Overview

Endovascular stents for abdominal aortic aneurysms

The overview is written by members of the Institute’s team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees’ comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Aortic aneurysms develop when the wall of the aorta weakens, causing it to bulge and form a balloon-like projection. This leads to further stretching of the wall of the aorta and an increase in tension. Eventually the wall may rupture, leading to massive internal bleeding.

Aneurysms are often a result of atherosclerosis and most occur in the abdominal section of the aorta. An abdominal aortic aneurysm (AAA) is defined as an enlargement of the aorta of at least 1.5 times its normal diameter or greater than 3 cm. Most AAAs occur in the lower (infra-renal) part of the abdominal aorta.

Symptoms that can occur as an aneurysm enlarges include a pulsating sensation in the abdomen, back pain and abdominal pain that may possibly spread to the back. Patients with a ruptured AAA require rapid medical attention. There is a mortality rate of about 80% in patients with ruptured AAA; even when patients undergo emergency surgery, only about half survive.
beyond 30 days. The risk of rupture increases with the size of the aneurysm. Each year about 25% of aneurysms larger than 6 cm rupture. A number of studies indicate that without surgery the 5-year survival rate for patients with aneurysms larger than 5 cm is about 20%.

The main risk factors for AAA include increasing age, high blood pressure, male sex (AAAs are about three times more common in men than in women), and smoking. 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. The incidence of symptomatic AAA in men is approximately 25 per 100,000 at age 50, increasing to 78 per 100,000 in those older than 70 years. The overall incidence of AAA has increased in recent years and is likely to increase further with the ageing of the general population.

Most AAAs are detected by chance during clinical investigation (for example, ultrasound or X-ray) for other conditions. National screening programmes for the early detection of AAAs are currently under consideration by the Department of Health.

1.2 Current management

Patients with AAA 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, because many patients with an AAA have significant comorbidities (for example, heart or kidney disease) that reduce their fitness for surgery. Open repair can also be performed laparoscopically, either by hand-assisted laparoscopic surgery (HALS) or total laparoscopic surgery (TLS). ‘Stent–graft placement in abdominal aortic aneurysm’ (NICE interventional procedure guidance 163) states that, current evidence on the efficacy and short-term
safety of stent–graft placement in abdominal aortic aneurysm appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.

In current UK clinical practice, elective surgery is generally recommended for patients with aneurysms larger than 5.5 cm in diameter and aneurysms larger than 4.5 cm in diameter that have increased by more than 0.5 cm in the last 6 months. The UK small aneurysm trial (UKSAT) and aneurysm detection and management (ADAM) trial indicated that there was no mortality advantage of immediate (open) surgical repair over imaging surveillance in patients with aneurysms of less than 5.5 cm diameter. Current guidelines from the Vascular Society and the National Screening Committee recommend that ultrasonography is used to follow up patients with asymptomatic aneurysms smaller than 4.5 cm annually, and patients with aneurysms of 4.5-5.5 cm every 3 months.

Approximately 25% of patients with an AAA requiring surgery are considered unfit for open surgery. Such patients will be kept under surveillance with an option to defer surgery, or until a decision is made to rule out surgery entirely. As age, fitness and the untreated risk of rupture change over time, the option to defer surgery makes the decision complex and dynamic. The best management policy for patients considered unfit for open surgery is unclear. A policy to improve patient fitness might be effective, with treatment offered to reduce risk – for example, to stop smoking and to reduce blood pressure. Such a policy has not yet been evaluated.

Endovascular aneurysm repair (EVAR) is a minimally invasive 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, carried to the site of the aneurysm using catheters and guide wires and placed in position under X-ray guidance. Once in position, the stent–graft is 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. EVAR is carried out under general, regional or local anaesthesia.

EVAR has been used to treat both patients considered fit for open repair and those considered unfit. It can be used as an elective procedure or to treat symptomatic and ruptured aneurysms. However EVAR is not suitable for all patients: 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, 55% did not have an absolute morphological contraindication to EVAR.

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. Potential disadvantages include the development of endoleaks, which occur when blood continues to flow through the aneurysm because the graft does not seal completely (type I endoleak) or because of backfilling of the aneurysm from other small vessels in the aneurysm wall (type II endoleak). Patients who have had open repair do not require any special follow-up, but patients who have undergone EVAR require regular CT scans to check for the presence of late endoleaks. In addition, if EVAR is unsuccessful or complications arise during the procedure, conversion to open repair may be necessary in patients initially considered unfit for open surgery.

2 The technologies

The main types of endovascular stent–grafts are:

- aortic tube grafts (no longer used in the UK)
- aorto-uni-iliac grafts
- aorto-bi-iliac (bifurcated) grafts (most common in the UK).
The stent–graft typically comprises a self-expanding nickel-titanium (nitinol) stent attached to a woven polyester fabric graft. Bifurcated grafts are modular with multiple segments: a proximal tube, a flow divider, a full-length ipsilateral iliac limb and a short contralateral stump for attachment of the second iliac limb. The stent–grafts are attached to the aortic wall by metallic wires, hooks and anchors. Additional modular components include aortic and iliac extender cuffs, which are used for the treatment of type I endoleaks.

Endovascular stents are not homogeneous products. There are a number of different endovascular stent devices made by different companies, each with a different cost. This is further complicated by the fact that patients who are fitted with the same manufacturer’s device may require different numbers of components. The manufacturers who produce the devices also offer different pricing structures (for example, some charge a price per patient regardless of the number of components needed while others base their charge on the number of parts required). If the price per patient is not fixed, then ideally the mean price per patient should be calculated based on an assessment of the expected number of extension parts required, which in turn depends on the population case-mix.
All the technologies in table 1 have been granted CE (Conformité Européene) marking for use within EU countries.

Table 1 Summary description of technologies

<table>
<thead>
<tr>
<th>Product (stent-grafts)</th>
<th>Manufacturer</th>
<th>Product list price (£)</th>
<th>Product named specifically in trials/registry in the assessment report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talent stent–graft</td>
<td>Medtronic</td>
<td></td>
<td>DREAM EVAR 1 Soulez et al EUROSTAR RETA</td>
</tr>
<tr>
<td>Excluder AAA endoprosthesis</td>
<td>WL Gore</td>
<td></td>
<td>DREAM EVAR 1 EUROSTAR RETA</td>
</tr>
<tr>
<td>The Aorfix AAA stent–graft</td>
<td>Lombard Medical</td>
<td>5,000</td>
<td>Fixed price per patient irrespective of components used</td>
</tr>
<tr>
<td>Zenith AAA endovascular graft</td>
<td>Cook Medical</td>
<td></td>
<td>DREAM EVAR 1 EUROSTAR RETA</td>
</tr>
<tr>
<td>Endologix Powerlink Systems</td>
<td>Le Maitre</td>
<td>The manufacturer did not provide price data</td>
<td></td>
</tr>
</tbody>
</table>

AAA: abdominal aortic aneurysm, DREAM and EVAR are randomised controlled trials, EUROSTAR and RETA are patient registries

The principal investigators of one of the large randomised controlled trials (RCTs) comparing EVAR with open surgery undertook a survey in June 2004 of prices paid by centres participating in the trial. The mean cost per patient, regardless of the number of extensions required, ranged from [ ] to [ ]. The mean cost of the stent–graft body alone ranged from [ ] to [ ]; the mean cost of limb sections, if required, ranged from [ ] to [ ]; and the
mean cost of cuff sections ranged from [x] to [y]. For further details, see table 3.2.1 on page 18 of the assessment report.

