BRITISH SOCIETY OF INTERVENTIONAL RADIOLOGY

SUBMISSION TO THE NICE HTA ASSESSMENT COMMITTEE ON ENDOVASCULAR STENT-GRAFTS FOR ABDOMINAL AORTIC ANEURYSMS (EVAR)

1. INTRODUCTION

The NICE 'Final Scope' document sets out the background, objectives and methods to be used for the forthcoming Health Technology appraisal of EVAR. The document also defines the standard comparators, outcome measures, economic factors and other criteria by which the EVAR technique will be assessed. The appraisal follows on the heels of recent guidance issued by NICE in March 2006 (IPG 163) [1] and a systematic review published on the NICE website in November 2005 [2].

The strict remit of the current HTA process is to consider the clinical effectiveness and cost effectiveness of EVAR within the NHS setting.

2. CLINICAL EFFECTIVENESS OF EVAR

Over the last 15 years, many technological advances have been made both in terms of the devices used in endovascular repair and in the imaging assessment of abdominal aortic aneurysms (AAA). Data regarding clinical effectiveness is available from cohort studies, national and international registries and prospective randomised trials.

2.1 Registry and cohort study data

The introduction of EVAR has resulted in a large body of literature worldwide [3-37]. However, until recently, the published evidence has been limited to level 2 data. Two European registries, the EUROSTAR and UK RETA registries have contributed a large amount of data that have greatly improved our understanding of the outcomes of EVAR and have provided valuable information on the outcomes of individual devices [10,11]. The EUROSTAR registry was established in 1996, not long after the arrival of the first commercial devices. The early data regarding the first generation devices were removed from the database in 2003, so that the database now describes devices currently in use. Over 8000 patients were registered in the EUROSTAR database, which has recently been closed to new registrations.

2.1.1 Early mortality

Most of the published evidence indicates a lower mortality for EVAR compared with open repair (OR). A recent analysis based on Eurostar showed a 30-day mortality for all patients of 2.4% [10]. This low mortality rate is supported by data from several cohort series involving different types of endograft. Moore et al reported a 1.7% 30-day mortality rate in 573 patients treated with the Ancure endograft (Guidant, Santa Clara, CA) compared with 3% mortality in 101 patients who underwent open surgery. Similarly, Matsumura et al reported 1% mortality in 334 patients treated with the Gore Excluder endograft (WL Gore, Flagstaff, AZ) and Criado et al reported 1% mortality in 240 patients treated with the Talent device (Medtronic, Minneapolis,

MN) [12-14]. In a non-randomised comparison with surgery, Greenberg et al reported 3.5% mortality in 200 patients treated with the Zenith endograft (W Cook, Bloomington, IND) compared with 3.8% in the surgical group [15].

2.1.2 Early complications

Morbidity rates are also reduced after EVAR compared with surgery. In the US multicenter trial evaluating the Zenith device, the incidence of significant adverse events within 30 days was significantly lower in the EVAR group compared with the OR group (57% vs 80% P<0.001) [15]. From the EUROSTAR analysis, non-fatal systemic complications (mainly pulmonary and renal) occurred in 11% of patients [10]. The accumulated data from all sources indicate that the conversion rate from EVAR to OR is negligible, for example 0.9% reported in the Eurostar analysis. Early device related complications such as graft thrombosis and graft migration occurred in 2.6% and access site complications occurred in 6% of procedures. Deterioration in renal function due to coverage of the renal artery by the endograft, due to occlusion of the artery by thrombus, or to embolization of the distal renal artery branches occurs in around 2% of cases [10].

2.1.3 Endoleaks

The endoleak is the most frequent delayed complication of EVAR and can be defined as the passage of blood into the aneurysm sac outside the endograft. Endoleaks are classified into 5 types: Type 1, are endoleaks around the proximal or distal attachment sites. Type 2, are retrograde aortic side branch leaks into the sac from the inferior mesenteric or lumbar arteries. Type 3, are leaks from the junction between two components or through tears in the graft fabric. Type 4, are related to porosity of the graft material. Type 5, represent those cases with increasing sac size but with no demonstrable leak.

There is evidence from the EUROSTAR and RETA registries that type 1 and type 3 endoleaks are independent risk factors for post-procedural aneurysm rupture and late aneurysm-related death. There is no evidence that type 2 leaks are similarly problematic. The incidence of type 1, type 2 and type 3 leaks on completion angiography are 4%, 10% and 2% respectively [28].

