ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4638–4651
doi:10.1093/eurheartj/ehab246

FASTTRACK CLINICAL RESEARCH
Interventional cardiology

Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis

Eliano P. Navarese[1,2,3]*, Alexandra J. Lansky[4], Dean J. Kereiakes[5], Jacek Kubica[1,3], Paul A. Gurbel[6], Diana A. Gorog[7,8], Marco Valgimigli[9], Nick Curzen[10,11], David E. Kandzari[12], Marc P. Bonaca[13], Marc Brouwer[14], Julia Umińska[15], Milosz J. Jaguszewski[16], Paolo Raggi[2], Ron Waksman[17], Martin B. Leon[18,19], William Wijns[20], and Felicita Andreotti[21,22]

[1]Interventional Cardiology and Cardiovascular Medicine Research, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland; [2]Faculty of Medicine, University of Alberta, Edmonton, Canada; [3]SIRIO MEDICINE research network, Poland; [4]Yale University School of Medicine, New Haven, CT, USA; [5]Christ Hospital and Lindner Research Center, Cincinnati, OH, USA; [6]Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD, USA; [7]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, UK; [8]Cardiology Department, East and North Hertfordshire NHS Trust, Stevenage, UK; [9]Department of Cardiology, Inselspital Universitätsspital, Bern, Switzerland; [10]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [11]University of Southampton, Southampton, UK; [12]Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, GA, USA; [13]CPC Clinical Research, University of Colorado School of Medicine, USA; [14]Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands; [15]Department of Geriatrics, Nicolaus Copernicus University, Bydgoszcz, Poland; [16]1st Department of Cardiology, Medical University of Gdansk, Gdansk, Poland; [17]Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, USA; [18]Division of Cardiovascular Medicine, Columbia University Irving Medical Center, New York, NY, USA; [19]Cardiovascular Research Foundation, New York, NY, USA; [20]The Lambe Institute for Translational Medicine and Curam, National University of Ireland Galway and Saolta University Healthcare Group, Galway, Ireland; [21]Direzione Scientifica, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; and [22]Cardiovascular Medicine, Catholic University Medical School, Rome, Italy

Received 4 March 2021; revised 28 March 2021; editorial decision 11 April 2021; accepted 13 April 2021; online publish-ahead-of-print 18 May 2021

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See page 4652 for the editorial comment for this article 'Impact of revascularisation on outcomes in chronic coronary syndromes: a new meta-analysis with the same old biases?', by D.L. Brown abd W.E. Boden, https://doi.org/10.1093/eurheartj/ehab330.

Aims The value of elective coronary revascularisation plus medical therapy over medical therapy alone in managing stable patients with coronary artery disease is debated. We reviewed all trials comparing the two strategies in this population.

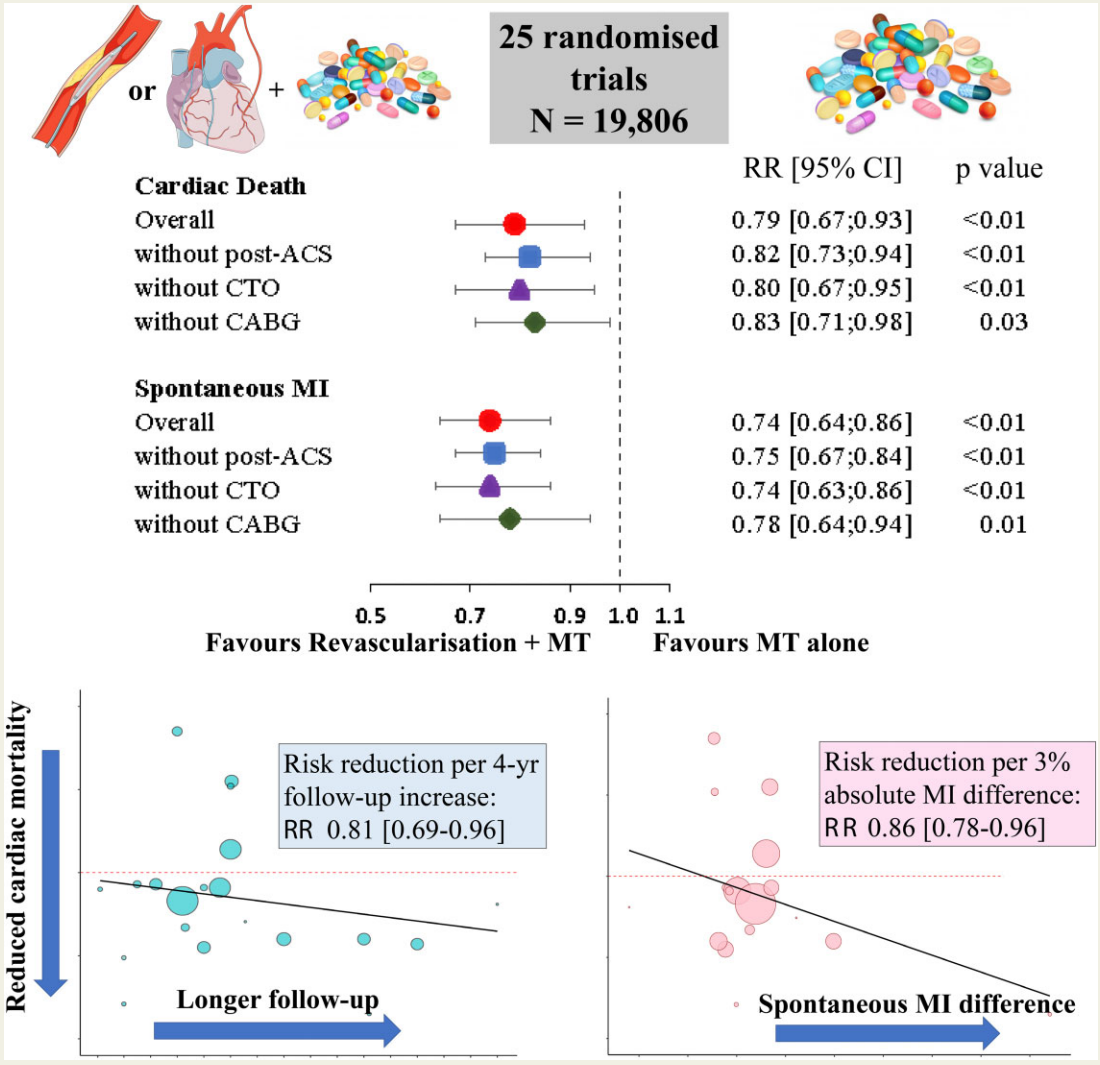
Methods and results From inception through November 2020, MEDLINE, EMBASE, Google Scholar, and other databases were searched for randomised trials comparing revascularisation against medical therapy alone in clinically stable coronary artery disease patients. Treatment effects were measured by rate ratios (RRs) with 95% confidence intervals, using random-effects models. Cardiac mortality was the pre-specified primary endpoint. Spontaneous myocardial infarction (MI) and its association with cardiac mortality were secondary endpoints. Further endpoints included all-cause mortality, any MI, and stroke. Longest follow-up data were abstracted. The study is registered with PROSPERO (CRD42021225598). Twenty-five trials involving 19 806 patients (10 023 randomised to revascularisation plus medical therapy and 9783 to medical therapy alone) were included. Compared with medical therapy alone, revascularisation yielded a lower risk of cardiac death [RR 0.79 (0.67–0.93), $P < 0.01$] and spontaneous MI [RR 0.74 (0.64–0.86), $P < 0.01$]. By meta-regression, the cardiac death risk reduction after revascularisation, compared with

* Corresponding author. Tel: +48 52 585 4023, Fax: +48 52 585 4024, Email: elianonavarese@gmail.com

medical therapy alone, was linearly associated with follow-up duration [RR per 4-year follow-up: 0.81 (0.69–0.96), $P = 0.008$], spontaneous MI absolute difference ($P = 0.01$) and percentage of multivessel disease at baseline ($P = 0.004$). Trial sequential and sensitivity analyses confirmed the reliability of the cardiac mortality findings. All-cause mortality [0.94 (0.87–1.01), $P = 0.11$], any MI ($P = 0.14$), and stroke risk ($P = 0.30$) did not differ significantly between strategies.

