Original Article

Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease

A Meta-Analysis

Georg Wolff, MD; Dimitrios Dimitroulis, MD; Felicita Andreotti, MD, PhD, FESC; Michalina Kołodziejczak, MD; Christian Jung, MD, PhD; Pietro Scicchitano, MD; Fiorella Devito, MD; Annapaola Zito, MD; Michele Occhipinti, MD; Battistina Castiglioni, MD; Giuseppe Calveri, MD; Francesco Maisano, MD; Marco M. Ciccone, MD; Stefano De Servi, MD; Eliano P. Navarese, MD, PhD, FESC

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Background**—**Heart failure with reduced ejection fraction caused by ischemic heart disease is associated with increased morbidity and mortality. It remains unclear whether revascularization by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) carries benefits or risks in this group of stable patients compared with medical treatment.

Methods and Results**—**We performed a meta-analysis of available studies comparing different methods of revascularization (PCI or CABG) against each other or medical treatment in patients with coronary artery disease and left ventricular ejection fraction ≤40%. The primary outcome was all-cause mortality; myocardial infarction, revascularization, and stroke were also analyzed. Twenty-one studies involving a total of 16 191 patients were included. Compared with medical treatment, there was a significant mortality reduction with CABG (hazard ratio, 0.66; 95% confidence interval, 0.61–0.72; $P<0.001$) and PCI (hazard ratio, 0.73; 95% confidence interval, 0.62–0.85; $P<0.001$). When compared with PCI, CABG still showed a survival benefit (hazard ratio, 0.82; 95% confidence interval, 0.75–0.90; $P<0.001$).

Conclusions**—**The present meta-analysis indicates that revascularization strategies are superior to medical treatment in improving survival in patients with ischemic heart disease and reduced ejection fraction. Between the 2 revascularization strategies, CABG seems more favorable compared with PCI in this particular clinical setting. **(*Circ Heart Fail*. 2017;10:e003255. DOI: 10.1161/CIRCHEARTFAILURE.116.003255.)**

Key Words: coronary artery bypass ■ coronary artery disease ■ heart failure ■ meta-analysis ■ myocardial infarction

Heart failure (HF) remains a major cause of morbidity and mortality worldwide.[1–4] With an incidence expected to rise steadily in the coming years, it represents an increasing public health issue.

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Systolic HF, also termed HF with reduced ejection fraction (HFrEF), accounts for ≈50% of the overall HF burden.[1,3,5] HFrEF is commonly defined as a reduction in left ventricular ejection fraction (LVEF) to ≤40%, with coronary artery disease (CAD) causing approximately two thirds of cases.[1,6] Recurrent or prolonged ischemic events lead to maladaptive remodeling of cardiomyocytes and expanding extracellular matrix, culminating in cavity dilation and systolic dysfunction.[7]

Previous studies have reported improved survival by revascularization with coronary artery bypass grafting (CABG)

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From the Systematic Investigation and Research on Interventions and Outcomes (SIRIO) MEDICINE Research Network, Milan, Italy (G.W., D.D., F.A., M.K., C.J., P.S., F.D., A.Z., M.O., M.M.C., S.D.S., E.P.N.); Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Düsseldorf, Germany (G.W., D.D., C.J.); Institute of Cardiology, Catholic University, Rome, Italy (F.A.); Collegium Medicum in Bydgoszcz, University of Nicolaus Copernicus, Toruń, Poland (M.K.); Department of Emergency and Organ Transplantation, Section of Cardiovascular Diseases, School of Medicine, University of Bari, Italy (P.S., F.D., A.Z.); Department of Heart Science, Ospedale di Circolo e Fondazione Macchi, University of Insubria, Varese, Italy (M.O., B.C., G.C.); Department of Cardiosurgery, University of Zurich, Switzerland (F.M.); Department of Emergency and Organ Transplantation, Section of Cardiovascular Diseases, School of Medicine, University of Bari, Italy (M.M.C.); and Department of Cardiology, Multimedica IRCCS, Milan, Italy (S.D.S., E.P.N.).
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Correspondence to Eliano P. Navarese, MD, PhD, FESC, Department of Cardiology, Multimedica IRCCS Via Milanese 300, 20099 Milan, Italy. E-mail elianonavarese@gmail.com
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compared with medical treatment (MT)[8–10] for patients with CAD and HFrEF, with CABG becoming the recommended strategy; however, other potential therapeutic options currently include percutaneous coronary interventions (PCIs) and intensified, evidence-based MT; moreover, single studies in the setting of HF have been underpowered to draw definite conclusions, ultimately contributing to the uncertainty of current recommendations on the optimal strategy for patients with CAD and HFrEF.[1,3] We aimed to perform an analysis of the totality of evidence of both randomized and observational studies evaluating the impact on mortality of available treatment options (CABG, PCI, and MT) for patients with HFrEF and CAD.