2.1.4 Late AAA rupture

Despite repair of the AAA, whether by open repair or by EVAR, there may still be late rupture of aneurysms leading to death in a small proportion of patients. However, it is generally difficult separating death due to late rupture from death due to other causes in this group of patients with a high degree of cardio-respiratory and renal comorbidity. The EUROSTAR registry has thus far provided the best data regarding late mortality [29]. A recent sub-set analysis evaluated the effect of aneurysm size on the delayed outcomes and divided patients into small aneurysms (4-5.4cm), medium size (5.5-6.4cm) and large aneurysms (6.5cm or above). The freedom from aneurysm related death rates at 5 years were 97%, 95% and 87.9% for the small, medium and large groups respectively, indicating a correlation between the largest aneurysms and late mortality and similar to the correlation between increasing aneurysm size and death before treatment [30]. In the NICE systematic review, the overall mortality rate for aneurysm-related death was quoted as 3%, while the pooled all cause mortality for patients after EVAR was 15.1% from follow-up of 7 up to 48 months.

2.2 Canadian HTA Field Evaluation of EVAR [31]

The Canadian Ministry of Health conducted a review of international and Canadian Health Technology Assessments in 2003 and supported an Ontario-based field evaluation of EVAR technology. This non-randomised observational study assessed the results of elective AAA repair on 342 patients between August 2003 and April 2005. The 140 patients allocated EVAR were all considered high risk for open repair. Of the 195 patients allocated to open repair, only 27% were unsuitable for EVAR on anatomical grounds and all these were also judged to be high risk for open surgery. As in all previous studies the EVAR group showed significant reductions in hospital stay, procedure time, blood transfusion, severe complications and operative mortality, as compared to the OR group. No re-interventions were required in the EVAR group and there was a significant reduction of one year mortality, 7.1% vs 17.3% for the OR group.

2.3 Randomised trials of EVAR

There are three prospective randomized trials, which have compared the outcomes of EVAR with other treatment methods, which deserve description in detail: the EVAR 1 trial, the DREAM trial, and the EVAR 2 trial [16-18].

2.3.1 EVAR 1 and the DREAM trials

In the EVAR 1 trial, 1082 UK patients with AAA of 5.5cm or larger, were randomized to EVAR or OR. The 30 day mortality for the EVAR group was 1.7% v 4.7% in the group undergoing OR (P = 0.009). At follow up, 4 years after randomization, although the advantage for EVAR was maintained with respect to aneurysm related deaths (4% in the EVAR group v 7% in the open surgery group), all cause mortality in the region of 28% was found in both groups. Complications and reinterventions were higher in the EVAR group compared with OR. Complications occurred in 41% of EVAR patients vs 9% of OR (P< 0.001). Similarly, reinterventions occurred in 20% of EVAR patients v 9% of OR (P< 0.001). There was no significant difference in the quality of life between the two groups. The cost analysis of both treatment arms revealed higher costs for the EVAR group over 4 years (£13,257 v £9946 for OR).

In the DREAM trial, 345 patients in the Netherlands with AAAs of 5cm or greater were randomized to either EVAR or OR. Similar to the EVAR 1 trial, the 30 day mortality of EVR was lower by a factor of 3 compared with OR (1.2% for EVR v 4.6% in the open repair group). Because of the relatively small numbers randomised in this trial statistical significance was not achieved. Two years after randomization the early advantage seen after EVAR had been abolished and the cumulative survival of both groups was around 90%. As in the EVAR 1 trial, the aneurysm related deaths were lower at 2 years in the EVAR group (2.1% v 5.7% {p=0.05}) but the complication rates were more common in the EVAR group compared with OR. In the first 9 months after aneurysm repair, the reintervention rates for EVAR were about three times the rate for surgery. After nine months, the reintervention rates were roughly similar for the two arms of the trial. Complications occurred in 19.4% of patients in the EVAR group v 16.9% in the open surgery group and reinterventions had been performed in 14% of EVAR patients versus 5% of OR patients (p = 0.03).

2.3.2 Comment on RCTs comparing EVAR to OR

Both trials reported a three-fold reduction in 30-day mortality for EVAR compared with OR, which was maintained in terms of aneurysm related mortality at 4-year follow-up. There was no apparent survival advantage for EVAR in terms of all cause mortality in either trial at follow-up.

However, it must be emphasised that interventions for aortic aneurysm are primarily aimed at reducing the mortality and morbidity associated with aneurysm rupture. Regarding the use of "all cause mortality" as a primary endpoint; every patient with atheromatous aneurysm has, by definition, vascular disease and is at higher than normal risk of eventual cardiovascular death. Death by these means will clearly not be reduced by the performance either of an open or an endovascular aortic intervention, assuming survival to discharge following intervention. However both patients and clinicians have appreciated the obvious difference in operative mortality between the two techniques within the RCTs. Patients, in particular, appreciate the benefits of a "minimally invasive" procedure. Thus the chance of a nearly three-fold reduction in early mortality has produced a further surge in popularity of the minimally invasive option over the two years since the publication of the mid-term results of the EVAR trials. The early advantage of EVAR may be offset by the apparent lack of lives gained beyond two years. But note that the number of patients followed to four years in EVAR trial I was less than 25% of the total. More accurate assessment may become possible only after analysis of the longer-term results in 2010 and by the results of other US and European national trials.