Conclusion In stable coronary artery disease patients, randomisation to elective coronary revascularisation plus medical therapy led to reduced cardiac mortality compared with medical therapy alone. The cardiac survival benefit after revascularisation improved with longer follow-up times and was associated with fewer spontaneous MIs.

Graphical Abstract



Major findings on cardiac mortality reduction with elective coronary revascularisation plus medical therapy vs. medical therapy alone. Abbreviations in text.

Keywords Coronary • Revascularisation • Medical therapy • Elective • Meta-analysis • Randomised trials

Introduction

Coronary artery disease is the most prevalent medical condition worldwide among individuals 50 years or older in terms of disease burden, disability, or early death.[1] Chronic coronary syndromes encompass clinically stable coronary artery disease patients, with or without acute coronary syndromes (ACS) or coronary revascularisation procedures in their natural history.[2] Compared with medical

therapy alone, timely revascularisation of epicardial artery obstructions with percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (MI) and with coronary artery bypass grafting (CABG) in patients with left ventricular ejection fraction <35% has been demonstrated to confer survival advantage.[3,4] In clinically stable patients with preserved or moderately impaired left ventricular systolic function, symptomatic benefit favouring revascularisation is well known,[3] but controversy remains regarding prognosis. Significant effects on cardiac mortality of one or the other strategy have not been reported so far. Moreover, no meta-analysis has comprehensively included data at longest follow-up for each available study.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial,[5] the largest and most recent randomised comparison of coronary revascularisation plus medical therapy vs. medical therapy alone in 5179 patients with stable coronary syndromes and moderate or severe inducible myocardial ischaemia, showed a non-significant difference between the two strategies for the primary composite endpoint of cardiovascular death, MI, hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest at a median follow-up of 3.2 years; at 5 years, the estimated cumulative composite event rates were 16.4% with revascularisation plus medical therapy vs. 18.2% with medical therapy alone, suggesting potential benefit with revascularisation at longer follow-up; the trial lacked statistical power to be conclusive on cardiac-related mortality. In the Fractional flow reserve vs. Angiography for Multivessel Evaluation 2 (FAME-2) study of 888 patients with stable coronary artery disease and functionally significant stenoses, the 5-year primary endpoint of death/MI/urgent revascularisation was significantly reduced, with lower rates of spontaneous MI, in the revascularisation plus medical therapy compared with the medical therapy alone arm.[6]

We conducted a meta-analysis of all trials comparing elective coronary revascularisation plus medical therapy vs. medical therapy alone in patients with preserved or moderately impaired left ventricular ejection fraction to appraise whether revascularisation in addition to medical therapy affects cardiac mortality at longest follow-up.

Methods

Search strategy and selection criteria

To be eligible, studies had to enrol clinically stable coronary artery disease patients undergoing, by protocol, randomisation to elective revascularisation plus medical therapy or medical therapy alone. Elective revascularisation was defined as a planned, deferrable, non-urgent/non-emergent procedure. Studies that enrolled only post-ACS patients had to include by protocol a myocardial stress test as an additional criterion of clinical stability, beyond the absence of symptoms or signs of ischaemia at rest. Studies with a comparator other than medical therapy, or investigating the acute phase of ACS, or focused only on heart failure patients were excluded. No limits were set for age, comorbidities, study language, publication status, or publication date.

Established methods recommended by the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement were used[7,8] to include all pertinent evidence. From inception through 28 November 2020, the following databases were searched: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar, TCTMD (https://www.tctmd.com/), EuroPCR, ClinicalTrials.gov, and Clinical Trial Results. The search was kept current by setting up automated reminders from MEDLINE for new publications. Backward snowballing was performed and abstracts from major congress proceedings were searched. Published meta-analyses on the subject were screened, and the data critically appraised and cross-checked with the original studies. The following keywords were used: coronary, coronary artery disease, ischaemic heart disease, revascularisation, medical therapy, and randomised. Supplementary material online, *Table S1* outlines the full electronic MEDLINE search process.

Two trained investigators (J.U. and D.A.G.) independently abstracted data on study design, patient characteristics, and clinical outcomes, using pre-specified data-extraction forms. Accuracy was appraised and any discrepancies were resolved by consensus after discussion with senior investigators (E.P.N. and F.A.). Non-relevant articles were excluded on the basis of title and abstract. For each trial, risk of bias was independently assessed by two investigators (J.U. and D.A.G.) using the revised Cochrane RoB2 tool involving five domains (randomisation process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results).

Outcome measures

Events at longest reported follow-up were abstracted. Cardiac or cardiovascular mortality was the pre-specified primary endpoint. Most studies ($n = 17$) reported cardiac, whereas three[5,9,10] reported cardiovascular mortality; these outcomes were considered together and referred to, briefly, as 'cardiac mortality'. As stated by the Academic Research Consortium-2 consensus, cardiac or cardiovascular death is more specific than all-cause death in relation to devices or procedures.[11] Spontaneous MI was analysed as a secondary endpoint and in association with cardiac mortality by meta-regression. Further endpoints were all-cause mortality, any MI, and stroke, as defined in the original studies. Stroke was considered of ischaemic origin unless otherwise specified.

Data synthesis and statistical analyses

Trial-level data were analysed according to the intention-to-treat principle. Rates rather than crude number of events were considered most appropriate because they incorporate trial duration,[12] which was variable across trials. Rate ratios (RRs) with 95% confidence intervals (CIs) were used as summary statistics. Continuity correction was applied to trials reporting no clinical events. Heterogeneity was assessed by the Cochran Q test and I^2 statistic,[13,14] with an I^2 value of 0% indicating no observed heterogeneity, up to 25% low heterogeneity, 26–50% moderate heterogeneity, and above 50% high heterogeneity. Potential publication bias was estimated visually and by linear regression.[15] For the meta-analyses, pooled RRs were calculated using the DerSimonian and Laird random-effects model. Fixed-effect models were performed as sensitivity analyses in the absence of high heterogeneity. The reliability of the meta-analysis for the primary endpoint was assessed by a *post hoc* trial sequential analysis (TSA) based on random-effects model assumptions,[16] with the cumulative Z-curve of the meta-analysis calculated and plotted against Lan-DeMets trial sequential monitoring boundaries.