3 The evidence

3.1 Clinical effectiveness

The Assessment Group identified studies of adult patients with asymptomatic or symptomatic, ruptured or unruptured infra-renal AAA that compared EVAR using stent–grafts with conventional open repair and/or to non-surgical treatment (sometimes referred to as watchful waiting).

The Assessment Group recognised that not all devices evaluated in the studies would have a CE mark and that several devices would have undergone a number of changes since the studies were undertaken. The Assessment Group also recognised that manufacturers’ devices would have different indications for use and contraindications. The Assessment Group considered studies of any EVAR device to be eligible but, where data allowed, analysis focused on devices commonly used in current UK practice.

In their systematic review, the Assessment Group included RCTs and large registries relevant to UK practice. The registries included were the NVD (4545 patients from 59 centres), RETA (1000 patients from 41 centres) and EUROSTAR (8345 patients from 177 centres). Where appropriate, the Assessment Group used meta-analysis to estimate a summary measure of treatment effect on relevant outcomes based on intention-to-treat (ITT) analyses.

A brief summary of the results of the systematic review is given below. Further details of the RCTs are provided in tables 5.2.4–5.2.7 on pages 47–51 of the assessment report. Further details of the registries are in table 5.2.21 on page 73 of the assessment report.
3.1.1 EVAR versus open surgery in patients with unruptured AAA

Four RCTs compared EVAR with open repair in patients with unruptured AAA (EVAR 1, n = 1082; DREAM, n = 351; Cuypers and co-workers, n = 76; and Soulez and co-workers, n = 40). Most patients in the RCTs were male, reflecting the disease profile, and the average age of patients ranged from late 60s to mid-70s. The four RCTs were relatively homogeneous in terms of average aneurysm diameter (6.0 cm, 6.5 cm, 5.4 cm and 5.2 cm respectively). The Assessment Group considered EVAR 1 and DREAM to be of high quality but in the trials by Cuypers and co-workers and Soulez and co-workers some methodological aspects were unclear in the published reports. In addition to the methodological quality issues, the Assessment Group stated that the Cuypers and co-workers and Soulez and co-workers trials were not designed to assess hard clinical endpoints such as mortality.

30-day mortality

All four RCTs comparing EVAR with open repair in patients with unruptured AAAs reported 30-day mortality. The pooled estimate of effect suggested a significant lower rate of 30-day mortality in patients in the EVAR group (pooled odds ratio 0.35; 95% confidence interval [CI] 0.19 to 0.63).

The 30-day mortality rate of 2.3% in patients in the EUROSTAR registry was comparable with 1.7% in patients from the EVAR arm of EVAR 1. In the UK NVD, crude operative mortality following open repair of unruptured aneurysms was 6.8%, compared with 4.7% for patients in the open repair arm of EVAR 1.

All-cause mortality

Of the four RCTs, only DREAM and EVAR 1 provided information on all-cause mortality at follow-up (at 2 years and 4 years respectively). Both RCTs reported no significant difference in medium-term mortality (at 35 and 42 months respectively) in patients treated with EVAR compared with open repair. 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 5.2.6 on page 56 of the assessment report shows the ITT survival curves for the randomised groups.

**Rupture**

The four RCTs provided limited information on rupture as a separate outcome. The limited data available suggest that rupture may be more of an issue following EVAR than following open repair. The cumulative rate of rupture in patients from EUROSTAR was 3.1%.

**Endoleak**

Only the EVAR 1 and Soulez and co-workers trials reported endoleak as an outcome. Across the RCTs, some form of endoleak occurred at varying frequencies (up to approximately 20%) following EVAR. Type II endoleaks were most common, followed by type I. The cumulative rate of endoleak in patients from the EUROSTAR registry was higher (32.5%).

**Device migration**

Only EVAR 1 reported on device migration following EVAR. In the trial, 12 of 529 (2.3%) patients experienced device migration during follow-up, of which 7(1%) required re-intervention.

**Re-intervention**

The EVAR 1 and DREAM trials compared overall re-intervention rates between patients treated with EVAR and open repair. In DREAM, the risk of re-intervention was significantly higher in the EVAR group for the first 9 months (hazard ratio 2.9; 95% CI 1.1, to 6.2, p = 0.03) but the groups were not significantly different thereafter (hazard ratio 1.1; 95% CI 0.1 to 9.3, p = 0.95). Across the mid-term follow-up, in EVAR 1 the hazard ratio for re-intervention was 2.7; 95% CI 1.8 to 4.1, indicating a higher risk in the EVAR
group. The 4-year point estimates for re-intervention in this trial were 20% for the EVAR group compared with 6% for the open repair group. The cumulative rate of re-intervention in the EUROSTAR registry was similar to the 4-year point estimate for the EVAR group in EVAR 1.

**Short-term adverse events**

Only the trial by Cuypers and co-workers reported cardiac events: three (5%) in the EVAR group and two (11%) in the open repair group.

**Health-related quality of life (HRQoL)**

All four RCTs reported some details of HRQoL. All used the Medical Outcomes Study short form 36 (SF-36) questionnaire, but different components were reported, making it difficult to compare results across studies. Overall, data from these trials suggested that there may be a short-term quality of life (QoL) advantage for EVAR patients compared with those who have open repair. Longer-term QoL data tended to favour open repair. The Assessment Group stated that these findings probably reflected the less invasive nature of the intervention in EVAR, but also the need for continuing surveillance and the higher rate of complications and re-interventions following EVAR compared with open repair.

**3.1.2 EVAR versus open repair in patients with ruptured AAA**

The RCT by Hinchcliffe and co-workers (n = 32) compared EVAR and open repair in patients with ruptured AAAs. Compared with the 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 (a two-piece aorto-uni-iliac stent–graft made with Gianturco stents with an uncovered supra-renal component) were used in patients receiving EVAR.

**30-day mortality**

Of 15 patients randomised to EVAR, one died before surgery, one was converted to open repair and subsequently died, and six died in the perioperative period following EVAR. Therefore, on an ITT basis, the mortality rate was 8/15 (53%) patients. Of 17 patients randomised to open repair, three
died before surgery, two died in surgery 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**
Cardiac events were recorded in 5/11 EVAR patients (45%) and 7/12 open repair patients (58%) who survived the procedure. 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.