Methods

Data Sources and Search Strategy

The meta-analysis was performed according to the established methods recommended by the Cochrane guidelines[11] and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for conducting systematic reviews and meta-analyses in healthcare interventions.[12]

A systematic literature search of articles until July 5, 2016, was performed, using the medical databases MEDLINE, EMBASE, Google Scholar, Web of Science, and the Cochrane Controlled Trials Register, as well as congress proceedings from major cardiovascular societies (American College of Cardiology [ACC], American Heart Association [AHA] Scientific Sessions, and European Society of Cardiology [ESC] Congress). Search terms according to the medical subjects headings included revascularization, impaired ejection fraction, LVEF, severe left ventricular dysfunction, reduced ejection fraction, heart failure, ischemic cardiomyopathy, percutaneous coronary intervention, coronary artery bypass grafting, and medical therapy. A bibliography search within landmark articles and guidelines of cardiac societies on the subject was additionally performed, and relevant articles were added. Relevant citations were screened at the title/abstract level and retrieved as full-text reports, where possible.

Study Design, Selection Criteria, and Outcome Measures

We designed the current meta-analysis to compare CABG, PCI, and MT treatment strategies for patients with ejection fraction ≤40%. All randomized or observational trials comparing at least 2 of the 3 treatment modalities against each other with a minimum follow-up of 12 months and reporting all-cause mortality were eligible for inclusion. No language or publication status restriction was imposed. Exclusion criteria were (1) <12 months of follow-up, (2) mortality not reported, and (3) single-arm study.

The primary clinical end point was mortality; secondary end points were myocardial infarction (MI), repeat revascularization (RR), and stroke. RR was considered to be any revascularization, including target vessel revascularization.

Data Abstraction and Quality Assessment

The most updated or inclusive data for each study were used for abstraction. Two independent investigators (D.D. and G.W.), who were not personally involved in any of the included trials, abstracted data from each report into prespecified forms. Data were abstracted according to the intention-to-treat principle, where possible. Internal validity was independently appraised by 2 investigators (D.D. and G.W.); divergences were resolved by discussion with a third investigator (E.P.N.). Bias assessment was performed based on the Cochrane Handbook recommendations.[11] Additional sensitivity analyses were conducted to account for different types of emerging bias.

Statistical Analyses

Presented data are time-to-event outcomes. For meta-analyses of these outcomes, the most appropriate statistic to use is the hazard ratio (HR), which takes into account both the number of events and the time to these events. HR and 95% confidence intervals (CIs) were derived from survival parameters in each study and used as summary statistics. Heterogeneity was assessed by the Cochran Q test, and statistical heterogeneity was summarized by the I^2 statistic, which quantifies the percent of variation in study results that is because of heterogeneity rather than to chance.[13] I^2 values >50% indicate substantial heterogeneity. Pooled HR for all outcomes were calculated using the more conservative DerSimonian and Laird random-effects model.[11,14]

To validate the overall analyses of the primary mortality outcome, 3 prespecified sensitivity analyses were performed, namely studies with matched patients only (either randomized or propensity score matched), studies comparing CABG against drug-eluting stent (DES)-PCI, and studies published in 2010 or later.

Statistical significance for the summary HRs was assumed at a 2-tailed P value <0.05. Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ) was used for statistical analyses.

Results

Study Selection and Patient Populations

Article screening and selection is described in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (Figure 1). Of 1108 articles retrieved from the primary searches using prespecified keywords, 879 were excluded for unmet inclusion criteria.

Twenty-one studies published between 1983 and July 2016 were finally included in the meta-analysis (Table 1), of which 16 available as full-text reports.[10,15,16,18–24,26,29–35] For the remaining 5 articles, data were abstracted from the study summaries.[8,17,25,27,28] Patient baseline characteristics are shown in Table 2. Of a total of 16 191 patients (mean age 64 years, 79% male), 7335 underwent CABG, 4439 underwent PCI, and 4417 received MT. Three trials involving 1779 patients had a randomized design, and 6 observational studies involving 2611 patients used propensity score or case–control matching, contributing to a total of 4410 patients in randomized or matched groups. For articles reporting both crude and propensity score–matched populations (Yang et al[35] and Velazquez et al[34]), these groups were included separately in the overall and sensitivity analyses. Median follow-up was 36 months. Only a minority of studies performed viability testing in over 50% of patients.

The risks of bias of the included randomized and observational studies are shown in Tables I and II in the Data Supplement, respectively. Overall, bias was low across randomized controlled trials and moderate in observational studies.

Mortality With CABG, PCI, or MT

Eight studies, of which 2 had a randomized design,[21,31] involved 6896 patients and reported mortality with CABG compared with contemporary MT (Figure 2A). A statistically significant reduction in mortality was observed with the use of CABG, 31.91% (791 of 2479 patients), compared with MT, 38.31% (1692 of 4417 patients; HR, 0.66; 95% CI, 0.61–0.72; P<0.001; heterogeneity P<0.001; I^2=77%).