A pre-specified sensitivity meta-analysis was conducted for the primary endpoint excluding trials that enrolled only post-ACS patients[17,18] or only chronic total occlusions (CTOs),[10,19,20] or trials with a per cent use of CABG in the invasive arm >30%.[21–25] An influence analysis omitting one study at a time was also conducted. Sensitivity analyses for cardiac death were further performed excluding trials at risk of bias, trials

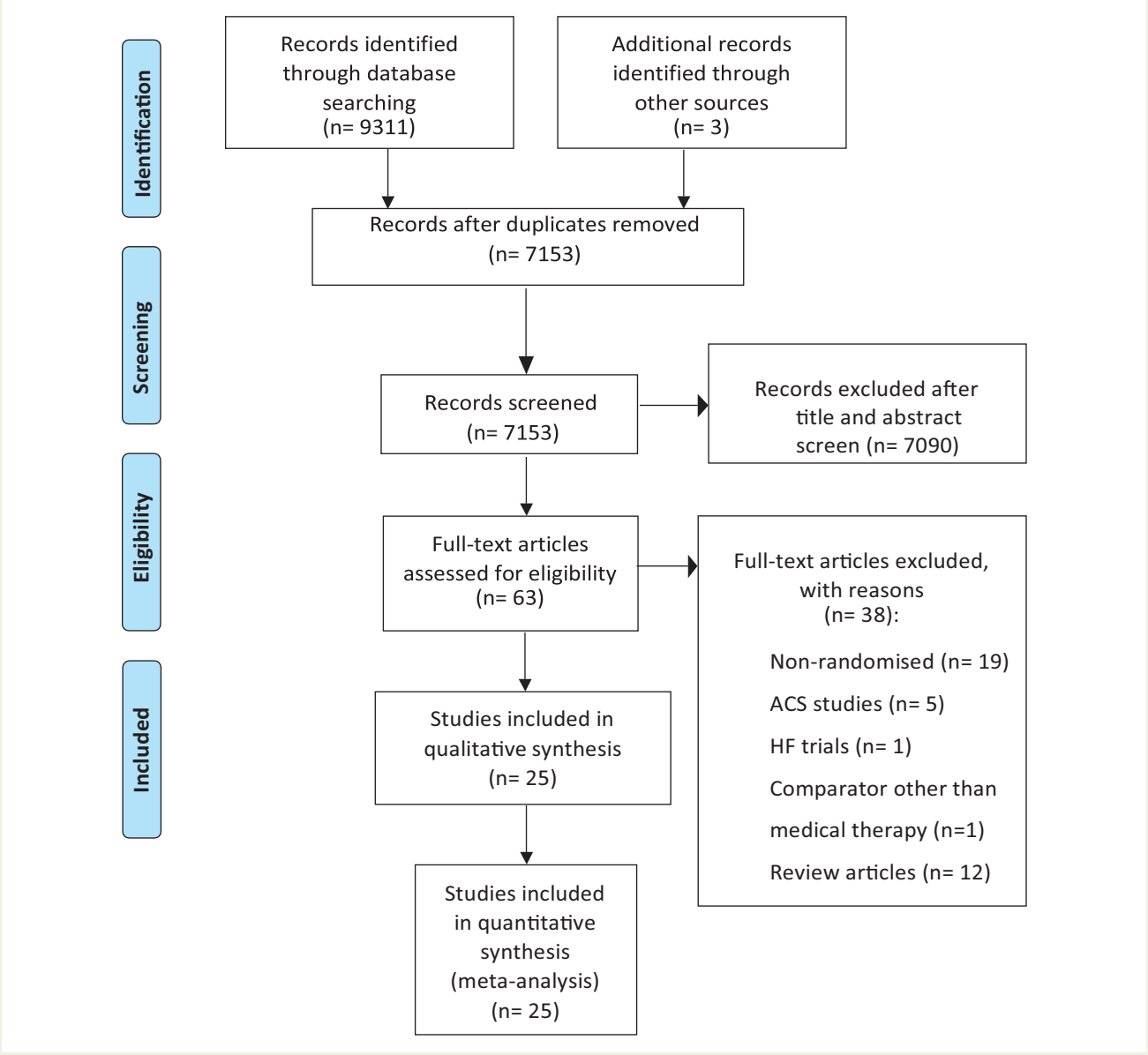


Figure 1 Study selection. ACS, acute coronary syndrome; HF, heart failure.

reporting cardiovascular mortality, or trials that could enrol, by protocol, within 2 months post-ACS (as per exclusion criterion set by the ISCHEMIA trial). The association between each trial's follow-up duration and the RR for cardiac death was investigated by random-effects meta-regression with follow-up time as covariate. Potential treatment-effect modifiers on cardiac death were further explored by meta-regression, including absolute per cent difference for spontaneous MI, trial year, percentage with multivessel disease and per cent use at randomisation of antithrombotic agents, statins, beta-blockers, or angiotensin-converting enzyme (ACE)-inhibitors/angiotensin II receptor blockers (ARBs). Meta-regression coefficients and corresponding *P*-values are reported. For summary estimates, a $P \leq 0.05$ (two-tailed) was considered statistically significant. Analyses were conducted using R Project version 4.0.2 for statistical computing and Comprehensive Meta-Analysis Software 2.0 (Biostat).

Results

Study selection and patient population

Twenty-five trials[5,6,9,10,17–49] involving a total of 19 806 clinically stable patients randomly allocated to elective revascularisation plus medical therapy ($n = 10\ 023$) or medical therapy alone ($n = 9783$) were included. The PRISMA flow diagram is shown in *Figure 1*. The key characteristics of the included trials are presented in *Table 1*. The

