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In the pool: dilution or drowning?

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This commentary refers to 'Cardiac mortality in patients randomized to elective coronary revascularization plus medical therapy or medical therapy alone: a systematic review and meta-analysis', by E.P. Navarese *et al.*, doi:10.1093/eurheartj/ehab246 and the discussion piece 'When a meta-analysis equals a single large-scale trial with meaningful follow-up', by E.P. Navarese *et al.*, doi:10.1093/eurheartj/ehab460.

PCI is solely directed to the 'culprit' lesion, while CABG aims to provide immediate surgical collateralization and to offer prophylaxis against new proximal disease. In essence, PCI treats the lesion and CABG treats the vessel. Considering that both strategies have different treatment objectives, it is not obviously intuitive to pool outcomes derived from both strategies when comparing with medical treatment.

In the meta-analysis from Navarese *et al.*,[1] the authors included all published randomized control trials that compared revascularization and medical treatment for patients with stable angina. The only treatment that has effectively not changed in the last 30 years is CABG. In contrast, PCI and medical treatment have both made significant advances over this time. It is noteworthy that of the 25 trials that were included, 7 included CABG procedures but that only 2 of them were isolated CABG.

The authors report that overall, revascularization decreased cardiac mortality with an RR of 0.79 (0.67–0.93; $P < 0.001$). Notwithstanding that cardiac, as opposed to total, mortality is notoriously susceptible to potential bias, to support this finding, the authors performed subgroup analysis excluding studies in which >30% of patients received CABG. While there is no formal explanation for this arbitrary 'cut-off', without CABG, the RR was 0.83 (0.71, 0.98; $P = 0.03$).

Pooling CABG and PCI together can generate potential biases with regard to the different meaning and results of these procedures. Indeed, the reported protective effect on cardiac mortality could result not only from the mixing of different interventional procedures over a very prolonged time span but also the choice of sensitive analysis. In particular, only excluding studies with >30% CABG does not appear reasonable, as it still maintains a quota of a mixed population that should, logically, be easily removed.

Replicating the subgroup meta-analysis in a less-biased setting that completely excludes trials with CABG, there is no evident advantage on cardiac mortality of PCI compared to medical treatment (random effect RR 0.79, 95% CI 0.57–1.05, *P*-value = 0.1). To avoid the controversial aspect of defining which studies fit into a stable angina meta-analysis, Head *et al.*[2] performed an individual patient data meta-analysis of patients with multivessel disease without acute myocardial infarction. They reported that CABG had a mortality benefit over PCI in patients with multivessel disease.

We believe that given their profound differences in medium- to long-term outcomes, PCI and CABG revascularization procedures should not be pooled during coronary revascularization trials. Furthermore, PCI and MT procedures from 30 years ago have very limited relevance to current outcomes. While each revascularization procedure has its inherent advantages and disadvantages, we are performing only one of them in our patients. Reporting a combined overall outcome is at serious risk of potentially masking the negative effect of a discrete procedure and does not provide clear evidence nor guidelines as to the best treatment for the individual patient.

Meta-analyses can increase the precision of estimates of treatment effect; however, pooling studies with questionable inclusion criteria introduce systematic errors, which may lead to inappropriate conclusions.

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