Two studies involved 931 patients and compared PCI versus MT (Figure 2B). A statistically significant mortality reduction was observed with PCI 34.70% (178 of 513 patients)

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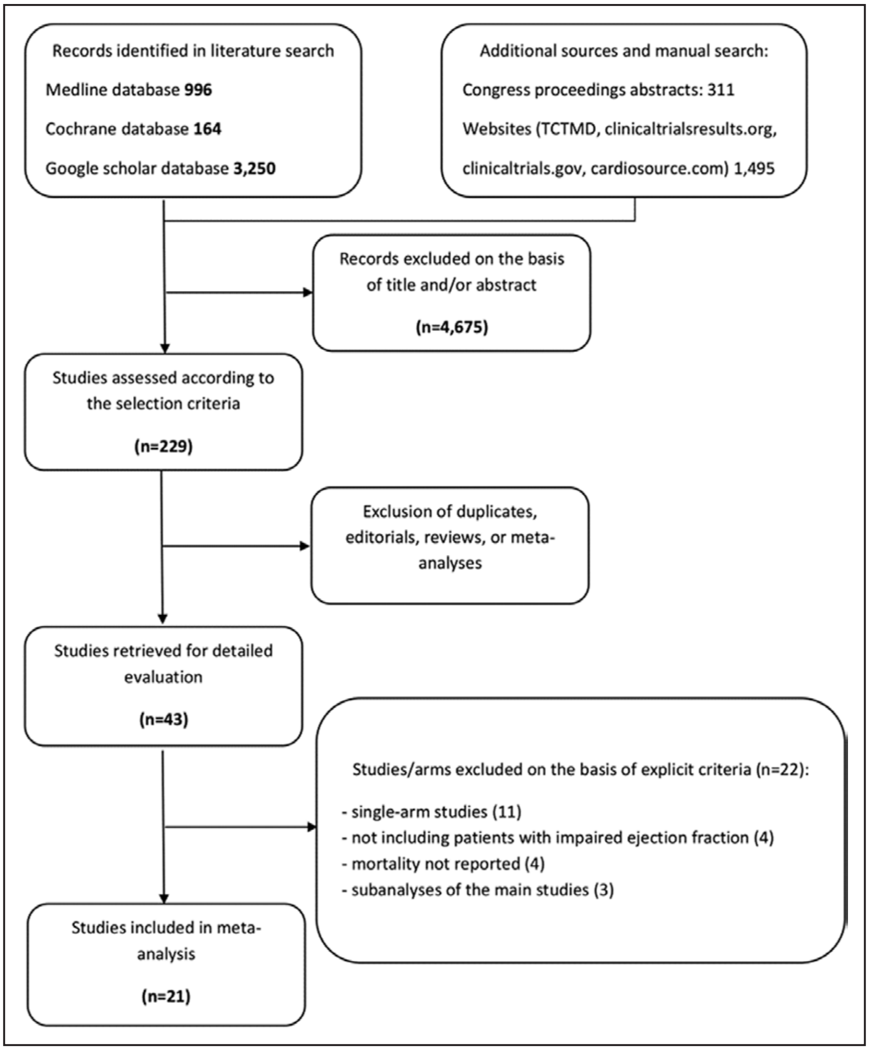

Figure 1. Flow diagram of meta-analysis.

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compared with MT 46.41% (194 of 418 patients; HR, 0.73; 95% CI, 0.62–0.85; P<0.001; heterogeneity P=0.96; I^2=0%).

Sixteen studies involving 8782 patients and including 2 randomized controlled trials compared CABG versus PCI (Figure 2C). There was a statistically significant reduction in mortality with CABG compared with PCI; the respective mortality rates were 18.95% (920 of 4856 patients) and 24.45% (960 of 3926 patients; HR, 0.82; 95% CI, 0.75–0.90; P<0.001; heterogeneity P=0.01; I^2=47%).

A sensitivity analysis limited to the randomized or matched cohorts was performed (Figure I in the Data Supplement). The results of CABG versus MT were confirmed by 3 studies[21,31,34] involving 1779 patients (HR, 0.75; 95% CI, 0.60–0.93; P=0.01; Figure IA in the Data Supplement). Seven studies[18,20,21,28–30,35] involving 2656 patients confirmed the results on CABG versus PCI (HR, 0.86; 95% CI, 0.77–0.96; P=0.009; Figure IB in the Data Supplement). Only 1 small randomized trial was available for the PCI versus MT comparison (Figure IC in the Data Supplement).

To account for the procedural and pharmacological progress made over the last years, a sensitivity analysis including only studies published since 2010 was performed (Figure II in the Data Supplement). The survival benefit seen in the overall analysis for CABG versus MT was confirmed by 5 studies[21,26,27,31,34] involving 3366 patients (HR, 0.67; 95% CI, 0.51–0.86; P=0.002; Figure IIA in the Data Supplement) and for CABG versus PCI by 10 studies[17,20–22,25,27–29,35] involving 5279 patients (HR, 0.79; 95% CI, 0.71–0.88; P<0.001; Figure IIB in the Data Supplement).

Secondary End Points With CABG Versus PCI

Myocardial Infarction

Eight studies with a total of 5122 patients reported data on first or recurrent MI (Figure 3A). Treatment with CABG resulted in a statistically significant reduction in MI compared with PCI; rates were 2.11% (62 of 2938) and 4.26% (93 of 2184), respectively (HR, 0.50; 95% CI, 0.36–0.68; P<0.001; heterogeneity P=0.51; I^2=0%).

Repeat Revascularization

Seven studies, involving 3886 patients, provided data on RR (Figure 3B).[20,22,23,25,28,30,33,35] There was a statistically significant reduction in RR with CABG compared with PCI treatment; the respective rates were 5.82% (116 of 1991 patients) and 20.74% (371 of 1788 patients; HR, 0.34; 95% CI, 0.24–0.47; P<0.001; heterogeneity P=0.03; I^2=57%).

