models is that

Epstein *et al.* assumed a greater difference in late aneurysm-related deaths (HR EVAR versus open repair = 6.0) than in the York model (HR = 1.5). The York model also used regression analysis to estimate baseline risks of operative mortality, late aneurysm-related mortality and non-aneurysm-related mortality in a wider range of patient groups than in Epstein *et al.*

The next section extends the York model to compare the cost-effectiveness of EVAR, open repair, watchful waiting and no intervention.

TABLE 68 Base-case and sensitivity analyses showing ICERs comparing EVAR and open repair for patients of different fitness, aneurysm size and age

		Fitness														
		Good					Moderate					Poor				
Scenario	AAA (cm)	Age (years)					Age (years)					Age (years)				
		70	75	80	85	85	70	75	80	85	85	70	75	80	85	
Base case	5.5	1,120,563	215,306	96,902	62,817	79,539	53,000	38,006	28,181	27,658	21,442	17,354	14,604	17,354	14,604	
	6.5	Dom	2,918,114	132,053	59,579	91,947	48,990	32,801	24,959	23,267	17,954	14,857	13,131	17,954	14,857	
	7.5	Dom	138,913	63,775	37,757	44,264	29,560	21,816	17,248	15,168	12,313	10,669	9855	12,313	10,669	
Lower cost of follow-up and lower rate of reinterventions	5.5	178,616	76,951	43,055	31,317	33,486	24,572	19,272	15,568	13,108	10,939	9588	8724	10,939	9588	
	6.5	Dom	338,899	61,553	31,980	40,766	24,227	17,735	14,631	11,615	9666	8670	8264	9666	8670	
	7.5	Dom	60,551	31,961	20,810	20,795	15,014	12,002	10,253	7686	6714	6299	6274	7686	6714	
Odds ratio of operative mortality 0.25 not 0.35	5.5	129,313	70,922	46,805	33,019	35,001	26,132	19,819	15,627	14,188	11,506	9647	8533	11,506	9647	
	6.5	346,307	77,388	43,933	28,413	31,102	21,922	16,737	13,499	11,602	9626	8418	7878	11,602	9626	
	7.5	74,231	38,924	25,945	18,974	18,792	14,233	11,441	9710	7978	6876	6273	6146	7978	6876	
Lower cost of follow-up, lower rate of reinterventions and equal cost of procedures	5.5	107,229	43,213	22,396	15,019	19,277	13,115	9457	7020	7183	5510	4412	3682	5510	4412	
	6.5	Dom	181,687	30,406	14,545	22,467	12,305	8252	6258	6069	4619	3776	3307	6069	4619	
	7.5	Dom	32,405	15,749	9434	11,436	7602	5561	4361	4001	3192	2724	2483	4001	3192	

Key: Dark grey shading, ICER > £30,001 per QALY or EVAR dominated; light grey shading, £20,001 per QALY < ICER < £30,000 per QALY; unshaded, ICER < £20,000 per QALY. The ICER is the difference in expected costs/difference in expected QALYs. Dominated (Dom) means that EVAR has less expected benefits and higher costs than open repair.

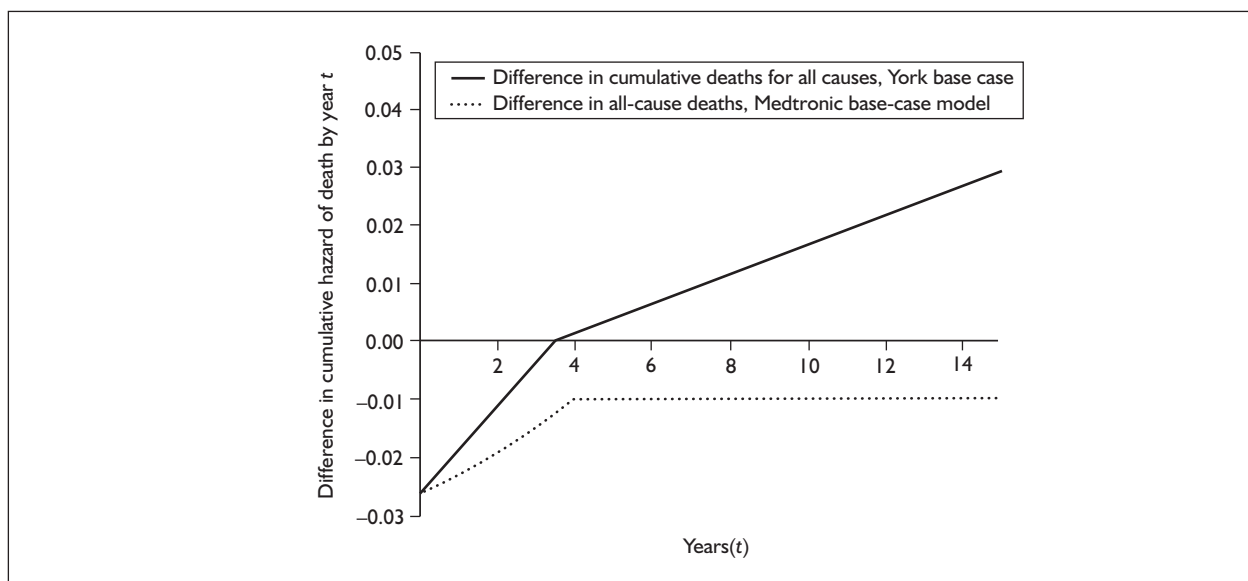


FIGURE 76 A comparison of the difference in cumulative deaths between EVAR and open repair over time for a patient aged 70 years with an aneurysm size of 6.5 cm and moderate fitness predicted by (a) the York model and (b) the Medtronic base-case model.

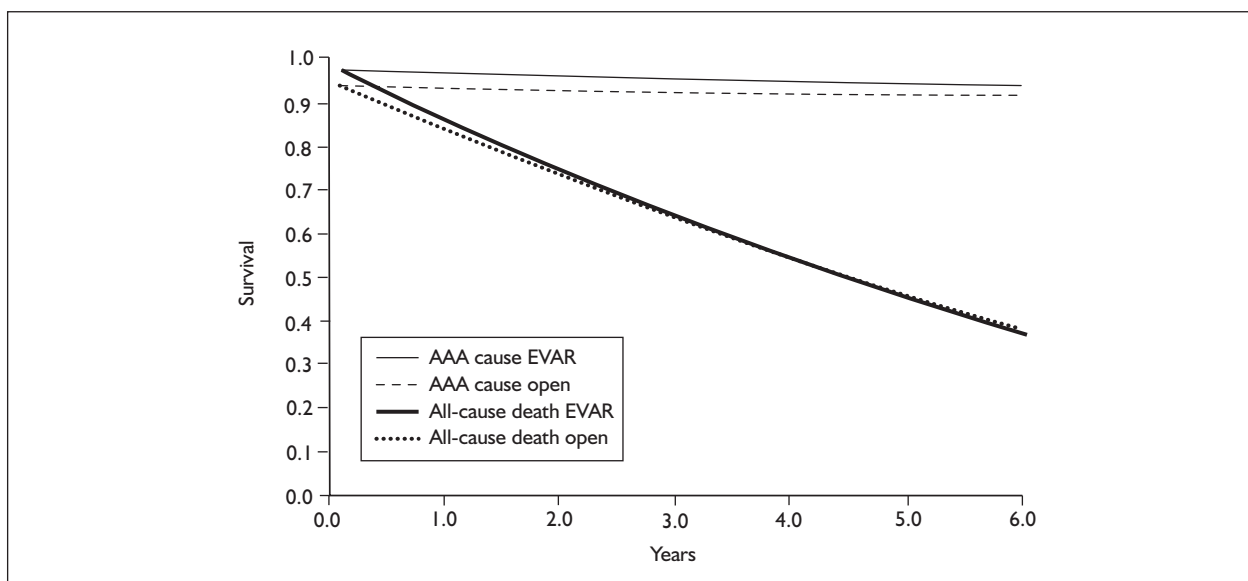


FIGURE 77 Predicted survival curves from the York model for a patient aged 70 years with moderate fitness and an aneurysm size of 6.5 cm. Survival curves converge by 3 years.

Model comparing immediate elective surgery, watchful waiting and no intervention

Methods of model comparing surgery and watchful waiting

Introduction

The objective of this second model was to broaden the nature of the comparisons made using the first

model. Specifically, the second model considers when surgery (with EVAR or open repair) might be cost-effective compared with no surgery or delaying the decision. The model brings together the sparse available evidence about natural history in untreated patients with evidence in treated patients to predict outcomes of a wide range of management policies in patients with diagnosed aneurysm. Given the uncertainties in these data,

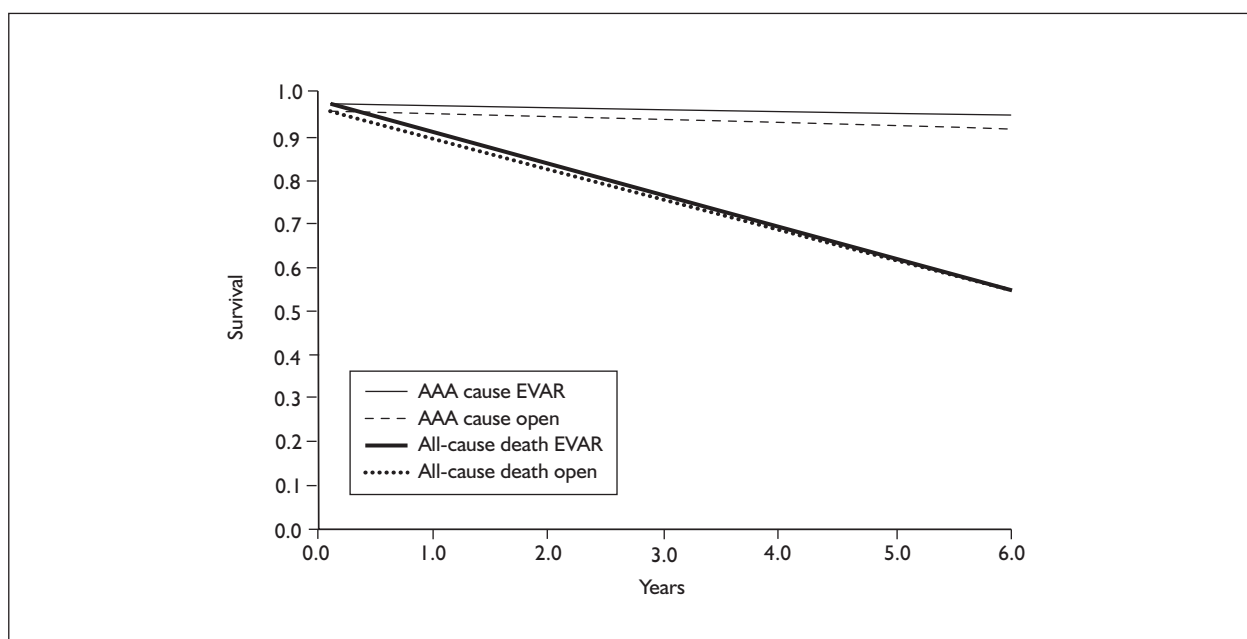


FIGURE 78 Predicted survival curves using Medtronic assumptions in the York model for a patient aged 70 years with moderate fitness and an aneurysm size of 6.5 cm. Survival curves do not converge. There is a small but cumulatively important difference in all-cause survival between the treatments.

the model is intended to be exploratory and suggest areas for further research.

Current guidelines for the management of AAA were discussed in Chapter 1. Briefly, patients are observed until the aneurysm reaches 5.5 cm in diameter, after which surgical intervention is considered.¹⁴¹ Patients considered fit for open surgery might be offered EVAR or open surgery; patients considered unfit for open surgery might be offered EVAR or no intervention. However, in practice there is a continuous range of probabilities of operative mortality and the optimum management policy should systematically weigh up all of the risks to the patient – that is, operative mortality and late mortality if treated versus the risks of rupture if untreated.¹¹ Furthermore, a publicly funded health-care system must also evaluate the use of health-care resources, which is not considered explicitly by the current clinical guidelines. This section presents a decision model to evaluate the cost-effectiveness of surgery, watchful waiting or no surgery for patients of different ages, operative fitness and aneurysm size.

Description of the watchful waiting strategy

At each consultation with the vascular surgeon the patient faces four options:

- immediate elective surgery with EVAR
- immediate elective surgery with open repair

- ruling out surgery entirely
- delaying the decision (watchful waiting).

We assume that the patient is evaluated every 6 months in the watchful waiting policy¹⁴⁶ and that the patient attends all scheduled follow-up visits. In practice, a substantial risk of patient non-compliance would diminish the value of a watchful waiting strategy, although we do not model this scenario. We assume that surveillance is discontinued if a decision is made to rule out surgery and there are no subsequent monetary costs to the health-care service. In practice, the patient may return if the aneurysm becomes symptomatic, but we do not model this scenario. The benefits of delaying the decision are that it allows more information on the aneurysm growth rate to be assembled, and preserves the option to commence immediate surgery in the future should the patient's health state (aneurysm size) worsen.¹⁰ The costs of deferral are monetary costs (the monitoring costs of CT and outpatient attendance) but also an important opportunity cost: patients may die from rupture while waiting. Waiting is also a source of uncertainty: people prefer current benefits rather than future benefits. We represent the cost of this impatience by discounting delayed benefits. Because AAAs are usually asymptomatic we assume that patients have normal HRQoL for their age while under surveillance, although there is some evidence that patients with diagnosed untreated aneurysm suffer anxiety.¹⁴⁶

The approach used to model watchful waiting is as follows:

- first, the model previously described to evaluate EVAR versus open surgery was used to estimate the maximum expected net benefit of surgery in patients of a given fitness for a range of aneurysm sizes (4–8 cm, in increments of 0.5 cm) and ages (70–85 years, in increments of 6 months)
- second, another model was constructed to evaluate an option of no surgery (i.e. natural history, with no treatment and no surveillance) for the same patient groups; this model is described in the following section
- finally, a dynamic programme was constructed using these data to estimate the net benefit of a watchful waiting strategy and to calculate the optimum policy (EVAR, open repair, no surgery or watchful waiting) for each aneurysm size and patient age.

Model to estimate the natural history of untreated aneurysm

To estimate the natural history of untreated aneurysm a Markov cohort model is used. The aim of the model is to estimate QALYs over a patient's lifetime if the patient is left untreated. As there is no surveillance and no surgery in this model there are no costs. The discrete health states are aneurysm size, from the size at diagnosis up to a maximum of 10 cm in diameter in increments of 0.5 cm. Rupture rate is conditional on aneurysm size. The mean growth rate and standard deviation and rupture rate were obtained from a review of the literature on the natural history of untreated aneurysm. It was assumed that the growth rate of aneurysms (g) is normally distributed with the mean and variance being a function of aneurysm size in the previous period. Markov transition probabilities for moving from one health state to another were derived from this continuous distribution as follows:

- $\text{Pr}(\text{aneurysm increases by 1 cm in a single 6-month period}) = \text{Pr}(g \geq 1)$
- $\text{Pr}(\text{aneurysm increases by 0.5 cm in a single 6-month period}) = \text{Pr}(0.5 \leq g < 1)$
- $\text{Pr}(\text{no change in aneurysm in the 6-month period}) = \text{Pr}(g < 0.5)$
- It is assumed that aneurysms do not diminish in size.

As the annual probability of rupture is estimated to be 90% for aneurysms of 10 cm in diameter¹¹ it was assumed unnecessary to predict growth beyond this

size. Consequently, when the aneurysm is 9.5 cm in diameter the above algorithm is amended to:

- $\text{Pr}(\text{aneurysm increases by 0.5 cm in a single 6-month period}) = \text{Pr}(g \geq 0.5)$
- $\text{Pr}(\text{no change in aneurysm in the 6-month period}) = \text{Pr}(g < 0.5)$.

In this model rupture is assumed to be fatal. Very few patients reach hospital alive after rupture and therefore the possibility of emergency surgery would be unlikely to affect the results.¹¹ Given the absence of evidence on how fitness might evolve over time, and the effect of fitness on aneurysm growth and rupture, it is assumed that fitness is constant over the duration of the model.

