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A new method of applying randomised control study data to the individual patient: A novel quantitative patient-centred approach to interpreting composite end points

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ABSTRACT

Background: Modern randomised controlled trials typically use composite endpoints. This is only valid if each endpoint is equally important to patients but few trials document patient preference and seek the relative importance of components of combined endpoints. If patients weigh endpoints differentially, our interpretation of trial data needs to be refined.

Methods and results: We derive a quantitative, structured tool to determine the relative importance of each endpoint to patients. We then apply this tool to data comparing angioplasty with drug-eluting stents to bypass surgery. The survey was administered to patients undergoing cardiac catheterisation. A meta-analysis comparing coronary artery bypass grafting (CABG) to percutaneous coronary interventuin (PCI) was then performed using (a) standard MACE and (b) patient-centred MACE.

Patients considered stroke worse than death (stroke 102.3 ± 19.6%, $p < 0.01$), and MI and repeat revascularisation less severe than death (61.9 ± 26.8% and 41.9 ± 25.4% respectively $p < 0.01$ for both). 7 RCTs (5251 patients) were eligible. Meta-analysis demonstrated that standard MACE occurs more frequently with PCI than surgery (OR 1.44; 95% CI 1.10 to 1.87; $p = 0.007$). Re-analysis using patient-centred MACE found no significant difference between PCI and CABG (OR 1.22, 95% CI 0.97 to 1.53; $p = 0.10$).

Conclusions: Patients do not consider the constituent endpoints of MACE equal. We derive a novel patient-centred metric that recognises and quantifies the differences attributed to each endpoint. When patient preference data are applied to contemporary trial results, there is no significant difference between PCI and CABG. Responses from individual patients in clinic could be used to give individual patients a recommendation that is truly personalised.

1. Introduction

Randomised clinical trials (RCTs) in many medical domains often use combined clinical end points when comparing competing therapies [1]. Major Adverse Cardiovascular Events (MACE) is a common example [2]; it combines the individual end points of death, myocardial infarction, stroke and unplanned revascularisation.

The use of composite end points such as MACE has been justified as an attempt to capture and express the overall treatment effect of a new therapy, rather than "simply" its effect on mortality [3]. In more practical terms, grouping events together in this way increases the observed event rate and therefore reduces the required sample size and cost of the trial [4].

However, the use of MACE to compare trial arms makes several assumptions [5]. First it assumes that all its components are of equal clinical severity. For example, a small peri-procedural myocardial infarct is given equal importance to death and stroke; for major disabling myocardial infarctions some may consider this appropriate, while this may be challenged for asymptomatic enzyme rises. Second, it assumes that clinicians' and patients' perception of each component is similar. For example, it assumes that the perception of repeat revascularisation is identical between clinicians and patients; any difference would mean that our interpretation of the relative merits of one therapy as clinicians may be at odds to those of patients in whom that therapy is being applied. Third, it assumes that the perception of each component is

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identical for every patient. For example, that the importance of a stroke to a 45-year-old male is the same as that of an 85-year-old female.

If these assumptions are not true then how we interpret the results of clinical trials comparing competing therapies in this manner should be revisited. A potential solution would be to appropriately weigh the severity of each component of MACE. This would provide a more refined interpretation of the trial data — that can be personalised to the individual patient being seen in clinic. This has been attempted previously, either with arbitrarily assigned weights [6], or through weighting derived purely by evaluation by an expert panel of clinicians [7].

In the first part of this study we perform a meta-analysis of randomised trials comparing revascularisation with drug eluting stents versus coronary artery bypass grafting (CABG) using conventional MACE. We then sought to determine the relative importance patients and clinicians place on each of the individual components of MACE. Finally we re-analyse the RCTs comparing percutaneous coronary intervention (PCI) to CABG using this data.

2. Methods

2.1. Search strategy

We re-analysed the 7 RCTs included in a recent meta-analysis [8] which compared coronary artery bypass grafting to PCI with drug eluting stents. In addition, we performed a systematic search of Medline, EMBASE and the Cochrane library to identify further articles published through March 2015, using the following keywords: "coronary angioplasty", "coronary artery bypass grafting", "drug eluting stents", "coronary artery bypass surgery", and "randomised control trial". Bibliographies were hand-searched for relevant studies, reviews and meta-analyses to identify further eligible studies. Abstracts were reviewed for suitability and articles accordingly retrieved. The search and meta-analysis were performed in accordance with published guidance [9].

