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RESEARCH ARTICLE

Coronary revascularization for heart failure with coronary artery disease: A systematic review and meta-analysis of randomized trials

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Aims Coronary artery disease (CAD) is a common cause of heart failure (HF). Whether coronary revascularization improves outcomes in patients with HF receiving guideline-recommended pharmacological therapy (GRPT) remains uncertain; therefore, we conducted a systematic review and meta-analysis of relevant randomized controlled trials (RCTs).

Methods and results We searched in public databases for RCTs published between 1 January 2001 and 22 November 2022, investigating the effects of coronary revascularization on morbidity and mortality in patients with chronic HF due to CAD. All-cause mortality was the primary outcome. We included five RCTs that enrolled, altogether, 2842 patients (most aged <65 years; 85% men; 67% with left ventricular ejection fraction ≤35%). Overall, compared to medical therapy alone, coronary revascularization was associated with a lower risk of all-cause mortality (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.79–0.99; $p = 0.0278$) and cardiovascular mortality (HR 0.80, 95% CI 0.70–0.93; $p = 0.0024$) but not the composite of hospitalization for HF or all-cause mortality (HR 0.87, 95% CI 0.74–1.01; $p = 0.0728$). There were insufficient data to show whether the effects of coronary artery bypass graft surgery or percutaneous coronary intervention were similar or differed.

Conclusions For patients with chronic HF and CAD enrolled in RCTs, the effect of coronary revascularization on all-cause mortality was statistically significant but neither substantial (HR 0.88) nor robust (upper 95% CI close to 1.0). RCTs were not blinded, which may bias reporting of the cause-specific reasons for hospitalization and mortality. Further trials are required to determine which patients with HF and CAD obtain a substantial benefit from coronary revascularization by either coronary artery bypass graft surgery or percutaneous coronary intervention.

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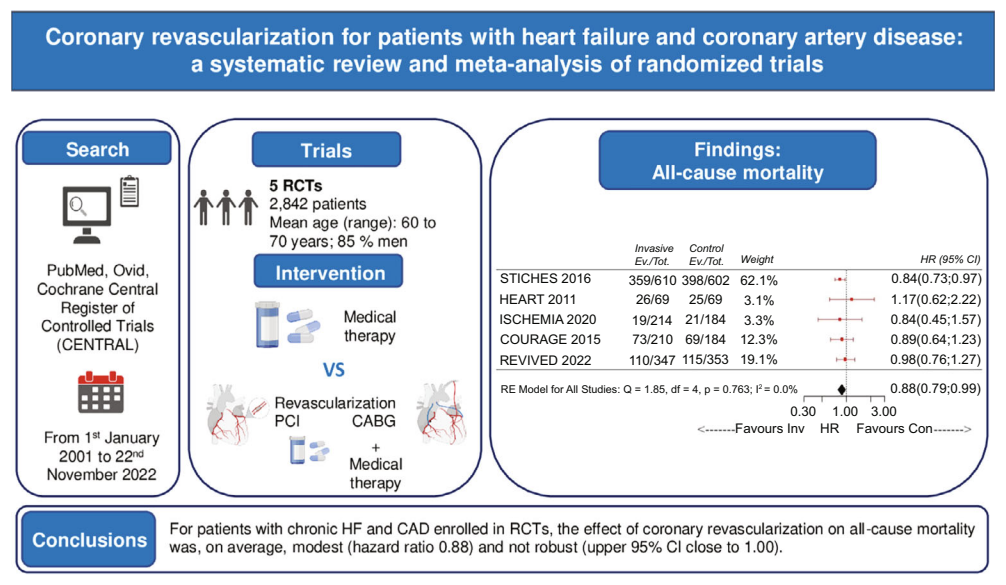
Graphical Abstract



In patients with heart failure (HF) and coronary artery disease (CAD), coronary revascularization was associated with a lower risk of all-cause mortality and cardiovascular mortality but not the composite of hospitalization for HF or all-cause mortality. Further trials are required to determine which patients with HF and CAD may obtain a benefit from coronary revascularization. CABG, coronary artery bypass; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

Keywords Heart failure • Coronary artery disease • Revascularization

Introduction

Coronary artery disease (CAD) is a common cause of heart failure (HF), present in more than half of patients with a reduced left ventricular ejection fraction.[1] Patients with HF and CAD have a poor prognosis, perhaps because they must contend not only with the effects of myocardial dysfunction but also recurrent myocardial ischaemia and infarction that can cause further myocardial damage and arrhythmias.[2] In contemporary clinical practice, many patients with HF and CAD are referred to, and undergo, coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in the hope that this might improve cardiac function, symptoms, and long-term outcomes[3] but it is uncertain that revascularization is superior in any respect to guideline-recommended pharmacological therapy (GRPT) alone for this population, other than for the relief of angina.[4–7]