Parameter estimation for natural history model

Rupture rate for untreated patients

Untreated patients face a risk of rupture of their aneurysm (*Table 69*). It is difficult to measure the risk of rupture in an untreated patient because the natural history is rarely fully observed. Interventions might be considered when the risks of rupture outweigh the operative risk and therefore censoring is not at random. Powell *et al.*¹⁵⁴ conducted a review of the literature and compared the results with estimated rupture rates in the EVAR trial 2. The EVAR trial 2 is the only study we know of that specifically measured untreated rupture rates in patients suitable for EVAR. Powell *et al.*¹⁵⁴ found that the patients with large aneurysms (> 6 cm) in the EVAR trial 2 had a lower untreated risk of rupture than patients in other studies and concluded that this might be due to the EVAR trial patients being anatomically suitable for EVAR (*Table 69*). However, there were few patients with further CT scans after randomisation and so growth after the baseline was not investigated in the EVAR trial 2. This limits the usefulness of these data to model a watchful waiting strategy. For patients with aneurysms of < 6 cm they found that the rupture rate in EVAR trial 2 was similar to that in other published studies. Because of time constraints the data on rupture rates used in this model were not identified by a systematic review of the literature. However, we believe we have identified the most important sources of evidence relevant to the UK (*Table 69*). We used the estimates from Michaels 1992¹¹ as the base case as these data were available for a wide range of aneurysm sizes and appeared to be broadly consistent with estimates from the EVAR trial 2.¹⁵⁴ Rupture rates were smoothed with respect to aneurysm size with an exponential function.

TABLE 69 Estimates of untreated rupture rates for different sizes of aneurysm: results from review of the literature

	AAA diameter (cm)	Rupture rate/year
Studies of patients considered fit for open surgery		
Limet 1991 ¹⁵⁶ (case series, based on last observed AAA diameter)	< 4	0
	4–5	N/A
	> 5	0.22
Michaels 1992 ¹¹ (meta-analysis, based on last observed AAA diameter)	3–3.9	0.005
	4–4.9	0.010
	5–5.9	0.050
	6–6.9	0.090
	7–7.9	0.125
	8–8.9	0.250
	9–9.9	0.500
Reed 1997 ¹⁵⁷ (case series, based on last observed AAA diameter)	10+	0.900
	3–3.9	0.000
	4–4.9	0.010
	5–5.9	0.110
UKSAT 1998 ¹⁵⁸ (surveillance arm of RCT)	6+	0.260
	4–5.5	0.010
Kim 2005 ¹⁵⁹ (MASS trial, based on baseline AAA diameter)	3–4.4	0.000
	4.5–5.4	0.009
	5.5+	0.063
Studies of patients refusing or unfit for open repair		
Powell 2008 ¹⁵⁴ (meta-analysis of five studies, ^a based on baseline AAA diameter)	5.0–5.9	0.103
	≥ 6	0.270
Powell 2008 ¹⁵⁴ (EVAR trial 2, based on baseline AAA diameter)	5.5–5.9	0.097
	≥ 6	0.174
Studies of patients both fit and unfit for open repair		
Brown 2003 ¹⁵⁵ (Canadian cohort, men)	5.0–5.9	0.010
		0.141
Brown 2003 ¹⁵⁵ (Canadian cohort, women)	5.0–5.9	0.039
	≥ 6	0.223
Brown 1999 ² (UKSAT randomised and unrandomised, based on last observed or estimated AAA diameter)	3–3.9	0.003
	4–4.9	0.015
	5–5.9	0.065

a The five studies used in the Powell review¹⁵⁴ were Jones 1998,¹⁶⁰ Brown 1999,¹⁶¹ Conway 2001,¹⁶² Lederle 2002¹⁶³ and Aziz 2004.¹⁶⁴

Powell *et al.*¹⁵⁴ and Brown *et al.*¹⁵⁵ found that rupture rates tended to be greater in women for a given aneurysm size, although Powell *et al.* found the result to be non-significant [HR women versus men 1.21 (95% CI 0.77 to 1.90)].

Expansion rate of untreated aneurysm

Table 70 shows the estimates of the expansion rate of untreated aneurysm from the literature review. Because of time constraints these data were not identified by a systematic review of the literature.

TABLE 70 Expansion rate of untreated aneurysm: results of review of the literature

	AAA diameter (cm)	Median expansion rate (cm/year)	Variability
Limet 1991 ¹⁵⁶ (case series, based on last observed AAA diameter)	< 4	0.53	N/A
	4–5	0.69	N/A
	> 5	0.74	N/A
			No increase (%)
Michaels 1992 ¹¹ (meta-analysis, based on last observed AAA diameter)	3–3.9	0.28	53
	4–4.9	0.60	22
	5–5.9	0.68	19
	6–6.9	0.96	5
	7–7.9	1.26	0
Reed 1997 ¹⁵⁷ (case series)	All	0.21	N/A
UKSAT 1998 ¹⁵⁸ (surveillance arm of RCT)	4–5.5	0.33	IQR 0.2–0.53 cm
			Rate of expansion to next size in 3 months
Kim 2005 ¹⁵⁹ (MASS trial, based on baseline AAA diameter)	3–4.4	N/A	0.025
	4.5–5.4	N/A	0.087
	> 5.5	N/A	N/A

IQR, interquartile range.

We used the mean expansion rate from Michaels¹¹ as the base case as these data were available for a wide range of aneurysm sizes and appeared to be consistent with estimates from the other sources. Not all of the studies reported the standard deviation or other measures of variability. We estimated the standard deviation of the expansion rate to be 0.15 cm/6 months in aneurysms of 4–4.4 cm, 0.30 cm/6 months in aneurysms of 4.5–6.9 cm and 0.34 cm/6 months for aneurysms > 7 cm, which seemed roughly consistent with the data on variability of the expansion rate estimated by Kim *et al.*,¹⁵⁹ UKSAT¹⁵⁸ and Michaels.¹¹ Table 71 calculates the transition probabilities of moving from the current aneurysm size to one or two sizes larger in one cycle of the natural history model assuming a normal distribution and the mean expansion rate from Table 70.

Illustration of the predicted rate of mortality of surgical treatment compared with no treatment at each age and aneurysm size

Figure 79 illustrates the rate of mortality estimated over time in the model for a patient with a starting age of 70 years, with poor fitness and with an initial aneurysm diameter of 4 cm. Without treatment the

aneurysm is predicted to grow exponentially and the risk of rupture increases according to aneurysm diameter.¹¹ Given these estimates of aneurysm growth, and the risk equation estimated from EUROSTAR (Table 58, equation 1), the expected operative mortality with EVAR would increase in relation to increasing age and aneurysm diameter, from about 1.5% at age 70 years to 10% after 7 years.

Cost-effectiveness analysis using dynamic programming

This section describes how dynamic programming was used to select the most cost-effective option (surgery, no intervention or watchful wait) for patients at each age and aneurysm size, using the results of the models for estimating the net benefits of surgery and the natural history described in the previous sections. The methods are closely based on the work of Driffield and Smith.¹⁰

This section has three parts:

1. We explain the concepts of dynamic programming and how the method can be used to simplify the modelling of watchful waiting.

TABLE 71 Mean and standard deviation of expansion assumed in the base case per 6 months, and calculated transition probabilities of expansion in a 6-month cycle, assuming a normal distribution for aneurysm growth

		Aneurysm size at start of 6-month cycle (cm)												
		4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
Mean and SD of expansion in 6 months (cm)														
Mean		0.24	0.28	0.34	0.40	0.48	0.57	0.67	0.80	0.96	0.96	0.96	0.96	0.96
SD		0.15	0.30	0.30	0.30	0.30	0.30	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Probability of 0- to 0.5-cm growth, 0.5- to 1-cm growth and 1- to 1.5-cm growth in 6 months														
No growth		0.96	0.77	0.71	0.63	0.53	0.41	0.31	0.19	0.09	0.09	0.09	0.09	0.09
0.5-cm growth		0.04	0.23	0.28	0.35	0.43	0.51	0.52	0.53	0.46	0.46	0.46	0.46	0.46
1-cm growth		0.00	0.01	0.01	0.02	0.04	0.07	0.17	0.28	0.45	0.45	0.45	0.45	0.45

Note: The data on mean aneurysm growth with respect to aneurysm size from Michaels¹¹ have been smoothed using an exponential function.

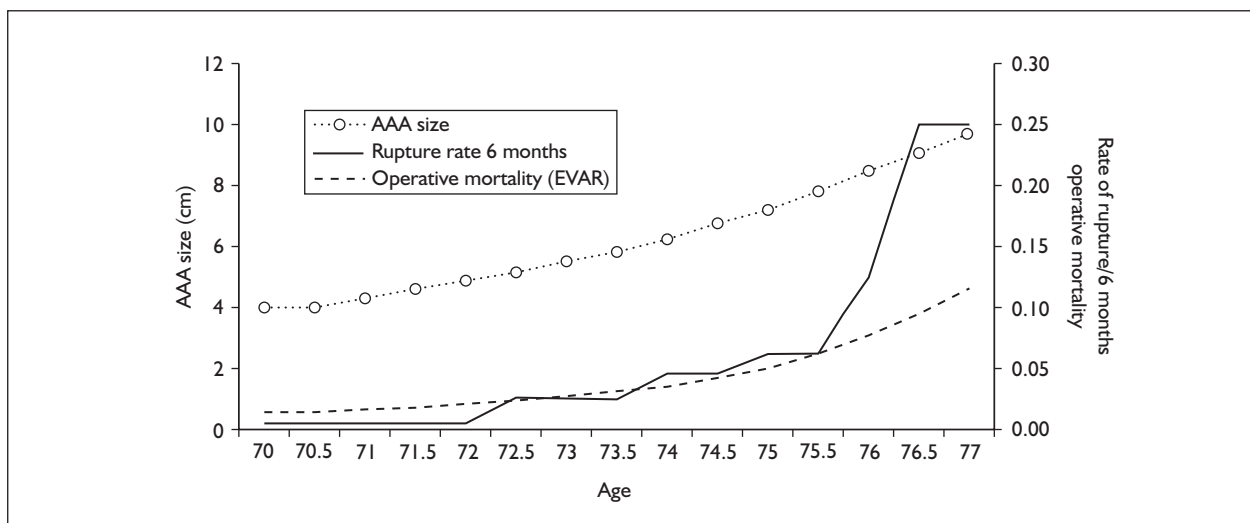


FIGURE 79 Illustration of mean rates of operative mortality and rupture estimated over time in the model for a patient aged 70 years, with poor fitness and with an aneurysm of diameter 4 cm at diagnosis. The figure also shows the change in aneurysm size over time.

2. We calculate the optimal policy for each aneurysm size in the final time period.
3. We calculate the optimal policy for each aneurysm size in each of the previous time periods.

Concepts of dynamic programming

Figure 80 illustrates the management options. The benefits and costs of the strategies of immediate elective repair versus no surgery depend only on future chance events, such as whether the aneurysm grows slowly or quickly in each cycle, or the patient dies. The previous sections described the Markov models used to estimate patients' lifetime expected benefits and costs for these two strategies, for any given starting age, aneurysm size and fitness. In principle, we could also use a decision tree or Markov model to calculate a watchful waiting strategy. However, this would quickly become intractable. The watchful waiting strategy is more complex than a decision simply to treat or not treat taken at diagnosis. At each future age and aneurysm size there are three decision options (immediate surgery, rule out surgery or watchful waiting) and an indeterminate time horizon. The problem is dynamic, i.e. the optimal strategy depends not only on future chance events but also on decisions made in the light of those events (Figure 80). This means that there are hundreds of possible strategies for watchful waiting (e.g. immediate EVAR, wait 6 months then surgery if the aneurysm is 0.5 cm larger, wait 1 year, etc.) for each starting age and aneurysm size.

To reduce this complexity we use a dynamic programming formulation to calculate the

optimum strategy for each age and aneurysm size.¹⁶⁵ Dynamic programming is based on a simple principle: that if a decision has a finite time horizon (N periods) and we know the optimal choices (payoffs) for each aneurysm size (model state) in period $N+1$ and we know the probabilities of transition between model states then we can work backwards to induce the optimal choices for each model state in the previous period (N , $N-1$ and so on) until the starting period ($t = 1$). Both surgery and a decision to discharge the patient are irreversible. Delaying a decision might have value because, as time progresses, the information regarding aneurysm size and growth rate is updated, resolving uncertainty and offering the option of changing the treatment policy. Continuing surveillance with an option to treat in the future if the aneurysm grows might give greater expected benefit than either of the irreversible decisions, which can be compared with the costs of obtaining this information. The output of the dynamic programme is a policy that states the optimal management option for each patient age and aneurysm size.

Calculating the optimal policy for each aneurysm size in the final time period

We begin by assuming that there is a maximum aneurysm size, say 8 cm, above which we will not continue watchful waiting, that is, we will either operate or discharge the patient. A size of 8 cm is arbitrary but as the risk of rupture at this size is 25% per year, and expected growth is over 1¼ cm per year,¹¹ the expected benefits of surveillance beyond this size would be very low. As we assume continued surveillance is not an option, the

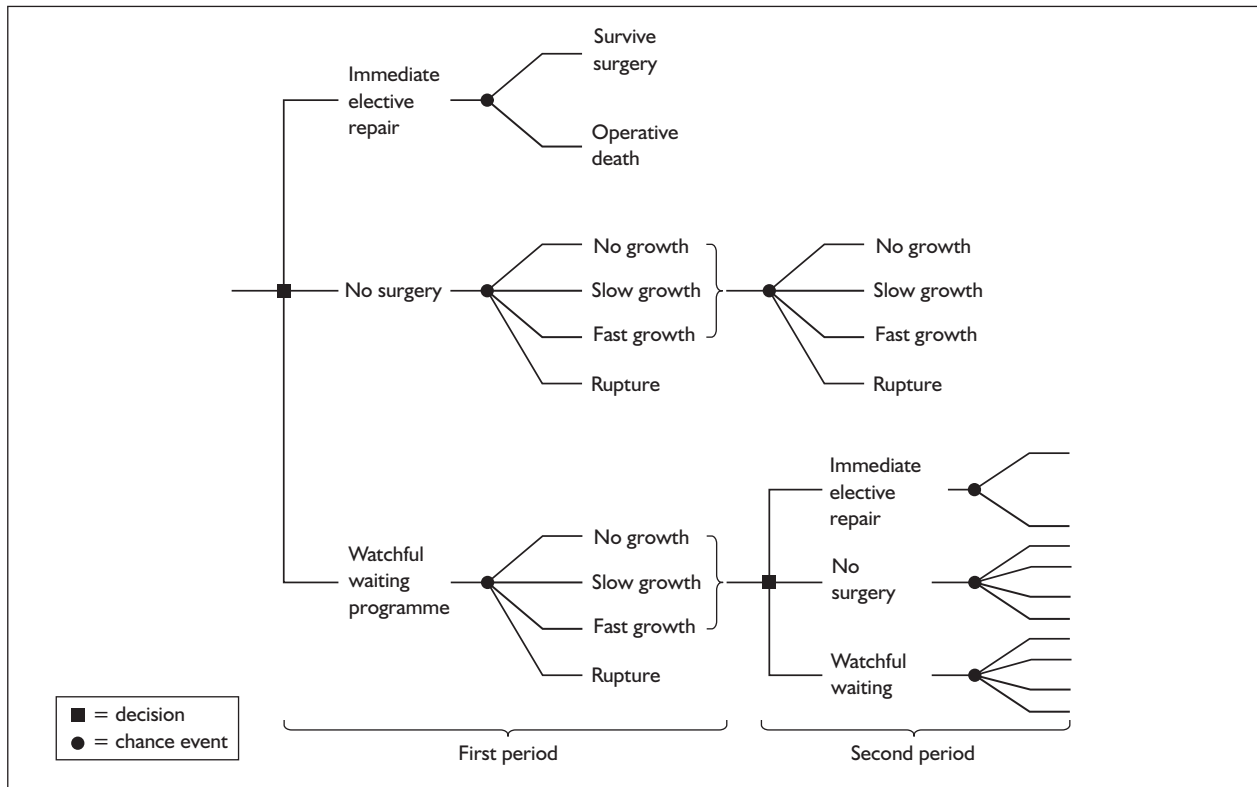


FIGURE 80 Management of a patient diagnosed with AAA, showing immediate elective repair, no surgery and watchful waiting strategies.

decision about whether to operate or discharge the patient at any given age when the aneurysm is 8 cm depends on whether the net benefits of surgery are greater than no surgery; the incremental net benefits of surgery versus no surgery will diminish with age (at a given aneurysm size) as operative mortality increases and life expectancy beyond surgery falls. On the other hand, the incremental net benefits of surgery versus no surgery will increase with aneurysm size (at a given age) as the risk of rupture outweighs the risk of operative mortality. We compare the net benefits of open surgery, EVAR and no surgery to find the maximum age at which it is no longer cost-effective to operate, even for aneurysms of 8 cm.

Under the base-case model, at a willingness to pay of £30,000 per QALY and assuming the rupture and growth rates from Michaels,¹¹ for patients in 'very poor' fitness (i.e. ineligible for EVAR trial 1) we find this age to be 80 years. That is, at age 80 years and above it is never cost-effective to operate, whereas at age 79.5 years it is cost-effective to operate on aneurysms of 8 cm but not on smaller aneurysms.