2.2. Inclusion and exclusion criteria

We considered studies of multi-vessel coronary artery disease, coronary artery disease and diabetes, left main coronary artery stenosis and proximal left anterior descending artery stenosis. We only considered randomised control trials comparing CABG to PCI with drug-eluting stents. We excluded animal studies, studies not in the English language, case reports, conference abstracts, meta-analyses and reviews from the final selection. We identified 7 suitable studies including 5251 patients [10–16].

2.3. Analysis

Outcome data regarding death, myocardial infarction, stroke and revascularisation were extracted from the included studies. These were then grouped together to provide outcomes for MACE, and a meta-analysis for this outcome was performed. Review Manager Version 5.2.1 software package [17] was used to perform this analysis. An inverse variance weighted random effects model was used and the z-score and confidence intervals calculated using standard methods. Heterogeneity was assessed using the I^2 statistic [18]. Mean values are expressed as mean ± SD unless otherwise stated. An unpaired t-test was used to compare between group data.

2.4. Determining the relative importance of each component of MACE

113 patients (from 7 hospitals in London: Hammersmith Hospital, St Mary's Hospital, Charing Cross Hospital, Watford Hospital, Luton and Dunstable Hospital, Ealing Hospital and West Middlesex Hospital) undergoing cardiac catheterisation (including patients with previous bypass surgery) in our institution were surveyed using a structured, quantitative assessment to determine the relative importance patients confer to the components of MACE.

A visual analogue scale was used (Fig. 1). The relative importance of each component of MACE was determined by measuring the distance from the bottom of the visual analogue scale to the intercept of the cross, marked by the patient along the vertical axis of the scale. This dimension was then indexed to the value the patient attributed to death — providing a relative measure of the importance of this component to death. Internal validation was performed using a scale from 1 to 10, to ensure consistency amongst responses. Patients were asked to rank the following components of MACE: death, myocardial infarction, stroke (permanent and non-permanent) and repeat revascularisation. 50 Cardiologists attending the British Cardiac Society 2014 congress were also asked to complete the same survey. The study underwent ethical review and was approved (reference: 11/NW/0777).

2.5. Application to RCTs

The relative importance of each component of MACE was then indexed to death to derive a weighting factor for that component.

$$\text{Weight}_{(\text{Indiv component of MACE})} = \text{importance attributed to outcome} \,/\, \text{importance attributed to death}.$$

The weighted event rate for each component was then calculated:

$$\text{Component Weighted event rate} = \text{Weight}_{(\text{Indiv component of MACE})} \times (\text{Number of component events}).$$

The overall weighted MACE was then calculated:

$$\text{MACE rate}_{(\text{weighted})} = \sum \text{Component Weighted events}.$$

This analysis was performed to determine the following:

1. Patient derived weights
2. Clinician derived weights.

The relative importance of each component of MACE according to each of the above weighting systems was then applied to the randomised controlled trials of PCI vs CABG.

3. Results

7 studies comparing PCI with drug eluting stents and CABG (5251 patients) were included in the meta-analysis (Fig. 2).

3.1. Characteristics and risk of bias of included studies

Characteristics of included studies are shown in Online Appendix Table 1; risk of bias using the Cochrane criteria [19] is shown in Online Appendix Table 2.

3.2. PCI vs CABG using conventional MACE

The unweighted meta-analysis of the 7 studies demonstrated higher MACE with PCI when compared to CABG (OR 1.44; 95% CI 1.10 to 1.87; $p = 0.007$, Fig. 3).

3.3. Patient opinion of clinical end points when compared to death

113 patients (73.9% male, age 58.19 ± 15.9 years) were surveyed (Table 1).

Patients did not consider all clinical end points equal (Table 2). Stroke was considered worse than death (stroke 102.3 ± 19.6%, $p < 0.01$). All other end point were considered less significant than death. Myocardial infarction was deemed 35% less significant as death