Guidelines on HF from both the European Society of Cardiology (ESC)[8] and American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA)[9] recommend coronary revascularization for patients with HF with reduced ejection fraction (HFrEF) and CAD but diverge in terms of strength of recommendation. Whereas ESC guidelines have a class IIa-B recommendation, meaning that revascularization should be considered based on one substantial trial,[5] AHA/ACC/HFSA guidelines have a class I-A recommendation, meaning a strong recommendation based on a substantial array of evidence. ESC guidelines on HF also suggest that PCI may be considered as an alternative to CABG, but AHA/ACC/HFSA guidelines recommend only CABG. In contrast, ESC guidelines on myocardial revascularization recommend CABG for severe left ventricular systolic dysfunction when coronary artery anatomy is suitable for intervention (I-B), with PCI as a less favoured alternative.[10] Recently, two new randomized controlled trials (RCTs) have reported on the effects of coronary revascularization with conflicting results (REVIVED[7] and the ISCHEMIA HF subset[11]).

In view of these conflicting recommendations, uncertainties, and new evidence, we conducted a systematic review and meta-analysis of RCTs to evaluate the effects of coronary revascularization on morbidity and mortality in patients with HF and CAD.

Methods

Search strategy

The protocol for analysis was registered prior to data extraction and analysis in PROSPERO (registration number: CRD42022367240).

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Using a set of pre-specified search terms developed by four cardiologists (AI, AR, MB and GP) informed by a senior co-author (PP) (online supplementary material), we searched public databases (PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) for RCTs that investigated the effects of elective coronary revascularization (PCI, CABG, or both) on morbidity and mortality in patients with CAD and HF. The search was conducted on 22 November 2022. Four authors (AI, AR, MB and GP) independently screened abstracts and full manuscripts; any disagreement was resolved by consensus or with the help of a senior co-author when required (PP, JGFC). Only manuscripts written in English and published between 1 January 2001 and 22 November 2022 were included. Four authors (AI, DD, NA, GP) extracted data independently. Data extraction included: trial data (number of patients enrolled, year of publication, type of revascularization, number on centres involved, mean length of follow-up, main inclusion and exclusion criteria), clinical information, including patient demographics, blood tests, comorbidities, severity of CAD, treatments and, after randomization, clinical events of interests. We report outcomes at the longest follow-up time point available for each trial, including the long-term extension of the STICH trial[5] (STICHES; median follow-up 9.8 years) but also conducted an additional analysis based on the primary publication of STICH (median follow-up 4.7 years).[12]

All-cause mortality was the primary endpoint; we also pre-specified several secondary endpoints including cardiovascular mortality, hospitalization for HF, composite of hospitalization for HF or all-cause mortality, incident stroke and, finally, all-cause mortality with the exclusion of deaths within 90 days of enrolment to exclude perioperative deaths.

Selection and risk of bias assessment

Assessment for risk of bias was conducted by AI and EC, using the components recommended by the Cochrane Collaboration as outlined by the Cochrane Handbook for Systematic Reviews, available online (www.training.cochrane.org/handbook): sequence generation of allocation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Statistical analyses

The meta-analysis was reported in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.training.cochrane.org/handbook). To compare coronary revascularization strategies versus medical therapy, pooled estimates of the hazard ratios (HR)s for the outcomes selected and corresponding 95% confidence intervals (CIs) were estimated through a meta-analysis, using a random-effect model to account for heterogeneity among studies. Heterogeneity across studies was assessed by Cochran's Q method and by Higgins and Thompson I^2. Low heterogeneity was defined as an I^2 value less than 25%, moderate heterogeneity as a value of 25–50%, and high heterogeneity as a value larger than 50%. Publication bias was assessed by visual asymmetry on funnel plots of HRs centred at comparison-specific effect against standard errors. We also performed Egger's regression test for funnel plot asymmetry, to verify whether the association between effect sizes and the related standard error was statistically significant. To evaluate the robustness of results and to show whether any trial influenced the overall estimate of the meta-analysis, a leave-one-out analysis, in which the results of the meta-analysis are recalculated each time leaving out one trial, was performed.

All statistical analyses were performed using the statistical software R (The R Project for Statistical Computing, Vienna, by 'metafor' package). The metafor R package was used for meta-analysis. The significance level for all the tests was set to $\alpha = 0.05$.

Since HRs and CIs for all-cause mortality were not provided by the HEART[6] trial, nor for the subset of patients with HF in the COURAGE[13] trial, we extracted these data from the Kaplan–Meier curves for the HEART trial and from the forest plots for the COURAGE trial, adopting the WebPlotDigitizer software (https://automeris.io/WebPlotDigitizer).