Table 1. Characteristics of Included Studies

Study	Year	Type	Patients, Total	Comparison	FU, mo	Reported Outcomes
Ahn et al[15]	2011	Registry	327	CABG vs PCI	36	Mortality, major adverse cardiac or cerebrovascular events
Appoo et al[16]	2004	Registry	2169	CABG vs MT	12	Mortality
ASAN-MAIN[17]	2015	Registry	213	CABG vs PCI	24	Mortality
AWESOME[18,19]	2004	RCT/Registry	386	CABG vs PCI	36	Mortality, survival free of angina, RR
Bangalore et al[20]	2015	Registry	396	CABG vs PCI	35	Mortality, MI, stroke, RR
Bounous et al[8]	1988	Registry	710	CABG vs MT	36	Mortality
CASS[10]	1983	Registry	651	CABG vs MT	36	Mortality, functional limitation
Cleland et al[21]	2011	RCT	109	CABG vs PCI vs MT	59	Mortality
CREDO-Kyoto[22]	2014	Registry	293	CABG vs PCI	60	Mortality, cardiac mortality, sudden death, readmission for HF, stroke, MI, RR
Gioia et al[23]	2007	Registry	220	CABG vs PCI	15	Mortality, cardiac mortality, MI, TVR, NYHA
Hannan et al[24]	2008	Registry	2673	CABG vs PCI	18	Mortality, MI
IRIS-MAIN[25]	2015	Registry	364	CABG vs PCI	12	Mortality, cardiac mortality, MI, RR, TVR, stroke
Kwon et al[26]	2012	Registry	450	CABG vs MT	70	Mortality
LaBarbera et al[27]	2012	Registry	1345	CABG vs PCI vs MT	60	Mortality
Nagendran et al[28]	2013	Registry	1436	CABG vs PCI	180	Mortality, RR
REAL[29]	2013	Registry	296	CABG vs PCI	60	Mortality
REHEAT[30]	2007	Case–control study	107	CABG vs PCI	12	Mortality, MI, arrhythmia, angina, RR, stroke
STICH/STICHES[31,32]	2011/2016	RCT	1212	CABG vs MT	118	Mortality, cardiovascular mortality
Toda et al[33]	2002	Registry	117	CABG vs PCI	36	Mortality, MI, TVR, HF
Velazquez et al[34]	2012	Registry	763	CABG vs MT	120	Mortality
Yang et al[35]	2013	Registry	953	CABG vs PCI	28	Mortality, MI, stroke, RR, TVR

Characteristics of included studies. ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CABG, coronary artery bypass graft; CASS, Coronary Artery Surgery Study; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; FU, follow-up; HF, heart failure; IRIS-MAIN, Observational Study for Left Main Disease Treatment; MI, myocardial infarction; MT, medical therapy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; RR, repeat revascularization; STICH/STICHES, Surgical Treatment for Ischemic Heart Failure; and TVR, target vessel revascularization.

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Stroke

Four studies, comprising 2113 patients, were included in the analysis of stroke (Figure 3C). The rates did not differ significantly between the 2 groups: 5.21% (58 of 1112 patients) who underwent CABG and 4.13% (37 of 894 patients) who underwent PCI (HR, 0.79; 95% CI, 0.52–1.18; P=0.24; heterogeneity P=0.76; I^2=0%).

CABG Versus PCI in Patients Stratified by Disease or Treatment Characteristics

We investigated whether CABG or PCI favored special patient populations or patients preferably treated with DESs in the PCI group.

Four studies, with a total of 987 patients, reported a prevalence of left main/proximal left anterior descending disease >50% in both groups (Figure 4A). Mortality was still significantly reduced with CABG versus PCI, with respective rates of 17.08% (103 of 603 patients) and 25.0% (96 of 384 patients; HR, 0.76; 95% CI, 0.59–0.98; P=0.03; heterogeneity P=0.96; I^2=0%).

Seven studies involving 2695 patients reported a prevalence of 3-vessel disease >50% in both groups (Figure 4B).[18,21–23,28,33] The overall incidence of all-cause mortality did not differ significantly between the 2 revascularization strategies: 27.85% (379 of 1361) among patients undergoing CABG and 30.51% (407 of 1334) among patients

