Non-comparable patients in non-randomised comparative studies – misleading study design?

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BACKGROUND

- Ideally effectiveness data should come from randomised controlled trials (RCTs), but in the absence of RCTs, non-randomised comparative studies can be a useful source.
- Given the risk of selection bias, it seems reasonable to expect non-randomised studies to make some attempt at comparability i.e. the populations allocated to each treatment are similar. One would not expect treatments to have been explicitly selected based on patient prognosis.
- Endovascular repair and open surgical repair (OSR) are two treatment options for large abdominal aortic aneurysms. However, endovascular repair of juxta-renal or thoraco-abdominal aneurysms require specially manufactured stent-grafts with openings to allow blood to reach branches of the aorta: these are called fenestrated endovascular aortic repair (fEVAR) and branched endovascular aortic repair (bEVAR).
- We were commissioned* to conduct a systematic review of the effectiveness of fEVAR and bEVAR versus no surgery or OSR for juxta-renal and thoraco-abdominal aortic aneurysms.

OBJECTIVE

To describe the extent to which non-randomised comparative studies are subject to explicit selection on the basis of prognosis, using the example of a systematic review of fEVAR or bEVAR aneurysm.

METHODS

- A systematic review was conducted following CRD's guidance and the Cochrane handbook.
- Bibliographic databases such as Medline (OvidSP), Embase and CENTRAL were searched on 1st October 2013 without date limits.
- Studies were included based on an intervention of either fEVAR or bEVAR and a comparator of either OSR or no surgery.
- To qualify as 'comparative', studies had to demonstrate that there had been some attempt to make the populations receiving each of the treatments comparable. Studies in which allocation of interventions was based on patient characteristics were excluded.

RESULTS

- The literature searches retrieved 3,268 records which were screened at title and abstract stage.
- Twenty four studies were ordered for full text screening but none satisfied our inclusion criteria.
- Of these, five studies purported to compare fEVAR or bEVAR with OSR. However, all five were found to have selected treatment on the basis of prognosis. Therefore, these studies were considered to have selection bias and thus they were not comparative.
- Moreover, the studies had included patients in the fEVAR/bEVAR group who were actually ineligible for the comparator, OSR due to, for example old age (Table 1).
- The quote from Greenberg et al 2008[4] clearly demonstrates that selecting patients based on their clinical characteristics can cause a significant baseline imbalance between groups making them non-comparable.

Study Name	Quotes from the study
Vallabhaneni 2011[1]	"All endovascular aortic repair (EVAR) patients were not considered suitable for [OSR]"
Chisci 2009[2]	"The policy for implanting a fenestrated stent-graft was based on high risk for open surgery (old age, severe comorbidities, previous aortic reconstruction, or need for suprarenal clamping) and whenever the quality of the neck was too poor to provide a seal with a standard stent-graft that would be durable for the expected lifespan of the patient"
Canavati 2013[3]	"When f-EVAR is technically feasible, the physicians usually recommended younger and generally fit patients to have an open repair, as was the case for patients with very large aneurysms. Older patients and those with multiple comorbidities were recommended to have f-EVAR. Exceptions occurred due to patient preference and availability of funding. Patients selected by the clinicians based on their characteristics"
Greenberg 2008[4]	"Patients treated with EVAR were on average 8.6 years older (71.3±12 versus 62.7±13 years, P<0.001) than those treated with an SR, but no gender differences between repair types were found. Our bias has been to treat patients who are younger or have fewer comorbid factors with conventional surgery, a tendency that is readily reflected in the preoperative patient characteristics"
Donas 2012[5]	"Patients who were deemed physiologically fit and young (68 years) underwent conventional OR"

Table 1: Quotes from the five studies suggesting that they were non-comparative

CONCLUSION

- In fEVAR/bEVAR not one non-randomised study attempted comparability of patients. Indeed, they explicitly used the same method of selection i.e. according to prognosis. Some patients treated with fEVAR/bEVAR were not even eligible for OSR. This review is only one example but it seems unlikely that it is unique.
- Indeed, it is appropriate to compare fEVAR/bEVAR and OSR, but only in patients eligible for both treatments i.e. the younger, fitter population.
- Researchers and publishers should take particular care when describing or assessing non-randomised studies, which appear to have a comparative study design.

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