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KEY CONCEPTS SERIES

Composite endpoints

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Abstract

Studies often combine several events, for example, death or myocardial infarction or stroke, into a single study outcome. This is called a composite endpoint. Composite endpoints make doing trials easier by reducing the sample size or follow-up period required to demonstrate the effectiveness of an intervention. However, interpreting the results of composite endpoints can be confusing. To avoid misleading conclusions about the effectiveness of an intervention, it is important for readers of studies reporting a composite endpoint to ascertain that the clinical importance, the frequency of events, and the effect of the intervention on each component of the composite endpoint are similar.

Keywords: Composite endpoint; Clinical trial; Treatment effect; Primary endpoint; randomized controlled trial, Outcome measures

1. Background

The effectiveness of a treatment is usually measured by how much it reduces the incidence of an undesirable event over a specific time period. Sometimes, the undesirable event is a single outcome, for example, death. Other times it can be any of several possible outcomes, for example, death or myocardial infarction or stroke (a composite endpoint). The number of participants who experience a composite endpoint will be higher than the number of participants who experience a single component. This higher number of events increases the ability of a trial to detect a difference between treatment and control, allowing recruitment of a smaller number of patients and follow-up for shorter periods [1].

2. Example

Although composite endpoints make it easier to do studies, they can sometimes lead to misleading conclusions. Readers should therefore be careful about how they interpret results of composite endpoints. For example, in the DREAM trial, rosiglitazone significantly reduced the composite outcome of death or incident diabetes compared with placebo [2]. Readers may interpret this result as rosiglitazone being effective in reducing both deaths and incident diabetes. However, on examining the results of each individual outcome, only incident diabetes was reduced significantly (hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.33 to 0.44). There was no significant difference in deaths between rosiglitazone and placebo (HR 0.91, 95% CI 0.55 to 1.49) (Table 1).

3. Pointers

To avoid misleading conclusions that make interventions appear more effective than they really are [3], Montori, et al. suggest three criteria:

1. The components of the composite endpoint must be of similar clinical importance to patients. For example, in Table 1, death was clearly more important than diabetes, so these two outcomes should not have been combined into a composite endpoint. In contrast, a composite outcome of death, stroke, or myocardial infarction would be more acceptable because these component outcomes are of arguably similar importance.
2. The frequency of the occurrence of the components over the same time period must be similar; otherwise, the effect on the composite will be largely determined by the predominant event. In Table 1, 938 patients in the DREAM study developed diabetes, whereas only 63 deaths were recorded. This means the reduction in

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Table 1. Incidence of the primary outcome (a composite of diabetes or death) and its components in patients with impaired fasting glucose given either rosiglitazone or placebo [2]

Outcome	Rosiglitazone $n = 2,635$	Placebo $n = 2,634$	Hazard Ratio (95% CI)	*P*
Diabetes	280 (10.6%)	658 (25.0%)	0.38 (0.33, 0.44)	<0.0001
Death	30 (1.1%)	33 (1.3%)	0.91 (0.55, 1.49)	0.7
Death or diabetes (composite)	306 (11.6%)	686 (26.0%)	0.40 (0.35, 0.46)	<0.0001

the composite was largely (or solely) determined by the reduction in diabetes (Table 1).

3. Finally, the effect of the treatment must be similar for each component of the composite. In Table 1, the outcome of diabetes is decreased in the rosiglitazone group, but there is no difference in the outcome of death. In such a situation, the reduction in the composite outcome (26.0% vs. 11.6%, $P < 0.0001$) could lead to a misleading suggestion that both events decreased.

When composite endpoints fulfill all these criteria, then we can be assured that the conclusions are probably credible. Otherwise, further investigation of the results is warranted.

References

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Further reading

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