Consequently, we need only consider watchful waiting up to age 79 years, as watchful waiting can only be more cost-effective than offering no treatment if surgery is a possible future option. In this case $N = 19$ periods for a starting age in the model of 70 years and a cycle length of 6 months $[(79-70) \times 2 + 1 = 19]$. Even though we only consider watchful waiting up to age 79 years, net benefits of surgery and no surgery have been calculated for a lifetime using the Markov models described in previous sections. Note that this maximum age is a function of willingness to pay and the fitness of the patient, as well as all of the parameters of the decision model.

Calculating the optimal policy for each aneurysm size in each of the previous time periods

Given that we have calculated the optimum choices for each health state (aneurysm size) at period $N + 1$ (corresponding to age 79.5 years) we use backward induction to calculate the optimum choices for each health state in the previous period N . Figure 81 illustrates the numerical solution method with a segment of the decision tree for a patient of very poor operative fitness, for example

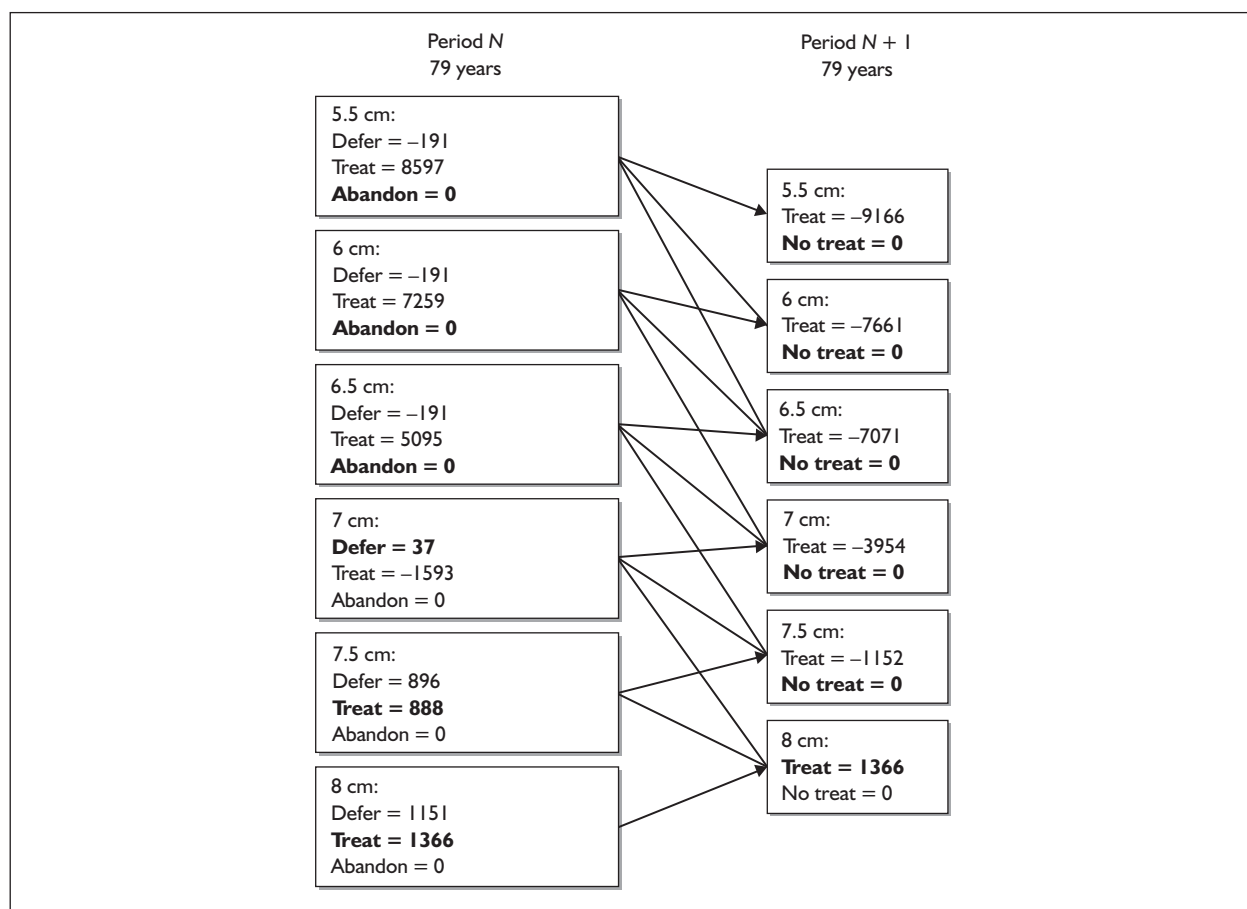


FIGURE 81 Illustration of the dynamic programme decision tree for the periods N and $N + 1$ for a patient of very poor operative fitness. The values shown are the incremental net benefits of deferring the decision (watchful waiting) or of immediate treatment compared with abandoning watchful waiting (never offering surgical treatment). The dynamic programme is evaluated from right to left, that is, the cost-effective policies are identified for each state in period $N + 1$ and then for each state in period N , $N - 1$, etc. Note: The cost of an outpatient visit with CT scan is £191. The probability of the aneurysm growing from 7 to 8 cm in 6 months is 0.17 and of growing from 7.5 to 8 cm in 6 months is 0.52. Cost-effective options at a threshold of £30,000 per QALY are highlighted in bold.

ineligible for EVAR trial 1 or the DREAM trial. The willingness to pay threshold is £30,000 per QALY.

The right-hand side of the figure shows the possible states of health in period $N + 1$ (age 79.5 years). The incremental net benefits of surgery (most cost-effective of EVAR versus open repair) compared with no surgery have been calculated using the decision models for treated and untreated patients previously described; the value for no surgical treatment is always shown as zero (relative to surgery). In the period $N + 1$ there is no option to defer and so the decision is merely whether the patient should receive treatment. This decision is straightforward (given the data), depending only on whether the incremental net benefits of surgery are positive (relative to

no surgery). At age 79.5 years surgery would be offered only if the aneurysm is 8 cm in diameter.

Moving back to period N (age 79 years) there is now the additional option to defer treatment. In each state we compare three possible actions: deferral, treatment and abandonment. If the aneurysm is 7 cm, deferral is calculated as the expected net benefits from waiting another period (6 months), in which three possible states of health could occur: no growth, growth by 0.5 cm (to 7.5 cm) or growth by 1 cm (to 8 cm). The probabilities of these outcomes were calculated in Table 71 to be 0.31, 0.52 and 0.17 respectively. Delaying a decision might generate benefits but it also has costs. Delaying a decision might have value because it allows resolution of the uncertainty

about whether the aneurysm will grow, which in turn would change the treatment decision, with greater benefit than either immediate treatment or never offering surgery. If delay is permitted in period N , the optimal strategy in period $N + 1$ is no surgery if the aneurysm does not grow, no surgery if the aneurysm grows to 7.5 cm and EVAR if the aneurysm grows to 8 cm. There are three sources of opportunity cost of delaying the decision. First, patients may rupture while waiting. Second, there is a time preference for current benefits and so future uncertain benefits are discounted. Third, there is a monetary cost of monitoring, which is assumed to be one outpatient visit with CT scan costing £191. These costs and benefits of delay are expressed in the following formula:

$$\text{Present value at 7 cm in period } N \text{ of future net benefit of deferral} = (1 - \text{Pr}(\text{rupture})) \times e^{-r/2} \times (0.31 \times 0 + 0.52 \times 0 + 0.17 \times 1366) - 191 = 37$$

where $\text{Pr}(\text{rupture})$ is the probability of rupture for a patient with a 7-cm aneurysm, e is the exponential function and r is the discount rate (0.035 per year).

This can be compared with the counterfactual, which is the present value of immediate elective EVAR at 7 cm in the period N . This was calculated using the decision model for EVAR described in the previous section. For convenience, this value is shown relative to a policy of no surgery, so that 'no treatment' is always shown with a value of zero. If surgery has been carried out there is no monetary cost of continued surveillance, nor will the patient rupture from untreated aneurysm.

Therefore, if the aneurysm is 7 cm at 79 years the optimal decision is to continue waiting, as the net benefits of waiting are greater than those of treatment. For aneurysms < 7 cm the optimal decision is to discharge the patient, because at period $N + 1$ it will never be cost-effective to treat, regardless of the aneurysm growth rate. For aneurysms > 7 cm it is not cost-effective to wait and the best strategy is immediate treatment.

The same algorithm is used to calculate the net benefits for each aneurysm size in period $N - 1$, and the process continues by backward induction until period 1 is reached. In most dynamic programming applications the main interest is in the decision at period 1 and the future period calculations are performed merely to inform that decision.¹⁰ In this application, however, we are also interested in the grid of policies for all ages and

aneurysm sizes, as this indicates the most cost-effective policy for any patient at diagnosis.

Results of the comparison of immediate surgery, watchful waiting and no intervention strategies

Results of watchful waiting model for patients of very poor operative fitness

Table 72 shows the optimum policy for patients of very poor operative fitness at each age and aneurysm size, under base-case assumptions and at thresholds of £20,000 and £30,000 per QALY. Patients are similar to those who were eligible for the EVAR trial 2. The results show that, for patients of very poor fitness, EVAR might be cost-effective at £20,000 per QALY up to 77 years in patients with an aneurysm of 8 cm, up to 74 years in patients with an aneurysm of 6 cm and up to 71.5 years in patients with an aneurysm of 5 cm. Increasing the threshold to £30,000 per QALY increases the age at which EVAR is cost-effective by about 2 years.

The model predicts that watchful waiting would be cost-effective for patients with a small aneurysm of 4 cm up to age 68.5 years at a threshold of £20,000 per QALY. For patients with a larger aneurysm, delaying treatment might be cost-effective for some patients on the margin of the treat/discharge decision. For patients with an aneurysm > 4 cm, waiting might be cost-effective for up to 18 months (three periods).

Scenario 17 in Table 67 showed that if EVAR has lower costs and a lower rate of reintervention than in the base case, the ICER for EVAR versus open repair for patients fit for open surgery was approximately £12,000 per QALY. We carried out a further sensitivity analysis comparing EVAR with watchful waiting for patients who are not fit for open surgery, that is, with a very poor risk of operative mortality, using the costs and rate of reinterventions in scenario 17. The results are shown in Table 73. In this scenario the decision about whether to treat with EVAR or to offer no treatment is broadly similar to that in the base case.

Results of watchful waiting model for patients of poor operative fitness

The previous analysis considered management options for patients who might be considered for the EVAR trial 2, that is, with very poor operative risk under open surgery. It is also possible to use this model to examine management options for patients who might be considered for EVAR trial 1, that is, when aneurysm repair might be

TABLE 72 Base-case results of the dynamic programme decision model for patients of very poor operative fitness, at thresholds of cost-effectiveness of £20,000 and £30,000 per QALY

Aneurysm size (cm)		Age (years)														
		68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
Threshold of £20,000 per QALY																
Small	4	W	W	W	N	N	N	N	N	N	N	N	N	N	N	N
	4.5	O	E	E	W	N	N	N	N	N	N	N	N	N	N	N
Medium	5	E	E	E	E	W	N	N	N	N	N	N	N	N	N	N
	5.5	E	E	E	E	E	E	N	N	N	N	N	N	N	N	N
Large	6	E	E	E	E	E	E	N	N	N	N	N	N	N	N	N
	6.5	E	E	E	E	E	E	W	N	N	N	N	N	N	N	N
Very large	7	E	E	E	E	E	E	E	W	N	N	N	N	N	N	N
	7.5	E	E	E	E	E	E	E	E	E	N	N	N	N	N	N
8	E	E	E	E	E	E	E	E	E	E	E	N	N	N	N	N
Threshold of £30,000 per QALY																
Small	4	W	W	W	W	W	N	N	N	N	N	N	N	N	N	N
	4.5	E	E	E	E	E	W	N	N	N	N	N	N	N	N	N
Medium	5	E	E	E	E	E	E	W	N	N	N	N	N	N	N	N
	5.5	E	E	E	E	E	E	E	W	N	N	N	N	N	N	N
Large	6	E	E	E	E	E	E	E	E	W	N	N	N	N	N	N
	6.5	E	E	E	E	E	E	E	E	E	W	N	N	N	N	N
Very large	7	E	E	E	E	E	E	E	E	E	E	W	N	N	N	N
	7.5	E	E	E	E	E	E	E	E	E	E	E	W	N	N	N
8	E	E	E	E	E	E	E	E	E	E	E	E	E	W	N	N

E, EVAR; N, no surgical intervention; O, open repair; W, watchful waiting.

TABLE 73 Sensitivity analysis: results of the dynamic programme decision model for patients of very poor operative fitness, at thresholds of cost-effectiveness of £20,000 and £30,000 per QALY

Aneurysm size (cm)		Age (years)														
		68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
Threshold of £20,000 per QALY																
Small	4	W	W	W	W	N	N	N	N	N	N	N	N	N	N	N
	4.5	E	E	E	E	N	N	N	N	N	N	N	N	N	N	N
	5	E	E	E	E	E	W	N	N	N	N	N	N	N	N	N
Medium	5.5	E	E	E	E	E	E	N	N	N	N	N	N	N	N	N
	6	E	E	E	E	E	E	E	N	N	N	N	N	N	N	N
	6.5	E	E	E	E	E	E	E	W	N	N	N	N	N	N	N
	7	E	E	E	E	E	E	E	E	W	N	N	N	N	N	N
Very large	7.5	E	E	E	E	E	E	E	E	E	E	N	N	N	N	N
	8	E	E	E	E	E	E	E	E	E	E	N	N	N	N	N
Threshold of £30,000 per QALY																
Small	4	W	W	W	W	W	N	N	N	N	N	N	N	N	N	N
	4.5	E	E	E	E	E	E	N	N	N	N	N	N	N	N	N
	5	E	E	E	E	E	E	E	W	N	N	N	N	N	N	N
Medium	5.5	E	E	E	E	E	E	E	E	N	N	N	N	N	N	N
	6	E	E	E	E	E	E	E	E	N	N	N	N	N	N	N
	6.5	E	E	E	E	E	E	E	E	W	N	N	N	N	N	N
	7	E	E	E	E	E	E	E	E	E	W	N	N	N	N	N
Very large	7.5	E	E	E	E	E	E	E	E	E	E	E	N	N	N	N
	8	E	E	E	E	E	E	E	E	E	E	E	N	N	N	N

E, EVAR; N, no surgical intervention; W, watchful waiting.

cost-effective compared with watchful waiting or discharging the patient, taking account of age, fitness and aneurysm size.

In this analysis we consider options for patients who have poor operative fitness. *Table 59* showed that such patients aged 75 years with an aneurysm of 6.5 cm would have a probability of operative mortality with EVAR of 0.04 and with open repair of 0.12. This would put them on the margins of eligibility for the EVAR trial 1 and EVAR trial 2. Current guidelines are unclear about the management of these patients. All other parameters are as in the base case.

The results of the dynamic programme are shown in *Table 74*. At a threshold of £20,000 per QALY, EVAR would be cost-effective up to age 82.5 years for an aneurysm of 8 cm and between 74 and 78 years for an aneurysm of 6 cm. With base-case assumptions, younger patients would be more cost-effectively treated with open repair, consistent with *Table 68*. At £30,000 per QALY, EVAR would be cost-effective up to 85 years for an aneurysm of 8 cm and up to 80 years for an aneurysm of 6 cm. For patients with an aneurysm of 5 cm the model predicts that EVAR is cost-effective up to about 78 years, with watchful waiting until 79 years. For patients with an aneurysm of 4 cm the model predicts that watchful waiting is cost-effective up to 75.5 years if the aneurysm does not grow.

Discussion

Conventionally, patients have been classified as fit or unfit for open surgery, and AAA repair has been offered to all patients fit for open surgery with an aneurysm size of ≥ 5.5 cm. This chapter has presented two models. The first examined EVAR versus open repair in patients according to the conventional classification of fit for open surgery and with large aneurysms of ≥ 5.5 cm. The second explored the cost-effectiveness of different policies concerning when, as well as how, surgery should be offered. In both models results have been presented by age, fitness and aneurysm size at diagnosis. Fitness in these models is defined in a general way so that a person of moderate fitness will have twice the operative mortality of a patient with the same size of aneurysm and of the same age with no pre-existing conditions.