Table 2. Baseline Patient Characteristics

Study	Age, y	Male (%)	HTN (%)	DM (%)	HLP (%)	CKD (%)	Previous CABG (%)	Previous PCI (%)	Previous MI (%)	DES Use >50%	Left Main/ Proximal LAD >50%	3-Vessel Disease >50%	Viability Test >50%
Ahn et al[15]	…	…	…	…	…	…	…	…	…	yes	no	yes	no
Appoo et al[16]	64	85	50	26	39	4	12	8	61	no	no	no	no
ASAN-MAIN[17]	…	…	…	…	…	…	…	…	…	no	yes	no	no
AWESOME[18,19]	65	…	66	33	…	…	29	23	…	no	no	yes	no
Bangalore et al[20]	65	72	…	40		5	0	…	41	yes	no	no	no
Bounous et al[8]	…	…	…	…	…	…	…	…	…	no	no	no	no
CASS[10]	55	89	…	…	…	…	…	…	…	no	no	yes	no
Cleland et al[21]	67	93	50	36	59	…	8	8	73	no	no	yes	yes
CREDO-Kyoto[22]	69	77	87	57	…	11	…	…	44	yes	yes	yes	no
Gioia et al[23]	68	81	69	43	68	…	17	20	56	yes	no	yes	no
Hannan et al[24]	66	70	…	…	36	4	…	…	42	yes	no	no	no
IRIS-MAIN[25]	66	79	…	…	…	…	…	…	…	no	yes	no	no
Kwon et al[26]	63	74	51	37	49	…	20	…	…	no	no	no	yes
LaBarbera et al[27]	…	…	…	…	…	…	…	…	…	no	no	no	no
Nagendran et al[28]	65	81	63	34	62	5	6	8	66	no	no	yes	no
REAL[29]	…	78	78	26	…	5	…	…	29	no	no	no	no
REHEAT[30]	61	77	62	25	66	…	…	…	62	no	no	no	yes
STICH/STICHES[31,32]	60	88	60	40	60	8	3	…	77	no	yes	yes	no
Toda et al[33]	64	74	…	42	…	3	20	26	23	no	yes	yes	no
Velazquez et al[34]	64	75	…	34	…	4	30	21	39	no	no	no	no
Yang et al[35]	66	76	60	50	27	13	5	25	29	yes	no	no	no

ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CABG, coronary artery bypass graft; CASS, Coronary Artery Surgery Study; CKD, chronic kidney disease; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; DES, drug-eluting stent; DM, diabetes mellitus; HLP, hyperlipoproteinemia; HTN, hypertension; IRIS-MAIN, Observational Study for Left Main Disease Treatment; LAD, left anterior descending; MI, myocardial infarction; PCI, percutaneous coronary intervention; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; and STICH/STICHES, Surgical Treatment for Ischemic Heart Failure.

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who underwent PCI (HR, 0.92; 95% CI, 0.82–1.03; P=0.16; heterogeneity P=0.66; I^2=0%).

Six studies comprising 4827 patients used only DES in the PCI group, allowing a comparison of CABG against contemporary PCI (Figure 4C). Revascularization by CABG still resulted in a statistically significant reduction of all-cause mortality compared with revascularization by PCI, with respective rates of 13.73% (380 of 2767) and 16.70% (344 of 2060; HR, 0.82; 95% CI, 0.69–0.96; P=0.01; heterogeneity P=0.79; I^2=0%).

Discussion

The present article, to the best of our knowledge, represents the largest evidence base comparing mortality outcome after surgical, percutaneous, or conservative treatment of HFrEF and CAD. The main findings of this analysis are that (1) revascularization with either CABG or PCI carried a significant improvement in long-term survival over MT, (2) CABG showed a significantly improved survival compared with PCI, that persisted among patients with left main/proximal left anterior descending disease and in studies conducted after the advent of DES, and (3) CABG compared with PCI was associated with a significant reduction in the risk of MI or need for RR, albeit with a numerically higher rate of stroke.

There are potential anatomic and functional reasons for the described different mortality rates among the investigated patients' cohorts. (1) A complete revascularization can be more frequently reached with CABG than with PCI[36]; completeness of revascularization by removing the ischemic burden might be a pivotal driver of improved prognosis, in particular in high-risk patients with HF caused by ischemic CAD. Although in the last years advances have been made in MT, the results on clinical outcomes offered by a complete revascularization could not be equalized by the sole MT in the high-risk subset with HFrEF. (2) In HF patients, CAD tends to be more complex and diffuse, leading to higher need for RRs and MI rates after coronary stenting than with CABG.[37,38] (3) CABG revascularization of prolonged epicardial segments versus PCI performed only on specific stenotic lesion can yield a better vessel patency due to often extensively diseased arteries in ischemic HF. (4) In HF patients with low cardiac reserve, it is conceivable that in-stent restenosis would be more negatively impacting in this group than in others without severe dysfunction. (5) Improved survival after CABG could