Table 1 **Characteristics of included studies**

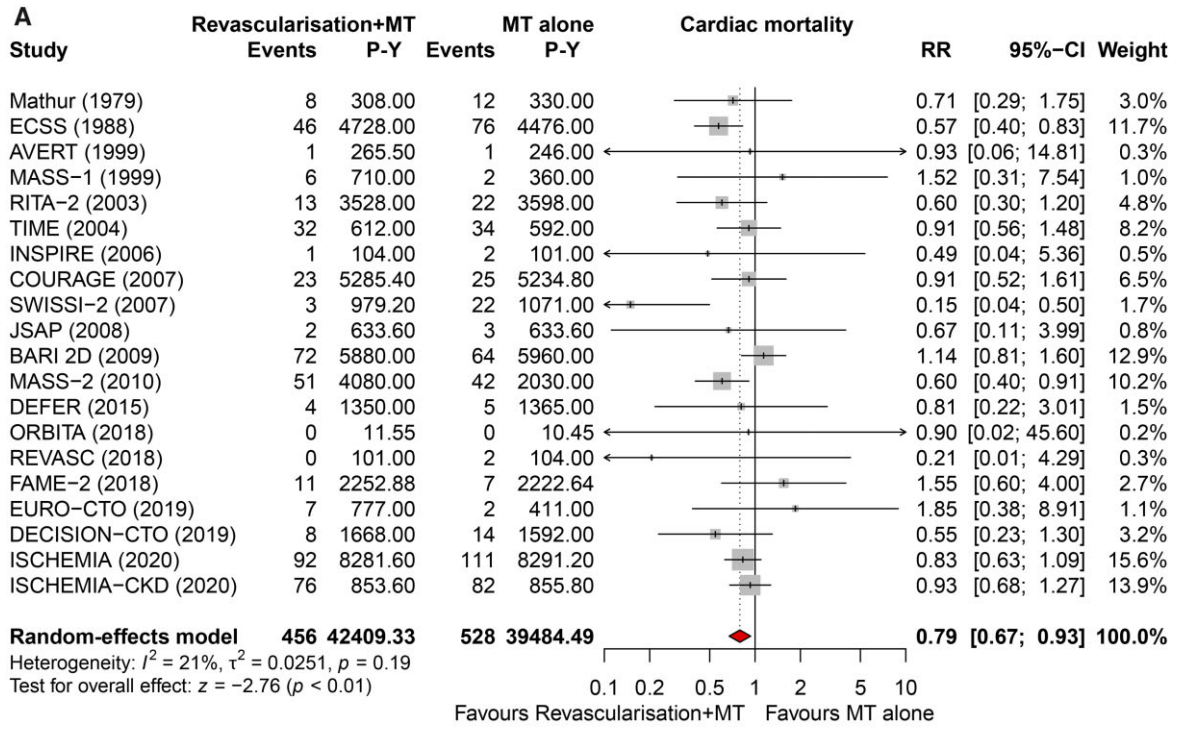
Study	Key qualifying event	Number of participants	Strategy	Mean age at onset (years)	Years of follow-up	Crossover from MT to revascularisation (%)
ACIP[26]	Asymptomatic positive stress test and ≥1 major coronary artery ≥50% stenosis at angiography	558	PCI/CABG vs. MT	61.2	2	29
ACME-1[27,28]	Men with stable angina, positive stress test, or MI within 3 months, 70–99% single-vessel coronary stenosis at angiography	227	PCI vs. MT	62.5	3	57
ACME-2[27]	Men with stable angina, positive stress test, or MI within 3 months, 70–99% double-vessel coronary stenosis at angiography	101	PCI vs. MT	NR	5	54
AVERT[29]	Negative stress test and ≥50% coronary stenosis at angiography	341	PCI vs. MT	58.5	1.5	11
BARI 2D[21,30]	Angina, diabetes, and ≥50% coronary stenosis at angiography	2368	PCI/CABG vs. MT	62.4	5	42
CASS[31,32]	Positive ECG or stress test and ≥70% coronary stenosis at angiography	780	CABG vs. MT	51.0	10	40
COURAGE[33]	Positive ECG or stress test and ≥70% coronary stenosis at angiography	2287	PCI vs. MT	61.7	4.6	31
DECISION-CTO[19]	Angina or silent ischaemia and 100% coronary stenosis at angiography	815	PCI vs. MT	62.6	4	11
DEFER[34,35]	≥50% coronary stenosis at angiography with FFR ≥0.75 and no ischaemia on stress test	181	PCI vs. MT	61.0	15	43
ECSS[25,36]	Angina and at least two-vessel ≥50% coronary stenosis at angiography	767	CABG vs. MT	50.0	12	36
EURO-CTO[10,37]	Angina and 100% coronary stenosis at angiography	396	PCI vs. MT	65.0	3	18
FAME-2[6,38]	Stable angina or documented silent ischaemia and ≥50% coronary stenosis at angiography	888	PCI vs. MT	63.7	5	51
INSPIRE[18]	Recent MI and large total (≥20%) and ischaemic (≥10%) adenosine-induced left ventricular perfusion defects	205	PCI vs. MT	63.5	1	NR
ISCHEMIA[5]	Moderate or severe ischaemia on non-invasive stress testing and eGFR ≥30 mL/min/1.73 m^2	5179	PCI/CABG vs. MT	64.0	3.2	21
ISCHEMIA-CKD[9]	Moderate or severe ischaemia and eGFR <30 mL/min/1.73 m^2 or on dialysis	777	PCI/CABG vs. MT	62.7	2.2	20
JSAP[39]	Positive ECG or other stress test and ≥75% coronary stenosis at angiography (≥60% on quantitative angiography)	384	PCI vs. MT	64.4	3.3	37
MASS-I[23,40]	≥80% single-vessel coronary stenosis at angiography	214	PCI/CABG vs. MT	57.0	5	17
MASS-II[22,41]	Positive stress test or angina and ≥70% proximal multivessel coronary stenosis at angiography	611	PCI/CABG vs. MT	60.0	10	39
Mathur[24,42]	Men with chronic angina despite >3 months intensive MT and >70% coronary stenosis in ≥1 major artery	116	CABG vs. MT	NR	5.5	13
ORBITA[43]	Angina and ≥70% single-vessel coronary stenosis at angiography	200	PCI vs. MT	66.0	0.115	0
REVASC[20]		205	PCI vs. MT	66.5	1	17

Continued

Table 1 *Continued*

Study	Key qualifying event	Number of participants	Strategy	Mean age at onset (years)	Years of follow-up	Crossover from MT to revascularisation (%)
	Angina and/or positive functional test with 100% coronary stenosis at angiography					
RITA-2[44,45]	Angina and ≥50% in two views or ≥70% in one view coronary stenosis at angiography	1018	PCI vs. MT	58.0	7	35
SWISSI-II[17]	MI within 3 months, positive stress test (without chest pain) and 1–2 vessel coronary stenosis at angiography	201	PCI vs. MT	55.3	10	44
TIME[46,47]	Age >75 years and chronic chest pain (CCS class >II) despite >2 antianginal drugs	301	PCI vs. MT	80.0	3.1	45
VA[48,49]	Chronic angina, positive ECG or other stress test and ≥1 major coronary artery ≥50% stenosis at angiography	686	CABG vs. MT	NR	22	66

ACIP, Asymptomatic Cardiac Ischaemia Pilot; ACME-1, Angioplasty Compared to MEdicine for single-vessel disease; ACME-2, Angioplasty Compared to MEdicine for double-vessel disease; AVERT, Atorvastatin VErsus Revascularisation Treatment; BARI 2D, Bypass Angioplasty Revascularisation Investigation 2 Diabetes; CABG, coronary artery bypass grafting; CASS, Coronary Artery Surgery Study; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularisation and AGgressive drug Evaluation; DECISION-CTO, Randomised Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion; DEFER, Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis; ECG, electrocardiogram; ECSS, European Coronary Surgery Study; eGFR, estimated glomerular filtration rate; EURO-CTO, A randomised multicentre trial to compare revascularisation with optimal medical therapy for the treatment of chronic total coronary occlusions; FAME 2, Fractional flow reserve vs. Angiography for Multivessel Evaluation 2; FFR, fractional flow reserve; INSPIRE, Adenosine Sestamibi Post-Infarction Evaluation; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-Chronic Kidney Disease trial; JSAP, Japanese Stable Angina Pectoris study; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; MT, medical therapy; NR, not reported; PCI, percutaneous coronary intervention; REVASC, A Randomised Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion; RITA-2, Second Randomised Intervention Treatment of Angina; SWISSI II, Swiss Interventional Study on Silent ischaemia Type II; TIME, Trial of Invasive vs. Medical therapy in Elderly patients; VA, Veterans Administration Cooperative Study. For each study the first reference corresponds to the longest available follow-up.