Summary of model results: patients considered suitable for surgical repair

The base-case decision model found that EVAR is not cost-effective on average for patients

who are fit for open surgery, with an ICER of £49,000 per QALY and decision uncertainty that EVAR might be cost-effective of 0.42. However, these assumptions are based on historical data, particularly the EVAR trial 1. First, as EVAR has become more widely used, it is plausible that the costs of the EVAR procedure, particularly the time spent in the intensive care unit and operating theatre, have fallen faster than those of open repair since the start of the decade. This hypothesis is difficult to test using observational data because the case mix of patients undergoing EVAR may also have changed over this period. Second, it is plausible that the EVAR trial 1 overestimates the relative rate of reinterventions of EVAR versus open repair because it does not include late laparotomies and it is now less common to reoperate on some types of endoleak. Third, and related to the previous point, the frequency and cost of routine surveillance after EVAR may have been diminishing in recent years. Under this more favourable scenario, EVAR has an ICER of £12,000 per QALY and a probability of being cost-effective of 0.74 versus open repair at a threshold of £20,000 per QALY.

The model also considered how cost-effectiveness might vary by subgroups defined by age, aneurysm size and fitness. If patients can be classified into good, average and poor operative risk, then for patients of most ages and aneurysm sizes, EVAR is cost-effective compared with open repair in patients of poor risk but not cost-effective in patients of good risk. The absolute benefit of EVAR compared with open repair is low in patients of good operative risk. Furthermore, there is a long-term risk of complications and reinterventions after EVAR. The decision is very uncertain in patients of moderate risk.

Summary of model results: management of patients with poor or very poor fitness

Current UK clinical practice is that elective surgery is generally recommended for patients with aneurysms of ≥ 5.5 cm or with aneurysms > 4.5 cm that have increased in diameter by more than 0.5 cm in the last 6 months. However, these guidelines are based on the risks and benefits of open surgery and do not take account of costs. Neither do they take account of the findings of the EVAR trial 2, which called into question whether aneurysm repair was effective for unfit patients. The decision model has been used to identify the cost-effective management of patients for whom EVAR is an option, according to age and aneurysm size.

TABLE 74 Results of the dynamic programme decision model for patients of poor operative fitness, at thresholds of cost-effectiveness of £20,000 and £30,000 per QALY, from 70 to 85 years of age

		Age (years)															
Aneurysm size (cm)		70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
Threshold of £20,000 per QALY																	
Small	4	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
	4.5	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
	5	O	O	O	O	O	O	O	W	O	O	O	O	O	O	O	O
Medium	5.5	O	O	O	O	O	O	O	E	E	E	E	E	E	E	E	E
	6	O	O	O	O	O	E	E	E	E	E	E	E	E	E	E	E
	6.5	O	O	O	O	E	E	E	E	E	W	W	W	W	W	W	W
Large	7	E	E	E	E	E	E	E	E	E	E	E	W	W	W	W	W
	7.5	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Very large	8	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Threshold of £30,000 per QALY																	
Small	4	O	O	W	W	W	W	W	W	W	W	W	W	W	W	W	W
	4.5	O	O	O	E	E	E	E	E	E	E	E	E	E	E	E	E
	5	O	E	E	E	E	E	E	E	W	W	W	W	W	W	W	W
Medium	5.5	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	6	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	6.5	E	E	E	E	E	E	E	E	E	E	E	E	W	W	W	W
Large	7	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	7.5	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Very large	8	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E

E, EVAR; N, no surgical intervention; O, open repair; W, watchful waiting.

For patients who would be considered unsuitable for open surgery according to current guidelines, that is, with very poor operative fitness, the model predicts that EVAR might be cost-effective at a threshold of £20,000 per QALY up to 77 years in patients with an 8-cm aneurysm, up to 74 years in patients with a 6-cm aneurysm and up to 71.5 years in patients with a 5-cm aneurysm. Increasing the threshold to £30,000 per QALY increases the age at which EVAR is cost-effective by about 2 years.

The model predicts that watchful waiting would be cost-effective for patients with a small aneurysm of 4 cm up to age 68.5 years at a threshold of £20,000 per QALY. For patients with a larger aneurysm, delaying treatment might be cost-effective for some patients on the margin of the treat/discharge decision. For patients with an aneurysm > 4 cm, waiting might be cost-effective for up to 18 months (three periods). These results are fairly robust to assumptions about the cost of EVAR.

The model was also used to explore management options in patients with poor fitness. Such patients could be considered on the margin of eligibility for EVAR trial 1. At a threshold of £20,000 per QALY, EVAR would be cost-effective up to age 82.5 years for an aneurysm of 8 cm and between 74 and 78 years for an aneurysm of 6 cm. With base-case assumptions, younger patients would be more cost-effectively treated with open repair. However, these results are sensitive to model assumptions. At a threshold of £30,000 per QALY, EVAR would be cost-effective up to age 85 years for an aneurysm of 8 cm and up to 80 years for an aneurysm of 6 cm.

For patients with a small aneurysm at the upper margin of fitness for open surgery the model suggests that current guidelines ought to be reassessed. The model predicts that watchful waiting is cost-effective for such patients with an aneurysm of 4 cm up to 75.5 years. For patients with an aneurysm of 5 cm the model predicts that EVAR is cost-effective at a threshold of £30,000 per QALY up to about 78 years, with watchful waiting until 79 years.

The model including watchful waiting and no treatment is exploratory because it is based on data on the natural history of AAAs rather than on a comparison between treatment and no treatment in a controlled experimental setting such as an RCT. We can compare the results of EVAR trial 2 with the model predictions. At up to 4 years follow-up the EVAR trial 2⁴⁶ did not find any benefit for EVAR in the intention to treat analysis (primary adjusted HR EVAR versus no intervention 1.00,

95% CI 0.54 to 1.84), with higher cost in the EVAR group. The RCT authors concluded that EVAR was not effective or cost-effective for patients with very poor fitness. Patients enrolled in EVAR trial 2⁴⁶ had a mean age of 77 years and a median aneurysm size of 6.4 cm (IQR 6–7.4 cm). The model broadly supports these conclusions, that is, for this ‘average’ patient, no intervention is cost-effective at a threshold of £20,000 per QALY, and watchful waiting is cost-effective at a threshold of £30,000 per QALY. A watchful waiting policy was not formally evaluated by the RCT. However, there was a high proportion of crossovers in the trial – 27% (47/172) of patients in the no intervention arm had an aneurysm repair by 4 years.⁴⁶ This might indicate a high degree of uncertainty about the optimal management of these patients, such that many clinicians followed a ‘de facto’ watchful waiting policy despite the trial protocol. The trial was not powered to formally undertake subgroup analysis and therefore the model results cannot be compared to the RCT results for different ages and aneurysm sizes.

Limitations of the model comparing EVAR and open repair

These conclusions are sensitive to the model assumptions. We discuss the strengths and limitations of the main assumptions in turn.

First, the base case assumes that the treatment effect is proportional to operative risk, that is, the OR for EVAR versus open repair is constant for all levels of fitness, aneurysm sizes and ages. This implies that the absolute difference between EVAR and open repair in the proportions who die within 30 days is low in patients at low operative risk. There is some evidence that this assumption is reasonable^{23,96} (see Chapter 3). Brown *et al.*²³ found no significant interaction between CPI risk score and treatment effect for the patients in the EVAR trial 1. Schermerhorn *et al.*⁹⁶ also found fairly constant ORs across all age ranges, and therefore the absolute risk reduction (the difference in the operative mortality rate between similar patients) increased with age. Although this comparison used unrandomised data from Medicare, the authors used propensity score matching to compare treatment effects across a much more heterogeneous set of patients than are usually entered in a clinical trial, and in a much larger sample (almost 23,000 patients).

Second, the base case assumes that the initial advantage of EVAR compared with open repair is not sustained in the medium term. For patients at low and moderate risk, with a modest initial

difference in operative mortality, the survival curves are predicted to meet between 1 and 3 years after the procedure. This assumption is supported by the results of the EVAR trial 1,⁴³ the DREAM trial⁴⁰ and Schermerhorn *et al.*⁹⁶

Third, the base-case model assumed that late aneurysm mortality after EVAR would be low, around 0.3% per year in patients with an aneurysm of 5–5.4 cm but constant over a patient's lifetime. The most recent generations of devices require longer follow-up to confirm these results. The base-case model also predicted, from survival analysis of the EUROSTAR data, that late aneurysm mortality after EVAR in patients with a large aneurysm (≥ 6.5 cm) was considerably and significantly greater than that in patients with a small aneurysm (*Table 62*; HR 3.75, SE 0.83), confirming earlier work on this data set.⁸² However, patient selection into EUROSTAR may limit its generalisability. AAA diameter is a major determinant of the decision about surgery and is also an independent predictor of suitability for EVAR so that any results for patients with large AAAs treated by EVAR are likely to be based on a highly selective sample of patients. Therefore, this result requires further investigation.

Fourth, the base case estimated the use of hospital resources from the EVAR trial 1, as this was recent randomised data relevant to the UK. Other non-randomised data,^{128,166,167} and the survey results in Appendix 3, have suggested that some elements of the hospital costs of EVAR procedures, such as length of stay in the intensive care unit, may have fallen more rapidly than the costs of open repair since 2003. As discussed in Chapter 1, there is considerable variation in the prices paid for the endovascular stent and accessories.¹⁶⁶

Fifth, the base case estimated the baseline rate of operative mortality after EVAR conditional on fitness, aneurysm size and age from the EUROSTAR registry,⁵⁴ and estimated the rate after open repair using the average OR from a meta-analysis of RCTs (Chapter 3). On average in this population, the predicted rate of operative mortality after open repair in the model (5.7%) is higher than that found by the DREAM and EVAR trial 1 (4.6%⁴⁰ and 4.2%²³ respectively), but similar to that in the UKSAT trial (5.8%¹⁵⁸) in a younger patient group with smaller aneurysms and lower than that in the NVD registry (6.8%). It may be that the EVAR and DREAM trials operated on a more selected patient group, or in more specialist centres, than UKSAT. The base-case analysis assumes that the rates of operative mortality in the model are achievable on average in the UK.

Finally, throughout this analysis, fitness has referred to the risk of operative mortality relative to a patient of that age and aneurysm size with no comorbidities. Although fitness is an important factor in the analysis, there is currently no validated risk score system to quantify this risk both for EVAR and for open surgery. This makes it difficult to translate the findings presented in this analysis into recommendations for clinical practice. The development of a recognised risk scoring instrument for operative mortality that is valid for EVAR and open surgery is a matter of urgency.¹⁴²

Despite the lack of such an instrument there is considerable evidence that clinicians are skilled at identifying patients of lower than average, average and higher than average risk of operative mortality,^{23,65} taking account of a range of factors including cardiac conditions, pulmonary disorders, malignant disease, obesity and previous laparotomy. Indeed, this subjective assessment is a component of the current guideline used to determine whether a patient is suitable for surgical repair and to obtain informed consent. The definition of 'good' fitness used in this analysis is simply the absence of any of these comorbidities, and it would therefore be straightforward to measure in individual patients. The results of this analysis suggest that EVAR is unlikely to be cost-effective in this good fitness group in any of the scenarios evaluated (*Table 68*).

Limitations of the model comparing surgery with watchful waiting

The watchful waiting model has two submodels: a model comparing EVAR with open repair, to estimate outcomes with surgery, and a model calculating the natural history of untreated aneurysm, to estimate QALYs without any surgical intervention. Therefore, all of the limitations listed above apply to the watchful waiting model. Below, we discuss the additional assumptions required by the natural history model.

The parameters comparing the relative risks of operative mortality, reinterventions and late mortality after open surgery and EVAR were obtained from recent RCTs.^{40,43} However, the model comparing surgery with watchful waiting did not use treatment effects from RCTs. This is because the crossovers, delays and absence of a watchful waiting protocol in EVAR trial 2⁴⁶ make the results difficult to use directly to identify the most cost-effective form of management. Although the UKSAT trial¹⁵⁸ did have a clear policy for interventions, it did not evaluate EVAR. Therefore, we could not use treatment effects from these two

RCTs to inform the model. Instead, the natural history of patients with untreated aneurysm was estimated using rupture rates and growth rates obtained from a review of the literature, and compared with outcomes estimated by the model of EVAR and open repair for patients with the same baseline characteristics.

Given the uncertainties in the data, and the potential for bias in this non-randomised comparison, the decision model and dynamic programme for watchful waiting are intended to be exploratory. Nevertheless, as discussed above, the results appear broadly consistent with those of the EVAR trial 2, if it is accepted that the crossovers and delays for surgery represent a 'de facto' watchful waiting strategy by the trial participants. It would be difficult to design an RCT that was able to compare all of the policies considered in this model and to stratify results by patient characteristics. Therefore, more precise data are needed from clinical studies of rupture rates and growth rates of untreated aneurysm and the risk factors for rupture. There is some evidence that rupture rates tend to be greater in women for a given aneurysm size.¹⁵⁴ The optimal treatment policy for women has not been fully addressed in this analysis and requires further work.

In the absence of information about the effectiveness of policies to improve fitness, it is assumed constant (relative to the patient's age and aneurysm size) over the patient's lifetime. In effect, elective operative mortality worsens because of advancing age and aneurysm growth in these analyses. It may be that fitness can be improved in some patients.¹⁴² The UKSAT trial¹⁵⁸ concluded that one reason for the slightly better long-term outcomes after early surgery compared with delayed surgery might be that patients were more likely to give up smoking after surgery. The effectiveness of policies with the aim of improving fitness should be a matter for urgent research.

Management of patients with small aneurysms with EVAR

The guideline that aneurysm repair should not be undertaken in patients with an aneurysm size of < 5.5 cm is based on the UKSAT trial.¹⁵⁸ However, this RCT did not include EVAR, nor do the guidelines consider costs. Our decision analysis

suggests that the cost-effectiveness of management strategies is sensitive to model assumptions and patient characteristics of age and aneurysm size. There is, therefore, continuing uncertainty about the cost-effectiveness of EVAR in patients with small aneurysms. The ongoing CAESAR trial,⁵² comparing EVAR and surveillance, will provide some evidence relating to this patient group.

Conclusions

The main conclusions of the decision analysis are:

- EVAR is not cost-effective compared with open repair on average given base-case assumptions at a threshold of £30,000 per QALY.
- The results are very sensitive to model assumptions. EVAR may be more cost-effective than open repair if the relative costs of the procedure are less, reinterventions are relatively less frequent and follow-up surveillance is currently less intensive than in the base-case assumptions.
- The results are sensitive to the baseline risk of operative mortality, with EVAR appearing to be most cost-effective compared with open repair in the least fit patients. A validated and accepted fitness score is needed.
- In patients considered to be of very poor fitness (unfit for open repair according to current guidelines), EVAR may be cost-effective at a threshold of £20,000 per QALY up to 77 years in patients with an 8-cm aneurysm, up to 74 years in patients with a 6-cm aneurysm and up to 71.5 years in patients with a 5-cm aneurysm. Increasing the threshold to £30,000 per QALY increases the age at which EVAR is cost-effective by about 2 years. The modelling of EVAR versus no intervention and watchful waiting is indicative and exploratory, based on assumptions about the natural history of untreated aneurysm in patients anatomically suitable for EVAR. Further research in these areas would be important to inform future modelling work.
- Indicative modelling results suggest that EVAR may be cost-effective in some patient groups for small aneurysms and the current guideline that aneurysm should not be treated in patients with an aneurysm of < 5.5 cm should be reviewed.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Endovascular repair for AAA is already a well-established and widely used technology throughout the NHS. It is, however, a difficult technology to research and hence the evidence base leaves many questions regarding best practice unresolved. This is a rapidly evolving technology, with improved and more specific devices being developed, and the range of patients eligible for EVAR is likely to expand as the technology develops. Furthermore, ongoing research into the natural history of AAA will further inform clinical practice. Thus, the treatment protocols relating to AAA and EVAR will continue to evolve.

The National Screening Committee for the UK (March 2007) has recommended that AAA screening be offered to men aged 65 years, provided that the men invited are given clear information about the risks of elective surgery. Screening will lead to an increase in the number of AAA cases being identified for treatment, particularly small aneurysms. Steps will need to be taken to create networks of vascular surgical services to allow further specialisation and a bigger throughput of cases. Provided adequate

resources and training are available, the increased volume should reduce the risk of surgery (open or EVAR) as there is evidence correlating volume and quality.¹⁶⁸

It is necessary, as with any treatment decision, to consider ethical issues when choosing between AAA procedures. EVAR has significantly improved the 30-day mortality rate compared with open repair and has an equivalent medium-term all-cause death rate. When deciding on the best treatment for a patient an individual surgeon may decide that the short-term gains of EVAR outweigh the lack of a long-term advantage.

