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Temporal trends in the efficacy of revascularization in stable ischaemic heart disease: A cumulative meta-analysis

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The use of revascularization added to optimal medical therapy (OMT) for stable ischaemic heart disease (SIHD) and its prognostic implications has been a longstanding debate in the cardiologic community. The ISCHEMIA trial is considered a landmark trial in the field, randomizing over 5000 patients; it essentially conferred no prognostic benefit of initial revascularization added to OMT vs. OMT alone in moderate to severe ischaemia [1]. Several meta-analyses have been conducted with mixed results. Most recently, Navarese et al. performed a large, yet debated, meta-analysis, and concluded that revascularization led to 21% and 26% relative decrease in cardiac mortality and spontaneous myocardial infarctions (MIs), respectively [2]. To further explore these controversial findings and because of the substantial timespan of publication of eligible trials (range from 1976 to 2020), we performed an in-depth meta-analysis of the same data and we specifically aimed, primarily, to explore the effect of time of publication on the pooled results, and, secondarily, to pool homogeneous studies with a robust definition of modern era OMT.

We regarded included trials from the most recent meta-analysis as eligible for our analysis [2]. We also performed an updated search in Medline from October 2020 to September 2021 and did not find any additional eligible trials. We extracted the longest follow-up published data on outcomes. We employed a random effects model cumulative meta-analysis, in which studies were included and pooled sequentially together in chronological order (from older to newer studies) and reverse chronological order (from newer to older studies) [3]. We inserted the studies in the cumulative meta-analysis based on the year of first publication for each trial, instead of the year of publication of the long-term outcomes (e.g. six years later for the MASS-2 trial), in order to capture the OMT used at the time of randomization and to avoid inserting results of long-term events of older studies after more contemporary studies. The incidence rate ratio (IRR) was used as effect measure. To homogeneously pool studies regarding the use of modern era OMT, we classified included trials into those with and without the use of modern OMT, which was defined as at least 50% use for each drug class (antithrombotic therapy, statins, beta-blockers, renin-angiotensin-aldosterone system inhibitors) at randomization (with the exception of ISCHEMIA-CKD because of the inherent discrepancies in this population) [4]. We performed a subgroup analysis of the outcomes based on the use or not of modern OMT use. Further, we performed a meta-regression analysis by using the absolute per cent difference for spontaneous MIs (all MIs minus periprocedural MIs) as a covariate to the cardiac mortality outcome. The *meta* package in R (version 3.6.3.) was used for all analyses.

Twenty-five trials were included. Efficacy of the revascularization arm in cardiac mortality achieved statistical significance by adding $k = 2$ studies in chronological order, whereas statistical significance was only achieved by adding $k = 17$ studies in reverse chronological order (Fig. 1A, B). A sensitivity analysis of trials without inclusion of recent ACS (INSPIRE, SWISSI-2), significant left main disease (ECSS), and chronic total occlusion (REVASC, DECISION-CTO, EURO-CTO) showed no benefit of revascularization on cardiac mortality (IRR 0.88, 95% CI 0.76 to 1.01).

All-cause mortality achieved statistical significance by adding k=5 studies in chronological order and k=20 studies in reverse chronological order. There was no statistical difference for any MI or stroke.

One in nine studies (11.1%) used OMT before the COURAGE trial, contrary to nine out of eleven studies (81.8%) after COURAGE. In the subgroup analysis, revascularization failed to show a reduction of cardiac mortality in SIHD among studies using OMT (IRR 0.93, 95% CI 0.79 to 1.10), whereas did so, among studies without OMT (IRR 0.64, 95% CI 0.51 to 0.80) (p for interaction = 0.007) (Fig. 1C). Spontaneous MIs were fewer in the revascularization arm in OMT-studies (IRR 0.73, 95% CI

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0.65 to 0.83) and not significantly fewer in without OMT-studies (IRR 0.80, 95% CI 0.58 to 1.10). However, the meta-regression analysis of the trials using OMT showed that the risk of cardiac death was not associated with the absolute difference of spontaneous MIs ($p = 0.3$) (Fig. 1D), in contrast to the studies without OMT ($p = 0.01$).

In summary, the principal findings of our analysis are that (i) there is significant effect of the time of publication of (not strictly selected) trials on the effect of revascularization added to OMT in SIHD on cardiac mortality, and (ii) there is no conclusive evidence of benefit of revascularization when homogeneous data are pooled from contemporary era trials . Our findings do not agree with results from a meta-regression analysis by using each trial's publication year as a covariate to show the impact of chronological order to the effect measure [2]. We believe that a meta-analysis' goal is to maintain homogeneity in order to answer a specific research question and that data obtained largely before 2000 in a constantly evolving clinical landscape are not relevant to current clinical decision-making. Therefore, we regard the subgroup analysis of studies with a robust definition of OMT, which are also studies in the modern era of OMT, as an inclusive pooling of eligible studies to investigate the role of revascularization added to OMT in SIHD. In addition, trials including patients with recent ACS, significant left main disease and chronic total occlusions may bias the pooled effect estimate. The meta-analysis by Shah et al. is also a good example of homogeneous pooling of studies to answer this specific research question [5].

Remarkable progress has been made in the field of disease-modifying drugs and, thus, only OMT may offer a survival benefit in patients with SIHD, except for certain higher risk subgroups. The meta-regression analysis shows that, although revascularization is efficient in reducing spontaneous MIs, this has no effect on cardiac mortality in the recent years. The latter may be explained by the improved management of spontaneous MIs, which results in reduced fatality rates than several decades ago. Also, a recent meta-regression analysis of large coronary artery disease trials showed that non-fatal MI is a poor surrogate outcome for all-cause or cardiovascular mortality [6]. We have to note as well that spontaneous MI was not a pre-specified endpoint of any of the eligible trials.