**EVAR versus open surgery: summary**
Compared with open repair, EVAR reduced operative mortality (odds ratio 0.35; 95% CI 0.19 to 0.73) and aneurysm-related mortality over the medium term (odds ratio 0.49; 95% CI 0.29 to 0.83) but offered no significant difference in all-cause mortality at mid-term. The Assessment Group stated that the reason that the short-term benefit of EVAR over open repair did not translate into an advantage in the longer term was unclear. They stated that 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 patients die as an immediate result of the procedure. However, these ‘high risk’ patients die within a relatively short time and so by 4 years after surgery the mortality rate in patients treated with EVAR or with open repair is 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 re-interventions in the EVAR group. EVAR was associated with an increased rate of complications and re-interventions, and these were not offset by the increase in HRQoL.
3.1.3 EVAR versus non-surgical management (patients with unruptured AAA considered unfit for open repair)

The Assessment Group identified one published RCT (EVAR 2, n = 338) that compared EVAR and non-surgical management in patients judged to be unfit for open repair. The Assessment Group considered the trial to be of high quality. The primary endpoint was all-cause mortality and secondary endpoints were aneurysm-related mortality, HRQoL, postoperative complications and hospital costs.

The trial found no differences in AAA-related and all-cause mortality outcomes between groups at mid-term. The Assessment Group stated that this may indicate that the benefits of EVAR over no intervention may require more than 4 years’ follow-up to become apparent.

3.1.4 Analysis by device type

Only EVAR 1 and EVAR 2 reported an analysis by device type. In EVAR 1 there were no statistically significant differences between outcomes with the Zenith and Talent devices. Adjusted hazard ratios were 0.79; 95% CI 0.51 to 1.21 for re-intervention, 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 2 there were also no statistically significant differences between outcomes with the Zenith and Talent devices. Adjusted hazard ratios were 0.69; 95% CI 0.29 to 1.62 for re-intervention, 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.
3.1.5 Analysis by neck angulation

Significant aortic neck angulation may lessen the chances of a good outcome after endovascular abdominal aortic aneurysm repair. Neck angulation is the angle between the infra-renal aortic neck and the longitudinal axis of the aneurysm. It can be defined as severe (≥ 60 degrees), moderate (40–59 degrees), and mild (< 40 degrees). The Assessment Group reported that none of the included RCTs reported data allowing an analysis of outcomes by neck angulation.

3.2 Assessment of risk factors for adverse outcomes during EVAR

In order to identify criteria for selecting patients appropriate for EVAR, the Assessment Group reviewed studies that modelled the spectrum of risk. Further details are provided in table 5.2.31 on page 96 of the assessment report.

There was evidence from single studies by Biancari and Timaran that the Glasgow aneurysm score (GAS) and Charlson comorbidity index (CCI) score respectively can independently predict short-term mortality (in-hospital or 30-day mortality) after EVAR. These scoring tools have previously been validated for prediction of mortality risk following open AAA repair. The GAS may also be able to predict longer term mortality risk after EVAR, based on the study by Biancari. Based on one study by Brown, there was no evidence that fitness rating based on a modified CCI score predicted benefit from EVAR compared with open repair.

The Assessment Group identified one study which focused on the development of an algorithm to assess baseline risks in patients after EVAR. Four factors were identified as having a statistically significant impact on survival rates: American Society of Anaesthesiologists (ASA) score, maximum aneurysm diameter, age and serum creatinine (p < 0.001 for each factor). The study indicated that the greatest predicted survival rate would be expected in younger patients (70 years) with lower ASA scores and creatinine levels.
(85 micromoles/litre), and smaller aneurysm size (5 cm). By contrast, patients expected to have lower survival rates were identified as older patients (83 years), with a higher ASA score (that is, grade IV), higher creatinine levels (125 micromoles/litre), and larger aneurysm size (7.4 cm). Survival rates for the older group of patients were 44% at 3-year 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. The expected mortality rate at 5 years was 15% for the younger patient group and 75% for the older patient group. However, the Assessment Group noted that the authors had stated that the data for the older patient group were unreliable because of the small sample sizes and should be interpreted with caution.

The Assessment Group identified 32 studies investigating specific risk factors after EVAR. The Assessment Group stated that the studies did not provide definitive evidence but age, gender, renal impairment, fitness, ASA score and aneurysm size may be predictive of lower 30-day survival. There may be a link between fitness for the open procedure, aneurysm size and device type and aneurysm-related mortality. In terms of all-cause mortality, pulmonary status, renal impairment, ASA score and aneurysm size might adversely affect this outcome. The Assessment Group did not find any consistent risk factors for re-intervention.

### 3.3 Cost effectiveness

The Assessment Group identified six published economic evaluations that met their inclusion criteria for the economic review. One economic evaluation was submitted by one of the manufacturers. In addition, the Assessment Group carried out their own economic evaluation.

#### 3.3.1 Published economic evaluations

Five of the economic evaluations considered EVAR for patients with unruptured aneurysms requiring surgery who were considered fit for open surgery. All five were cost-utility analyses. A summary of the economic
evaluations is shown in table 2. The Assessment Group’s commentary on the studies can be found on pages 144–165 of the assessment report.

Table 2 Endovascular aneurysm repair (EVAR) studies in patients with unruptured abdominal aortic aneurysm (AAA) who were fit for open repair surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Country where study was performed</th>
<th>Summary</th>
<th>Patient population (average age in years)</th>
<th>QALYs</th>
<th>Costs</th>
<th>ICER (per QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al</td>
<td>USA</td>
<td>Markov model comparing EVAR with open repair</td>
<td>Men aged 70 years with an AAA of 5 cm in diameter</td>
<td>0.42</td>
<td>$9587</td>
<td>$22,836</td>
</tr>
<tr>
<td>Bosch et al</td>
<td>USA</td>
<td>Markov model comparing EVAR with open repair</td>
<td>Men aged 70 years with an AAA between 5 and 6 cm in diameter</td>
<td>0.22</td>
<td>$179</td>
<td>$9,905</td>
</tr>
<tr>
<td>Epstein et al</td>
<td>UK</td>
<td>Markov model comparing EVAR with open repair</td>
<td>Men aged 74 years with an AAA of diameter greater than or equal to 5.5 cm</td>
<td>-0.020</td>
<td>£3578</td>
<td>EVAR is dominated</td>
</tr>
<tr>
<td>Michaels et al</td>
<td>UK</td>
<td>Markov model comparing EVAR with open repair</td>
<td>Fit patients aged 70 years with an AAA of 5.5 cm diameter</td>
<td>0.10</td>
<td>£11,449</td>
<td>£110,000</td>
</tr>
<tr>
<td>Prinssen et al</td>
<td>Netherlands</td>
<td>Within-trial analysis comparing EVAR with open repair</td>
<td>Fit patients with an AAA of greater than or equal to 5 cm in diameter</td>
<td>-0.01</td>
<td>4968 euros</td>
<td>EVAR is dominated</td>
</tr>
</tbody>
</table>

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Two economic evaluations considered EVAR for patients with unruptured aneurysms requiring surgery who were considered unfit for open repair. The economic evaluation by Michaels and co-workers also considered EVAR for patients with unruptured aneurysms who were considered unfit for surgery. EVAR 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, the Assessment Group included it in their cost-effectiveness review 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. A summary of the economic evaluations is shown in table 3. The Assessment Group’s commentary on the studies can be found on pages 178–185 of the assessment report.