Irrespective of the potential benefits of EVAR, a significant proportion of all AAA patients (55% in an unselected series¹³) are unsuited to EVAR on the grounds of anatomy. Even with developments in EVAR device design it is unlikely that the requirement for open repair will diminish in the near future. It is therefore essential that the NHS maintains provision of, and continues to develop expertise in, open repair.

Chapter 6

Discussion

Statement of principal findings

Currently, EVAR trial 1,^{42,43} EVAR trial 2⁴⁶ and the DREAM trial^{40,41} represent the best randomised evidence for evaluating EVAR. In patients fit for both procedures EVAR reduces operative mortality compared with open repair and is associated with a reduction in aneurysm-related mortality over the medium term but there is no significant difference in all-cause mortality between EVAR and open repair at mid-term follow-up. The lack of a long-term mortality benefit with EVAR is compounded by an increased rate of complications and reinterventions and these are not offset by any increase in HRQoL, possibly because of the increased level of monitoring required with EVAR because of the risk of complications.

There is limited RCT evidence comparing EVAR with non-surgical management in patients unfit for open repair. EVAR trial 2⁴⁶ found no differences in mortality outcomes between groups but this finding cannot be taken as definitive because substantial numbers of patients randomised to non-surgical management crossed over to receive surgical repair of their aneurysms. This may indicate that the benefits of EVAR over 'watchful waiting' may only be apparent in the very long term.

The results from these trials are complemented by data from registries, in particular the EUROSTAR registry data relating to devices in current use.⁵⁴

Although not formally part of our review, the findings of the very large observational study recently published by Schermerhorn *et al.*⁹⁶ reflect those of the RCTs. Importantly, this study suggests that, although across all age groups the initial benefit of EVAR over open repair diminishes over time, the rate of conversion between the two treatments is slower in older patients. This suggests that less fit patients may benefit from EVAR more than fit patients.

Very few data on the use of EVAR for ruptured aneurysms are available and, as yet, it is unclear whether EVAR is an appropriate or beneficial intervention in this indication. An ongoing

study⁴⁸ should contribute data to help inform this question.

The base-case decision models developed by the York assessment team found that EVAR is unlikely to be cost-effective compared with open repair on average. For patients of poor or very poor fitness, the base-case model found that EVAR is more cost-effective than open repair. This result is sensitive to model assumptions and EVAR may be more cost-effective than open repair under other plausible assumptions, particularly about costs and reinterventions.

In patients with very poor fitness EVAR should be compared with options of no surgery or delayed surgery. In patients unfit for open repair and eligible for EVAR trial 2, with an aneurysm of 6.5 cm and aged 77 years, the model suggests that no intervention is cost-effective at a threshold of £20,000 per QALY, and watchful waiting is cost-effective at a threshold of £30,000 per QALY. These results appear broadly consistent with the results of the EVAR trial 2. The model suggests that EVAR may be cost-effective at £20,000 per QALY up to 77 years in patients with an 8-cm aneurysm, up to 74 years in patients with a 6-cm aneurysm and up to 71.5 years in patients with a 5-cm aneurysm. Increasing the threshold to £30,000 per QALY increases the age at which EVAR is cost-effective by about 2 years. This modelling work is based on unrandomised comparisons and is intended to be exploratory.

Strengths and limitations of the assessment

This review of the evidence used established systematic review methods.³⁷ We defined inclusion and exclusion criteria in advance. We applied a rigorous search strategy to a range of electronic and print sources. We also ensured that the review was kept up to date by using a current awareness strategy. Finally, we quality assessed RCTs before performing a meta-analysis when possible and appropriate. A more definitive analysis would be an individual patient data analysis of all completed and currently ongoing trials of EVAR.

We attempted to obtain any extra trial data on EVAR for unruptured aneurysms above that used in a previous systematic review of the RCT literature.³⁵ Data from EVAR trial 1 and EVAR trial 2 were supplied on an academic-in-confidence basis. Additional analyses of data from the EVAR trials have been published and were also included in the review as appropriate. Our synthesis of the RCT data differs slightly from that of Lederle *et al.*³⁵ in that they used ORs whereas we used HRs in our meta-analysis to provide a more precise measure of effect. However, this did not affect the findings of the meta-analysis.

The best RCTs in the review included patients with aneurysms of at least 5.5 cm in diameter. Ongoing trials that have included patients with aneurysms of 5 cm will contribute to the general evidence base of EVAR versus open repair but will also specifically inform the debate about the lower aneurysm size limit that can be treated beneficially with EVAR.^{49,50}

This review found a limited number of RCTs, particularly for patients unfit for open repair and for those with ruptured aneurysms. The lack of RCTs limits the strength of the conclusions that may be drawn. In addition, the data from both the RCTs and the registries are derived almost entirely from male patients. Although a very high proportion of the patients in the studies is representative of patients who develop AAA, the estimates of clinical effect will reflect the treatment of male patients more than female patients.

The registries included in the review were selected based on perceived relevance to the review question. The main strength of registry data is that they may give an indication of outcomes achieved in routine clinical practice. However, it should be noted that some data are old and thus may not reflect current practice. This is particularly the case for the RETA registry,⁵⁶ which stopped adding new cases in 2000 when the EVAR trial 1 and EVAR trial 2 studies began. The EUROSTAR registry⁵⁴ provides data on a large sample of patients undergoing EVAR, with most data being recorded prospectively. Although probably the strongest source of registry data on EVAR, a possible limitation of EUROSTAR is that it includes relatively few centres from the UK and may not entirely reflect UK practice. The UK NVD¹⁶ currently concentrates on open repair of AAAs almost exclusively and therefore (because patients are not routinely followed up after open repair) includes only short-term outcomes (i.e. 30-day mortality) in its published reports.

The studies on risk models provide pointers for further research and show decision-makers where data are limited, contradictory or uncertain. The majority of studies assess relationships between preoperative risk factors and patient outcomes following EVAR. We have provided a narrative and graphical synthesis of these studies and this illustrates which factors have generally been found to be significant independent risk factors in multivariate analyses. We are conscious, however, of potential reporting bias as factors not found to be significant in analyses may not always have been reported in the included studies. Therefore we have been cautious in our summary statements, indicating which may be significant risk factors overall. In addition, there is inconsistency in the combinations of factors used in multivariate models and this supports the decision to use broad categories of patient fitness rather than any specific risk scoring system in the economic model included in this report (see Chapter 4, York economic assessment).

A further limitation of most of the included risk modelling studies is that methodology was poorly reported. This, together with a lack of validated quality assessment tools for such studies, makes it difficult to stratify the studies in terms of quality. We have focused on the studies that evaluated existing risk algorithms^{23,59,86} and the one study that developed a risk algorithm from scratch^{21,60,92} because these appear to be potentially the most useful for clinical decision-making. Further research is required to develop tools to compare possible outcomes of EVAR and alternative strategies (open repair and non-surgical management with or without later surgery).

The modelling undertaken by the York assessment team builds on earlier work undertaken by a subset of authors. In general, a strength of the modelling is that it uses both RCT and registry data in an attempt to identify the most cost-effective form of management for each type of patient (in which fitness, age and aneurysm diameter are the key variables characterising patients). This approach highlights the heterogeneity in cost-effectiveness in this area and suggests that it may not be appropriate to define one form of management as the most cost-effective in all types of patients. The modelling approach has also sought to handle the issue of appropriate comparators by presenting two models. The first model assumes (as was the case in EVAR trial 1) that a decision has been taken to operate on a patient and the question is whether EVAR or open surgery should be provided. The second model widens the comparators by including

two additional strategies: watchful waiting and the decision not to intervene.

All models in this area are subject to uncertainty in the assumptions made and the evidence used. These have been dealt with using appropriate sensitivity and scenario analyses. Different perspectives on structural assumptions and choice of evidence also largely explain differences between the York model, those in the published literature and that submitted to NICE by Medtronic. These uncertainties are considered in the following section.

Uncertainties

In general, the main uncertainties that may influence this assessment are:

- the uncertainty regarding the natural history of AAA if left untreated
- the uncertainty regarding the effect size of EVAR in smaller aneurysms; this question is currently being addressed in two ongoing trials, ACE and OVER (see Chapter 3, Ongoing RCTs)
- the uncertainty regarding the effect size of EVAR compared with watchful waiting
- the uncertainty regarding the impact of various levels of risk on the outcome following EVAR.

For the economic modelling in particular there are some specific uncertainties about assumptions and data sources:

- The base case assumes that the treatment effect is proportional to operative risk, that is, the odds ratio for EVAR versus open repair is constant for all levels of fitness, aneurysm sizes and ages. This implies that the absolute difference between EVAR and open repair in the proportion who die within 30 days is low in patients at low operative risk. There is some evidence that this assumption is reasonable^{23,96} (see Chapter 5).
- The base case assumes that the initial advantage for EVAR compared with open repair is not sustained in the medium term. For patients at low and moderate risk, with a modest initial difference in operative mortality, the survival curves are predicted to meet between 1 and 3 years after the procedure. This assumption is supported by the results of EVAR trial 1,⁴³ the DREAM trial⁴⁰ and Schermerhorn *et al.*⁹⁶

- The base-case model assumes that late aneurysm mortality after EVAR would be low, around 0.3% per year in patients with an aneurysm of 5–5.4 cm, but constant over a patient's lifetime. It also predicted, from survival analysis of the EUROSTAR data, that late aneurysm mortality after EVAR in patients with a large aneurysm (≥ 6.5 cm) was considerably and significantly greater than that in patients with a small aneurysm, confirming earlier work on this data set.⁸² However, patient selection into EUROSTAR may limit its generalisability. AAA diameter is a major determinant of the decision about surgery and is also an independent predictor of suitability for EVAR and so any results for patients with large AAA treated by EVAR are likely to be based on a highly selective sample of patients.
- The base case estimated the use of hospital resources from EVAR trial 1 as this was recent randomised data relevant to the UK. Other non-randomised data^{127,166,167} have suggested that the hospital costs of EVAR procedures may have fallen more rapidly than the costs of open repair since 2003, although, as discussed in Chapter 1, there is also considerable variation in the prices paid for the endovascular stent and accessories.¹⁶⁶
- The base case estimated the baseline rate of operative mortality after EVAR conditional on fitness, aneurysm size and age from the EUROSTAR registry,⁵⁴ and estimated the rate after open repair using the average odds ratio from a meta-analysis of RCTs. The predicted rate of operative mortality after open repair (5.7%) is greater than that found by the DREAM trial and EVAR trial 1 (4.6%⁴⁰ and 4.2%,²³ respectively), and similar to that found in the UKSAT trial in a younger patient group with smaller aneurysms (5.8%¹⁵⁸). It may be that the EVAR and DREAM trials operated on a more selected patient group, or in more specialist centres, than UKSAT. The base-case analysis assumes that the rates of operative mortality in the model are achievable on average in the UK.
- Throughout this analysis, fitness has referred to the risk of operative mortality relative to a patient of that age and aneurysm size with no comorbidities. This has been done because, although fitness is an important consideration in the management of patients, there is no validated risk scoring system to quantify this risk both for EVAR and for open surgery. It may be that fitness can be improved in some patients, but there has been very little

evaluation to date of policies having this objective.

- The model comparing surgery with watchful waiting did not use treatment effects from RCTs. This is because the crossovers, delays and absence of a watchful waiting protocol in EVAR trial 2⁴⁶ make the results difficult to use directly to identify the most cost-effective form of management. Although the UKSAT trial¹⁵⁸ did have a clear policy for interventions, it did not evaluate EVAR. Therefore, we could not use treatment effects from these two RCTs to inform the model. Instead, the natural history of patients with untreated aneurysm was estimated using rupture rates and growth rates obtained from a review of the literature,

and compared with outcomes estimated by the model of EVAR and open repair for patients with the same baseline characteristics. Given the uncertainties in the data, and the potential for bias in this non-randomised comparison, the decision model and dynamic programme for watchful waiting are intended to be exploratory.

- As noted in Chapters 3 and 4, the RCT data on EVAR were predominantly collected in men. Although Chapter 3 reported that there was no evidence that either baseline risks or treatment effects were influenced by gender, it is feasible that untreated rupture rates may differ between men and women, and this may influence the cost-effectiveness of the management options.

Chapter 7

Conclusions

- Compared with open repair EVAR reduces operative mortality and aneurysm-related mortality over the medium term but offers no significant difference in all-cause mortality at mid-term follow-up.
- EVAR is associated with an increased rate of complications and reinterventions and these are not offset by any increase in HRQoL.
- Analysis of the EVAR trial data did not find any evidence that a benefit of EVAR over open repair could be predicted using the CPI score for preoperative fitness.
- There is evidence from single studies that the GAS and CCI scores can independently predict in-hospital or 30-day mortality after EVAR. The GAS may also be able to predict longer-term mortality following EVAR.
- A large number of studies have modelled risks for adverse outcomes following EVAR. These do not provide definitive evidence but age, possibly gender, renal impairment, fitness, ASA class and aneurysm size may be predictive of poorer 30-day survival. There may be a link between fitness for open repair, aneurysm size and possibly device type and aneurysm-related mortality. In terms of all-cause mortality, pulmonary status, renal impairment, ASA class and aneurysm size might adversely affect this outcome. We did not consistently find any risk factors for reintervention. For the outcome of endoleak, only age was a possible independent risk factor.
- There is limited RCT evidence comparing EVAR with non-surgical management or watchful waiting in patients unfit for open repair. The EVAR trial 2 found no differences in mortality outcomes between groups but this finding cannot be taken as definitive.
- There is no high-quality evidence for the efficacy of EVAR in the treatment of ruptured aneurysms.
- EVAR is not cost-effective compared with open repair on average using base-case assumptions.
- The results are very sensitive to model assumptions. EVAR may be cost-effective on average under alternative reasonable scenarios of how hospital costs and rates of reintervention have changed in recent years.
- In subgroup analysis, EVAR is likely to be cost-effective in patients with a poor risk of operative mortality. EVAR is unlikely to be cost-effective compared with open repair in patients of good fitness, that is, in the absence of comorbidity.
- In an exploratory analysis of the management of patients considered of very poor fitness or unfit for open repair, EVAR may be cost-effective at a threshold of £20,000 per QALY up to 77 years in patients with an 8-cm aneurysm, up to 74 years in patients with a 6-cm aneurysm and up to 71.5 years in patients with a 5-cm aneurysm. Increasing the threshold to £30,000 per QALY increases the age at which EVAR is cost-effective by about 2 years.
- The results are sensitive to assumptions and data about the risk of late aneurysm death, reinterventions and the hospital cost of the procedures. The modelling of no intervention and watchful waiting is indicative and exploratory, based on assumptions about the natural history of untreated aneurysm in patients anatomically suitable for EVAR. Further research in all of these areas would be important to inform future modelling work.

Implications for service provision

- Based on the results of this assessment of clinical effectiveness and cost-effectiveness, open repair should be the treatment of choice for patients with AAA who have good or moderate fitness.
- For patients with poorer fitness, whether suitable for open repair or not, EVAR may be cost-effective but this will depend upon a patient's age.
- EVAR cannot currently be recommended for the treatment of ruptured aneurysms.

Suggested research priorities

- Further follow-up of the existing UK trials (EVAR trial 1, EVAR trial 2) should be undertaken.

- Opportunities for individual patient meta-analysis of all RCTs relating to EVAR should be sought.
- Further research is needed on the rate of late aneurysm-related mortality after EVAR, in particular for the most recent generations of devices.
- The extent to which the relative treatment effect of EVAR on operative mortality can be assumed constant across subgroups of patients should be further investigated.
- Research is required into how to implement the best available risk scoring systems for the management of AAA into decision-making in routine clinical practice.
- Research is required into the natural history of untreated AAA to determine more reliably when surgical intervention is optimal. The analysis should investigate the impact of different levels and determinants of patient fitness as well as aneurysm size and anatomy.
- A well-defined and well-conducted RCT of EVAR versus watchful waiting reflecting current clinical practice is warranted. However, given the difficulties of conducting RCTs in the management of AAA, it is probably advisable that the collection of data through the existing, established registries in the UK, particularly RETA (for EVAR) and NVD (for open repair), should be continued.



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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Contributions of authors

Duncan Chambers (Research Fellow) was involved in all stages of the clinical review, from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report. David Epstein (Research Fellow) was involved in all stages of the review, design and analysis of the economic model and production of the final report. Simon Walker (Research Fellow) was involved in the cost-

effectiveness section, study selection, development of the economic model and report writing. Debra Fayter (Research Fellow) was involved in all stages of the review, from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report. Fiona Paton (Research Fellow) provided input for the design and implementation of data extraction, analysed the registry data and contributed to the final report. Kath Wright (Information Officer) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Jonathan Michaels (Professor of Vascular Surgery) provided input at all stages of the review, assisted in the development of the model structure for the economic modelling and the natural history of aortic aneurysm and commented on the results and draft report. Stephen Thomas (Senior Lecturer and Consultant Vascular Radiologist) provided input at all stages of the review, assisted in the development of the model structure for the economic modelling and the natural history of aortic aneurysm and commented on the results and draft report. Mark Sculpher (Professor of Health Economics) provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the economics section. Nerys Woolacott (Senior Research Fellow) provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the review.