Results

Trial selection and risk of bias

After removing 74 170 records by screening titles and abstracts, the remaining 491 articles were fully evaluated. Of these, 31 manuscripts from five clinical trials of patients with stable CAD and HF and/or a reduced left ventricular ejection fraction (LVEF) were considered for inclusion in this meta-analysis (*Figure 1*, *Table 1*). One trial (STICH[4,12,14–18] and with extended follow-up STICHES[5,19]) investigated the effect of CABG in patients with HFrEF. Two trials (HEART[6] and ISCHEMIA[11,20–30]) investigated a strategy of coronary angiography with the intent to do CABG or PCI if and as appropriate. Two trials (COURAGE[13,31–37] and REVIVED[7]) investigated the effect of PCI. No trial was designed to blind either the patient (technically feasible only for PCI) or investigators (technically feasible to blind those doing assessments although not procedures). All RCTs were otherwise deemed to have a low risk of bias in all domains (online supplementary *Figure S1*).

Baseline characteristics and outcomes

A total of 2842 patients with HF (mean age ranging among trials from 60 to 70 years; 85% men; 67% with LVEF ≤35%) were enrolled (*Table 2*). The great majority of patients were aged <70 years except in the REVIVED trial, where the median age was 70 years.

Outcomes for each trial are reported in *Table 3*. No trial found that revascularization reduced all-cause mortality, including the primary analysis of the STICH trial (HR 0.86, 95% CI 0.71–1.04). However, with longer-term follow-up of the STICH trial (STICHES), an effect was observed in a second analysis (HR 0.84, 95% CI 0.73–0.97), although it is not clear if the analysis was adjusted for the additional comparison. The difference between STICH and STICHES reflected a reduction in the CIs around the treatment effect rather than a larger benefit. Of the five trials included in this meta-analysis, only STICH identified an effect on other outcomes, including cardiovascular mortality and hospitalization for HF.

Meta-analysis

Coronary revascularization was associated with a lower risk of all-cause mortality with no between-trial heterogeneity ($I^2 = 0$) (online supplementary *Figure S2*), although the effect was small and

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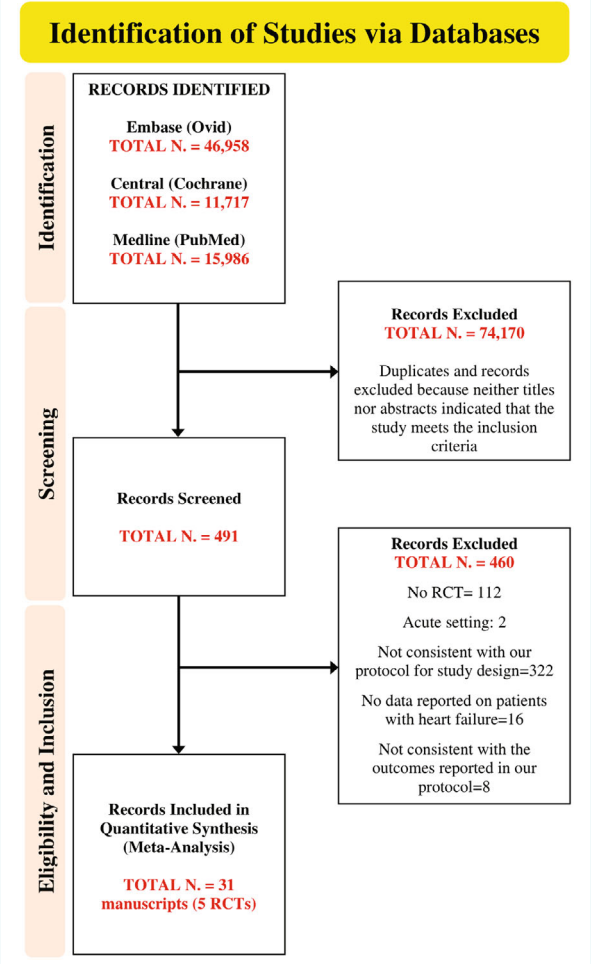

Figure 1 Study selection. RCT, randomized controlled trial.

not robust (HR 0.88, 95% CI 0.79–0.99; $p = 0.0278$) (*Figure 2A*). Coronary revascularization was also associated with a reduction in the risk of cardiovascular mortality (HR 0.80, 95% CI 0.70–0.93; $p = 0.0024$) (*Figure 2B*), but the effects on the composite of hospitalization for HF or all-cause death (HR 0.87, 95% CI 0.74–1.01; $p = 0.0728$) (*Figure 2C*) and hospitalization for HF alone (HR 0.80, 95% CI 0.62–1.03; $p = 0.0889$) (*Figure 2D*) were not statistically significant.