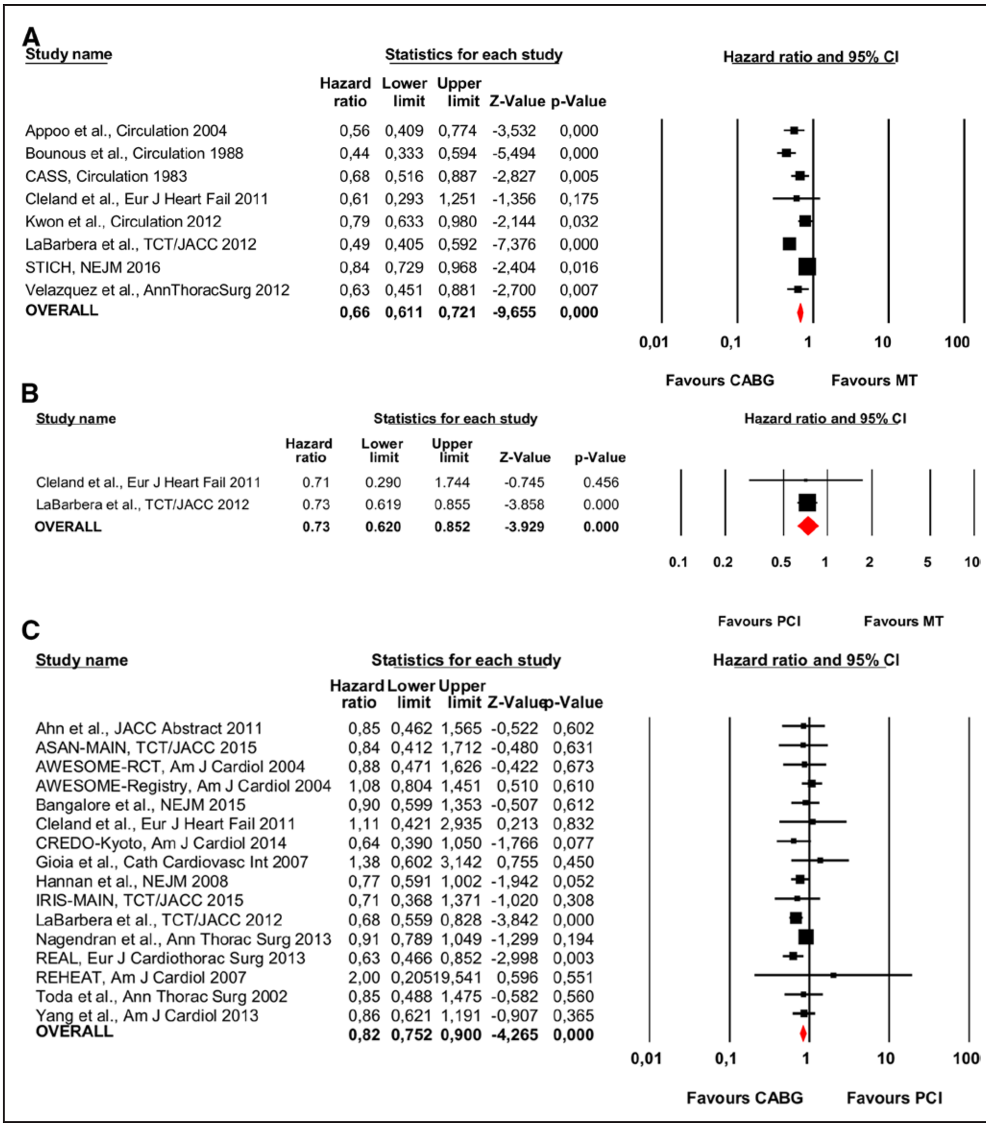

Figure 2. Individual and summary hazard ratios for mortality of studies stratified by treatment comparison: (**A**) coronary artery bypass grafting (CABG) vs medical treatment (MT)[8,10,16,21,26,27,31,32,34]; (**B**) percutaneous coronary intervention (PCI) vs MT[21,27]; and (**C**) CABG vs PCI.[15,17–25,27–30,33,35] ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CASS, Coronary Artery Surgery Study; CI, confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; IRIS-MAIN, Observational Study for Left Main Disease Treatment; REAL, Regional Registry of Coronary Angioplasties; REHEAT, Revascularization in Heart Failure Trial; and STICH, Surgical Treatment for Ischemic Heart Failure.

be related to fewer lethal ventricular arrhythmias or to reverse remodeling. The risk of contrast-induced acute nephropathy after PCI is also increased in more complex patients with HFrEF, potentially contributing to higher mortality rates when compared with CABG.[39]

Findings from early randomized trials comparing medical therapy to CABG for the treatment of stable angina cannot be automatically extrapolated to the care of CAD patients with HF because this is a specific population that was largely excluded from the early stable angina trials.[31] The only randomized trial specifically addressing HF patients is STICH (Surgical Treatment for Ischemic Heart Failure), with its recently published 10-year extended follow-up (STICHES).[32] For similar reasons, the randomized trials comparing PCI to CABG in CAD patients have failed to provide definite answers on patients with comorbid HF. Indeed, only ≈2% of patients enrolled in the SYNTAX trial (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) had LVEF <30%.[40] More recently, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) reported similar outcomes with PCI using DESs and CABG in patients with LVEF <40%, but only 32 patients (2.5%) were in this prespecified subgroup.[41] Thus, the available randomized data comparing PCI and CABG in patients with severe left ventricular dysfunction are insufficient.

Current guidelines from the American and European cardiac societies are not uniform with respect to the class and level of treatment recommendations for CAD patients with HFrEF. The ESC guidelines recommend CABG over PCI for patients with HFrEF and significant CAD in the