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Appendix I

Literature search strategies

Literature searches were carried out to identify systematic reviews, guidelines, ongoing trials, RCTs, risk modelling studies, reports from specified EVAR registries and economic studies.

Systematic reviews

To identify systematic reviews the following were searched:

Cochrane Database of Systematic Reviews, DARE, HTA database

Via Cochrane Library – 2007 Issue 4
Searched 17 September 2007

Search strategy:

- #1 (evar):ti,ab,kw or “endovascular stent*”:ti,ab,kw or “endovascular repair*”:ti,ab,kw or “endovascular treat*”:ti,ab,kw or “endovascular surg*”:ti,ab,kw
- #2 “endovascular aneurysm repair*”
- #3 “endoluminal stent*”:ti,ab,kw or “endoluminal repair*”:ti,ab,kw or “endoluminal treat*”:ti,ab,kw or “endoluminal surg*”:ti,ab,kw
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Aortic Aneurysm, Abdominal explode all trees
- #6 (AAA):ti,ab,kw or “abdominal aortic aneurysm*”:ti,ab,kw or “abdominal aneurysm*”:ti,ab,kw
- #7 (#5 OR #6)
- #8 (#4 AND #7)

Guidelines

To identify guidelines the following databases and web pages were searched/scanned:

TRIP database

www.tripdatabase.com/index.html
Searched 11 September 2007

NLH National Library of Guidelines

www.library.nhs.uk/guidelinesFinder/
Searched 11 September 2007

National Guideline Clearinghouse

www.guideline.gov/
Searched 29 October 2007

NICE web pages

www.nice.org.uk/
Searched 29 October 2007

RCTs, risk studies and registry data

The following bibliographic databases were searched to identify RCTs (2005–7), risk studies and papers based on registry data:

BIOSIS Previews®

Via Dialog
Searched 18 September 2007

Search strategy:

- S1 131 EVAR/TI,AB,DE
- S2 641 ENDOVASCULAR(W)STENT?/TI,AB,DE
- S3 506 ENDOVASCULAR(W)REPAIR?/TI,AB,DE
- S4 1078 ENDOVASCULAR(W)TREAT?/TI,AB,DE
- S5 169 ENDOVASCULAR(W)SURG?/TI,AB,DE
- S6 166 ENDOVASCULAR(W)ANEURYSM(W) REPAIR?/TI,AB,DE
- S7 155 ENDOLUMINAL(W)STENT?/TI,AB,DE
- S8 49 ENDOLUMINAL(W)REPAIR?/TI,AB,DE
- S9 51 ENDOLUMINAL(W)TREAT?/TI,AB,DE
- S10 5 ENDOLUMINAL(W)SURG?/TI,AB,DE
- S11 2497 S1:S10
- S12 2931 AAA/TI,AB,DE
- S13 2767 ABDOMINAL(W)AORTIC(W) ANEURYSM?/TI,AB,DE
- S14 215 ABDOMINAL(W)ANEURYSM?/TI,AB,DE
- S15 4836 S12:S14
- S16 544 S11 AND S15
- S17 3 AAA(W)ENDOGRAFT?/TI,AB,DE
- S18 546 S16 OR S17
- S19 44179 RANDOM?/TI
- S20 45754 TRIAL/TI
- S21 36106 DOUBLE(W)BLIND?/AB
- S22 3073 SINGLE(W)BLIND?/AB
- S23 99005 S19:S22
- S24 20 S18 AND S23
- S25 6 S24/2005:2007
- S26 11 (EUROSTAR(2W)(REGISTRY OR REGISTER OR PROJECT OR DATABASE OR DATA OR COLLABORAT? OR GROUP?))/TI,AB
- S27 16 (EUROSTAR AND (EVAR OR STENT? OR GRAFT? OR ANEURYSM?))/TI,AB

- S28 16 RETA/TI,AB
 S29 0 REGISTRY(2W)ENDOVASCULAR(W)
 TREATMENT(2W)ANEURYSMS/TI,AB
 S30 1 NATIONAL(W)VASCULAR(W)DATABASE/
 TI,AB
 S31 33 S26:S30
 S32 2 (HARDMAN(W)(INDEX OR SCORE? OR
 SCORING OR MEASURE?)/TI,AB
 S33 2 GLASGOW(W)ANEURYSM(W)SCORE?/
 TI,AB
 S34 22 (POSSUM(W)(INDEX OR SCORE? OR
 SCORING OR MEASURE?)/TI,AB
 S35 1 MODIFIED(W)LEIDEN(W)SCORE/AB
 S36 1 MODIFIED(W)COMORBIDITY(W)
 SEVERITY(W)SCORE/AB
 S37 26 S32:S36
 S38 212323 (RISK? OR MORTALITY OR
 SURVIVAL OR DEATH)/TI
 S39 131 EVAR/TI,AB,DE
 S40 641 ENDOVASCULAR(W)STENT?/TI,AB,DE
 S41 506 ENDOVASCULAR(W)REPAIR?/TI,AB,DE
 S42 1078 ENDOVASCULAR(W)TREAT?/TI,AB,DE
 S43 169 ENDOVASCULAR(W)SURG?/TI,AB,DE
 S44 166 ENDOVASCULAR(W)ANEURYSM(W)
 REPAIR?/TI,AB,DE
 S45 155 ENDOLUMINAL(W)STENT?/TI,AB,DE
 S46 49 ENDOLUMINAL(W)REPAIR?/TI,AB,DE
 S47 51 ENDOLUMINAL(W)TREAT?/TI,AB,DE
 S48 5 ENDOLUMINAL(W)SURG?/TI,AB,DE
 S49 3 AAA(W)ENDOGRAFT?/TI,AB
 S50 2499 S39:S49
 S51 71 S38 AND S50
 S52 134 S25 OR S31 OR S37 OR S51
 S53 1453415 (RAT OR RATS OR MOUSE OR
 MICE OR HAMSTER OR HAMSTERS OR
 ANIMAL OR ANIMALS OR DOG OR DOGS
 OR CAT OR CATS OR BOVINE OR SHEEP
 OR FLY OR FLIES OR FISH OR FISHES OR
 BAT OR BATS OR BEE OR BEES OR GRASS
 OR GRASSES OR FOSSIL OR FOSSILS OR
 LICHEN OR LICHENS OR MUSHROOM
 OR MUSHROOMS)/AB, TI
 S54 129 S52 NOT S53
 S55 534304 ANIMAL
 S56 4001770 HUMAN
 S57 413787 S55 NOT (S55 AND S56)
 S58 129 S54 NOT S57
- CINAHL – Cumulative Index to Nursing
 and Allied Health Literature**
 Via Ovid – 1982 to August Week 5 2007
 Searched 10 September 2007
- Search strategy:
 1. EVAR.ti,ab. (25)
 2. endovascular stent\$.ti,ab. (83)
 3. endovascular repair\$.ti,ab. (93)
 4. endovascular treat\$.ti,ab. (94)
 5. endovascular surg\$.ti,ab. (17)
 6. endovascular aneurysm repair\$.ti,ab. (24)
 7. endoluminal stent\$.ti,ab. (12)
 8. endoluminal repair\$.ti,ab. (6)
 9. endoluminal treat\$.ti,ab. (3)
 10. endoluminal surg\$.ti,ab. (0)
 11. or/1–10 (296)
 12. AAA\$.ti,ab. (382)
 13. exp aortic aneurysm/(995)
 14. abdominal aortic aneurysm\$.ti,ab. (390)
 15. abdominal aneurysm\$.ti,ab. (11)
 16. or/12–15 (1265)
 17. 11 and 16 (144)
 18. AAA endograft\$.ti,ab. (3)
 19. 17 or 18 (147)
 20. vascular surgery/(477)
 21. 20 and 16 (119)
 22. 19 or 21 (197)
 23. exp clinical trials/(47023)
 24. clinical trial.pt. (22538)
 25. (clinic\$adj trial\$.tw. (11002)
 26. ((singl\$or doubl\$or trebl\$or tripl\$) adj
 (blind\$3 or mask\$3)).tw. (6495)
 27. randomi?ed control\$trial\$.tw. (9627)
 28. random assignment/(16139)
 29. random\$allocat\$.tw. (1061)
 30. placebo\$.tw. (9144)
 31. placebos/(3742)
 32. quantitative studies/(3400)
 33. allocat\$random\$.tw. (62)
 34. or/23–33 (65834)
 35. 22 and 34 (17)
 36. (EUROSTAR adj2 (registry or register or
 project or database or data or collaborat\$or
 group\$)).ti,ab. (3)
 37. (EUROSTAR and (evar or stent\$or graft\$or
 aneurysm\$)).ti,ab. (3)
 38. reta.ti,ab. (2)
 39. registry of endovascular treatment of
 aneurysms.ti,ab. (0)
 40. national vascular database.ti,ab. (0)
 41. 36 or 37 or 38 or 39 or 40 (5)
 42. (Hardman adj (index or score\$or scoring or
 measure\$)).ti,ab. (0)
 43. Glasgow aneurysm score\$.ti,ab. (0)
 44. (POSSUM adj (index or score\$or scoring or
 measure\$)).ti,ab. (4)
 45. Modified Leiden Score.ti,ab. (0)
 46. Modified Comorbidity Severity Score.ti,ab. (0)
 47. 42 or 43 or 44 or 45 or 46 (4)
 48. risk assessment/(9540)
 49. risk factors/(21665)
 50. survival analysis/(4131)
 51. mortality/(5604)

52. roc curve/(1418)
53. "Sensitivity and Specificity"/(10462)
54. (risk\$or mortality or survival or death).ti.
(47061)
55. (roc curve\$or sensitivity or specificity).ab.
(10517)
56. 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
(89143)
57. EVAR.ti.ab. (25)
58. endovascular stent\$.ti.ab. (83)
59. endovascular repair\$.ti.ab. (93)
60. endovascular treat\$.ti.ab. (94)
61. endovascular surg\$.ti.ab. (17)
62. endovascular aneurysm repair\$.ti.ab. (24)
63. endoluminal stent\$.ti.ab. (12)
64. endoluminal repair\$.ti.ab. (6)
65. endoluminal treat\$.ti.ab. (3)
66. endoluminal surg\$.ti.ab. (0)
67. AAA endograft\$.ti.ab. (3)
68. vascular surgery/(477)
69. or/57-68 (682)
70. 56 and 69 (91)
71. 35 or 41 or 47 or 70 (109)
72. from 71 keep 1-109 (109)

Cochrane Central Register of Controlled Trials

Via Cochrane Library – 2007 Issue 4
Searched 11 September 2007

Search strategy:

- #1 (evar):ti,ab,kw or "endovascular stent*":ti,ab,kw or "endovascular repair*":ti,ab,kw or "endovascular treat*":ti,ab,kw or "endovascular surg*":ti,ab,kw in Clinical Trials (52)
- #2 "endovascular aneurysm repair*":ti,ab,kw or "endoluminal stent*":ti,ab,kw or "endoluminal repair*":ti,ab,kw or "endoluminal treat*":ti,ab,kw or "endoluminal surg*":ti,ab,kw in Clinical Trials (21)
- #3 (#1 OR #2) (84)
- #4 (AAA*):ti,ab,kw or "abdominal aortic aneurysm*":ti,ab,kw or "abdominal aneurysm*":ti,ab,kw in Clinical Trials (507)
- #5 MeSH descriptor Aortic Aneurysm, Abdominal explode all trees (395)
- #6 (#4 OR #5) (728)
- #7 (#3 AND #6) (60)
- #8 "AAA endograft*":ti,ab,kw in Clinical Trials (0)
- #9 (#7 or #8) (60)
- #10 MeSH descriptor Vascular Surgical Procedures explode all trees (4141)
- #11 (#6 and #10) (141)
- #12 (#9 or #11) (161)
- #13 (#12), from 2005 to 2007

EMBASE

Via Ovid – 1980 to 2007 Week 35
Searched 6 September 2007

Search strategy:

1. EVAR.ti.ab. (422)
2. endovascular stent\$.ti.ab. (1345)
3. endovascular repair\$.ti.ab. (1373)
4. endovascular treat\$.ti.ab. (2990)
5. endovascular surg\$.ti.ab. (385)
6. endovascular aneurysm repair\$.ti.ab. (438)
7. endoluminal stent\$.ti.ab. (280)
8. endoluminal repair\$.ti.ab. (171)
9. endoluminal treat\$.ti.ab. (140)
10. endoluminal surg\$.ti.ab. (24)
11. or/1-10 (6306)
12. AAA\$.ti.ab. (5101)
13. exp aorta aneurysm/(15874)
14. abdominal aortic aneurysm\$.ti.ab. (6740)
15. abdominal aneurysm\$.ti.ab. (515)
16. or/12-15 (18921)
17. 11 and 16 (2246)
18. AAA endograft\$.ti.ab. (14)
19. 17 or 18 (2254)
20. vascular surgery/(10955)
21. 20 and 16 (1022)
22. 19 or 21 (3162)
23. clinical trial/(469549)
24. randomized controlled trial/(146648)
25. randomization/(23723)
26. single blind procedure/(6886)
27. double blind procedure/(65699)
28. crossover procedure/(19208)
29. placebo/(103122)
30. randomi?ed controlled trial\$.tw. (25624)
31. rct.tw. (1969)
32. random allocation.tw. (584)
33. randomly allocated.tw. (9232)
34. allocated randomly.tw. (1293)
35. (allocated adj2 random).tw. (547)
36. single blind\$.tw. (6783)
37. double blind\$.tw. (78511)
38. ((treble or triple) adj blind\$).tw. (122)
39. placebo\$.tw. (100415)
40. prospective study/(68159)
41. or/23-40 (619632)
42. case study/(5041)
43. case report.tw. (106789)
44. abstract report/or letter/(443249)
45. or/42-44 (553223)
46. 41 not 45 (598087)
47. 22 and 46 (390)
48. limit 47 to yr="2005 – 2007" (134)
49. (EUROSTAR adj2 (registry or register or project or database or data or collaborat\$or group\$)).ti.ab. (50)

50. (EUROSTAR and (evar or stent\$or graft\$or aneurysm\$)).ti,ab. (62)
51. reta.ti,ab. (11)
52. registry of endovascular treatment of aneurysms.ti,ab. (1)
53. national vascular database.ti,ab. (7)
54. 49 or 50 or 51 or 52 or 53 (80)
55. (Hardman adj (index or score\$or scoring or measure\$)).ti,ab. (9)
56. Glasgow aneurysm score\$.ti,ab. (19)
57. (POSSUM adj (index or score\$or scoring or measure\$)).ti,ab. (86)
58. Modified Leiden Score.ti,ab. (2)
59. Modified Comorbidity Severity Score.ti,ab. (1)
60. 55 or 56 or 57 or 58 or 59 (108)
61. risk assessment/(151661)
62. risk factor/(205117)
63. survival rate/(48556)
64. survival time/(24668)
65. overall survival/(3310)
66. survival/(55421)
67. mortality/(149265)
68. roc curve/(1438)
69. "Sensitivity and Specificity"/(37627)
70. (risk\$or mortality or survival or death).ti. (238237)
71. (roc curve\$or sensitivity or specificity).ab. (359551)
72. 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 (1014439)
73. EVAR.ti,ab. (422)
74. endovascular stent\$.ti,ab. (1345)
75. endovascular repair\$.ti,ab. (1373)
76. endovascular treat\$.ti,ab. (2990)
77. endovascular surg\$.ti,ab. (385)
78. endovascular aneurysm repair\$.ti,ab. (438)
79. endoluminal stent\$.ti,ab. (280)
80. endoluminal repair\$.ti,ab. (171)
81. endoluminal treat\$.ti,ab. (140)
82. endoluminal surg\$.ti,ab. (24)
83. AAA endograft\$.ti,ab. (14)
84. or/73–83 (6314)
85. 72 and 84 (1297)
86. 48 or 54 or 60 or 85 (1505)
87. from 86 keep 1–1505 (1505)

ISI Proceedings

Via Web of Science

Searched 18 September 2007

Search strategy:

TS=evar (140)

TS=(endovascular SAME (stent* OR repair* OR treat* OR surger*)) (1639)

TS=(endoluminal SAME (stent* OR repair* OR treat* OR surger*)) (241)

