
Editorial

The importance of cumulative meta-analyses and implications for B-type natriuretic peptide research in non-cardiac surgery

It is a travesty to waste resources. In medicine, a persistence of futile research depletes the already limited resources available for research. Furthermore, ignoring clinical trial evidence of benefit is unethical and negatively impacts on public health.

Cumulative meta-analyses have contributed substantially to limiting waste in research. A cumulative meta-analysis provides a "running total" of the overall effect for an intervention through sequentially adding each published trial (or study) to an ongoing meta-analysis. This technique led to an appreciation of the significant delay from the time that clinical trials show unequivocal benefit of a treatment, to subsequent awareness of this benefit by practising clinicians. The turning point was a cumulative meta-analysis of the use of oral beta blockers for the secondary prevention of mortality following myocardial infarction (MI). As early as 1977, there was sufficient evidence of a survival benefit, with only 3 522 patients randomised.^{1,2} However, clinical trials continued for a further 10 years, and 17 000 more patients were randomised prior to an appreciation of the evidence supporting this indication for beta blockers.^{1,2} This situation has major negative public health implications. Firstly, patients are randomised into trials where the benefit should be known. Hence, the placebo group is essentially randomised to harm as they are denied efficacious therapy. Secondly, the public and population are denied the benefit of the therapy, despite evidence to support its use. In this example, patients with an MI over a period of 10 years were denied therapy associated with a relative risk reduction in subsequent mortality of approximately 20%.^{1,2} It is now standard practice to present a systematic review when applying for a grant for an interventional clinical trial because of these startling facts. This prevents wasteful clinical trials from being conducted in the presence of sufficient existing evidence of efficacy.

However, it is not standard practice to present a meta-analysis prior to conducting an observational study. The work by Ryan et al, presented in this edition of *SAJAA*,³ supports the important public health contribution that a cumulative meta-analysis may play in observational studies. They may identify a time when it is appropriate to shift the research focus. The point estimate

associated with an adverse cardiovascular outcome in non-cardiac surgery for elevated B-type natriuretic peptides (BNPs) has been fairly consistent since 2011.³ Therefore, it is wasteful to persist in this line of observational research. Rather, a shift is needed in preoperative BNP research from merely documenting its prognostic importance addressing its integration into clinical practice.

Preoperative BNP research has fulfilled the first four of the six progressive stages of evaluation necessary before BNP can be adopted in preoperative cardiac evaluation guidelines and algorithms.⁴ Proof of concept, prospective validation, incremental value and clinical utility have been demonstrated.⁵

It is now time to demonstrate that the modification of perioperative management, based on preoperative BNP, improves perioperative outcomes (stage 5). If this can be achieved, and only if it is cost-effective (stage 6), it is likely that preoperative BNPs will be written into perioperative clinical guidelines.⁴ The most important candidate study to achieve this objective would be a prospective, multi-centred, randomised trial of preoperative BNP-guided medical optimisation, to improve outcomes following non-cardiac surgery.

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