If the results of STICHES are replaced with those of STICH, then the effect of revascularization on all-cause mortality was no longer statistically significant (HR 0.91, 95% CI 0.79–1.05; $p = 0.1970$) (online supplementary *Figure S3A*), the effect on cardiovascular death was less certain (HR 0.82, 95% CI 0.69–0.97; $p = 0.0235$) (online supplementary *Figure S3B*) but there was little change in the effect on the composite of hospitalization for HF and all-cause death (HR 0.88, 95% CI 0.77–1.00; $p = 0.0477$) (online supplementary *Figure S3C*) or hospitalization of HF alone (HR 0.80, 95% CI 0.61–1.04) (online supplementary *Figure S3D*).

Compared to management with pharmacological and device therapy alone, there was little evidence of a survival advantage for revascularisation either by PCI or when the method of revascularisation was chosen by investigators (online supplementary Figure S4) but the effect of CABG did not appear substantially different from other revascularisation strategies (*Figure 2*).

Leave-one-out analysis was performed only for all-cause mortality. Other outcomes were not assessed because few trials reported them. Pooled estimates were recalculated by excluding one trial at a time and arranged in ascending order of the size effect. Using data from the longest follow-up, the pooled estimates remained mostly unchanged, except when the STICHES was omitted. Omission of STICHES resulted in a loss of statistical significance for the pooled effects (online supplementary *Figure S5*).

Discussion

In patients with HF due to CAD it is still uncertain if, how, and in whom elective coronary artery revascularization should be attempted. In the present analysis, we found that revascularization might reduce the risk of all-cause mortality in patients with HF due to CAD, but the effect is not substantial, largely driven by the long-term extension of the STICH trial, and the 95% CI barely excludes neutrality (*Graphical Abstract*). Although there may have been fewer cardiovascular deaths or hospitalizations for HF after revascularization, these outcomes may be prone to bias because the trials were not blinded.

The clinical decision to advise a patient with HF and CAD to have CABG or PCI may currently be based more on opinion than on objective evidence, and influenced by the oculo-stenotic reflex.[38] The hypothesis that revascularization might protect the myocardium from further damage and therefore retard the progression of HF and reduce the risk of sudden death is perfectly reasonable, but requires robust proof to justify the procedural morbidity, risk and cost.[39,40] Strongly held opinions may be the barrier to the conduct of RCTs that might prove that revascularization actually does improve outcomes. A clinician may believe that one patient is an ideal candidate for and must have coronary revascularization but deem it very unwise to intervene on another. Only when the clinician is in doubt about what to do, will they be willing to approach a patient and ask them to participate in a randomized trial. After receiving information about the trial, a patient is only likely to agree to participate when they concur that the balance of potential risks and benefits is acceptable. However, RCTs with neutral results are likely to shift the equipoise of both patients and physicians; greater uncertainty may enable randomization of patients that were previously considered ideal candidates for revascularization. Accordingly, clinical trials and the nature of the patients enrolled in them may evolve over time.

Coronary artery bypass graft surgery carries a substantial perioperative morbidity and mortality for patients with HF. Perioperative mortality was 5% in the STICH trial and it took >2 years before there was a trend to a survival benefit from CABG, which did not become statistically significant until follow-up was substantially longer than 5 years. Even so, the effect on mortality after almost 10 years of follow-up was modest (HR 0.84) and the upper 95% CI (0.97) barely excluded neutrality. Estimating outcome based

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Table 1 Key aspects of the design of the trials included in the meta-analysis