#1 or #2 or #3 (1804)

TS=(AAA OR abdominal aortic aneurysm* OR abdominal aneurysm*) (2273)

#5 or #4 (619)

MEDLINE®

Via Ovid – 1950 to August Week 5 2007

Searched 6 September 2007

Search strategy:

1. EVAR.ti,ab. (404)
2. endovascular stent\$.ti,ab. (1354)
3. endovascular repair\$.ti,ab. (1394)
4. endovascular treat\$.ti,ab. (2595)
5. endovascular surg\$.ti,ab. (374)
6. endovascular aneurysm repair\$.ti,ab. (417)
7. endoluminal stent\$.ti,ab. (286)
8. endoluminal repair\$.ti,ab. (169)
9. endoluminal treat\$.ti,ab. (126)
10. endoluminal surg\$.ti,ab. (20)
11. or/1–10 (5920)
12. AAA\$.ti,ab. (5868)
13. exp aortic aneurysm, abdominal/(8427)
14. abdominal aortic aneurysm\$.ti,ab. (7979)
15. abdominal aneurysm\$.ti,ab. (713)
16. or/12–15 (14579)
17. 11 and 16 (1838)
18. AAA endograft\$.ti,ab. (13)
19. 17 or 18 (1846)
20. vascular surgical procedures/(16153)
21. 20 and 16 (1121)
22. 19 or 21 (2645)
23. RANDOMIZED CONTROLLED TRIAL.pt. (242026)
24. CONTROLLED CLINICAL TRIAL.pt. (76175)
25. RANDOMIZED CONTROLLED TRIALS.sh. (50846)
26. RANDOM ALLOCATION.sh. (58962)
27. DOUBLE BLIND METHOD.sh. (93291)
28. SINGLE BLIND METHOD.sh. (11312)
29. or/23–28 (410206)
30. (ANIMALS not HUMANS).sh. (3178675)
31. 29 not 30 (384781)
32. CLINICAL TRIAL.pt. (441091)
33. exp CLINICAL TRIALS/(196388)
34. (clin\$adj25 trial\$.ti,ab. (135407)
35. ((singl\$or doubl\$or trebl\$or tripl\$) adj25 (blind\$or mask\$)).ti,ab. (92729)
36. PLACEBOS.sh. (26592)
37. placebo\$.ti,ab. (104970)
38. random\$.ti,ab. (385021)
39. RESEARCH DESIGN.sh. (49242)
40. or/32–39 (870519)
41. 40 not 30 (807906)
42. 41 not 31 (442725)

43. 31 or 42 (827506)
44. 22 and 43 (379)
45. limit 44 to yr="2005 – 2007" (126)
46. (EUROSTAR adj2 (registry or register or project or database or data or collaborat\$or group\$)).ti,ab. (50)
47. (EUROSTAR and (evar or stent\$or graft\$or aneurysm\$)).ti,ab. (60)
48. reta.ti,ab. (12)
49. registry of endovascular treatment of aneurysms.ti,ab. (1)
50. national vascular database.ti,ab. (5)
51. 46 or 47 or 48 or 49 or 50 (77)
52. (Hardman adj (index or score\$or scoring or measure\$)).ti,ab. (11)
53. Glasgow aneurysm score\$.ti,ab. (21)
54. (POSSUM adj (index or score\$or scoring or measure\$)).ti,ab. (85)
55. Modified Leiden Score.ti,ab. (2)
56. Modified Comorbidity Severity Score.ti,ab. (1)
57. 52 or 53 or 54 or 55 or 56 (109)
58. risk assessment/(81774)
59. risk factors/(326347)
60. survival analysis/(63460)
61. mortality/(27549)
62. roc curve/(11339)
63. "Sensitivity and Specificity"/(171061)
64. (risk\$or mortality or survival or death).ti. (313939)
65. (roc curve\$or sensitivity or specificity).ab. (419309)
66. 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (1155607)
67. EVAR.ti,ab. (404)
68. endovascular stent\$.ti,ab. (1354)
69. endovascular repair\$.ti,ab. (1394)
70. endovascular treat\$.ti,ab. (2595)
71. endovascular surg\$.ti,ab. (374)
72. endovascular aneurysm repair\$.ti,ab. (417)
73. endoluminal stent\$.ti,ab. (286)
74. endoluminal repair\$.ti,ab. (169)
75. endoluminal treat\$.ti,ab. (126)
76. endoluminal surg\$.ti,ab. (20)
77. AAA endograft\$.ti,ab. (13)
78. vascular surgical procedures/(16153)
79. or/67–78 (21316)
80. 66 and 79 (2246)
81. 45 or 51 or 57 or 80 (2470)
82. from 81 keep 1–2470 (2470)

**MEDLINE® In-Process & Other
Non-Indexed Citations**

Via Ovid

Searched 7 September 2007

Search strategy:

1. EVAR.ti,ab. (37)
2. endovascular stent\$.ti,ab. (66)
3. endovascular repair\$.ti,ab. (74)
4. endovascular treat\$.ti,ab. (127)
5. endovascular surg\$.ti,ab. (15)
6. endovascular aneurysm repair\$.ti,ab. (33)
7. endoluminal stent\$.ti,ab. (9)
8. endoluminal repair\$.ti,ab. (1)
9. endoluminal treat\$.ti,ab. (4)
10. endoluminal surg\$.ti,ab. (1)
11. or/1–10 (291)
12. AAA\$.ti,ab. (181)
13. abdominal aortic aneurysm\$.ti,ab. (185)
14. abdominal aneurysm\$.ti,ab. (12)
15. AAA endograft\$.ti,ab. (0)
16. or/13–15 (189)
17. 11 and 16 (67)
18. RANDOMIZED CONTROLLED TRIAL.pt. (373)
19. CONTROLLED CLINICAL TRIAL.pt. (22)
20. CLINICAL TRIAL.pt. (354)
21. (clin\$adj25 trial\$).ti,ab. (4733)
22. ((singl\$or doubl\$or trebl\$or tripl\$) adj25 (blind\$or mask\$)).ti,ab. (1686)
23. placebo\$.ti,ab. (2174)
24. random\$.ti,ab. (17378)
25. or/18–24 (21406)
26. 17 and 25 (8)
27. (EUROSTAR adj2 (registry or register or project or database or data or collaborat\$or group\$)).ti,ab. (1)
28. (EUROSTAR and (evar or stent\$or graft\$or aneurysm\$)).ti,ab. (1)
29. reta.ti,ab. (0)
30. registry of endovascular treatment of aneurysms.ti,ab. (0)
31. national vascular database.ti,ab. (0)
32. 27 or 28 or 29 or 30 or 31 (1)
33. (Hardman adj (index or score\$or scoring or measure\$)).ti,ab. (2)
34. Glasgow aneurysm score\$.ti,ab. (1)
35. (POSSUM adj (index or score\$or scoring or measure\$)).ti,ab. (2)
36. Modified Leiden Score.ti,ab. (0)
37. Modified Comorbidity Severity Score.ti,ab. (0)
38. 33 or 34 or 35 or 36 or 37 (4)
39. (risk\$or mortality or survival or death).ti. (8672)
40. (roc curve\$or sensitivity or specificity).ab. (12211)
41. 39 or 40 (20606)
42. EVAR.ti,ab. (37)
43. endovascular stent\$.ti,ab. (66)

44. endovascular repair\$.ti,ab. (74)
45. endovascular treat\$.ti,ab. (127)
46. endovascular surg\$.ti,ab. (15)
47. endovascular aneurysm repair\$.ti,ab. (33)
48. endoluminal stent\$.ti,ab. (9)
49. endoluminal repair\$.ti,ab. (1)
50. endoluminal treat\$.ti,ab. (4)
51. endoluminal surg\$.ti,ab. (1)
52. AAA endograft\$.ti,ab. (0)
53. or/42-52 (291)
54. 26 or 32 or 38 or 53 (295)
55. from 54 keep 1-295 (295)

Science Citation Index

Via Web of Science

Searched 18 September 2007

Three separate searches carried out to identify RCTs, specified registry reports, risk modelling studies:

RCT search strategy (limited to 2005-7)

TS=EVAR (253)

TS=(endovascular SAME (stent* OR repair* OR treat* OR surger*)) (2965)

TS=(endoluminal SAME (stent* OR repair* OR treat* OR surger*)) (252)

TS=(AAA OR abdominal aortic aneurysm* OR abdominal aneurysm*) (2954)

#3 or #2 or #1 (3143)

#5 AND #4 (798)

TS=(RANDOMIZED CONTROLLED-TRIAL or RANDOMISED CONTROLLED-TRIAL) (21120)

TI=(trial* or random*) (40781)

#8 or #7 (55388)

#9 and #6 (121)

Registry reports search strategy, no date limits

TS=(EUROSTAR SAME (registry OR register OR project OR database OR data OR collaborat* OR group*)) (55)

TS=(EUROSTAR SAME (evar OR stent* OR graft* OR aneurysm*)) (41)

TS=(reta OR "registry of endovascular treatment of aneurysms" OR "national vascular database") (38)

TS=(hardman SAME (index OR score* OR scoring OR measure*)) (12)

TS=("glasgow aneurysm score*" OR "modified leiden score" OR "modified comorbidity severity score") (23)

TS=(possum same (index OR score* OR scoring OR measure*)) (190)

#6 OR #5 OR #4 OR #3 OR #2 OR #1 (313)

Risk modelling studies search strategy, no date limits

TS=EVAR

TS=(endovascular SAME (stent* OR repair* OR treat* OR surger*))

TS=(endoluminal SAME (stent* OR repair* OR treat* OR surger*))

TS=("AAA endograft*")

#4 OR #3 OR #2 OR #1

TI=(risk* OR mortality OR survival OR death)

#6 and #5 (248 papers)

Zetoc Conferences

Searched 18 September 2007

Series of searches carried out using terms: EVAR, endovascular stents, endovascular repair/treatment/surgery AND aneurysm (170 papers identified)

Ongoing studies

To identify any ongoing studies the following were searched:

Clinicaltrials.gov

<http://clinicaltrials.gov/>

Searched 11 September 2007

Search terms: aneurysm AND endovascular (no date limits)

Results: 23

Current Controlled Trials

www.controlled-trials.com/

Searched 11 September 2007

Search terms: aneurysm AND endovascular (no date limits)

Results: 45

National Research Register

2007 Issue 3

Searched 11 September 2007

Search strategy:

#1 evar (67)

#2 (endovascular next stent*) (38)

#3 (endovascular next repair*) (49)

#4 (endovascular next treat*) (37)

#5 (endovascular next surger*) (16)

#6 (endoluminal next stent*) (2)

#7 (endoluminal next repair*) (6)

#8 (endoluminal next treat*) (0)

#9 (endoluminal next surger*) (0)

#10 (endovascular next aneurysm next repair*) (60)

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (180)

#12 aaa* (104)

- #13 (abdominal next aortic next aneurysm*) (196)
- #14 (abdominal next aneurysm*) (12)
- #15 AORTIC ANEURYSM ABDOMINAL explode all trees (MeSH) (128)
- #16 #12 or #13 or #14 or #15 (246)
- #17 #11 and #16 (80)
- #18 (aaa next endograft*) (1)
- #19 (#17 or #18) (80)
- #20 VASCULAR SURGICAL PROCEDURES explode tree 1 (MeSH) (483)
- #21 (#16 and #20) (17)
- #22 (#19 or #21) (83)

Economics searches

EconLIT

Via WebSPIRS

Searched 12 October 2007

Search strategy:

- #1 EVAR in ti,ab (0 records)
- #2 endoluminal (0 records)
- #3 endovascular (0 records)
- #4 aaa (38 records)
- #5 abdominal aortic aneurysm* (5 records)
- #6 abdominal aneurysm* (1 records)
- #7 aaa endograft* (0 records)
- #8 vascular surgery (0 records)
- #9 vascular surgical procedure* (0 records)
- #10 (abdominal aortic aneurysm*) or (aaa) or (abdominal aneurysm*) (42 records)

EMBASE

Via Ovid

Searched 11 October 2007

Search strategy:

- #1 Health Economics/(9545)
- #2 exp Economic Evaluation/(91514)
- #3 exp Health Care Cost/(93030)
- #4 exp PHARMACOECONOMICS/(48656)
- #5 or/1-4 (176440)
- #6 (econom\$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$.ti,ab. (206766)
- #7 (expenditure\$not energy).ti,ab. (8791)
- #8 (value adj2 money).ti,ab. (390)
- #9 budget\$.ti,ab. (8045)
- #10 or/6-9
- #11 5 or 10 (305033)
- #12 (metabolic adj cost).ti,ab. (356)
- #13 ((energy or oxygen) adj cost).ti,ab. (1607)
- #14 ((energy or oxygen) adj expenditure).ti,ab. (9073)
- #15 or/12-14 (10558)

- #16 11 not 15 (302646)
- #17 editorial.pt. (198373)
- #18 note.pt. 9219980)
- #19 letter.pt. (394199)
- #20 or/17-19 (812552)
- #21 16 not 20 (261791)
- #22 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh. (1900407)
- #23 exp animal/(18204)
- #24 Nonhuman/(2965844)
- #25 or/22-24 (3281976)
- #26 exp human (5941940)
- #27 exp human experiment/(240151)
- #28 26 or 27 (5942804)
- #29 25 not (25 and 28) (2713634)
- #30 21 not 29 (241038)
- #31 EVAR.ti,ab. (430)
- #32 endovascular stent\$.ti,ab. (1359)
- #33 endovascular repair\$.ti,ab. (1392)
- #34 endovascular treat\$.ti,ab. (3038)
- #35 endovascular surg\$.ti,ab. (388)
- #36 endovascular repair\$.ti,ab. (442)
- #37 endoluminal stent\$.ti,ab. (281)
- #38 endoluminal repair\$.ti,ab. (171)
- #39 endoluminal treat\$.ti,ab. (141)
- #40 endoluminal surg\$.ti,ab. (24)
- #41 or/31-40 (6391)
- #42 AAA\$.ti,ab. (5142)
- #43 exp aorta aneurysm/(15998)
- #44 abdominal aortic aneurysm\$.ti,ab. (6795)
- #45 abdominal aneurysm\$.ti,ab. (518)
- #46 or/42-45
- #47 41 and 46
- #48 AAA endograft\$.ti,ab. (14)
- #49 47 or 48 (2282)
- #50 vascular surgery/(11029)
- #51 50 and 46 (1030)
- #52 49 or 51 (3196)
- #53 30 and 52 (138)
- #54 limit 53 to yr="2006 - 2008" (24)

HEED

Searched 11 October 2007

Search strategy:

(EVAR OR endovascular OR endoluminal) AND (AAA OR abdominal OR aneurysm OR aneurysms) (57 records retrieved)

IDEAS

Via <http://ideas.repec.org/>

Searched 11 October 2007

Series of searches using the following terms:
endovascular, aneurysm (three records retrieved)

MEDLINE

Via Ovid

Searched 11 October 2007

Search strategy:

- #1 economics/(25182)
- #2 exp "costs and cost analysis"/(132702)
- #3 economics, dental/(1702)
- #4 exp "economics, hospital"/(14981)
- #5 economics, medical/(6910)
- #6 economics, nursing/(3749)
- #7 economics, pharmaceutical/(1842)
- #8 (economic\$or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$.tw. (248787)
- #9 (expenditure\$not energy).tw. (10815)
- #10 (value adj1 money).tw. (10)
- #11 budget\$.tw. (11233)
- #12 or/1-11 (352654)
- #13 ((energy or oxygen) adj cost).ti,ab. (1938)
- #14 (metabolic adj cost).ti,ab. (455)
- #15 ((energy or oxygen) adj expenditure).ti,ab. (10439)
- #16 or/13-15 (12303)
- #17 12 not 16 (349802)
- #18 EVAR.ti,ab. (423)
- #19 endovascular stent\$.ti,ab. (1374)
- #20 endovascular repair\$.ti,ab. (1422)
- #21 endovascular treat\$.ti,ab. (2632)
- #22 endovascular surg\$.ti,ab. (375)
- #23 endovascular aneurysm repair\$.ti,ab. (430)
- #24 endoluminal stent\$.ti,ab. (286)
- #25 endoluminal repair\$.ti,ab. (169)
- #26 endoluminal treat\$.ti,ab. (128)
- #27 endoluminal surg\$.ti,ab. (20)
- #28 or/18-27(6011)
- #29 AAA\$.ti,ab. (5930)
- #30 exp aortic aneurysm, abdominal/(8526)
- #31 abdominal aortic aneurysm\$.ti,ab. (8061)
- #32 abdominal aneurysm\$.ti,ab.
- #33 or/29-32 (14725)
- #34 28 and 33
- #35 AAA endograft\$.ti,ab. (13)