Most of the events quoted as complications in the RCTs and the many non-randomised studies within the systematic review, did not require re-intervention and there was no additional mortality. The experience of most UK centres now involved in EVAR procedures is that the level of re-intervention has generally reduced as devices have evolved and more centres become accustomed to the low risk associated with most of the sub-clinical 'complications' seen on follow up CT. The incidence of delayed complications has appeared mainly to be related to the use of first generation devices and to deployment in the presence of adverse anatomical features. Certainly there is single centre data showing significant reductions in re-intervention rates (< 10%) in parallel with the use of more technically refined (fourth generation) devices in selected cases [32,33].

The reduction in the aneurysm related mortality after EVAR is a real benefit and most patients given the choice between surgery and EVAR would likely choose endovascular repair on the basis of the reduced mortality alone. Both trials had methodological flaws but perhaps the greatest was that a mature procedure i.e. open aneurysm surgery, perfected over a 50-year period, was compared with a new, still evolving technique using a variety of devices that were still undergoing modification. The EVAR results thus represent the cumulative experience with a heterogeneous group of old and new stent-grafts.

2.3.3 Randomised trial of EVAR vs conservative management, the EVAR 2 trial:

In the EVAR 2 trial, patients with AAAs of 5.5cm or larger, who were unfit for OR were randomized to endovascular repair plus best medical therapy or to best medical therapy (BMT) alone. Three hundred and thirty eight patients were randomized to either EVAR (n=166) or to conservative management (n=172). The 30 day mortality for the patients in the EVAR group was 9%. The overall mortality at four years was 64%. There was no significant difference in all-cause mortality between the two groups and neither was there a difference for aneurysm-related mortality between the two groups. Similar to the EVAR 1 trial, the mean hospital costs per patient were substantially increased over the time of follow-up in the EVAR group - £13, 632 v £4,983 in the no intervention group. There was no difference in the quality of life scores whether patients were treated or managed conservatively. It was emphasised that EVAR had a considerable 30 day operative mortality in patients already unfit for OR. Moreover EVAR did not improve patients survival compared with BMT and was associated with a need for continued surveillance and re-interventions at a substantially increased cost. The conclusion was that attention should be directed at improving the fitness of these patients rather than subjecting them to early endovascular therapy.

2.3.4 Comment on RCT comparing EVAR to BMT (EVAR 2)

There are several contentious issues concerning the data interpretation. The determination of whether patients were fit for surgery or not was left to local clinicians to decide; patients considered unfit at one hospital might have been considered to be fit for surgery in another hospital. The fact that EVAR Trial 2 patients who underwent EVAR had a 30-day mortality of 9% has been used to support the view that patients unfit for surgery should not be offered EVAR. However, the mortality figure of 9% is of the same order as the mortality figures for open repair in *fit* high-risk patients. Therefore, the relatively low 30-day mortality rate in this selected high- risk group might equally be interpreted as supporting EVAR in unfit patients.

In the BMT group, 47 (27%) of the 172 patients originally randomized, crossed over to the interventional group (35 undergoing EVAR and 12 OR) for various reasons including aneurysm tenderness and patient preference. The 30-day mortality in the patients who crossed over and underwent EVAR was only 2.1%. The large proportion of patients who crossed over has made analysis of the outcomes of the conservative group problematic for two main reasons: First, the data on the outcomes of patients who are managed conservatively compared with intervention has been rendered imperfect making it difficult to compare conservative management with active intervention i.e. EVAR. Second, complete data on rupture rates and cause of death in patients managed conservatively have not been provided by the trial.

In addition, there was a significant increase in the length of time between randomization and treatment in the EVAR group. The protocol indicated that patients allocated to EVAR would undergo the procedure within 30 days. In the event, the median time from randomization to implantation was 57 days, indicating that a large proportion of patients in the EVAR arm exceeded the 30-day stipulated time. Thirty percent of the deaths in the EVAR group occurred before the procedure could be performed (14 patients, 6 from aneurysm rupture).

2.4 Conclusions regarding clinical effectiveness

- EVAR is clearly an extremely safe and effective procedure in the short and medium term.
- Specific categories of patients with AAA can be identified in whom a durable EVAR result, with minimal need for re-intervention, is expected.
- The results for EVAR on patients thought to be at high risk for open repair are encouraging, despite the data provided by the one RCT to address this subject.
- Protocols in evolution should include a range of anatomical parameters, patient fitness and co-morbidities.