	COURAGE (2007)[a]	HEART (2011)	STICH (2011) and STICHES (2016)	ISCHEMIA (2020)	REVIVED (2022)
Type of revascularization	PCI	Angiography with intention for PCI or CABG	CABG	Angiography with intention for PCI or CABG	PCI
Country (enrolling centres)	US and Canada (50 centers)	UK (13 centres)	Multinational (127 centres)	Multinational (320 centres)	UK (40 centres)
Patients (intervention:control)	394[b] (210:184)	138 (69:69)	1212 (610:602)	398[b] (214:184)	700 (347:353)
Standard of care	Standard of care	Standard of care	Standard of care	Standard of care	Standard of care
Mean follow-up (months)	55	59	56 (for STICH) 118 (for STICHES)	38	41
Main inclusion criteria					
LVD/HF criteria	HF LVEF 30–50%	HF LVEF ≤35%	HF LVEF ≤35%	Diagnosis of HF before randomization regardless of LVEF	LVEF ≤35% +/− HF
CAD criteria	>1 substantial vessel amenable to PCI	CAD amenable to revascularization	CAD amenable to CABG	NA	Extensive CAD[c], amenable to PCI
Ischaemia/viability criteria	Objective evidence of myocardial ischaemia or severe symptoms	Viability in ≥5 myocardial segments with contractile dysfunction[e]	Not required	At least moderate ischaemia on a qualifying stress test	Viability in ≥4 myocardial segments with contractile dysfunction[e]
Main exclusion criteria					
NYHA class				III or IV	IV
LVEF	<30%[d]			<35%	
Recent ACS or stroke	+	+	+	+	+
Recent revascularization	+			+	
LMCA	+			+	
Coronary lesions unsuitable	For PCI			+	For PCI
Angina requiring revascularization		+		+	
Need for valve surgery	+	+	+	+	+
Ventricular arrhythmias	+	+		+	+
Definition of primary and secondary outcomes					
Primary outcome	• Non- fatal MI or all-cause mortality	• All-cause mortality	• All-cause mortality	• Composite of hospitalization for MI, UA, HF or resuscitated cardiac arrest or CV death	• Hospitalization for HF or all-cause mortality
Secondary outcomes	• All-cause mortality • MI • Stroke • Hospitalization for angina		• CV mortality • CV hospitalization or CV death	• MI or CV death • • Angina-related QoL	• LVEF at 6 and 12 months • QoL scores

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; CV, cardiovascular; HF, heart failure; HEART, Heart Failure Revascularization Trial; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; LAD, left anterior descending artery; LMCA, left main coronary artery; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QoL, quality of life; REVIVED, Revascularization for Ischemic Ventricular Dysfunction; STICH, Surgical Treatment for Ischemic Heart Failure; STICHES, Surgical Treatment for Ischemic Heart Failure Extension Study; UA, unstable angina; UK, United Kingdom; US, United States.

[a]Data reported for this trial refer to the overall population since data from the subgroup on patients with HF were not provided.

[b]These numbers refer only to patients with HF.

[c]Defined as BCIS Jeopardy score ≥6.

[d]If three-vessel CAD – including >70% LAD proximal stenosis.

[e]17 segment model.

on published Kaplan–Meier curves for STICHES, for every 100 patients enrolled, about eight more patients would be alive at 10 years if assigned to CABG, but for 92 patients it would make no difference. Also, it is conventional to apply statistical adjustments when repeating analyses; it is not clear that the STICHES *p*-value ($p = 0.02$) was adjusted for the previous analysis of STICH. If a life expectancy of many years is required to reap the benefits of CABG, then older patients or those with multiple comorbidities are unlikely to benefit. Most patients with HF are aged >70 years. Analysis of STICHES suggested no reduction in cardiovascular or all-cause mortality for patients aged >60 years.[41] Older patients may be more prone to perioperative complications and mortality. Should guidelines recommend a treatment that carries serious risk when the great majority of patients with HF and CAD appear not to benefit? Overall, STICH did not show improvements in ventricular function,[42] symptoms (other than angina)[43] or exercise capacity,[44] although some improvement in quality-of-life scores was observed.[45] Reported reductions in hospitalization after CABG disregard the hospitalization required for the surgical procedure, which might be considered biased.

Analysis of patient subgroups from STICH/STICHES suggested that those with three-vessel disease, those who were not of

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Table 2 Baseline characteristics of the trial populations

	COURAGE (2007)[a]	HEART (2011)	STICH (2011) and STICHES (2016)	ISCHEMIA (2020)	REVIVED (2022)
No. of patients					
Invasive arm	210	69	610	214	347
Control arm	184	69	602	184	353
Age (years)	61[b]	67	60[b]	66	70[b]
Men, *n* (%)	1947 (85)	129 (93)	1064 (88)	315 (79)	614 (88)
Hypertension, *n* (%)	1521 (66)	69 (50)	728 (60)	322 (81)	391 (56)
DM, *n* (%)	766 (33)	51 (37)	478 (39)	184 (46)	289 (41)
Previous AMI, *n* (%)	876 (38)	101 (73)	934 (77)	146 (37)	372 (53)
Previous PCI, *n* (%)	359 (16)	11 (8)	156 (13)	137 (34)	142 (20)
Previous CABG, n (%)	248 (11)	11 (8)	36 (3)	31 (8)	34 (5)
NYHA class I–II, *n* (%)	NA	88 (64)	765 (63)	286 (72)	513 (74)
NYHA class III–IV, *n* (%)	NA	50 (36)	447 (37)	NA	182 (26)
LVEF (%)	NA	All patients have EF ≤35%	27[b]	44	27
LM CAD, *n* (%)	NA	NA	32 (3)	3 (1)	95 (14)
Three-vessel CAD, *n* (%)	696 (30)	NA	733 (60)	38/175 (22)	281 (40)
BBs, *n* (%)	1983 (87)	128 (93)	1036 (85)	351 (88)	634 (91)
ACE-I/ARBs, *n* (%)	1451 (63)	128 (93)	1111 (92)	328 (82)	587 (84)
ARNi, *n* (%)	NA	NA	NA	NA	38 (5)
SGLT2i, *n* (%)	NA	NA	NA	NA	NA
MRAs, *n* (%)	NA	49 (35)	556 (46)	36 (9)	346/697 (49)
Loop diuretics, *n* (%)	NA	130 (94)	791 (65)	146 (37)[c]	460/697 (66)[c]
ICD only, *n* (%)	NA	NA	203 (17)	NA	82 (12)
CRT, *n* (%)	NA	NA	NA	NA	67 (10)

ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; ICD, implantable cardioverter-defibrillator; LM, left main; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

[a]Data reported here refer to the overall population since numbers from the subgroup of patients with heart failure were not provided.

[b]These values refer to the intervention group since data on the overall population were not provided by the investigators and numbers on the control arm were similar to ones referring to intervention.

[c]It refers to number (proportion) of patients on a loop and/or a thiazide diuretic.

European descent and patients who were randomized to CABG plus surgical ventricular remodelling compared to medical therapy may have received more benefit.[5] It makes sense that more extensive CAD predicts a better response to CABG; the patient is at higher risk, there is less opportunity for the generation of an effective endogenous collateral blood supply and therefore more myocardium should be protected by revascularization. Patients with a better exercise capacity were more likely to obtain a prognostic benefit from CABG; such patients were younger, had fewer comorbidities and better quality-of-life scores and had lower perioperative mortality.[46] A low competing risk of dying from conditions that revascularization does not improve may be required to obtain substantial benefit from CABG. Rather like trials of implantable cardioverter-defibrillators (ICDs), long-term follow-up of patients with a relatively good prognosis may be most likely to show benefit.[47] The issue of race and age may be confounded. The striking benefit (HR for all-cause mortality 0.72, 95% CI 0.57–0.89) for patients who were neither from Europe nor North America (mainly India) may reflect both the younger age of patients as well as excellent surgery.[5] The surgical ventricular remodelling arm of the STICH trial did not show a difference in outcome with this procedure compared to CABG alone.[48]

Prior to RCTs of revascularization, there was much speculation that myocardial viability might predict response. However, what researchers mean by the term 'myocardial viability' varies.[49,50] In STICH, the term simply meant that the myocardium was viable, and included normally functioning myocardium supplied by an artery without significant stenosis, myocardial segments with reversible ischaemia, partial-thickness myocardial scar and 'hibernating' myocardium[51] with severe contractile dysfunction but without transmural scar. In the STICH trial, the presence of viability[42] was not associated with greater benefit from revascularization. The definition of 'myocardial viability' in the HEART and REVIVED trials was restricted to segments that had contractile dysfunction at rest or during stress imaging, but the outcome of these trials was neutral.[52]

No RCT has compared PCI to CABG in patients with HF despite an abundance of observational data that suggest greater long-term survival after CABG compared to PCI.[53] A large propensity-score adjusted analysis demonstrated that, in patients with LVEF ≤35% and multivessel or left main disease, PCI was associated with

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Table 3 **Endpoints of the trials included in the meta-analysis**

	COURAGE[a] (2007)[b]	HEART (2011)	STICH (2011)	STICHES (2016)	ISCHEMIA[a] (2020)	REVIVED (2022)
All-cause mortality						
Treatment *n* (%) vs Control *n* (%)	73 (35) vs 69 (37)	26 (38) vs 25 (36)	218 (36) vs 244 (41)	359 (59) vs 398 (66)	19 (9) vs 21 (11)	110 (32) vs 115 (33)
HR [95% CI]	0.89 [0.64–1.23]	1.17 [0.62–2.22]	0.86 [0.71–1.04]	0.84 [0.73–0.97]	0.84 [0.45–1.57]	0.98 [0.76–1.27]
Cardiovascular mortality						
Treatment *n* (%) vs Control *n* (%)	NA	NA	168 (28) vs 201 (33)	247 (40) vs 297 (49)	14 (6) vs 19 (10)	76 (22) vs 88 (25)
HR [95% CI]			0.81 [0.66–1.00]	0.79 [0.67–0.93]	0.69 [0.34–1.39]	0.88 [0.65–1.20]
Hospitalization for HF						
Treatment *n* (%) vs Control *n* (%)	NA	NA	127 (21) vs 169 (28)	157 (26) vs 201 (33)	8 (4) vs 9 (5)	51 (15) vs 54 (15)
HR [95% CI]			0.70 [0.56–0.88]	0.71 [0.57–0.89]	0.91 [0.35–2.39]	0.97 [0.66–1.43]
Composite (HFH OR ACM)						
Treatment *n* (%) vs Control *n* (%)	NA	NA	290 (48) vs 324 (54)	404 (66) vs 450 (75)	25 (12) vs 27 (15)	129 (37) vs 134 (38)
HR [95% CI]			0.84 [0.72–0.98]	0.81 [0.71–0.93]	0.88 [0.51–1.52]	0.99 [0.77–1.27]
Myocardial infarction						
Treatment *n* (%) vs Control *n* (%)	NA	NA	NA	NA	18 (8) vs 26 (14)	37 (11) vs 38 (11)
HR [95% CI]					0.58 [0.32–1.06]	1.01 [0.64–1.60]
Incident stroke						
Treatment *n* (%) vs Control *n* (%)	NA	NA	NA	NA	NA	NA
HR [95% CI]						
All-cause mortality[c]						
Treatment *n* (%) vs Control *n* (%)	NA	NA	NA	NA	NA	NA
HR [95% CI]						

