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REVIEWS

Criteria for use of composite end points for competing risks—a systematic survey of the literature with recommendations

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Abstract

Background: Composite end points are frequently used in reports of clinical trials. One rationale for the use of composite end points is to account for competing risks. In the presence of competing risks, the event rate of a specific event depends on the rates of other competing events. One proposed solution is to include all important competing events in one composite end point. Clinical trialists require guidance regarding when this approach is appropriate.

Objectives: To identify publications describing criteria for use of composite end points for competing risk and to offer guidance regarding when a composite end point is appropriate on the basis of competing risks.

Methods, Data Sources, Study Selection and Data Extraction: We searched MEDLINE, CINAHL, EMBASE, The Cochrane's Central & Systematic Review databases including the Health Technology Assessment database, and the Cochrane's Methodology register from inception to April 2015, and candidate textbooks, to identify all articles providing guidance on this issue. Eligible publications explicitly addressed the issue of a composite outcome to address competing risks. Two reviewers independently screened the titles and abstracts for full-text review; independently reviewed full-text publications; and abstracted specific criteria authors offered for use of composite end points to address competing risks.

Results: Of 63,645 titles and abstracts, 166 proved potentially relevant of which 43 publications were included in the final review. Most publications note competing risks as a reason for using composite end points without further elaboration. None of the articles or textbook chapters provide specific criteria for use of composite end points for competing risk. Some advocate using composite end points to avoid bias due to competing risks and others suggest that composite end points seldom or never be used for this purpose. We recommend using composite end points for competing risks only if the competing risk is plausible and if it occurs with sufficiently high frequency to influence the interpretation of the effect of intervention on the end point of interest. These criteria will seldom be met. Review of heart failure trials published in the *New England Journal of Medicine* revealed that many of them use the composite end point of death or hospitalization; none of the trials, however, satisfied our criteria.

Conclusion: The existing literature fails to provide clear guidance regarding use of composite end point for competing risks. We recommend using composite end points for competing risks only if the competing risk is plausible and if it occurs sufficiently often. Published by Elsevier Inc.

Keywords: Competing risks; Composite end points; Combined end points

1. Introduction and Background

Clinical trialists often specify composite end points as their primary outcome. A composite end point combines all patients who experience at least one event included in the composite in a single endpoint. For example, a commonly used composite end point in the field of cardiology is a composite of death, myocardial infarction (MI), or stroke; this would include all patients who experienced any of these events. Reasons for the use of composite end points include increasing statistical power by increasing the number of events, simplifying the interpretation for patients (it may be easier for patients to consider 1 risk estimate rather than several in considering risks and benefits of interventions for decision making), and accounting for competing risks.

Competing risks is a concern in randomized trials because of the possibility that an intervention may result in an apparent decrease in a less serious end point

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What is new?

Key findings

- A systematic survey of the literature revealed limited guidance on when to use composite end points in the presence of competing risks.
- We provide guidance on this topic and propose that composite outcomes be used to overcome the problem of competing risks only when
- Competing risk is plausible (i.e., understanding of the biology suggests that the intervention might realistically increase more serious events, thus misleadingly reduce the less serious)
- The more serious outcome occurs frequently enough that, if the intervention truly increases its frequency—appreciably decreasing the possibility of the less serious outcome occurring—the result would be a misleading decrease in the less serious event.

(e.g., MI) as a result of the intervention increasing a more serious end point (e.g., death). In other words, there is a competing risk if the intervention results in the death of individuals, some of whom, had they lived, would have experienced an MI.

One suggestion for dealing with the problem of competing end points is to construct a composite outcome that accounts for all competing risks in one outcome measure (e.g., a composite of MI and death). There are, however, concerns with the use of composite outcomes including challenges in interpretation, in particular making the impact of the intervention appears more important than it really is. Consider, for instance, if an intervention in fact has no impact on death but does decrease the incidence of MI. Providing a single relative risk reduction for the composite may suggest to many that the intervention reduces both death and MI and does so to the same degree, resulting in an overestimation of the impact or importance of the intervention on death and a possible underestimation of the importance on MI. The greater the gradient in importance between components, the greater is the seriousness of such a misinterpretation. For example, the gradient between death and percutaneous coronary interventions is greater than the gradient between death and MI.

Recent publications have highlighted the frequency of the use of composite end points in published trials and have underscored concerns related to this practice [1–6]. Consistent findings of these studies has been that clinical trialists very frequently—particularly in cardiology—choose composites as their primary outcomes, that components often include a large gradient of importance, that the less important end points typically occur more frequently than the more important end points, and that relative effects often differ substantially between components (with relative effects typically larger for less important outcomes).

These results suggest two fundamental problems with the use of composite end points. The first is an issue of interpretation: are clinicians to assume that relative effects on the composites apply to each of the components, and the absolute impact on components should be calculated accordingly, or make no such assumption and look at the composite without making any inferences about distribution of effects across components? Second, when the more important components contribute few outcomes and/or the effect is less in these components, there is high risk of spurious inferences from trials with composite end points, with treatment effects appearing more important than they actually are. Thus, confident interpretation of composite end points requires relatively small gradients of importance to patients and similar relative risk reductions across components [6].

The difficulties in interpretation, and risk of misinterpretation, can arise either if the composite is chosen to increase power or to address competing risks. The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) randomized trial [7] highlights the problem in the latter context. The DREAM trial implemented strategies to minimize risk of bias and enrolled 5,269 participants with impaired glucose tolerance, assigned them to a hypoglycemic drug, rosiglitazone, or placebo, and documented the impact on a primary end point of a composite of incident diabetes or death from any cause. The Section 2 of the study justifies the composite using the competing endpoint criteria: ‘‘death was included to account for the possibility that diabetes might develop at a different rate in individuals who die than in those who survive.’’

Although rosiglitazone reduced the outcome of death or diabetes (306 events in the rosiglitazone group, 686 in placebo, hazard ratio [HR] 0.40 [95% confidence interval {CI} 0.35–0.46], $P < 0.0001$), the drug had no effect on all-cause mortality (30 deaths with rosiglitazone, 33 with placebo HR 0.91 [95% CI 0.55–1.49], $P = 0.7$). Thus, a decrease in diabetes accounted for all the drug’s impact on the composite. The authors nevertheless concluded that ‘‘this large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes,’’ potentially leading readers to infer that rosiglitazone decreased mortality—clearly a problematic inference [6,8].

Given the problems of interpretation, it may be that composite end points should not be used gratuitously, and criteria for their parsimonious use should be available. We therefore undertook a systematic survey of the literature to identify publications that provide criteria for use of composite end points for competing risks. Considering the findings, we offer guidance for use of composite end points to address competing risks.