Incorporating non-randomised evidence in systematic reviews: a case study

Duncan Chambers, Debra Fayter, Fiona Paton, Kath Wright, Nerys Woolacott
Centre for Reviews and Dissemination, University of York (dc510@york.ac.uk)

Background

Endovascular (EVAR) is a less-invasive alternative to open surgery for repair of abdominal aortic aneurysms (AAAs), which involves the use of an endovascular stent-graft inserted through a small incision in the femoral artery in the groin. Compared with open repair, EVAR is potentially less traumatic for the patient and requires less time in hospital.

What are the problems associated with restricting systematic reviews to RCTs?

Systematic reviews limited to RCTs may lack clinical credibility if:

- there is a large volume of evidence from other study designs available
- the procedure has been widely adopted

As surgical procedures are frequently supported in clinical practice by non-randomised and observational studies, it might therefore be reasonable to expect a systematic review of a surgical procedure to go beyond the RCT evidence.

Methods

A systematic review was performed to investigate the clinical and cost effectiveness of EVAR compared with open repair.[1]

Recent systematic reviews were identified and searched, with additional searches conducted to identify recent RCTs (2005–7) and publications relating to named registries. Nine bibliographic databases were searched with no language restrictions. Regular current awareness searches were carried out up to February 2008.

Included studies were of:

- patients with asymptomatic or symptomatic, ruptured or unruptured infrarenal AAAs
- EVAR versus conventional open repair in patients for whom this was a treatment option, and non-surgical management in patients for whom open repair was not considered a treatment option

Table 1: Comparison of RCT (EVAR 1), registry (EUROSTAR) and matched cohort (Medicare) results

	EVAR 1 (EVAR arm)[3]	EUROSTAR[8]	Medicare[11]
Patients	1,082 (543 randomised to EVAR)	8,345 (treated with newer EVAR devices)	45,660 (matched cohorts from USA)
Last date treated	December 2003	June 2006	2004
Follow-up	Maximum 4-5 years (median 2.9 years)	Maximum 8 years	Maximum 5 years
30-day mortality	9/531 (1.7%)	190/8,345 (2.3%)	4.8%
Cumulative mortality	26% (4-year point estimate)	23% (cumulative mortality at 4 years)	Not reported
Duration of mortality benefit from EVAR	EVAR was associated with a reduction in aneurysm related mortality (but not all-cause mortality) over the medium term (up to 4 years after randomisation)	Not relevant (EVAR only)	The early survival benefit from EVAR persisted for about 3 years in the whole population, after which time the survival curves were similar
Other findings	The lack of long-term mortality benefit with EVAR was compounded by an increased rate of complications and re-interventions and these were not offset by any increase in HRQOL; possibly due to the increased level of monitoring required with EVAR due to the risk of complications	Late aneurysm mortality after EVAR in patients with large aneurysm (6.5cm or more) was considerably and significantly greater than patients with small aneurysm	Survival benefit of EVAR may be greater in the older than the younger age groups The benefit lasted less than 18 months in patients aged 67–74 years but for at least 4 years in those aged 85 years and older

Results

Six RCTs,[2-7] reports from three pre-specified registries,[8-10] and a matched control cohort study[11] were included. Of these, the most useful for comparing EVAR with open repair were the EVAR 1 RCT and the Medicare matched cohort study. EUROSTAR was the most useful of the pre-specified registries (Table 1).

Discussion

A well designed RCT like EVAR 1 has high internal validity (low risk of bias) but involves a relatively small and selected group of patients. The time lag involved in running trials means that the outcomes in the trial may not represent the best results achieved today as current devices and surgical techniques may be better than those used in the trial. Registries can be more up to date and follow larger samples but the absence of a control group means they are not suitable for assessing treatment effect and there are potential biases in selecting patients and reporting outcomes.

The matched cohort study combined some of the advantages of the other two types of evidence but it had its own limitations: vulnerability to unrecognised confounders (because non-randomised) and limitations on information available (because dependent on data collected for other purposes).

Conclusions

- Specific challenges in systematic reviews of surgical interventions demand adaptations of standard methods
- There is a need for a rigorous approach, but flexibility is necessary to ensure that conclusions are timely, useful and generalisable
- Reviews that incorporate all the evidence seen as relevant by clinicians may have greater credibility than those that do not
- The balance between the strengths and limitations of different types of evidence will depend on the review topic and methods used for data synthesis

References

1. Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, et al. Endovascular stents for abdominal aortic aneurysms: a systematic reveiw and economic model. *Health Technology Assessment* (Forthcoming).
2. Blankensteijn JD, de Jong SEC, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *New England Journal of Medicine*, 2005, 352(23), 2398-405.
3. EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet*, 2005, 365(9478), 2179-86.
4. Cuypers PMW, Gardien M, Buth J, et al. Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair. *British Journal of Surgery*, 2001, 88(8), 1059-65.
5. Hinchliffe RJ, Bruijstens L, MacSweeney ST, Braithwaite BD. A randomised trial of endovascular and open surgery for ruptured abdominal aortic aneurysm - results of a pilot study and lessons learned for future studies. *European Journal of Vascular And Endovascular Surgery*, 2006, 32(5), 506-13.
6. Soulez G, Thérasse E, Monfared AA, et al. Pain and quality of life assessment after endovascular versus open repair of abdominal aortic aneurysms in patients at low risk. *Journal of Vascular And Interventional Radiology*, 2005, 16(8), 1093-100.
7. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet*, 2005, 365(9478), 2187-92.
8. Progress report: endografts in current use only (Anaconda, Ancure, AneuRx, Endologix, Excluder, Fotron, Lifepath, Talent & Zenith). Eindhoven, the Netherlands: EUROSTAR Data Registry Centre; 2006, 31.
9. Thomas SM, Beard JD, Ireland M, Ayers S. Results from the prospective Registry of Endovascular Treatment of Abdominal Aortic Aneurysms (RETA): mid term results to five years. *European Journal of Vascular and Endovascular Surgery*, 2005, 29(6), 563-70.
10. Ashley S, Ridler B, Baker S, et al. Fourth National Vascular Database report 2004. Henley-on-Thames: Dendrite Clinical Systems; 2005, 136.
11. Schermerhorn M, O'Malley A, Jhaveri A, et al. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *New England Journal of Medicine*, 2008, 358, 464-74.

This poster is based on a research commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence. The views expressed in this poster are those of the authors and not necessarily those of NICE, the NHS, NIHR or the Department of Health.