3. COST-EFFECTIVENESS OF EVAR

3.1 Costs related to the primary procedure

The intra-operative effects of EVAR on the patient are well known to be significantly less than for OR, primarily because of the absence of aortic clamping, a consistent reduction in blood loss and the absence of a trans-abdominal wound. Thus the great majority of patients are discharged from hospital a few days after the procedure. During the early days of the technique, many patients spent the first post-operative day in intensive care or the high dependency unit. However, with increasing experience it soon became clear that this was unnecessary, unless there was severe comorbidity. Now the post-procedural care for the majority of patients involves a short stay in the recovery area in theatre, early ambulation from the vascular surgical ward and discharge 2 -5 days after EVAR. This undoubtedly leads to large potential savings of in-patient costs.

3.2 Device costs

The main cost of the EVAR procedure is still that of the endovascular device and the ancillary kit with which it is inserted. Commercial custom-built endovascular stent-grafts have been expensive items since their first use in the NHS more than 13 years ago. The average cost of the current devices listed in the Final Scope Document is of the order of £5,000, but this price has not changed since commercially produced endografts first became available for purchase in 1994. This is despite significant improvements in the quality of individual devices and in the range of available sizes. The likely primary cost of an average case with ideal anatomical features will currently exceed the cost of an open repair by some £1,500 and the difference increases to around £3,000 over the first 4 years of follow up [16]. However, this current cost differential, based on standard devices, may reduce both as a result of increasing automation of the manufacturing process and with evolution of the introduction systems. The mean size of the hole in the access artery has been reduced over the last decade, now requiring an opening of 18-22F (or 6-7mm) in diameter, even with the larger sizes of endograft. There are percutaneous closure devices now available that can safely close such wounds and thus it may well be that as techniques evolve further there will be a reduced need for surgical cut-down and general or regional anaesthesia.

3.3 Costs related to EVAR follow-up

The other major factor influencing cost is the requirement for follow-up imaging of stent-grafts. The detailed imaging assessment of every device inserted is currently mandatory within the randomised trials and the national registry. While it has been clear for some time that plain radiographs are the single most useful examination with which to permanently record the integrity of the stent-graft framework, it is also becoming evident that in many cases Doppler ultrasound examination may be as useful as a post-contrast CT scan [34-36]. Ultrasound can detect late aneurysm expansion, migration and concurrent endoleaks, which are the arbiters of re-intervention being considered. Although published data on use of ultrasound follow-up is small and retrospective, many centres have adopted this method in order to reduce exposure to ionising radiation and iodinated contrast media, as well as for cost savings. .

3.4 Resource data from the Canadian HTA study

As in the EVAR trials, the very detailed Ontario field evaluation showed a significantly higher initial mean cost of hospitalisation for EVAR ($28,139) than for OR ($15,494) [31]. But it was also confirmed that the costs incurred by treating high-risk patients by OR ($31,181) were greater than those for EVAR. Despite the additional imaging costs of EVAR in the first year of follow-up, the difference in the total average one-year health costs between the two high-risk groups (all the EVAR cases and 27% of the OR group) was slightly in favour of EVAR. In the high-risk patients OR was more expensive and gave less QALY benefit. If extrapolated to 10 years the cost per QALY of EVAR compared to OR was estimated to be $18,616.

3.5 Conclusions regarding cost effectiveness

- There is still a large cost associated with the primary procedure but this is likely to be reduced over time.
- As further reductions in re-intervention rates and less expensive forms of imaging follow up predominate, follow-up costs are likely to reduce.
- For patients at increased risk of surgical mortality and morbidity it seems, as suggested by the Canadian HTA, that EVAR is more cost-effective than open repair.
- Cost-effectiveness calculations based on the published results of the EVAR Trials 1 & 2 probably do not reflect current clinical practice in most centres.
- Because certain subgroups of patients do not need such intensive surveillance, there will be an even more marked mismatch as the surveillance protocols evolve to reflect the improved results of EVAR.

4. SUMMARY

Endovascular repair of abdominal aortic aneurysms is now the standard method of intervention for nearly 75% of elective cases within Europe and North America, despite the apparent high cost of the procedure. The consistent message emerging from the vascular units engaged in aneurysm repair is that the patients derive great benefit from this minimally invasive experience. There is currently a cost issue but this is likely to be reduced over time with relative reduction in device costs, with further reductions in re-intervention rates and as less expensive forms of imaging follow up predominate.

Patients who are fit for both open and EVAR procedures almost invariably opt for EVAR once they appreciate the faster discharge rates and the three-fold higher chance of attending the first post-operative outpatient review. Short-term survival is important to all of us.

Further clarification of indications, standardisation of procedures and introduction of agreed protocols for follow-up are required in order to ensure continued improvements in long-term clinical and cost effectiveness. It may be that the centralisation of vascular services in the UK will be required to bring about the necessary changes.

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