Table 3 Endovascular aneurysm repair (EVAR) studies in patients with unruptured abdominal aortic aneurysm (AAA) who were unfit for surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
<th>Patient population (average age, in years)</th>
<th>Incremental QALYs of EVAR</th>
<th>Incremental costs of EVAR</th>
<th>ICER (per QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaels et al.</td>
<td>Markov model comparing EVAR with medical management</td>
<td>Patients aged 80 years with an AAA of 6.5 cm diameter, who were considered unfit for open surgery</td>
<td>1.64</td>
<td>£14,077</td>
<td>£8,579</td>
</tr>
<tr>
<td>EVAR 2</td>
<td>Within-trial analysis comparing EVAR with no intervention</td>
<td>Patients aged 76 years with mean AAA diameter of roughly 6.3 cm who were considered unfit for open repair</td>
<td>Not stated</td>
<td>£8,649</td>
<td>EVAR is dominated by no intervention arm</td>
</tr>
</tbody>
</table>

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

3.3.2 Manufacturer’s economic model

Medtronic conducted a cost-utility analysis comparing EVAR with open repair in patients with an unruptured infra-renal AAA of at least 5.5 cm in diameter who were considered fit for open surgery. The average age of the population was 70 years and 90% of the patients were men.

Medtronic developed a two-stage model to estimate the lifetime cost and quality-adjusted life years (QALYs) for EVAR and open repair in this patient population. The model comprised a decision tree for the first 30 days after surgery and then a Markov model from 30 days after surgery until death. At the end of the first 30 days patients in the EVAR arm entered one of four states: successful EVAR with no complications; EVAR with complications; conversion to open surgery; or death. Patients in the open repair arm entered...
one of three states: open repair with no complications; open repair with complications; or death.

The effectiveness data used to set parameters for the model were largely drawn from EVAR 1 supplemented with data from clinical expert opinion and from registries. The key effectiveness parameters from the manufacturer’s submission are shown in table 4; further details can be found on pages 168-170 of the assessment report.

Table 4 Key effectiveness parameters from Medtronic’s submission

<table>
<thead>
<tr>
<th>Key parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality of open repair (%)</td>
<td>4.19</td>
</tr>
<tr>
<td>Mortality of primary EVAR (%)</td>
<td>1.62</td>
</tr>
<tr>
<td>Probability of conversion of EVAR to open repair (%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mortality (all-cause, monthly, EVAR) (%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Mortality (all-cause, monthly, open repair) (%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mortality (AAA-related, monthly, EVAR) (%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Mortality (AAA-related, monthly, open repair) (%)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm

Utility scores for health states have been taken directly from EVAR 1. These found that in the first 3 months after surgery, patients in the open repair arm had a lower utility (0.67), and patients in the EVAR arm had a slightly higher utility (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.

The resource use data used in the study were drawn largely from EVAR 1 for open repair. The key procedure-related costs from Medtronic’s submission are shown in table 5. The Assessment Group’s commentary on the manufacturer’s resource utilisation and cost data can be found on pages 171–172 of the assessment report.
Table 5 Procedure-related costs from the Medtronic submission

<table>
<thead>
<tr>
<th>Resource</th>
<th>EVAR</th>
<th>OSR</th>
<th>Cost (£)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theatre time (min), (mean, SD)</td>
<td></td>
<td>205 (69)b</td>
<td>£525/hour</td>
<td>Information Services Division (ISD) Scotland. Cost book-detailed tables, theatre services: R142X-average theatre running costs, and usage by specialty, by board (2006).</td>
</tr>
<tr>
<td>ICU ward (days), (mean, SD)</td>
<td></td>
<td>2.4 (5.9)b</td>
<td>£1345/day</td>
<td>Department of Health reference cost 2005-06. CC1L2, ITU/ICU-level 2 care (December 2006).</td>
</tr>
<tr>
<td>High dependency or coronary care units (days), (mean, SD)</td>
<td></td>
<td>1.9 (2.8)b</td>
<td>£480/day</td>
<td>Department of Health reference cost 2005-06. CC7L2, coronary care unit-level 2 care (December 2006).</td>
</tr>
<tr>
<td>Postoperative ward (days), (mean, SD)</td>
<td></td>
<td>9.2 (13.6)b</td>
<td>£100/day</td>
<td>Department of Health reference cost 2005. Service code 107, vascular surgery ward (April 2006).</td>
</tr>
<tr>
<td>Blood products used (ml), (mean, SD)</td>
<td></td>
<td>896 (1060)b</td>
<td>£289/pack</td>
<td>Varney et al, 2003 (92).</td>
</tr>
<tr>
<td>Contrast agents (ml), (mean, SD)</td>
<td></td>
<td>6 (34)b</td>
<td>£3.50/50 ml</td>
<td>Freeman Hospital, Newcastle upon Tyne.</td>
</tr>
<tr>
<td>Device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key resource cost parameters- (total procedure costs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EVAR: endovascular aneurysm repair; OSR: open surgical repair; SD: standard deviation; ICU: intensive care unit

*Multicentre EVAR data (Hayes et al, BSET, data on file, 2007)

Results from the manufacturer’s model

Medtronic found that, in the base case, patients treated with EVAR were expected to receive compared with for those treated with open surgery. This resulted in an incremental cost-effectiveness ratio (ICER) of £15,681 per QALY gained for EVAR when compared with open repair.
Medtronic conducted univariate sensitivity analyses for all the parameters in the model, using the values for the lower and upper confidence limits of each parameter. Further details of the values used in the sensitivity analyses can be found in table 6.1.18 on page 173 of the assessment report. The manufacturer found that the ICER was most sensitive to the short-term relative risk of operative mortality. The lower confidence limit for short-term relative risk of mortality resulted in an ICER of ******* per QALY gained, while the upper confidence limit for short-term relative risk of mortality resulted in *******.

The Assessment Group identified three main issues about the assumptions used by the manufacturer that favoured EVAR over open surgery. The first issue highlighted by the Assessment Group related to the manufacturer’s assumption that there was no disutility associated with secondary interventions and no risk of perioperative complications. The Assessment Group stated that, if these assumptions do not hold, then they bias the results in favour of EVAR being cost-effective because EVAR has a higher rate of secondary interventions.