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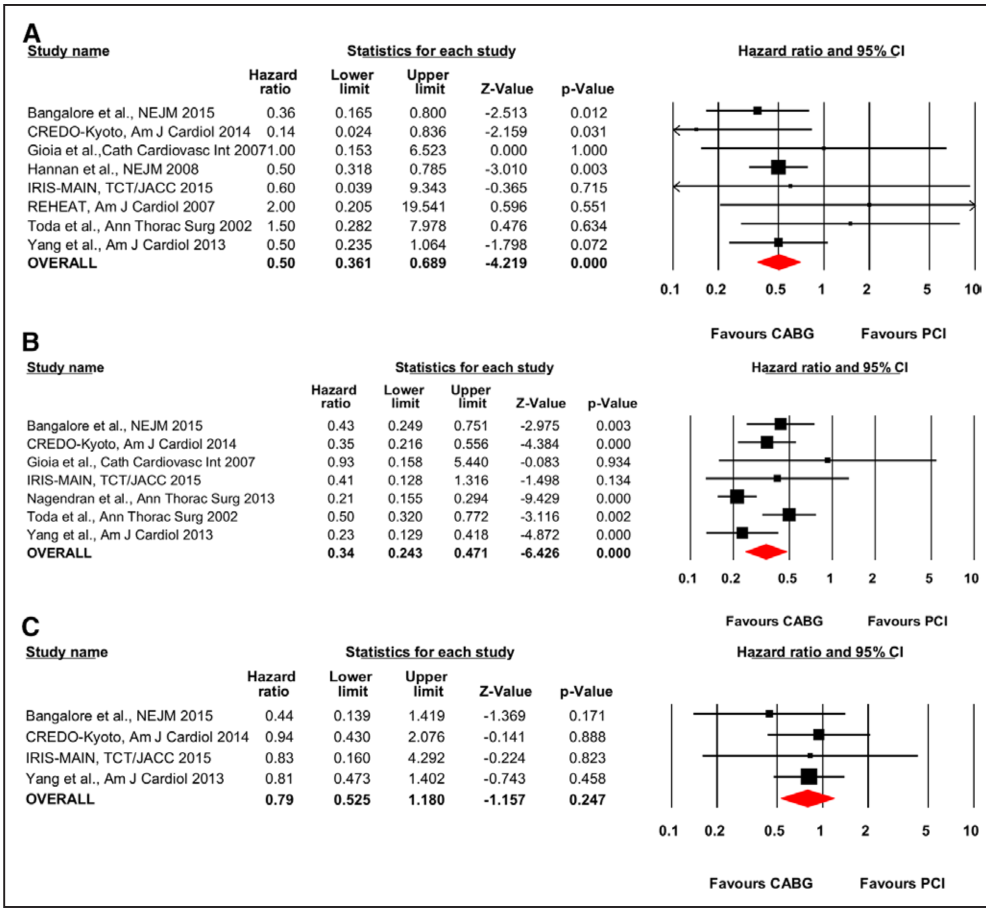

Figure 3. Individual and summary hazard ratios for secondary end points of studies comparing coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI): (**A**) myocardial infarction[20,22–25,30,33,35]; (**B**) repeat revascularization[20,22,23,25,28,33,35]; and (**C**) stroke.[20,22,25,35] CI indicates confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; IRIS-MAIN, Observational Study for Left Main Disease Treatment; and REHEAT, Revascularization in Heart Failure Trial.

presence of angina or viable myocardium.[42] PCI receives IIb C strength of recommendations for patients unsuitable for surgery, who have viable myocardium or significant left main stenosis or 2/3-vessel disease. The American College of Cardiology Foundation (ACCF)/AHA guidelines take a more liberal approach, suggesting CABG or PCI in patients with left main or multivessel disease in the case of angina and suitable coronary anatomy.[3] However, for patients with severely impaired left ventricular function and significant CAD in the absence of angina, only CABG is recommended as an alternative to MT, even in the absence of myocardial viability (Class IIb; Level of Evidence B).[3] The discrepancy among international recommendations, stemming from the lack of evidence from adequately powered randomized trials, challenges physicians in choosing the optimal strategy.[1,3,42,43] Our findings derived from a large-scale analysis agree with those from STICH, unequivocally supporting the revascularization option in this high-risk group of patients. Our data for the first time add comprehensive information on the efficacy of percutaneous revascularization versus medical therapy, providing evidence that revascularization, irrespective of modality, in this specific population has the potential to improve the patients' outcomes. Moreover, they further expand current evidence by investigating the comparison between surgical and percutaneous revascularization, with a consistent long-term survival benefit provided by the surgical revascularization strategy. According to our meta-analysis and to the results of the STICH trial, surgical revascularization should be regarded as the preferred revascularization modality in these high-risk patients, followed by percutaneous interventions. These results suggest that current international guidelines should upgrade CABG to receive a higher class of recommendation and a higher level of evidence over PCI or MT.

An interesting finding of our study is that a significant mortality reduction is observed not only for patients with a classical indication for surgical revascularization (left main disease or 3-vessel disease), but possibly for all patients with significant CAD and impaired left ventricular function.

The comparison of CABG and PCI in patients with HFrEF shows a significant survival benefit for CABG in the present analysis. The low heterogeneity and the narrow 95% CIs suggest consistency of the findings that remained statistically significant in the subanalyses of CABG versus PCI using DES and of the randomized/matched cohorts. The reduction in mortality, however, was numerically smaller for CABG versus PCI than for CABG versus MT, in line with the findings of the present article on the benefits of PCI over MT. In a subanalysis of secondary end points, we found significantly reduced risk for MI and RR in patients treated with CABG versus PCI.