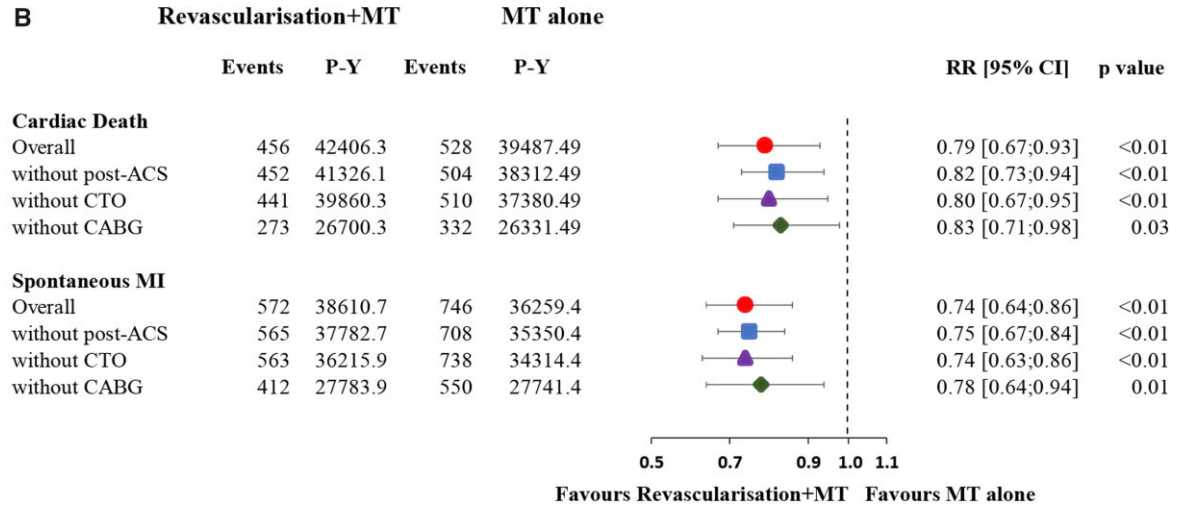


Figure 2 (*A*) Rate ratios and 95% confidence intervals for cardiac mortality with revascularisation plus medical therapy vs. medical therapy alone. Size of data markers is proportional to weight in meta-analysis. CI, confidence interval; MT, medical therapy; P-Y, person-years; RR, rate ratio. (*B*) Meta-analyses for cardiac death and spontaneous myocardial infarction excluding studies enrolling only post-acute coronary syndrome patients, chronic total occlusions, and use of coronary artery bypass grafting >30% in the revascularisation plus medical therapy arm. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CTO, chronic total occlusion; MT, medical therapy; P-Y, person-years; RR, rate ratio. (*C*) Meta-regression of rate ratios for cardiac mortality with revascularisation plus medical therapy vs. medical therapy alone in relation to follow-up duration. Size of data markers is proportional to size of trial. The solid line represents the meta-regression slope of the change in cardiac death rate ratio for revascularisation plus medical therapy vs. medical therapy alone with increasing length of follow-up. Rate ratios lower than 1 indicate cardiac death reduction with revascularisation. RR, rate ratio; MT, medical therapy.

main inclusion and exclusion criteria and the risk of bias assessment are reported in Supplementary material online, *Tables S2 and S3*. Eligible trials did not include left main lesions, except for the European Coronary Surgery Study (ECSS)[25] (<8%) and Veterans Administration Cooperative Study (VA) (13%).[48] Average follow-up was 5.7 years (95% CI 3.60–7.76). Overall, 13 trials were at low risk of bias in all domains, 11 presented some concern, and 1 was at high risk of bias (Supplementary material online, *Table S3*). The patterns of

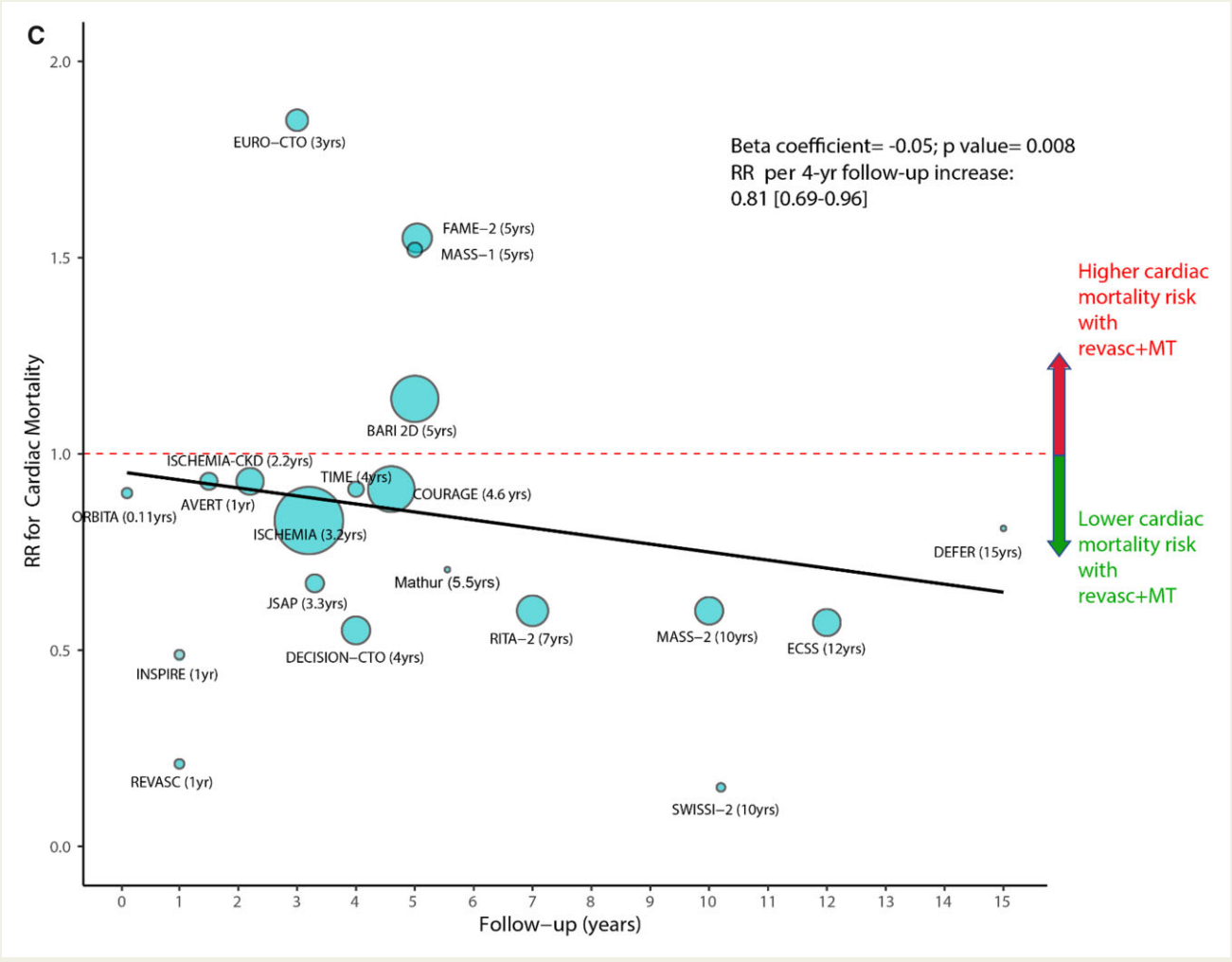


Figure 2 Continued.

medical therapy for trials reporting cardiac mortality are shown in Supplementary material online, *Table S4*.

Cardiac mortality

A total of 20 trials including 17 454 patients contributed to the cardiac mortality outcome. Overall, 456 of 8946 patients (5.09%) randomised to elective revascularisation plus medical therapy vs. 528 of 8508 patients (6.20%) randomised to medical therapy alone died of cardiac causes. Heterogeneity was low (I^2 = 21%). Funnel plot distributions of RRs and Egger's test indicated absence of publication bias (Supplementary material online, *Figure S1* and *Table S5*). Cardiac mortality was significantly lower with allocation to revascularisation plus medical therapy compared with medical therapy alone: RR 0.79 [0.67–0.93], $P < 0.01$ (random-effects model, *Figure 2A*). A comparable result was observed using a fixed-effect model: RR 0.80 [0.70–0.90], $P < 0.01$ (Supplementary material online, *Figure S2*).

A lower risk of cardiac death with revascularisation plus medical therapy vs. medical therapy alone persisted after excluding trials enrolling only post-ACS patients [RR 0.82 (0.73–0.94), $P < 0.01$], trials of CTOs [RR 0.80 (0.67–0.95), $P < 0.01$], and trials with CABG use in the revascularisation arm >30% [RR 0.83 (0.71–0.98), $P = 0.03$] (*Figure 2B*). In a further sensitivity analysis excluding studies that could enrol, by protocol, within 2 months post-ACS, the cardiac mortality benefit of revascularisation plus medical therapy compared with medical therapy alone was substantially unchanged: RR 0.82 [0.70–0.96], $P = 0.01$ (Supplementary material online, *Figure S3*). The lower risk of cardiac death with revascularisation plus medical therapy vs. medical therapy alone was also maintained omitting each study one at a time (Supplementary material online, *Figure S4*), omitting the three studies that reported cardiovascular mortality (Supplementary material online, *Figure S5*), or omitting studies presenting a potential risk of bias [RR 0.76 (0.65–0.87), $P < 0.01$; Supplementary material online, *Figure S6*].