The pathophysiologic concept of coronary artery disease has also evolved over the years; from a stenosis-focused approach to a more systemic view, which incorporates not only the intracoronary atherosclerotic burden, but also the prothrombotic and inflammatory background as well as the individualized activity of the disease [7]. Future trials should focus primarily on identifying and treating the right patient rather than solely a lesion in SIHD, whether that may require revascularization or not.

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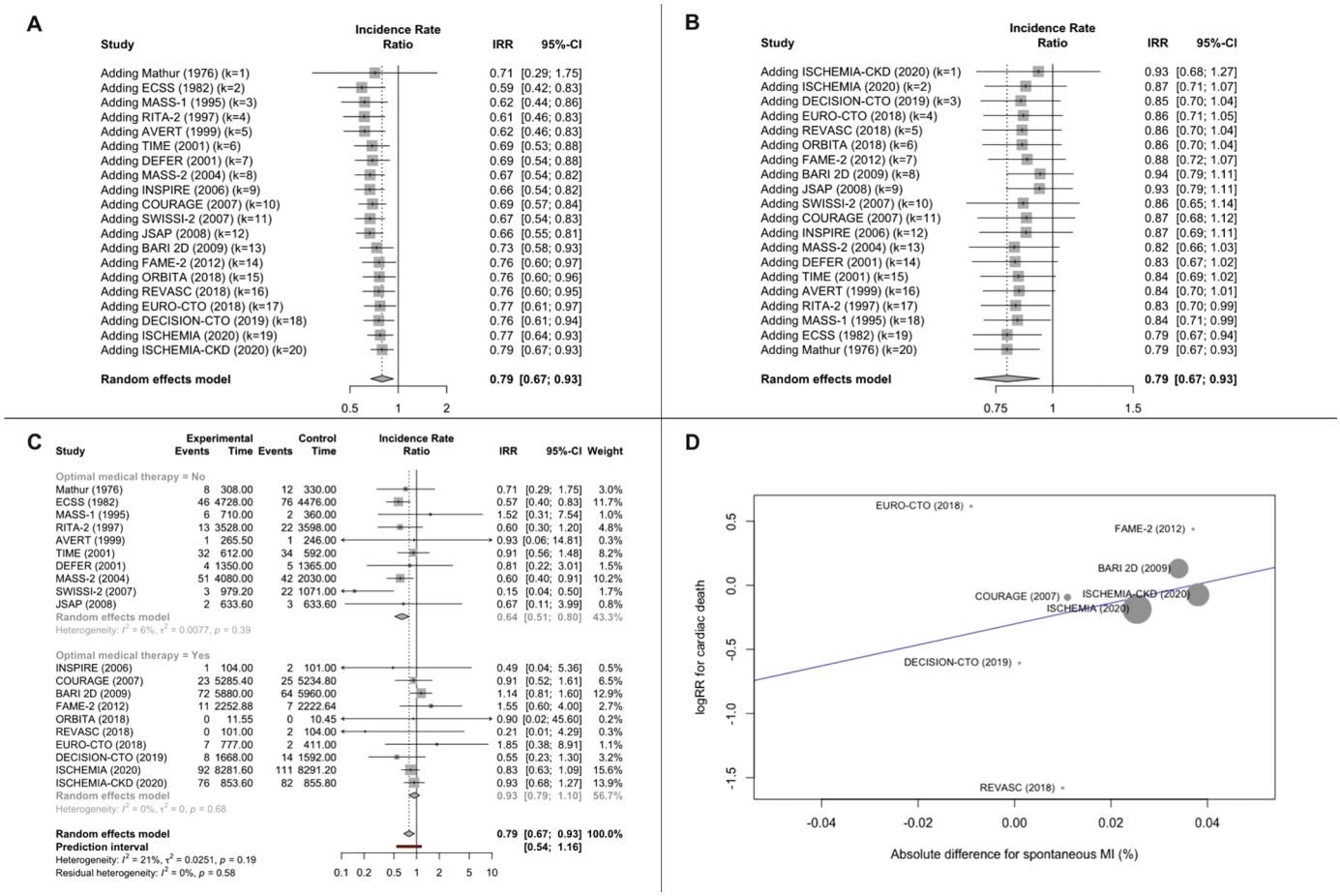

Fig. 1. A: Cumulative meta-analysis for cardiac mortality of studies in chronological order (from older to more recent studies), B: Cumulative meta-analysis for cardiac mortality of studies in reverse chronological order (from more recent to older studies), C: Subgroup meta-analysis of studies based on optimal medical therapy for cardiac mortality, D: Meta-regression analysis for the cardiac death adjusted for the absolute difference for spontaneous myocardial infarction in studies using optimal medical therapy.

CRediT authorship contribution statement

Ioannis T. Farmakis: Conceptualization, Methodology, Writing – original draft, Data curation. **Stefanos Zafeiropoulos:** Conceptualization, Methodology, Writing – original draft. **Ioannis Doundoulakis:** Conceptualization, Methodology, Writing – original draft. **Andreas S. Papazoglou:** Writing – review & editing. **Efstratios Karagiannidis:** Supervision, Writing – review & editing. **George Giannakoulas:** Supervision, Writing – review & editing.

Declaration of Competing Interest

None to declare.

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