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Cardiac death should be the primary endpoint for revascularization trials and meta-analyses

Harvey D. White *

Green Lane Cardiovascular Research Unit, Auckland City Hospital, Private Bag 92024, Victoria St West, Auckland 1142, New Zealand

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This commentary refers to 'Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis', by E.P. Navarese *et al.*, https://doi.org/10.1093/eurheartj/ehab246; 'In the pool: dilution or drowning?', by V. Dayan *et al.*, https://doi.org/10.1093/eurheartj/ehab443; 'When a meta-analysis equals a single large-scale trial with meaningful follow-up', by E.P. Navarese *et al.*, https://doi.org/10.1093/eurheartj/ehab460; and the discussion pieces 'Cardiac mortality, adequate power, and objective inclusion of the entire evidence are key to accurately define the long-term effect of revascularisation vs. medical therapy alone in stable coronary syndromes', by E.P. Navarese and F. Andreotti, https://doi.org/10.1093/eurheartj/ehab677.

The meta-analysis by Navarese *et al.*[1] of 25 revascularization vs. medical therapy trials in stable coronary disease showed a 21% risk reduction in cardiac mortality over 5.7 years but no effect on total mortality. These findings raise the issue of what should be the primary endpoint in revascularization trials and meta-analyses.

Navarese *et al.* prespecified cardiac mortality as primary and total mortality as secondary endpoint of their analysis. Total mortality has been advocated to be the best endpoint in clinical trials as it embraces both benefits and harms of treatments. However, for precise treatment effect estimates, primary endpoints should be more specific than total mortality.

In revascularization trials, deaths not possibly affected by revascularization, e.g. from cancer or chronic diseases, should not be counted in the primary endpoint for several reasons. Treatments of ischaemic events during trial follow-up such as myocardial infarction have dramatically improved due to reduced reperfusion times and use of evidence-based medicine (EBM) leading to low cardiovascular mortality in both randomized groups and consequently reducing statistical power. The longer the follow-up the more likely non-cardiac deaths will occur diluting the impact of a randomized treatment on total mortality even if there is an effect on cardiac mortality. Contemporary trials show that longer follow-up results in decreasing cardiac death rates and increasing non-cardiac death rates. For example, in COURAGE that compared elective PCI with optimal medical therapy, at 4.6 years follow-up, cardiac deaths made up only 26.7% of total deaths.[2] In parallel, with longer follow-up, all-cause mortality will tend towards the null regardless of treatment. Because cardiac mortality is the most specific endpoint to detect intervention effects and is not swamped by non-cardiac causes of death, many trials that form the basis of EBM have not used total mortality as the primary endpoint (*Table 1*).[3–5]

Table 1 Examples of evidence–based cardiovascular medicine trials not using total mortality as the primary endpoint

Trial	Treatment	Endpoint
ISIS 2	Aspirin/streptokinase vs. placebo	Vascular death
CURE	Clopidogrel vs. placebo	Cardiovascular death, nonfatal MI, or stroke
PLATO	Ticagrelor vs. clopidogrel	Death from vascular causes, MI, or stroke
ISCHEMIA	Revascularization vs. conservative strategy	Cardiovascular death, MI, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest

MI, Myocardial infarction.

* Corresponding author. Tel: +64 9 630 9992, Fax: +64 9 630 9915, Email: harveyw@adhb.govt.nz

The meta-analysis results by Navarese *et al.*[1] are consistent with the ISCHEMIA trial, which randomized 5179 patients with stable coronary disease and moderate or severe ischaemia to an invasive strategy or a conservative strategy. Cardiovascular death rate at 5 years was non-significantly lower in the invasive strategy [5.2% invasive vs. 6.5% conservative; difference—1.3%, (-3.1% to 0.6%)]. All-cause mortality was non-significantly higher in the invasive arm 9.0% vs. 8.3% conservative; difference 0.7% (-1.6% to 3.1).[5] Long-term follow-up of ISCHEMIA will provide additional information on all-cause death rates by strategy arm but will be impacted by increasing non-cardiac deaths, which made up ∼30% of all-cause deaths at 5 years.

The rising competing risk from non-cardiac mortality suggests that revascularization trials will be increasingly difficult to power statistically for treatment effects on total mortality and meta-analyses will similarly be challenged. For the above reasons, cardiac death should remain the primary endpoint for coronary revascularization trials and meta-analyses.

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Data availability

Data are available upon request.

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