#36 34 or 35 (1884)

#37 vascular surgical procedures/(16286)

#38 37 and 33 (1148)

#39 36 or 38 (2702)

#40 17 and 39 (134)

#41 limit 40 to yr="2006 - 2007" (27)

NHS EED

Via internal CAIRS software

Searched 10 October 2007

Search strategy:

S EVAR

S endovascular(w)stent\$

S endovascular(w)repair\$

S endovascular(w)treat\$

S endovascular(w)surg\$

S endovascular(w)aneurysm(w)repair\$

S endoluminal(w)stent\$

S endoluminal(w)repair\$

S endoluminal(w)treat\$

S endoluminal(w)surg\$

S S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR

S8 OR S9 OR S10

S AAA

S aortic(w)aneurysm(w)abdominal

S abdominal(w)aortic(w)aneurysm\$

S abdominal(w)aneurysm

S s12 or s13 or s14 or s15

S s11 and s16

S AAA(w)endograft\$

S vascular(w)surgical(w)procedures

S s18 or s19

S s17 or s20

(25 records retrieved)

Appendix 2

Quality assessment

Checklists for studies included in the systematic review of existing cost-effectiveness evidence

TABLE 75 Checklist for Patel et al.¹⁰⁵ – The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✗	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	Effectiveness data are drawn from a large range of sources and supplemented with a range of assumptions
10. Effectiveness data from RCT or review of RCTs	✗	
11. Potential biases identified (especially if data not from RCTs)	✗	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	Details are given, i.e. they have taken an average, but such methods are not considered suitable
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✗	Large number of assumptions made regarding resource use
15. Appropriate unit costs estimated (with methodology)	?	Unit costs have been taken from the literature and cost accounting system at New York Presbyterian Hospital
16. Unit costs reported separately from resource use data	✗	
17. Productivity costs treated separately from other costs	N/A	Productivity costs are not considered

continued

TABLE 75 Checklist for Patel et al.¹⁰⁵ – The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model (continued)

Study question	Grade	Comments
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	Methods to value health states are given although they appear inappropriate
21. Details of the individuals from whom valuations were obtained are given	✗	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓/✗	Results are presented but, with the exception of the base case, costs and QALYs are not reported separately and only ICERs are reported
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✗	Discounted at 3% per annum rather than 3.5%
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	✗	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	✗	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	✗	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✗	
32. Are the probability distributions adequately detailed and appropriate?	✗	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	?	Not stated but both one-way and threshold sensitivity analyses are undertaken
35. The choice of variables for sensitivity analysis is justified	?	They tested parameters based on their original assumptions
36. The ranges over which the variables are varied are stated	✗	

TABLE 75 Checklist for Patel et al.¹⁰⁵ – The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model (continued)

Study question	Grade	Comments
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	X	
39. Applicable to the NHS setting	X	US based

TABLE 76 Checklist for Bosch et al.¹⁰⁸ – Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	?	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓/?	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	X	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	X	
15. Appropriate unit costs estimated (with methodology)	?	
16. Unit costs reported separately from resource use data	X	

continued

TABLE 76 Checklist for Bosch et al.¹⁰⁸ – Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair (continued)

Study question	Grade	Comments
17. Productivity costs treated separately from other costs	X	Productivity costs were included in the total costs
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	Costs in 2000 US dollars
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	X	
21. Details of the individuals from whom valuations were obtained are given	X	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Markov model
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓/X	Only described adequately for the base case, all sensitivity analyses given in terms of thresholds
Discounting		
25. Discount rate used for both costs and benefits	✓	Both discounted at 3%
26. Do discount rates accord with NHS guidance?	X	Discounted at 3% per annum rather than 3.5%
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	X	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	X	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	X	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	X	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	X	
32. Are the probability distributions adequately detailed and appropriate?	X	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	X	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	

TABLE 76 Checklist for Bosch et al.¹⁰⁸ – Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair (continued)

Study question	Grade	Comments
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	✓/X	QALYs and costs are only disaggregated for the base-case analysis
39. Applicable to the NHS setting	X	

TABLE 77 Checklist for Michaels et al.¹⁰⁷ – Cost-effectiveness of endovascular abdominal aortic aneurysm repair

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	NHS
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓/X	
11. Potential biases identified (especially if data not from RCTs)	X	Not discussed in this article
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	X	Not discussed in this article as most of the parameters are drawn from a NICE review
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	X	This study does not consider productivity costs

continued

TABLE 77 Checklist for Michaels et al.¹⁰⁷ – Cost-effectiveness of endovascular abdominal aortic aneurysm repair (continued)

Study question	Grade	Comments
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	X	Parameters are drawn from other studies and no discussion of any statistical tests conducted in these other studies is given here
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	✓	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓/X	Beta distributions have been used appropriately for probabilities, but normal distributions have been used for costs, which is inappropriate
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	

TABLE 77 Checklist for Michaels et al.¹⁰⁷ – Cost-effectiveness of endovascular abdominal aortic aneurysm repair (continued)

Study question	Grade	Comments
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	✓/X	Incremental QALYs and costs are disaggregated from one another, but the study does not give the actual level of costs or QALYs for each arm separately
39. Applicable to the NHS setting	✓	

TABLE 78 Checklist for Epstein et al.¹⁰⁶ – Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	?	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	

continued

TABLE 78 Checklist for Epstein et al.¹⁰⁶ – Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm (continued)

Study question	Grade	Comments
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	✗	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	2004 UK pounds
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✗	Values are reported in paper but no information on how they were valued is given here, although it is referenced to Kind 1999 ³¹⁵ and so is clearly EQ-5D
21. Details of the individuals from whom valuations were obtained are given	✗	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	✓	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✗	No discussion of probability distributions in the paper although the model code is available on the internet
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	

TABLE 78 Checklist for Epstein et al.¹⁰⁶ – Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm (continued)

Study question	Grade	Comments
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	They have conducted scenario analyses
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	✓/X	Incremental QALYs and costs are disaggregated from one another, but the study does not give the actual level of costs or QALYs for each arm separately
39. Applicable to the NHS setting	✓	

TABLE 79 Checklist for Prinssen et al.¹²⁶ – Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	X	Viewpoint is not stated but would appear to be societal because of the inclusion of productivity costs (in terms of sick leave)
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
<i>continued</i>		

TABLE 79 Checklist for Prinssen et al.¹²⁶ – Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial (continued)

Study question	Grade	Comments
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓/X	Unit costs are reported but resource use data are not
17. Productivity costs treated separately from other costs	✓/X	Productivity costs are given separately but are also included in the total cost estimates
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	2003 euros
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	N/A	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	N/A	
24. All model outputs described adequately	N/A	
Discounting		
25. Discount rate used for both costs and benefits	X	Study has only a 1-year time horizon and so even if discounting was performed any changes would be marginal
26. Do discount rates accord with NHS guidance?	X	
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	✓/X	Uncertainty in estimates of incremental costs and QALYs is represented by the presentation of the results of the bootstrapping on the cost-effectiveness plane
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	X	

TABLE 79 Checklist for Prinssen et al.¹²⁶ – Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial (continued)

Study question	Grade	Comments
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	X	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?		
32. Are the probability distributions adequately detailed and appropriate?	X	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	X	
<i>Deterministic analysis</i>		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	X	
35. The choice of variables for sensitivity analysis is justified	X	
36. The ranges over which the variables are varied are stated	X	
<i>Presentation of results</i>		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	X	
39. Applicable to the NHS setting	X	

TABLE 80 Checklist for Medtronic submission¹²⁷ – Endovascular aneurysm repair (EVAR) for the treatment of infra-renal abdominal aortic aneurysms (AAA)

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
<i>Selection of alternatives</i>		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
<i>Form of evaluation</i>		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	

continued

TABLE 80 Checklist for Medtronic submission¹²⁷ – Endovascular aneurysm repair (EVAR) for the treatment of infra-renal abdominal aortic aneurysms (AAA) (continued)

Study question	Grade	Comments
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓/X	
11. Potential biases identified (especially if data not from RCTs)	✓/X	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	X	Study does not consider productivity costs
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	?	Costs are in UK pounds but the price year is unclear. Some of the reference costs are for 2005/6 but others are from earlier dates
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓/X	Costs and QALYs are not always disaggregated
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	Both costs and QALYs are discounted at a rate of 3.5%
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓/X	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	✓	

TABLE 80 Checklist for Medtronic submission¹²⁷ – Endovascular aneurysm repair (EVAR) for the treatment of infra-renal abdominal aortic aneurysms (AAA) (continued)

Study question	Grade	Comments
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	?	This is unclear from the report but has been carried out in the model
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	?	This is unclear from the report but has been carried out in the model
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	
<i>Deterministic analysis</i>		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	Univariate sensitivity analyses have been conducted
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
<i>Presentation of results</i>		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	✓/X	QALYs and costs have been disaggregated for the base-case analysis, but only ICERs are reported for the sensitivity analyses
39. Applicable to the NHS setting	✓	

TABLE 81 Checklist for EVAR trial participants⁴⁶ – Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	X	Viewpoint is not clearly stated, although from reading the paper it is clear that it is NHS
<i>Selection of alternatives</i>		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
<i>Form of evaluation</i>		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	X	

continued

TABLE 81 Checklist for EVAR trial participants⁴⁶ – Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial (continued)

Study question	Grade	Comments
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	✓	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	?	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	X	
Costs		
13. All of the important and relevant resource use included	✓	
14. All of the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	X	
17. Productivity costs treated separately from other costs	X	Productivity costs were not considered
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	X	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	X	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	N/A	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	N/A	
24. All model outputs described adequately	N/A	
Discounting		
25. Discount rate used for both costs and benefits	X	Only costs are discounted
26. Do discount rates accord with NHS guidance?	?	Discount rate is not stated
Allowance for uncertainty		
<i>Stochastic analysis of patient-level data</i>		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	X	

TABLE 81 Checklist for EVAR trial participants⁴⁶ – Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial (continued)

Study question	Grade	Comments
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	X	
<i>Stochastic analysis of decision models</i>		
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	N/A	
<i>Deterministic analysis</i>		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	N/A	
35. The choice of variables for sensitivity analysis is justified	N/A	
36. The ranges over which the variables are varied are stated	N/A	
<i>Presentation of results</i>		
37. Incremental analysis is reported using appropriate decision rules	N/A	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	?	
39. Applicable to the NHS setting	✓	

Appendix 3

Survey of health-care resource use after EVAR and open repair

Concerns have been raised by Medtronic¹²⁷ that the resource use collected from the EVAR trial 1⁴² may no longer accurately reflect current practice. To inform this issue a postal survey was conducted on behalf of the evaluation team in January 2008 of members of the Vascular Society and the British Society of Interventional Radiology in hospitals in which both EVAR and open repair are undertaken. In total, 55 replies were received from 50 centres by 25 March 2008 (it should be noted that there has been some duplication from centres but because of differences in the responses we have treated each response as an individual case). The results of this survey are presented in *Table 82*.

According to the results of the survey, mean days spent in both intensive care units and general wards are lower in 2008 after both open repair and EVAR than were found by the EVAR trial 1 for patients enrolled between 1999 and 2003.

The survey results also indicate that length of stay in general wards may have fallen slightly more after EVAR than after open repair, but there is no evidence that the difference between EVAR and open repair in the use of high dependency unit and intensive care unit facilities has changed substantially since the EVAR trial 1. The difference in ward length of stay between the treatments in the EVAR trial 1 was 2.3 days,⁴³ and the survey estimates a mean difference in 2008 of 4.3 days. The difference in intensive care unit use between the treatments estimated by EVAR trial 1 was 1.7 days,⁴³ and the survey estimates a mean difference of 1.1 days.

The EVAR trial 1 found that patients attended on average two follow-up visits in the first year after EVAR and one per year thereafter.⁴³ The results of this survey indicate that this is still current practice but that the frequency of surveillance tends to diminish over time.

TABLE 82 Results of the survey of resource use after EVAR and open repair

	EVAR (55 replies)		Open repair (55 replies)	
	Mean (proportion)	Median (proportion)	Mean (proportion)	Median (proportion)
Prior to EVAR/open repair does a critical care bed have to be booked? ^a	0.345	0	0.909	1
If one is not available would the procedure be cancelled? ^a	0.222	0	0.855	1
Standard planned postoperative arrangements for EVAR/open repair				
	Mean	Median	Mean	Median
Days in ICU	0.019	0	1.167	1
Days in HDU	0.519	1	1.600	1
Days in general ward	3.037	3	7.309	7
Current routine follow-up policy for a patient who has undergone EVAR/open repair				
	Mean	Median	Mean	Median
<i>Number of follow-up outpatient appointments per year</i>				
Year 1	2.000	2	1.333	1
Year 2	0.759	1	0.164	0
Year 3	0.648	1	0.109	0
Year 4	0.623	1	0.073	0
After year 4	0.635	1	0.073	0
<i>Number of CT follow-up appointments per year</i>				
Year 1	1.755	2	0.018	0
Year 2	0.827	1	0.036	0
Year 3	0.712	1	0.018	0
Year 4	0.653	1	0.055	0
After year 4	0.614	1	0.019	0
<i>Number of ultrasound follow-up appointments per year</i>				
Year 1	1.265	1	0.057	0
Year 2	0.776	1	0.037	0
Year 3	0.673	1	0.037	0
Year 4	0.681	1	0.037	0
After year 4	0.644	1	0.038	0
CT, computed tomography; HDU, high dependency unit; ICU, intensive care unit. a 1 indicates yes, 0 indicates no.				

Appendix 6

Characteristics of the average UK population

The decision model requires inputs such as operative mortality and non-aneurysm-related mortality that are representative of the UK population. The characteristics of the UK population who require aneurysm repair (either with EVAR or open repair) may not be the same as those of patients recruited to clinical trials or reported in registers. For example, clinical trials may select patients who are most anatomically suitable for EVAR. If the case mix of the target population differs from that of the trial or sample population then the estimates from the trial that are used as inputs to the model must be adjusted for the appropriate case mix in a consistent manner.

We identify and compare three data sets in which patients might have similar characteristics to the UK population for aneurysm repair: EVAR trial 1,^{42,43} RETA⁵⁶ and EUROSTAR.⁵⁴ *Table 83* compares the mean age and aneurysm size and operative mortality of these patients. The study characteristics and design of EVAR trial 1 and the RETA and EUROSTAR registries are described in detail in the assessment of clinical effectiveness assessment report (Chapter 3; see section on assessment of effectiveness from RCTs for EVAR trial 1 and section on assessment of effectiveness from registries for RETA and EUROSTAR). In brief, EVAR trial 1 included only UK patients judged suitable for open repair. The low operative mortality rate (1.7%) may be partly due to favourable anatomic selection criteria. RETA is a register of UK patients. The average operative mortality rate was 5.8%, but was 1.7% in patients considered fit for open surgery using commercially

available aorto-bi-iliac devices.⁵⁶ EUROSTAR included patients from centres in several European countries using the current generation of devices. The reported operative mortality rate of 2.3% in EUROSTAR includes patients both suitable and unsuitable for open repair, and patients with smaller aneurysms than are normally operated on in the UK. On the basis of these sources and clinical opinion it was thought that an operative mortality rate of EVAR of approximately 2% would be fairly representative of average UK practice.

In the model in the assessment report, operative mortality is an endogenous variable, that is, it is calculated as a function of age, aneurysm size and comorbidities (fitness). This is necessary because age and comorbidities have an independent effect on both operative mortality and late mortality. There is a correlation between operative mortality and late non-aneurysm mortality, operating through age, aneurysm size and comorbidity, that has been incorporated in the structure of the model. To populate the model we must select the average age, aneurysm size and level of comorbidity (relative fitness) of the UK population that is consistent with the average mean operative mortality rate after EVAR in the UK population. The risk equation shown in *Tables 58* and *59* of the assessment report indicates that patients aged 75 years with moderate fitness and an aneurysm size of 6.5 cm are predicted to have an operative mortality rate of 2.1%, similar to our estimate of the expected operative mortality rate after EVAR in the UK population of 2%. From this, we consider that these characteristics are representative on average of the UK population for aneurysm repair.

TABLE 83 Comparison of mean age, aneurysm size and operative mortality of patients in EVAR trial 1 and the RETA and EUROSTAR registries

	EVAR trial 1 ^{42,43}	RETA ⁵⁶	EUROSTAR ⁵⁴
Age	74 (SD 6.0) years	73 years (range 44–93 years)	73 (SD 7.8) years
Aneurysm size	6.5 (SD 0.9) cm	Median 6 cm	5.84 (SD 1.16) cm
Operative mortality after EVAR	1.7%	5.8%	2.3%



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