

Composite end points in cardiovascular clinical trials

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Abstract: Composite end points in which two or more end points are combined are commonly used in randomized clinical trials. This approach is often used in order to improve statistical efficiency and also to capture the overall effect of therapies in clinical trials. In this narrative review, we discuss the definitions, interpretation, limitations, and future directions regarding the use of composite end points in contemporary cardiovascular clinical trials. ■ *Heart Metab.* 2019;78:28-31

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Why do we use composite end points?

The randomized clinical trial is considered as one of the major advances in medicine in the last century, and represents the gold standard for establishing the efficacy of cardiovascular therapies.

Results from large-scale trials have established practice-changing advances in cardiovascular medicine, such as reperfusion strategies in myocardial infarction, use of potent antithrombotic therapy, lipid-lowering therapies, blood pressure control, and newer antidiabetic drugs. These therapies have dramatically improved cardiovascular disease mortality rates over the past decades. On the other hand, the current lower mortality rates have provided increasing challenges for clinical trialists, as smaller incremental benefits from novel therapies would require studies with larger sample sizes and longer follow-up.

The statistical power of a randomized controlled trial is directly related to the number of events observed. The larger the number of events observed, the larger the statistical power. In the 1970s and 1980s, it was possible to conduct trials using all-cause mortality as the primary end point (such as trials comparing aspirin and placebo or fibrinolytic with placebo in

patients with myocardial infarction).¹ Currently, if one aims to design a trial with all-cause mortality as the primary end point, depending on the included patient characteristics, a trial would require a sample size of over 50 000 patients and several years of follow-up in order for a minimal number of events to accrue. One potential solution to overcome unfeasible sample sizes is to increase the number of observed events by using composite end points.²

Composite (or combined) end points (or outcomes) in which two or more end points are combined are commonly used in contemporary cardiovascular clinical trials. This approach is often used in order to improve statistical efficiency and also to capture the overall effect of therapies in clinical trials. However, the correct interpretation of composite end points may be challenging for some physicians.

Interpretation of composite end points

The use of composite end points may lead to a misleading interpretation of results if the individual end points (components) differ in clinical relevance, if the frequency between components is different, and if the effect sizes differ markedly across the individual

components.³ Thus, when the gradient of importance for patients is large, and the more important components are less frequent and show small or non-clinically relevant treatment effects, use of composite end points can be misleading (*Box 1*).

1. The components of the composite end point of similar importance to patients
2. The event rates for the components of the composite end point occur with similar frequency
3. The effect sizes for the components of the composite end point are of similar magnitude

Box 1 Criteria for an appropriate composite end point.

In this sense, the components of a composite end point should be of similar clinical relevance and importance to patients. For example, in a trial in which the primary end point is composed of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, all the components are clinically relevant and important to patients. This is a typical end point used in trials of acute and chronic coronary artery disease, as well as in cardiovascular prevention trials. Conversely, in a trial which uses a composite end point of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, need for revascularization, or stent thrombosis, the components are not of equal clinical relevance and importance to patients. Despite being an important variable to be measured, need for revascularization, for example, is not directly related to the natural history of the disease and may carry a component of medical decision or bias. Thus, it cannot be considered as having the same importance to patients as a fatal event such as cardiovascular mortality or a disabling stroke. The larger the difference in clinical relevance between the most and least important component end points, the larger our skepticism about the appropriateness of the composite end point.

In addition, in the case where the authors have found a statistically significant result in the primary composite end point, if the more important component occurs with far less frequency (lower event rates) than the less important ones, the difference may be due to the less important component. In this case, the composite end point becomes less informative. Finally, it is vital to evaluate not only the results in terms of the primary composite end point but also to evaluate the results in terms of the individual compo-

nents. In this sense, if the magnitude of effects (effect sizes) varies between the individual components, the clinical implication of the results is also problematic.

The HOPE trial represents a classic example of adequate usage of composite end points.⁴ In this trial, 9297 high-risk patients who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of 5 years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Thus, all the components were clinically relevant. The frequency of the components was also consistent. Moreover, the authors found a 22% statistically significant relative risk reduction of the primary end point, but equally found consistent results with regard to the individual components (26% relative risk reduction of cardiovascular mortality, 20% relative risk reduction of myocardial infarction, and 32% relative risk reduction of stroke).

Composite end points in the medical literature

Systematic reviews have assessed the frequency and appropriateness of the use of composite end points in clinical trials. Freemantle et al⁵ assessed the incidence and quality of reporting composite end points in clinical trials published in major journals such as *Annals of Internal Medicine*, *BMJ*, *Circulation*, *Clinical Infectious Diseases*, *Journal of the American College of Cardiology*, *JAMA*, *Lancet*, *New England Journal of Medicine*, and *Stroke* from 1997 through 2001. The authors were able to find 167 original reports of randomized trials (with a total of 300 276 patients) that included a composite primary outcome that incorporated all-cause mortality. Sixty-three trials (38%) were neutral both for the primary end point and the mortality component. Sixty trials (36%) reported significant results for the primary outcome measure but not for the mortality component. Only 6 trials (4%) were significant for the mortality component but not for the primary composite end point, whereas 19 trials (11%) were significant for both. Twenty-two trials (13%) were inadequately reported.

