When a meta-analysis equals a single large-scale trial with meaningful follow-up

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Dayan et al. point out that our meta-analysis does not compare medical therapy (MT) alone against either coronary bypass surgery (CABG)+MT or percutaneous coronary intervention (PCI)+MT.[1] Indeed, as the title of our paper indicates, our meta-analysis compares cardiac mortality in randomised trials of elective coronary revascularisation+MT vs. MT alone, *not* of CABG+MT vs. PCI+MT vs. MT alone.[2] Of 20 trials reporting cardiac mortality, two enrolled CABG-only patients in the revascularisation arm.[2] The largest and most recent trial (ISCHEMIA)[3] and four other trials enrolled and followed 38,013 person-years revascularised by PCI or CABG in the revascularisation arm;[2] most of the latter trials, however, did not provide stratified outcomes by revascularisation mode.

Dayan et al. state that PCI and MT, unlike CABG, have changed in the last 30 years.[1] We have observed an increasing prevalence of arterial grafting over the years. Further, a major strength of randomised studies is the balance of baseline characteristics in study arms. Indeed, in all trials of our meta-analysis, MT was generally comparable in both arms regardless of trial date.[2] Trial chronology, study year and percentage of MT components did not impact our cardiac mortality findings.[2]

Although Dayan et al. challenge the choice of cardiac or cardiovascular (not total) mortality as the primary endpoint,[1] this prespecified endpoint was registered (PROSPERO protocol ID CRD42021225598) and chosen to avoid masking potential signals on cardiac death by noncardiac death.[4] Indeed, in recent decades, five-year or longer follow-up post-PCI shows an incremental increase of noncardiac, compared to cardiac, death over time, attenuating any specific effect of coronary intervention (e.g., revascularisation) on all-cause deaths.[5] The ISCHEMIA trial also elected to use cardiovascular (not total) mortality within its primary endpoint.[3] In our meta-analysis, heterogeneity for cardiac death was low, explained by variable length of follow-up; the effect of revascularisation+MT vs. MT alone on all-cause mortality was consistent with that on cardiac death, significantly favouring revascularisation after removing bias (as recommended by Cochrane)[6] related to one very high cross-over trial.

Exclusion of trials with >30% CABG use was not arbitrary but prespecified, based on the 26% CABG rate in ISCHEMIA[3] rounded up to 30%.[2] In our exploratory analysis, excluding trials with >30% CABG use yielded a cardiac death rate ratio favouring revascularisation of 0.83(0.71-0.98), P=0.03.[2] Excluding the two entirely CABG-based revascularisation trials yielded a rate ratio of 0.84(0.73-0.96), P=0.04.

Dayan et al. propose to exclude the seven trials with any CABG use.[1] Unfortunately, this entails removing a large portion of PCI-treated patients, including the largest, namely the ISCHEMIA trial, losing necessary power for infrequent, individual, hard endpoints such as cardiac death. This will lead to very significant bias. The size of our meta-analysis for the primary endpoint (n=17,454)[2] is comparable to that of a single large-scale drug-to-drug comparative trial in stable patients. Conversely, the analysis proposed by Dayan et al. involves only 7,422 patients, with a rate ratio for PCI+MT vs. MT alone of 0.76(0.56-1.02), P=0.07 (P=0.1 reported by Dayan), which is directionally consistent with our entire meta-analysis [rate ratio 0.79(0.67-0.93), P<0.01]. The sample size mandated by our trial sequential analysis to reach robust conclusions for cardiac death is at least 15,234 patients,[2] more than twice the analysis proposed by Dayan et al.

The meta-analysis referenced by Dayan et al.[1] to support mortality reduction with CABG vs. PCI antedates ISCHEMIA and includes relatively short follow-up durations as well as studies employing bare metal and first-

generation drug-eluting stents. The relative merits of CABG vs. PCI (not the aim of our meta-analysis) can be determined by adequate head-to-head comparisons and person-years.

Our simple prespecified inclusion criteria relate to *elective* revascularisation (indicated in the title and detailed in main text).[2] Cochrane mandates comprehensive meta-analyses of all pertinent, available evidence.[6] Lack of power, self-selection, limited expertise in evidence based medicine, and unsupported statements can seriously distort truth.

Further discussion is available at the Society for Cardiovascular Angiography and Interventions video roundtable: **https://www.youtube.com/watch?v=AIYZB5BN1tQ**.

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