The second issue raised by the Assessment Group related to the manufacturer’s choosing to supplement data from EVAR 1 with other evidence. In particular, the Assessment Group highlighted that the manufacturer *******.
Third, the Assessment Group stated that the manufacturer’s assumption that mortality was the same in both arms from 4 years onwards however at 4 years, a slightly higher proportion of patients in the EVAR arm survived in the manufacturer’s economic model (77.2% after open repair versus 78.3% after EVAR), this assumption results in the 4 year survival benefit being extrapolated over a lifetime and thus over the long term is favourable to EVAR.

3.3.3 Assessment Group model

The Assessment Group’s economic evaluation was divided into two parts. The first part compared the cost effectiveness of EVAR with open repair in patients with large aneurysms. This analysis assumed that the decision to operate had already been taken. The second part of the Assessment Group’s economic evaluation estimated the cost effectiveness of policies about when, as well as how, the aneurysm repair should be carried out. In this second part, the Assessment Group compared surgery (EVAR or open repair) with no surgery and watchful waiting as alternative policies.

In the analyses for both parts of their economic evaluation, the Assessment Group stratified their results according to three key patient characteristics: age, fitness (risk of operative mortality) and aneurysm size. Fitness in the model was represented by pre-existing conditions such as cardiac, pulmonary or renal insufficiency, which might predict operative mortality. The Assessment Group considered that because of the large number of combinations of potential risk factors and levels it would be more convenient to express fitness according to a single scale. In their analysis, the Assessment Group defined four levels of 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.

The Assessment Group stated that, from a clinical perspective, these relative (un)fitness scores could in principle arise from any combination of factors.

**EVAR compared to open repair: methods**

The model compared open repair with EVAR in patients with a diagnosed AAA of at least 5.5 cm in diameter and who were considered fit for open repair. The perspective of the model was that of the NHS. The time horizon of the model was for the patient’s lifetime. All costs were measured in UK sterling using 2007 prices. Costs and health benefits in future years were discounted at a rate of 3.5% per year. The model was closely based on the previously published model by Epstein and co-workers. The main difference was that the Assessment Group’s model extended the analysis for patients of different ages, fitness levels and aneurysm sizes at the time of the decision to undertake surgery. The base-case model assumed that these factors influenced baseline risks, but that the effect of treatment on operative mortality (odds ratio of EVAR versus open repair) was constant for all patient groups.

Patients enter the model after the decision to operate has been made, and have a primary aneurysm repair procedure (that is, 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.

For each of the subgroups, stratified by patient fitness, age and aneurysm diameter, parameter estimates were calculated using the risk equations detailed on pages 188–204 of the assessment report. The parameter
estimates calculated were operative mortality after EVAR and open repair, the rate of non-aneurysm deaths more than 30 days after aneurysm repair, rate of late aneurysm-related death and rate of late readmission for complications. The parameter estimates used in the Assessment Group’s economic model are shown in tables 6.2.1–6.2.6 on pages 190–205 of the assessment report.

Costs were incurred in the model during the primary admission, in surveillance after surgery and if the patient was readmitted to hospital for an aneurysm-related complication. The costs and resources used during the primary procedures were estimated from the ITT analysis of EVAR 1. Resource use and costs for intensive care during the primary procedure were based on the actual use of intensive care and high dependency units as recorded in EVAR 1. All patients undergoing EVAR, whether they experienced adverse events or not, were assumed to require regular specialist hospital outpatient attendances and computed tomography (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, the Assessment Group assumed that patients required two surveillance visits during the first year and one visit per year thereafter. Based on the findings of EVAR 1, the Assessment Group assumed that HRQoL declined by 0.077 in the 6-month period following open surgery, by 0.027 following EVAR and by 0.077 after readmission. Patients without the need for re-interventions were assumed to recover to age- and sex-specific average population values of HRQoL 6 months after the procedure. For patients aged 75 years or younger and for patients older than 75 years, the HRQoL values more than 6 months after successful surgery were 0.78 and 0.75 respectively.

**EVAR compared to open repair: results**

The cost-effectiveness results for EVAR compared with open repair were stratified by the Assessment Group by age, aneurysm size and fitness at baseline and are shown in table 6.
Table 6 Expected ICER by age, aneurysm size and fitness

### Good fitness

<table>
<thead>
<tr>
<th>Aneurysm size (cm)</th>
<th>Age (years)</th>
<th>70</th>
<th>72.5</th>
<th>75</th>
<th>77.5</th>
<th>80</th>
<th>82.5</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>Dom</td>
<td>Dom</td>
<td>1,420,044</td>
<td>184,812</td>
<td>93,320</td>
<td>64,037</td>
<td>46,591</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Dom</td>
<td>Dom</td>
<td>967,319</td>
<td>159,988</td>
<td>82,865</td>
<td>57,688</td>
<td>42,380</td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>172,922</td>
<td>70,824</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>491,853</td>
<td>102,492</td>
<td>53,933</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>153,636</td>
<td>68,273</td>
<td>41,549</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>Dom</td>
<td>405,063</td>
<td>83,217</td>
<td>48,232</td>
<td>32,539</td>
</tr>
</tbody>
</table>

### Moderate fitness

<table>
<thead>
<tr>
<th>Aneurysm size (cm)</th>
<th>Age (years)</th>
<th>70</th>
<th>72.5</th>
<th>75</th>
<th>77.5</th>
<th>80</th>
<th>82.5</th>
<th>85</th>
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</thead>
<tbody>
<tr>
<td>5.5</td>
<td>118,599</td>
<td>71,964</td>
<td>50,953</td>
<td>39,306</td>
<td>31,198</td>
<td>26,484</td>
<td>22,346</td>
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<tr>
<td>6</td>
<td>100,770</td>
<td>62,304</td>
<td>44,748</td>
<td>34,921</td>
<td>28,008</td>
<td>24,047</td>
<td>20,485</td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>Dom</td>
<td>363,892</td>
<td>88,775</td>
<td>51,000</td>
<td>34,964</td>
<td>27,765</td>
<td>22,351</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Dom</td>
<td>115,831</td>
<td>56,678</td>
<td>37,715</td>
<td>27,708</td>
<td>22,743</td>
<td>18,820</td>
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<tr>
<td>7.5</td>
<td>162,735</td>
<td>63,156</td>
<td>39,366</td>
<td>28,650</td>
<td>22,217</td>
<td>18,716</td>
<td>15,914</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>71,042</td>
<td>40,766</td>
<td>28,805</td>
<td>22,269</td>
<td>17,997</td>
<td>15,516</td>
<td>13,485</td>
<td></td>
</tr>
</tbody>
</table>