Another systematic review⁶ assessed specifically cardiovascular trials published in the *Lancet*, *Annals of Internal Medicine*, *Circulation*, *European Heart Journal*, *JAMA*, and *New England Journal of Medicine*,

from 1 January 2002 to 30 June 2003. Of 114 identified randomized controlled trials that included a composite end point of importance to patients, 68% (n=77) reported complete component data for the primary composite end point; almost all (98%; n=112) primary composite end points included a fatal end point. Of 84 composite end points for which component data were available, 54% (n=45) showed large or moderate gradients in both importance to patients and magnitude of effect across components. When analyzed by categories of importance to patients, the most important components were associated with lower event rates in the control group (medians of 3.3 to 3.7% for fatal, critical, and major outcomes; 12.3% for moderate outcomes; and 8.0% for minor outcomes). Components of greater importance to patients were associated with smaller treatment effects than less important ones (relative risk reduction of 8% for death and 33% for components of minor importance to patients).

A more recent study⁷ reviewed four leading general/cardiology journals (*Circulation*, *JAMA*, *The Lancet*, and *New England Journal of Medicine*) from January 1, 2011 to December 31, 2016 and identified 140 trials with a cardiovascular composite end point as their primary result. The median number of components in the composite end point was 3, with 36.5% of those based solely on the combination of mortality, MI, or stroke (23 of 63 three-component composite end point trials). The inclusion of revascularization (rather than stroke) in the composite end point was also quite common (22 of 63 three-component composite end point trials). All but 12 trials included death, arguably the least ambiguous and most important end point, with the remaining components comprising nonfatal clinical events, and the need for, or outcomes of, procedures.

Taken together, these systematic reviews suggest that the use of composite end points is generally inadequate, given that higher event rates and larger treatment effects associated with less important components may lead to result in misleading interpretations of trial results.

Future directions in the use of composite end points

Several authors are proposing a rethinking and a reappraisal of composite end points in cardiovascular

clinical trials (*Box 2*). A summary of some of the proposed solutions is presented below.^{7,8} A detailed discussion of the methodologies is beyond the scope of this narrative review.

1. Establish a consensus of event definitions, including recommended composite end points for each major cardiovascular area (heart failure, coronary artery disease, hypertension, etc).
2. Harmonize adjudication criteria between trials
3. Use weighting scheme methods
4. Perform analysis based on total number of events

Box 2 Future directions in the use of composite end points in cardiovascular trials.

Adapted from reference 7: Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation*. 2017;135:2299–2307. Copyright © American Heart Association 2017.

For trials with similar design and objectives, it would be desirable to establish a consensus that would provide more homogeneity of common components within composite end points across trials. It would also be very important that the definitions used to adjudicate the events are similar between trials. These would facilitate trial interpretation and also would enable better conduct of systematic reviews and meta-analysis of such trials.

Another potential solution would be to differentially weight the components of a composite end point. For example, a stroke characterized by transient arm paresis does not have the same relevance as one resulting in disabling persistent hemiplegia. Similarly, a myocardial infarction defined by a small troponin rise would carry a much lower risk than a much larger one complicated by heart failure. Similarly, equal treatment in the analysis of fatal and nonfatal events may be misleading. Thus, further refinement of weights within an event type (ie, the weighting of the weights) and use of weighting or a ranking scheme in time-to-all-event approach to primary analysis represent potential solutions. Several methods have been proposed to achieve this.⁹

Finally, in most cardiovascular trials, the analysis is based on time to first adjudicated event. Nevertheless, analytic methods based on a total number of events or recurrent events may better inform clinical practice.^{10,11} ■

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REFERENCES

1. Braunwald E, Cannon CP, McCabe CH. Use of composite endpoints in thrombolysis trials of acute myocardial infarction. *Am J Cardiol.* 1993; 72:3G–12G.
2. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ.* 2010;341:c3920.
3. Montori VM, Permanyer-Miralda G, Ferreira-Gonzalez I, Busse JW, et al. Validity of composite end points in clinical trials. *BMJ.* 2005;330:594–596.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.
5. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA.* 2003;289:2554–2559.
6. Ferreira-González I, Busse JW, Heels-Ansdell D, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ.* 2007;334:786.
7. Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation.* 2017;135:2299–2307.
8. Stolker JM, Spertus JA, Cohen DJ, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation.* 2014;130:1254–1261.
9. Armstrong PW, Westerhout CM, Van de Werf F, et al. Refining clinical trial composite outcomes: an application to the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial. *Am Heart J.* 2011;161:848–854.
10. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Statist.* 1982;10:1100–1120.
11. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distribution. *J Am Stat Ass.* 1989;84:1065–1073.