ACM, all-cause mortality; CI, confidence interval; HF, heart failure; HFH, hospitalization for HF; HR, hazard ratio; NA, not available.

[a]Data reported here refer to the longest follow-up available and published in 2015.

[b]Data referring to the events occurred in the subset of patients with HF has beed collected from Sedlis SP et al.[13] and Lopes RD et al.[11] for COURAGE and ISCHEMIA, respectively.

[c]With the exclusion of the events occurred within 90 days after the enrollment.

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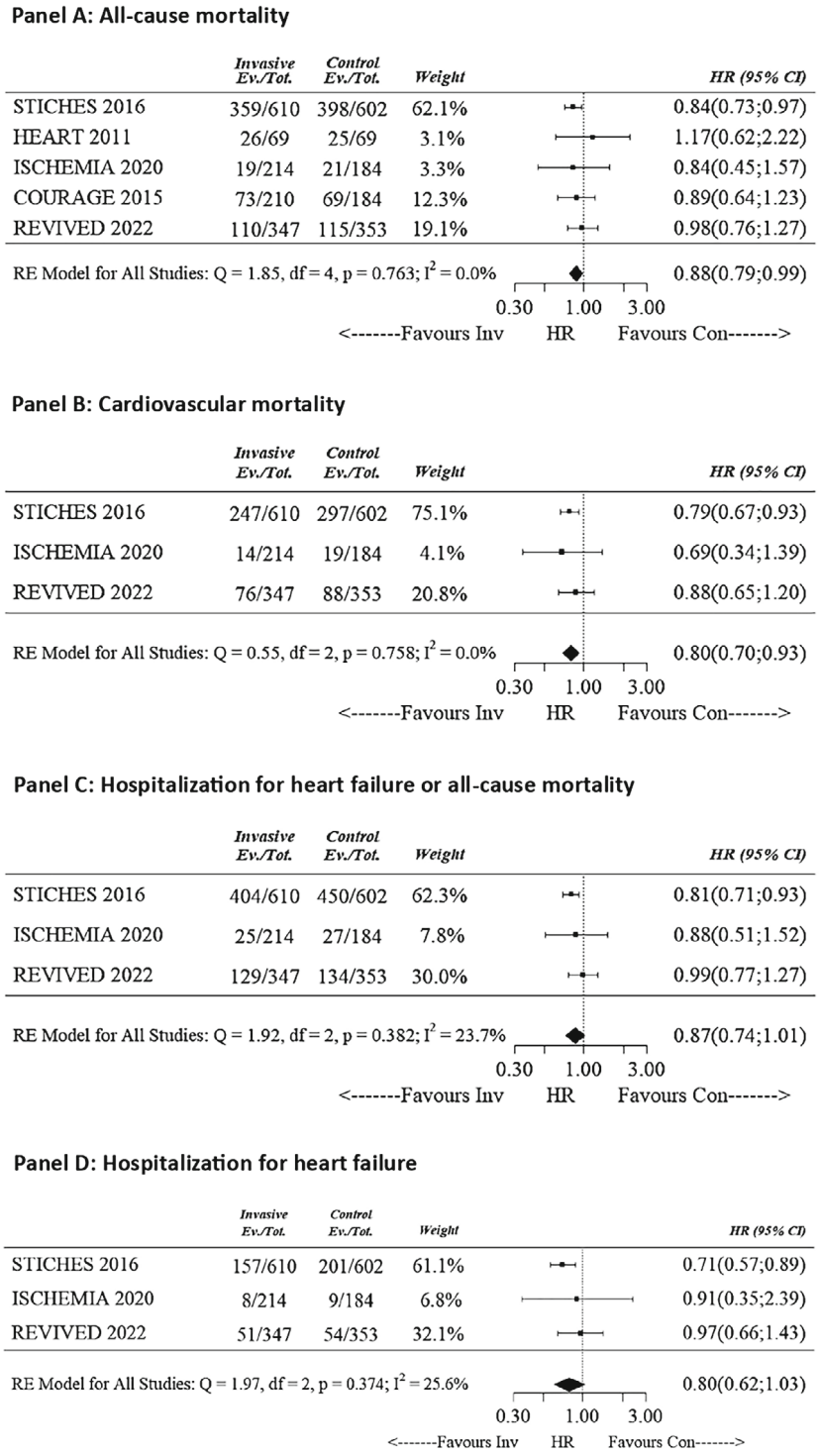