### Poor fitness

<table>
<thead>
<tr>
<th>Aneurysm size (cm)</th>
<th>Age (years)</th>
<th>70</th>
<th>72.5</th>
<th>75</th>
<th>77.5</th>
<th>80</th>
<th>82.5</th>
<th>85</th>
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</thead>
<tbody>
<tr>
<td>5.5</td>
<td>26,807</td>
<td>22,237</td>
<td>19,105</td>
<td>16,742</td>
<td>14,764</td>
<td>13,542</td>
<td>12,319</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>23,454</td>
<td>19,631</td>
<td>17,053</td>
<td>15,125</td>
<td>13,499</td>
<td>12,552</td>
<td>11,578</td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>28,455</td>
<td>21,939</td>
<td>18,183</td>
<td>15,687</td>
<td>13,756</td>
<td>12,718</td>
<td>11,688</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>21,560</td>
<td>17,373</td>
<td>14,841</td>
<td>13,071</td>
<td>11,694</td>
<td>10,955</td>
<td>10,218</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>16,755</td>
<td>13,971</td>
<td>12,237</td>
<td>10,979</td>
<td>9,996</td>
<td>9,497</td>
<td>8,996</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>13,304</td>
<td>11,392</td>
<td>10,196</td>
<td>9,303</td>
<td>8,607</td>
<td>8,284</td>
<td>7,967</td>
<td></td>
</tr>
</tbody>
</table>

Fitness is defined as a relative risk of operative mortality, where good fitness indicates no other pre-existing conditions and poor fitness represents 4 times greater odds of operative mortality for a person of a given age and abdominal aortic aneurysm diameter (AAA) diameter.

ICER: the incremental cost-effectiveness ratio, the difference in expected costs/difference in expected QALYs. Dominated (Dom): means EVAR has less expected benefit and higher cost than open repair.

The base-case model did not distinguish between male and female patients, other than to use life tables for men to estimate non-aneurysm mortality in the general population. However, the Assessment Group identified one large...
study by Timaran and co-workers that found an independent effect of gender on 30-day operative mortality (odds ratio women versus men 1.46; 95% CI 1.26 to 1.68). The Assessment Group undertook a secondary analysis exploring the cost effectiveness of EVAR specifically in women, further details of which can be found on pages 213–215 of the assessment report.

One-way sensitivity analyses of the base case were carried out by varying key parameters in the model. Analyses suggested that the estimates of cost effectiveness were sensitive to the following factors.

- If the EVAR procedure were cost-saving by about £600 compared with open repair, EVAR would be cost effective for older patients with moderate fitness at a threshold range of £20,000–£30,000 per QALY gained.

- If there were no differences in late aneurysm deaths (after 30 days) between EVAR and open repair, EVAR would be more cost effective than open repair in all patients with moderate fitness and older patients with good fitness at a threshold of £30,000 per QALY gained.

- If the treatment odds ratio for operative mortality were more favourable to EVAR, EVAR would be more cost effective than open repair in older patients with moderate fitness, but still unlikely to be cost effective in patients with good fitness.

- If the baseline odds of operative mortality (affecting both EVAR and open repair) were three times greater than estimated in the base case, EVAR would be cost effective compared with open repair in all patients with moderate fitness and older patients with good fitness.

- EVAR would not be cost effective in any of the patient groups considered if the mean list price per patient of the stent–graft was the highest of the values quoted by the manufacturers.
• The analysis for women indicated that EVAR would be unlikely to be cost effective at a threshold of £20,000 per QALY gained in women with good fitness, but it might be cost effective in older women with moderate fitness and women with poor fitness. However, the Assessment Group emphasised that over 90% of the patients in the RCTs were men and therefore it was difficult to verify the assumption that the average treatment effect applied to women. For this reason the Assessment Group stated that the analysis for women was highly uncertain.

A probabilistic sensitivity analysis was undertaken to estimate the probability that EVAR was more cost effective than open repair as a function of the threshold ICER. They suggested that at a threshold of £20,000 per QALY gained, EVAR was more cost effective than open surgery in more than half of the simulations for patients aged 75 and 80 years with poor fitness and aneurysm size of 5.5 cm and for patients aged 75 and 80 years with poor fitness and an aneurysm size of 6.5 cm.

Probabilistic sensitivity analysis also suggested that, at a threshold of £30,000 per QALY gained, EVAR was more cost effective than open surgery in more than half of the simulations for patients aged 75 years with moderate fitness and an aneurysm size of 6.5 cm; patients aged 70, 75 and 80 years with poor fitness and an aneurysm size of 5.5 cm; and patients aged 70, 75 and 80 years with poor fitness and an aneurysm size of 6.5 cm.

Immediate elective surgery (EVAR or open surgery) compared with watchful waiting and no intervention: methods

The model considered when surgery (with EVAR or open repair) might be cost effective, compared with no surgery or delaying the decision for patients at each age and aneurysm size. The Assessment Group assumed that the patient was evaluated every 6 months in the watchful waiting policy. The Assessment Group assumed that surveillance was stopped if a decision was made to rule out surgery and there were no subsequent monetary costs to the health-care system. The costs of deferral were the monitoring costs of CT and
outpatient attendance, deaths while waiting and a time preference for current benefits rather than future benefits. The Assessment Group assumed patients had normal HRQoL for their age while under surveillance, although it was recognised that there was some evidence that patients with diagnosed untreated aneurysm suffer anxiety. The approach used by the Assessment Group to model watchful waiting was as follows.

- First, the model constructed 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 (that is, natural history, with no treatment and no surveillance) for the same patient groups. To estimate the natural history of untreated aneurysm, a Markov cohort model was used. The aim of the model was to estimate QALYs over the patient’s lifetime if untreated. As there was no surveillance and no surgery in this model, there were no costs. The discrete health states were aneurysm sizes, from size at diagnosis in increments of 0.5 cm up to a maximum of 10 cm. The mean growth rate, standard deviation and rupture rate were obtained from a review of the literature on the natural history of untreated aneurysm. In the model, rupture was assumed to be fatal. Although emergency surgery is possible for patients who reach hospital alive, this scenario was not considered in the model. It was assumed that death from non-aneurysm causes was dependent upon current age, current aneurysm size and baseline fitness. This is as per the Assessment Group’s model comparing EVAR and open repair in patients with aneurysm of 5.5 cm or larger and considered fit for open repair. Given the absence of evidence on how fitness might change over time, and the effect of fitness on aneurysm growth and rupture, it was assumed that fitness was constant over the duration of the model.
The Assessment Group used estimates from the study by Michaels and co-workers for the rupture rate for untreated patients and the expansion rate of untreated aneurysms, because the Assessment Group considered these to be broadly consistent with other sources. Without treatment, the aneurysm was predicted to grow exponentially and the risk of rupture increases according to aneurysm diameter. Given these estimates of aneurysm growth, and the results from the risk equation for operative mortality (table 6.2.1 on page 190 of the assessment report), the Assessment Group estimated that the expected operative mortality with EVAR would increase due to increasing age and aneurysm diameter from about 1.5% at age 70 to 10% after 7 years.

