Balancing the morbidity benefit of a novel treatment with the potential for harm

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Introduction

Contemporary clinical trials that show a beneficial effect on morbidity for a novel treatment often give an indeterminate result for mortality, which may be a component of a composite primary endpoint. Although a beneficial effect on a composite endpoint is often perceived by clinicians as indicating a beneficial effect on each of the components, this is often not the case. Typically, only one or two of the morbidity components are clearly demonstrated to benefit, with an indeterminate effect on mortality and the other morbidity components.

For example, consider a trial assessing the effect of a novel treatment for coronary artery disease on the composite endpoint of death or need for revascularization. A beneficial effect on this composite endpoint might be presented as a reduced risk of death and need for revascularization, but the actual benefit might be confined to a reduced need for revascularization, with an indeterminate effect on mortality. The trial then provides no information as to whether the novel treatment reduces or increases the risk of death.

We cannot assume that a reduced risk of morbidity necessarily translates into a reduced risk of mortality. Further, an indeterminate result for mortality might hide an underlying modest increase in mortality that the trial is underpowered to detect. The difficulty for the clinician and indeed patients (who are increasingly demanding to be better informed on the risks and benefits of treatments) is that unless a treatment has been demonstrated to reduce mortality, the possibility of increased mortality cannot be excluded.

Interpretation of clinical trials with an indeterminate effect on mortality

In the light of the foregoing, how can we interpret trials that have demonstrated a novel treatment to have a beneficial effect on morbidity, while not ignoring the potential for harm when the effect on mortality is indeterminate? To address this, it is helpful to consider the principles of non-inferiority trials. Such trials are appropriate where a novel treatment has beneficial properties (cost, ease of administration, etc.) but is not expected to offer an advantage in terms of mortality. In the current setting, the beneficial properties are the favourable effects on morbidity. It is not possible to demonstrate that two treatments are identical in a mathematical sense, so we seek to demonstrate that they are sufficiently similar that any differences are of no practical interest. This entails choosing a priori (often with some considerable difficulty) the maximum potential difference between the treatments of no practical interest: δ. The object of the trial is then to demonstrate that the difference between the treatments is less than δ. If this is achieved, non-inferiority is established.

An extension of this has been proposed1 that entails defining δ as the amount of the efficacy of the
standard treatment that we are potentially prepared to sacrifice to obtain the beneficial properties of the novel treatment. We can apply this principle to put an upper bound on the potential for harm from a novel treatment. We use a one-sided test, as the lower bound defines the limit for benefit, which we are not seeking a limit on. When a trial result is indeterminate for mortality (whether or not it is a component of the primary endpoint), we cannot exclude the potential for harm, but using this approach we can define an upper limit for the potential harm. Clinicians are then in a better position to make informed judgements on the balance of risks and benefits of treatments, and to be able to communicate this to patients. It should be emphasized that we are not seeking to demonstrate retrospectively that a novel treatment is non-inferior for mortality. This will only be the case if the 95% upper bound for mortality is less than the pre-specified δ, or at least an established δ taken from the literature. It is not appropriate for δ to be chosen retrospectively.

To exemplify this principle, consider two trials with composite endpoints. The CURE Trial compared the effect of clopidogrel in addition to standard treatment vs. standard treatment alone in patients with non-ST elevation acute coronary syndromes. The composite primary endpoint was death from cardiovascular causes, non-fatal myocardial infarction or stroke. The relative risk of the composite endpoint for clopidogrel was 0.8 (95% CI 0.72–0.90). The components of the composite endpoint had relative risks of: cardiovascular death 0.93 (0.79–1.08), myocardial infarction 0.77 (0.67–0.89) and stroke 0.86 (0.63–1.18). Thus, the significant benefit in terms of the composite endpoint was ‘driven’ by a reduced risk of non-fatal myocardial infarction. The trial is uninformative with regards to the effect of clopidogrel on cardiovascular mortality or stroke, and does not exclude the possibility of harm. If we apply the above principle, the information on relative risk can be used to compute a one-sided upper 95% bound for the relative risk of cardiovascular death of 1.05. Thus we can conclude that the use of clopidogrel has a beneficial effect on the risk of non-fatal myocardial infarction, and although the effect on cardiovascular mortality is not known, we can state, with 95% confidence, that any relative excess risk is <16%.

Summary

Contemporary clinical trials may demonstrate a morbidity benefit, but give an indeterminate result for mortality. Consequently, the possibility that such a novel treatment may increase mortality should be considered. This possibility is not usually discussed in publications presenting trial results. Rather, the matter is dismissed by a statement to the effect that the study was not powered to assess mortality, and consequently it is to be expected that the trial gives an indeterminate result. This may be true, but for the clinician and patient it is not a satisfactory state of affairs.

In many situations, it is not feasible to conduct trials to look for small differences (which may be clinically meaningless) in mortality. We propose that the data on mortality should be used to provide a one-sided 95% upper bound on the potential for harm (increase in mortality). This would allow the clinician and patient to better understand the risks and benefits of novel treatments. Publications of trial results (and editorials) should incorporate this issue into the discussion of the potential value of a novel treatment. The judgement between benefit and harm may not be easy to make. For example, in the two examples given, the treatment reduced the risk of sustaining a non-fatal myocardial infarction, but may have increased the risk of death.

This discussion has focused on the retrospective interpretation of clinical trails. The principle, however, can be applied prospectively. Thus when consideration is being given to stopping a trial because of a morbidity benefit, consideration should also be given to the need to put an upper limit on the potential for harm as a consequence of an indeterminate mortality result.
References