The effect of follow-up duration on risk of cardiac death was explored by meta-regression: for each 4-year follow-up increase, the risk of dying from cardiac causes declined significantly by 19% with allocation to revascularisation plus medical therapy vs. medical therapy alone [RR 0.81 (0.69–0.96), $P = 0.008$; *Figure 2C*]. The inter-trial

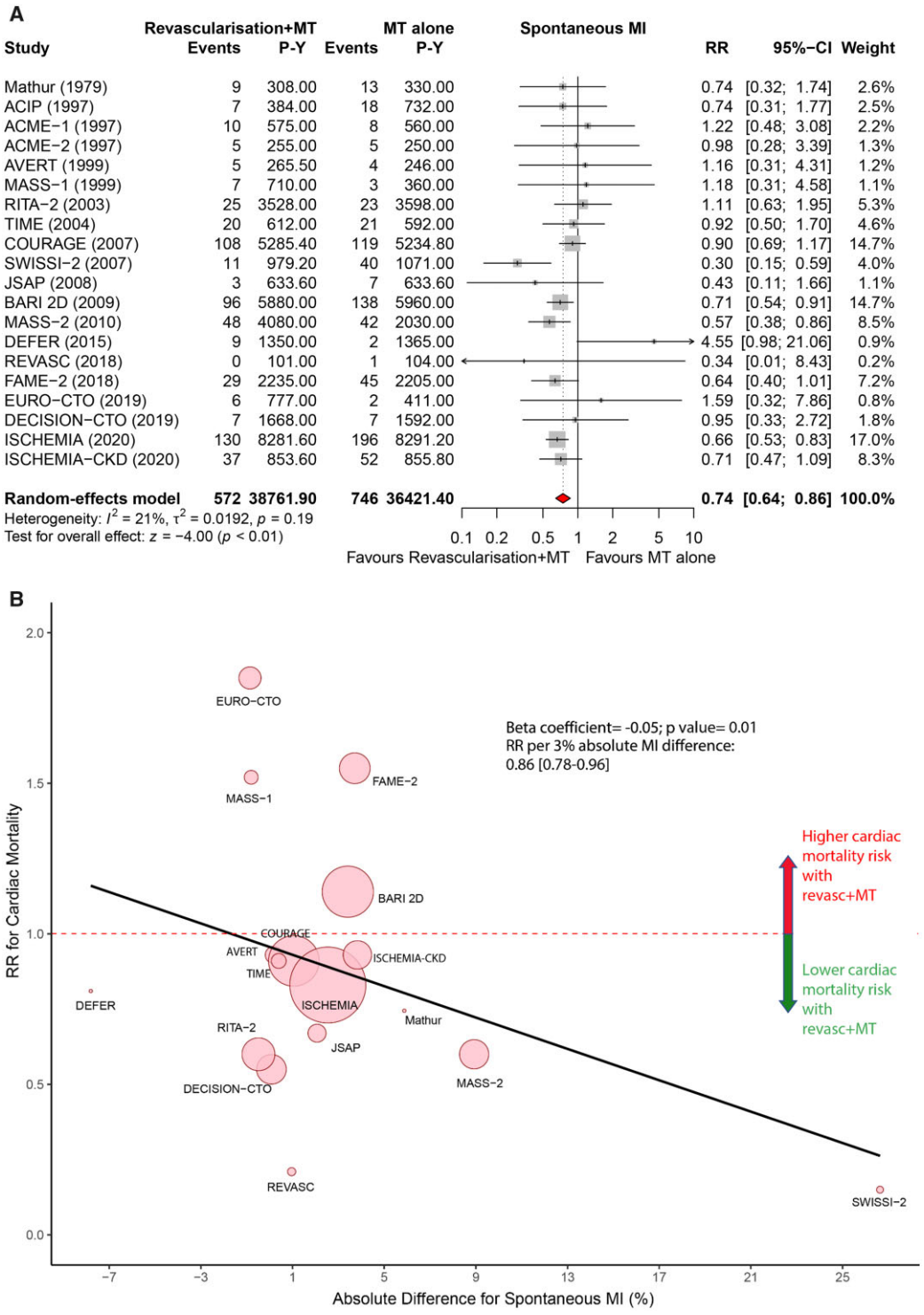


Figure 3 (*A*) Rate ratios and 95% confidence intervals for spontaneous myocardial infarction with revascularisation plus medical therapy vs. medical therapy alone. Size of data markers is proportional to weight in meta-analysis. CI, confidence interval; MI, myocardial infarction; MT, medical therapy; P-Y, person-years; RR, rate ratio. (*B*) Meta-regression of rate ratios for cardiac mortality with revascularisation plus medical therapy vs. medical therapy alone in relation to absolute difference in spontaneous myocardial infarction. Size of data markers is proportional to size of trial. The solid line represents the meta-regression slope of the change in cardiac death rate ratio for revascularisation plus medical therapy vs. medical therapy alone across increasing absolute differences for myocardial infarction. Rate ratios lower than 1 indicate cardiac death reduction with revascularisation. MI, myocardial infarction; RR, rate ratio; MT, medical therapy.

variance for the cardiac mortality outcome appeared to be entirely attributable to length of follow-up, with an adjusted R^2 = 100%.

The percentage of multivessel disease was found, by meta-regression, to predict greater cardiac death reduction with revascularisation plus medical therapy compared with medical therapy alone (beta = -0.006, P = 0.004; Supplementary material online, *Figure S7A*). The per cent use of the most frequently employed drug types, i.e. antithrombotic agents (P = 0.27), statins (P = 0.71), beta-blockers (P = 0.91), or ACE-inhibitors/ARBs (P = 0.12), did not significantly influence the effect of revascularisation vs. medical therapy alone on the risk of cardiac death, nor did study year (P = 0.16; Supplementary material online, *Figure S7B–F*). The inter-trial variance for the cardiac mortality outcome was not attributable to medical therapy (R^2 = 0%).

On TSA, crossing of the cumulative Z-curve into both the traditional boundaries for statistical significance and the trial sequential monitoring boundary for benefit indicated that a sufficient level of evidence was reached to demonstrate superiority of revascularisation plus medical therapy over medical therapy alone in reducing cardiac mortality (Supplementary material online, *Figure S8*).

All-cause mortality

A total of 23 trials involving 19 260 patients contributed to the analysis of all-cause mortality. Overall, 1234 of 9745 patients (12.66%) randomised to elective revascularisation plus medical therapy vs. 1276 of 9515 (13.41%) randomised to medical therapy alone died of any cause. Heterogeneity was absent (I^2 = 0%). There was evidence of publication bias on visual inspection and by Egger's test (Supplementary material online, *Figure S9* and *Table S5*). Overall, no significant difference in all-cause mortality was observed between treatment arms using the random-effects [RR 0.94 (0.87–1.01), P = 0.11; Supplementary material online, *Figure S10*] or a fixed-effect [RR 0.93 (0.86–1.01), P = 0.08; Supplementary material online, *Figure S11*] model. We investigated potential reasons for publication bias by excluding the trial at highest risk, given a 66% crossover rate from medical therapy to revascularisation;[48] this resulted in absence of publication bias (Egger's P = 0.14) and in a significant 10% all-cause mortality reduction for revascularisation plus medical therapy over medical therapy alone: RR 0.90 [0.83–0.99], P = 0.03 (Supplementary material online, *Figure S12*).