Finally, a dynamic programme was constructed using data from the models to evaluate EVAR versus open surgery and an option of no surgery. This estimated the net benefit of a watchful waiting strategy, and calculated the optimum policy (EVAR, open repair, no surgery or watchful waiting) for each aneurysm size and age.

Immediate elective surgery (EVAR or open surgery) compared with watchful waiting and no intervention: results

The base-case model (EVAR compared to open repair) estimated open repair to be more cost effective than EVAR for patients with good and moderate operative fitness. Including a watchful waiting or no surgery strategy would not alter the conclusion that, on average, open repair is more cost effective than EVAR in these patients.

The results of the watchful waiting model for patients with poor and very poor operative fitness at each age and aneurysm size, under base-case assumptions and at a threshold range of £20,000 and £30,000 per QALY gained, are shown in tables 6.2.16 and 6.2.17 on pages 237 of the assessment report. The results are summarised in table 7 below for a threshold of £20,000 per QALY gained. If the threshold was £30,000 per QALY gained, EVAR would be cost effective for patients with poor and very
poor fitness for an older age range compared with a threshold of £20,000 per QALY gained.

Table 7 The management policies predicted by the base-case model to be cost effective for patients with different levels of fitness at a threshold of £20,000 per QALY gained

<table>
<thead>
<tr>
<th>Aneurysm size</th>
<th>Good and moderate fitness</th>
<th>Poor fitness</th>
<th>Very poor fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5–7.4 cm</td>
<td>EVAR is unlikely to be cost effective</td>
<td>EVAR is cost effective between approximately age 74 and 78 years. Open repair is more cost-effective for younger patients, and no surgery or waiting until the aneurysm is larger is cost-effective for older patients</td>
<td>EVAR is cost effective up to about age 74 years. No surgery or waiting until the aneurysm is larger is cost effective for older patients</td>
</tr>
<tr>
<td>7.5 cm and larger</td>
<td>EVAR is more cost effective than open repair in elderly patients of moderate fitness</td>
<td>EVAR is cost effective up to about age 83 years</td>
<td>EVAR is cost effective up to about age 78 years</td>
</tr>
</tbody>
</table>

EVAR: endovascular aneurysm repair

3.3.4 Comparison of the manufacturer and Assessment Group models

EVAR versus open repair

The Assessment Group base-case model found that EVAR was not expected to be cost effective for patients aged 70–75 years with good or moderate fitness and with an aneurysm of between 5.5 and 6.5 cm. In comparison, the manufacturer found that under their base-case assumptions EVAR was a cost-effective alternative to open repair for patients aged 70 years with an aneurysm of at least 5.5 cm.

The Assessment Group stated that the main differences between their base-case model and that provided by the manufacturer were the difference between EVAR and open repair non-aneurysm-cause mortality rates in the medium term, and the difference in late aneurysm-related mortality and hospital costs (intensive care, ward and operating theatre time) of the EVAR procedure. In the manufacturer’s model, there was a slower rate of convergence of the survival curves than in the Assessment Group base case.
a lower relative cost of EVAR and no difference in late aneurysm deaths between EVAR and open surgery. The values used in the respective models are shown in table 8.

Table 8 Comparison of the key parameters in the manufacturer and Assessment Group models

<table>
<thead>
<tr>
<th>Key parameter</th>
<th>Medtronic values</th>
<th>Assessment Group values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of convergence in survival curves for EVAR compared with open (hazard ratio)</td>
<td>1.055</td>
<td>1.072</td>
</tr>
<tr>
<td>Rate of late aneurysm-related deaths (hazard ratio)</td>
<td>1.00</td>
<td>2.46</td>
</tr>
<tr>
<td>Relative cost of the initial procedure</td>
<td>Open repair costs £612 more than EVAR</td>
<td>EVAR procedure costs £523 more than open repair</td>
</tr>
</tbody>
</table>

EVAR: endovascular aneurysm repair

The Assessment Group used these values as part of the sensitivity analysis undertaken on their base-case model, the results of which are shown as scenario 4 in table 6.2.11 on page 214 of the assessment report. The manufacturer’s model presented results for a patient aged 70 years with an aneurysm size of 5.5 cm or larger. Fitness was unspecified in the model (that is, results were for the average level of fitness in patients in EVAR 1). When these assumptions were used in the Assessment Group’s model, the ICER was predicted to be between £11,000 and £24,000 per QALY gained for patients aged 70 years with good or moderate fitness, and therefore consistent with the results reported in the manufacturer’s submission (ICER for average population £15,681 per QALY gained).

Figure 6.2.8 on page 219 of the assessment report illustrates the differences between the assumptions for all-cause mortality made in the Assessment Group’s model and the manufacturer’s model. The figure shows the difference in cumulative deaths between EVAR and open repair predicted by the models. The Assessment Group’s 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 death rate after EVAR. The Assessment
Group considered this scenario to be consistent with the results of EVAR 1, DREAM and a large USA matched-cohort study. In contrast, the manufacturer’s base-case model assumed that the rate of convergence of the survival curves would be slightly slower, and the survival curves would not meet. There would be no further difference in deaths beyond 4 years and, therefore, a long-term survival advantage would be maintained in favour of EVAR.

**Immediate elective surgery (EVAR or open surgery) compared with watchful waiting and no intervention**

No economic evaluations were received from the manufacturers for a comparison of immediate elective surgery with watchful waiting and no intervention.

# 4 Issues for consideration

The major trials comparing EVAR with open repair, EVAR 1 and DREAM, randomised patients between November 2000 and December 2003 and between September 1999 and August 2004, respectively. It has been suggested by some of the consultees that these studies are out-of-date and that the devices and other details of the procedures (including improved outcome due to experience in using the EVAR procedure, and use of resources) may not represent current best practice. It has been suggested by consultees that certain assumptions should be reconsidered.

- Consultees stated that the Assessment Group’s model did not account for the fact that open surgical repair is more invasive, physical recovery takes longer, and patients often require support at home. They highlighted that the publication by Schermerhorn and co-workers showed that after open surgical repair, 18.4% of patients needed further rehabilitation or discharge to a nursing home, compared with 5.6% of EVAR patients.

- Consultees have suggested that the follow-up costs for EVAR used in the Assessment Group’s economic model are higher than those in current clinical practice. Consultees have highlighted that many centres use
ultrasound scanning rather than CT scans. They stated that the NHS reference cost for an ultrasound scan of up to 20 minutes is £49 compared with £108 for a CT scan. In addition they highlighted that many units have a nurse-led clinic, costing £56 per visit (NHS non-consultant out-patient department (OPD follow-up cost) rather than consultant outpatient clinic (at a cost of £83 per attendance).