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greater risk of subsequent myocardial infarction, admissions for HF and mortality compared to CABG.[54] Recently, Pathak and colleagues used routinely collected electronic health records in the UK and a complex computational methodology to simulate a trial that compared CABG with PCI in patients with HF and CAD.[55] They suggested that CABG might be associated with a lower risk of cardiovascular hospitalization or mortality compared to PCI. Although the REVIVED trial was neutral (HR for all-cause mortality 0.98), the 95% CIs were wide (0.76 to 1.27) and did not exclude substantial harm or benefit. Moreover, the effect of PCI on the primary composite endpoint of REVIVED for patients aged <70 years (HR 0.86, 95% CI 0.59–1.24) was similar to that for the primary all-cause mortality endpoint of STICH (HR 0.86, 95% CI 0.72–1.04), which included few patients aged >70 years. From the perspectives of both patients and physicians, PCI has many advantages over CABG including more rapid recovery, fewer immediate post-procedural complications and potentially lower costs. When the reason for revascularization is relief of angina, this makes PCI an attractive option.

Limitations

We did not include observational studies in our analysis, which are susceptible to bias and confounding that render them an unreliable source of evidence and, accordingly, are given little weight in guidelines.[56] The trials were unblinded and this may have biased assessments of cause-specific hospitalizations and mortality. We could not allow for cross-over between randomized groups. Some patients assigned to revascularization did not receive it and many patients assigned not to receive revascularization nonetheless did so. Trials of revascularization should be considered as randomization to a strategy of 'immediate and routine' compared to 'delayed and selective' revascularization. Re-analysis of the STICH trial suggested a larger effect of revascularization if analyses were done according to assigned treatment but this deviates from the principle of analysis by intention-to-treat principle with all the confounding that introduces.[16] We did not include the results of older trials, such as CASS,[57] that enrolled patients in the 1970s, because we considered that the patient population, background pharmacological therapy and operative procedures had little relevance to contemporary clinical practice. However, the RCTs included in this analysis also pre-date recent advances in GRPT, which might further diminish the benefits of revascularization. Alternatively, contemporary GPRT could enhance the benefits of revascularization by reducing death from causes other than myocardial ischaemia and infarction. Moreover, although ESC guidelines on HF have given a class IA recommendation for implantation of an ICD for patients with CAD and an LVEF ≤35% since 2008, few patients in these trials received an ICD. Whether implantation of more ICDs would have changed the results of the RCTs is uncertain; prevention of arrhythmic deaths may or may not have improved survival similarly for patients with or without revascularization.

Some deviations from the original protocol should be acknowledged. For instance, we did not perform a meta-regression analysis to assess the role of covariates on outcomes due to the small number of trials identified. Moreover, we planned to assess the effect of different therapeutic strategies on stroke, myocardial infarction and on all-cause mortality excluding deaths within 90 days of enrolment, but we did not find this information, or it was very limited, which precluded additional meaningful analyses. Moreover, we used aggregated data and therefore could not investigate effects in subgroups according to the severity of CAD or presence of valve disease, type of stent used, use of HF medications and their dose, and use of device therapy including cardiac resynchronization therapy or ICDs.

Conclusions

This systematic review and meta-analysis of patients with stable HF and CAD found that revascularization was probably associated with some reduction in the risk of all-cause and cardiovascular mortality. However, these results were not robust, and the confidence around the point-estimate of effect barely excluded neutrality. Neither does this analysis provide evidence that the effect of CABG and PCI differ. Further RCTs are required to determine whether coronary revascularization can substantially improve outcomes compared to contemporary medical therapy alone for a subset of patients with HF and CAD, and whether this should be by PCI or CABG or a mixture of the two. RCTs should be embedded within a registry to find out which patients were deemed unsuitable for randomization and why.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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