Myocardial infarction

A total of 20 trials involving 17 168 patients contributed to the analysis of spontaneous MI. Overall, 572 of 8701 patients (6.57%) randomised to elective revascularisation plus medical therapy vs. 746 of 8467 patients (8.81%) randomised to medical therapy alone experienced a spontaneous MI. Heterogeneity was low (I^2 = 21%). Funnel plot inspection and Egger's test indicated absence of publication bias (Supplementary material online, *Figure S13* and *Table S5*). Compared with medical therapy alone, revascularisation plus medical therapy yielded a significantly lower risk of spontaneous MI, with an RR of 0.74 [0.64–0.86], P < 0.01 (*Figure 3A*). Consistent results were observed using a fixed-effect model (Supplementary material online, *Figure S14*). The association between absolute difference for spontaneous MI and risk of cardiac death was explored by meta-regression: the risk of cardiac death with revascularisation plus medical therapy vs. medical therapy alone declined significantly [RR 0.86 (0.78–0.96), P = 0.01] for each 3% absolute reduction of spontaneous MI (*Figure 3B*). A lower risk of spontaneous MI favouring revascularisation plus medical therapy vs. medical therapy alone persisted after excluding specific settings: post-ACS [RR 0.75 (0.67–0.84), P < 0.01], CTOs [RR 0.74 (0.63–0.86), P < 0.01], and bypass use >30% [RR 0.78 (0.64–0.94), P = 0.01] (*Figure 2B*).

A total of 20 trials including 17 168 participants contributed to the results of any MI (procedural or spontaneous). Funnel plot distributions of RRs and Egger's test indicated absence of publication bias (Supplementary material online, *Figure S15* and *Table S5*). Heterogeneity was high (I^2 = 54%). Overall, 787 of 8701 patients (9.04%) allocated to revascularisation plus medical therapy vs. 849 of 8467 (10.02%) allocated to medical therapy alone experienced an MI episode, with no significant difference between treatment arms: RR 0.87 [0.73–1.05], P = 0.14 (Supplementary material online, *Figure S16*). Procedural MI was sparsely and heterogeneously reported (Supplementary material online,*Table S2*). By definition, rates of procedural MI were higher with revascularisation plus medical therapy compared with medical therapy alone [RR 2.13 (1.27–3.58), P < 0.01]. Heterogeneity was high (I^2 = 57%), likely driving the high heterogeneity for any MI. By meta-regression, unlike spontaneous MI, the absolute difference in procedural MI did not impact cardiac death (beta = -0.14; P = 0.16; Supplementary material online, *Figure S17*).

Stroke

A total of 13 trials involving 14 882 patients contributed to the analysis of stroke. Overall, 170 of 7588 patients (2.24%) receiving elective revascularisation plus medical therapy vs. 131 of 7294 (1.80%) receiving medical therapy alone suffered a stroke. Heterogeneity was moderate (I^2 = 27%). The risk for stroke did not differ significantly between strategies: RR 1.18 [0.86–1.60], P = 0.30 (Supplementary material online, *Figure S18*). The fixed-effect model yielded comparable results (Supplementary material online, *Figure S19*). Funnel plot distribution of RRs and Egger's test indicated absence of publication bias (Supplementary material online, *Figure S20* and Supplementary material online, *Table S5*).

Discussion

The main new findings of the present meta-analysis comparing elective revascularisation plus medical therapy to medical therapy alone in a total of 19 806 clinically stable coronary artery disease patients (17 454 for the cardiac mortality outcome) are at least three-fold. First, a significantly lower risk of cardiac death was observed among patients randomised to revascularisation plus medical therapy compared with medical therapy alone. Of note, trial chronological order did not impact the findings and overall heterogeneity was low. Second, the cardiac survival benefit of revascularisation plus medical therapy increased progressively over time, with an incremental relative risk reduction of 19% for every 4 years of follow-up extension. Third, there was an association between the reduced risk of cardiac death and the difference between treatment arms in spontaneous MI. The cardiac survival benefit of revascularisation was enhanced by increasing percentages of multivessel disease across trials. Major findings on cardiac mortality reduction with revascularisation plus medical therapy vs. medical therapy alone are displayed in the *Graphical Abstract*.

Compared with medical therapy alone, timely coronary revascularisation is known to offer survival advantage in patients with ST-segment elevation ACS.[3] Similarly, clinically stable patients with a recent ACS might derive enhanced benefit from revascularisation in addition to medical therapy, compared with other chronic coronary syndrome patients. In a sensitivity analysis excluding trials that, by protocol, could enrol patients within 2-month post-ACS, we found that the cardiac mortality benefit of revascularisation remained substantially unchanged.

On meta-regression, longer follow-up was associated with an incremental cardiac survival benefit after randomisation to a revascularisation strategy. Remarkably, the totality of inter-trial variance in cardiac mortality was attributable to variability in length of follow-up (R^2 = 100%). Thus, the magnitude of cardiac mortality reduction appeared to be a function of both revascularisation and follow-up duration. Possible reasons for incremental cardiac survival benefits at longer follow-ups include: durable benefits of revascularisation in contrast to attenuation of medical adherence over time; fewer spontaneous MIs, and temporal dilution of early procedural complications following revascularisation.

The risk of spontaneous MI was significantly reduced in the revascularisation plus medical therapy arm compared with medical therapy alone. In contrast, the risk of any MI (procedural and spontaneous) did not differ significantly between treatments. We observed an association between reduction of spontaneous MI and reduced risk of cardiac death, offering a mechanistic understanding of the underpinnings for the cardiac death reduction observed with revascularisation plus medical therapy compared with medical therapy alone. In a previous analysis of trials comparing revascularisation plus medical therapy to medical therapy alone in chronic and ACS patients, spontaneous MI was found to predict cardiovascular death.[50] In ISCHEMIA, spontaneous MI events using either primary or secondary definitions during a 5-year follow-up (i.e., well beyond the dual antiplatelet therapy period in the revascularisation arm) were significantly more frequent with medical therapy alone and associated with subsequent cardiovascular death.[51] Evidence indicates an association between extent of myocardial ischaemia and risk of cardiovascular events, as well as between coronary atherosclerotic burden and adverse prognosis.[3] Our meta-regression supports this, as the percentage of multivessel disease at baseline was found to enhance the cardiac survival benefit of revascularisation plus medical therapy compared with medical therapy alone.

In the present meta-analysis, all-cause mortality was not significantly different after elective revascularisation plus medical therapy compared with medical therapy alone. Although directionally consistent, the strong cardiac, but non-significant all-cause, survival signal following revascularisation plus medical therapy can be attributed, at least in part, to opposing directions of cardiac vs. non-cardiac mortalities[50]: whereas cardiac mortality declined compared with medical therapy alone, deaths other than cardiac were bound to accrue over time (as total death rates will ultimately reach 100% regardless of treatment). Long-term all-cause mortality tends to be biased towards the null, based on competing risks that are not influenced by the interventions being studied and on the uncontrolled effects of care received late following study interventions.[52] The competing risk of non-cardiovascular modes of death, which may blunt the effect of revascularisation on all-cause mortality, becomes amplified with longer follow-up, limiting the reliability of all-cause mortality as a main endpoint.[52] Additionally, one relatively large and extended trial with a particularly high (66%) crossover from medical therapy alone to revascularisation plus medical therapy may have blunted a potential all-cause mortality benefit of revascularisation. Indeed, in a sensitivity analysis excluding the above trial, a significant reduction in all-cause mortality emerged favouring revascularisation, presumably driven by the reduced risk of cardiac death, which accounted for 39% of all deaths. Stroke risk did not differ significantly with revascularisation plus medical therapy vs. medical therapy alone.