- Consultees have suggested that the length of stay data used in the Assessment Group’s model is higher than from other data sources. They stated that few patients who have EVAR require admission to intensive care units (ITU) or high dependency units (HDU) unless there are complications. All patients undergoing open surgical repair need admission to ITU or HDU for at least 1 or 2 days. Similarly, patients undergoing EVAR are discharged after about 48 hours, while those undergoing open surgical repair require bed stays of 3 to 10 days.

- A consultee has stated that the odds ratio of 0.35 related to operative mortality used in the Assessment Group’s economic model is not the most appropriate value to use. The odds ratio of 0.35 was based on EVAR 1 data using 30-day ITT. The consultee suggested that it would be more appropriate to use hospital per-protocol data to take into account patients who die without leaving hospital. They suggest that an odds ratio of 0.25, based on EVAR 1 per-protocol data and DREAM would be the most appropriate value to use.

- One consultee stated that the hazard ratio of 6.7 used in the Assessment Group’s economic model was excessive, as it was based on the EVAR 1 re-intervention rates. The consultee considered the re-intervention rates in EVAR 1 to be out-of-date and not representative of current practice. The consultee highlighted that many EVAR-related re-interventions concerned technical issues about patient and device selection. As the experience of operators improves alongside the technology, there is clear evidence that re-intervention rates are falling.
• One consultee suggested that the use of all-cause mortality as an outcome measure in the assessment report was at odds with many publications concerning the adoption of aneurysm screening, which have used aneurysm-related mortality.

• Consultees highlighted that the assumptions used by the Assessment Group for changes in HRQoL after open repair surgery compared with EVAR may underestimate the potential differences of HRQoL in the post-operative period. The Assessment Group estimated that HRQoL would decrease by 0.077 following open repair surgery and by 0.027 following EVAR and that the decrease would exist for 6 months following both procedures. Consultees stated that given the less invasive nature of EVAR, they would anticipate a return to baseline more quickly for patients having EVAR than for patients undergoing open repair.

Does the Committee consider the results from these trials to be applicable to current UK clinical practice?

Medtronic assumed that mortality is the same for patients receiving EVAR or open repair from 4 years onwards. The Assessment Group’s base case assumed that the initial advantage for EVAR compared with open repair is not sustained in the medium term. Which rate of convergence in survival curves for EVAR compared with open repair does the Committee consider being the most appropriate for use in the economic modelling?

In both of the Assessment Group’s cost effectiveness evaluations ‘fitness’ has referred to the risk of operative mortality relative to a patient of that age and aneurysm size with no comorbidities. The Assessment Group did this because, although fitness is a crucial factor in their analysis, there is no validated risk-score system to quantify this risk both for EVAR and open surgery. Consultees acknowledged that there is no adequate scoring system to predict the outcome of patients undergoing EVAR, however there were concerns that the Assessment Group’s ‘fitness’ scale was unreliable and would require further definition to allow it to be put into practice. Does the
Committee consider the Assessment Group’s definitions of ‘fitness’ for surgery to be appropriate?

Given the lack of published clinical data on EVAR for ruptured aneurysms, highlighted by the Assessment Group and consultees, does the Committee consider it appropriate to issue guidance on the treatment of ruptured aneurysms?

The current list price per patient of the EVAR device quoted by Medtronic (Talent), Gore (Excluder) and Lombard (Aorfix) [...]. The Assessment Group’s base-case economic model assumes that the average list price in 2007 for EVAR across all manufacturers and patients [...]. Do the Committee consider these stents as a class even though there are differences in prices?

EVAR 2 is the only RCT to have addressed the comparison of EVAR and continued non-surgical management of patients considered unfit or unsuitable for open repair. Although the Assessment Group considered it to be a high-quality RCT in terms of design and methodology, the Group stated that there were problems with its execution that complicated the analysis and interpretation of the trial. Does the Committee consider the results from this trial to be applicable to current UK clinical practice?

The model comparing surgery with watchful waiting did not use treatment effects from RCTs. Instead, the Assessment Group estimated the natural history of patients with untreated aneurysm using rupture rates and growth rates obtained from a review of the literature, and compared these with outcomes estimated by the model of EVAR and open repair for patients with
the same baseline characteristics. Given the uncertainties highlighted by the Assessment Group in the data for rupture rates and growth rates, and the potential for bias in this non-randomised comparison, how accurate does the Committee consider the rates to be?

The RCT data on EVAR were predominantly collected from men. Although the Assessment Group reported that there was no evidence that either baseline risks or treatment effects were influenced by gender, the Group stated that it was feasible that untreated rupture rates may differ between men and women, and this may influence the cost effectiveness of the management options. Are the cost-effectiveness estimates for EVAR versus open repair and surgery versus watchful waiting applicable to women?

The economic models were based on data from trials and registries in which patients were treated predominantly by clinicians with high levels of clinical expertise in units with significant numbers of patients treated each year. Would carrying out EVAR in settings with developing expertise and lower patient numbers affect the guidance on endovascular stent–graft devices?

NICE has issued guidance on stent–graft placement in abdominal aortic aneurysm (NICE interventional procedure guidance 163). The guidance states that the current evidence on the efficacy and short-term safety of stent–graft placement in abdominal aortic aneurysm appears adequate to support the use of the procedure provided that the normal arrangements are in place for consent, audit and clinical governance. The guidance also states that patient selection is important, particularly for patients who would normally be considered unfit for surgery, and it recommends that all patients who have the procedure are entered onto one of the existing registries. (Available from: www.nice.org.uk/IPG163)

5 Ongoing research

ACE is a French RCT comparing EVAR and open repair in patients aged 50 years and older with an AAA measuring 5 cm or more in diameter (4 cm or
more if rapidly growing). The primary outcomes were 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 the Assessment Group of a possible first publication in January 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. The primary outcome was 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 trial is scheduled to end in August 2008.

OVER (open surgery versus endovascular repair) is a large USA RCT comparing EVAR and open repair in patients aged 50 years and older with an AAA measuring 5 cm or more in diameter (4.5 cm or more if expanding rapidly). The primary outcome was 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.

CAESAR (Comparison of surveillance versus aortic endografting for small aneurysm repair) is a RCT conducted in Italy to compare 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. The primary outcome was all-cause mortality. Secondary outcomes included 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 were considered for surgery if the aneurysm reached 5.5 cm in diameter, grew rapidly (> 1 cm/year) or became symptomatic. The planned sample size is 740 patients. In November 2007, the investigators informed the Assessment
Group that 325 patients had been enrolled and results were not expected until the end of 2008.

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by for Reviews and Dissemination/Centre for Health Economics, University of York.


B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Cook Medical (Cook UK)
- Le Maitre
- Lombard Medical Cardiovascular Devices Division
- Medtronic Limited
- W L Gore and Associates

II Professional/specialist, patient/carer and other groups:

- British Society of Endovascular Therapy (BSET)
- British Society of Interventional Radiologists (BSIR)