Sensitivity meta-analyses excluding studies conducted entirely in post-ACS patients or entirely for CTOs or with CABG use >30% in revascularised patients confirmed the significant reduction of cardiac mortality following revascularisation plus medical therapy compared with medical therapy alone. Deleting each included trial in turn did not result in significant deviations from the original overall estimate, indicating that the overall association of cardiac mortality reduction with revascularisation plus medical therapy is sound.

By current standards, medical management in older trials was suboptimal and, it has been argued, may have favoured elective revascularisation plus medical therapy over medical therapy alone. In each trial, however, both treatment arms received medical therapy, which was generally comparable, preserving the capacity to assess the role of revascularisation on top of standard medical treatment. In the present analysis, the per cent use of any of the more frequently employed drug types, such as statins, antithrombotic agents, beta-blockers or ACE-inhibitors/ARBs, and study year did not influence the cardiac mortality findings, nor did any of the different drug types explain the variance of effect across trials (R^2 = 0%). A recent pooled analysis of trials in patients with diabetes showed a significant reduction of the composite of death, MI, and stroke with revascularisation plus medical therapy vs. medical therapy alone that accrued over time.[53] In that analysis, the benefit of revascularisation plus medical therapy was attenuated when lipid-lowering was suboptimal.[53] Thus, the benefits of revascularisation and of optimised medical therapy appear additive and the combination may be required to achieve maximal and durable prevention of adverse events.[54]

The findings of this meta-analysis may be insightful when interpreting the results of the ISCHEMIA trial, the largest and most recent comparing revascularisation plus medical therapy vs. medical therapy alone in patients with stable ischaemic syndromes. In that study, coronary revascularisation with percutaneous intervention or bypass grafting plus medical therapy did not significantly improve the primary composite endpoint nor reduce cardiovascular mortality at a median follow-up of 3.2 years. However, the primary endpoint time-to-event curves for the two treatment arms crossed at ~2 years and then continued to diverge in favour of revascularisation plus medical therapy. Although ISCHEMIA was underpowered to conclude on single hard endpoints, a signal for reduced cumulative cardiovascular death at 5 years in favour of revascularisation plus medical therapy was present, with a 1.3% absolute reduction. None of the trials was powered for cardiac mortality. The present meta-analysis allows less frequent events such as cardiac mortality to be estimated in a powered fashion.

Our analysis differs from a recent one, which did not observe a cardiac mortality reduction after elective coronary revascularisation plus medical therapy compared with medical therapy alone.[55] In that

analysis, longest follow-up times were not always considered; a lower number of pertinent trials was included, and the impact of follow-up duration as treatment-effect modifier was not explored in depth.[55] We expanded upon this previous analysis to encompass the longest and broadest randomised evidence comparing elective revascularisation plus medical therapy to medical therapy alone in clinically stable patients, after excluding predefined subgroups with proven benefits from revascularisation. By pooling data at longest follow-up, expanding sample size, focusing on follow-up duration, extracting homogeneous modes of death from included trials and exploring plausible causal relations, the present meta-analysis shows a robust and consistent reduction of cardiac mortality in favour of elective coronary revascularisation plus medical therapy, directly associated with duration of follow-up and with lower risk of spontaneous MI.

Limitations

Trial-level data were included. However, consistency between the overall and the sensitivity analyses supports the robustness of the findings. Deleting each trial in turn did not produce significant deviations from the original overall estimate. Plausibility is supported by the meta-regressions associating cardiac mortality benefits with length of follow-up and with absolute risk difference for spontaneous MI. Trial sequential analysis confirmed reliability of the meta-analysis. Crossover from medical therapy alone to revascularisation plus medical therapy may have diluted the effect of revascularisation.[56] High heterogeneity observed for any MI was likely driven by heterogeneous reporting and definitions of procedural MI. Heterogeneity across studies in the per cent use and type of coronary stents, and lack of individual patient data, prevent a precise characterisation of stent effects on outcomes. Similarly, lack of outcome data stratified by number and type of diseased vessels prevents precise characterisation of disease extent on outcomes, although an association between cumulative percentage of multivessel disease at baseline and cardiac survival benefit of revascularisation was found.

Conclusions

The present large-scale analysis of randomised trials shows a significant and consistent reduction of cardiac mortality in favour of elective coronary revascularisation plus medical therapy compared with medical therapy alone in stable coronary artery disease patients, the magnitude of which is directly associated with duration of follow-up and a lower risk of spontaneous MI. Lower cardiac mortality with revascularisation plus medical therapy was confirmed in all sensitivity analyses performed. The findings have direct implications for elective cardiac catheterisation procedures in stable patients with documented coronary artery disease. Recommendations for medical therapy alone based on trials with limited follow-up have likely underestimated the benefits of revascularisation plus medical therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The authors report no specific funding related to this article. All authors had full access to all the data and accept responsibility for the decision to submit for publication.

Conflict of interest: Dr E.P.N. reports research grants from Abbott, Amgen, and lecture fees/honoraria from Amgen, AstraZeneca, Bayer, Pfizer, and Sanofi-Regeneron, outside the submitted work. Dr D.J.K. reports personal fees from SINO Medical Sciences Technologies, Inc., Boston Scientific Corporation, Elixir Medical, Inc., Svelte Medical Systems, Inc., Caliber Therapeutics/Orchestra Biomed, and Shockwave, other from Ablative Solutions, Inc., outside the submitted work. Dr P.A.G. reports grants and personal fees from Bayer HealthCare LLC, Otitopic Inc, Amgen, Janssen, and US WorldMeds LLC, from Instrumentation Laboratory, Haemonetics, Medicure Inc, Idorsia Pharmaceuticals, and Hikari Dx, Novartis, personal fees from UpToDate, outside the submitted work; in addition, Dr P.A.G. has a patent Detection of restenosis risk in patients and Assessment of cardiac health and thrombotic risk in a patient issued; Dr P.A.G. is a relator and expert witness in litigation involving clopidogrel. Dr D.A.G. reports institutional research grants from Bayer and Bristol Myers Squibb and speaker fees from AstraZeneca, Bayer and Boehringer-Ingelheim. Dr D.E.K. reports grants from Boston Scientific, personal fees from Biotronik, grants and personal fees from Cardiovascular Systems, Inc., grants from Medtronic, outside the submitted work. Dr N.C. reports grants, personal fees, and non-financial support from Boston Scientific, Haemonetics, and Heartflow; grants from Beckmann Coulter; non-financial support from Biosensors and Medtronic; personal fees and non-financial support from Abbott, outside the submitted work. Dr M.V. reports personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFLOW, IDORSIA PHARMACEUTICALS LTD, Universität Basel | Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, iVascular, Medscape, and Biotronik; grants and personal fees from Terumo, outside the submitted work. Dr M.B. has received consulting fees/honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo, outside the submitted work. Dr R.W. reports consulting fees/honoraria from Amgen inc., Biotronik, Abbott Vascular, Boston Scientific, Medtronic, Cardiovascular Systems Inc., Chiesi, MedAlliance, Pi-Cardia LTD, and Transmural Solutions. Dr M.B.L. reports Consultant Fees/Honoraria from Abbott, Boston Scientific, and Medtronic. Research grants from Edwards Lifesciences, Ownership: Claret. Dr W.W. reports institutional grant and honoraria from MicroPort; medical advisor of Rede Optimus Research and co-founder of Argonauts, an innovation facilitator. Dr F.A. reports lecture/consultancy fees from Amgen, Bayer, BMS/Pfizer, and Daiichi Sankyo. The other authors have no conflicts to declare.

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