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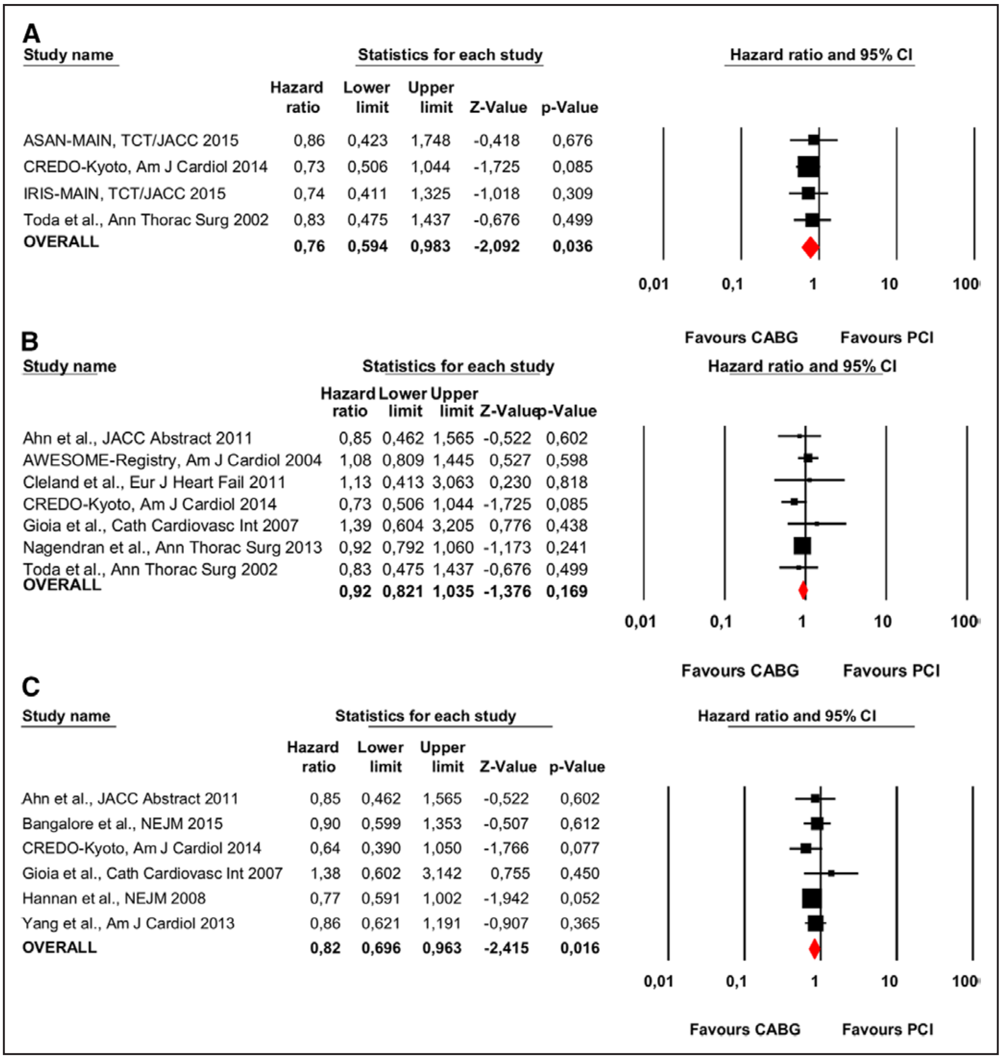

Figure 4. Individual and summary hazard ratios for mortality in studies comparing coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI) stratified by patient characteristics or treatment: (**A**) in patients with left main/proximal left anterior descending disease[17,22,25,33]; (**B**) in patients with 3-vessel disease[15,18,19,21–23,28,33]; and (**C**) in studies using drug-eluting stents in the PCI group.[15,20,22–24,35] ASAN-MAIN indicates Asan Medical Center—Left Main Revascularization; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CI, confidence interval; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; and IRIS-MAIN, Observational Study for Left Main Disease Treatment.

Although left main and 3-vessel disease have long been a domain of CABG rather than PCI for revascularization, because of an established prognostic benefit of CABG, 3 recent randomized trials, LE MANS (Left Main Coronary Artery Stenting),[44] SYNTAX,[45] and PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease)[46] and subsequent meta-analyses[47] have suggested that intermediate-term mortality after interventional revascularization using modern stent systems is comparable to CABG, with a reduced risk of stroke but a higher need for RR. Revascularization guidelines[42,43] have thus expanded PCI indications in stable coronary heart disease, leaving the sole CABG recommendation to complex coronary anatomy with high SYNTAX scores or diabetes mellitus.[41,48] Our findings indicate that surgical revascularization in patients with HFrEF should be regarded as the preferred strategy, with significant survival benefits in patients with left main/proximal left anterior descending disease and a numeric but nonsignificant mortality reduction in patients with 3-vessel disease.

Another important finding of the present report is that the significant survival improvement with CABG over MT or PCI occurred in patients largely without previous viability testing. The indication for revascularization in patients with HFrEF is most often based on clinical symptoms, for example, angina or decompensation, in the presence of significant CAD. The relevance of myocardial viability testing to determine the benefit/risk ratio of revascularization remains uncertain, with only a minority of studies providing signal for possible benefit[49] and guidelines generally recommending it as a reasonable procedure.[1,3] European guidelines clearly advise against revascularization with either CABG or PCI in patients who have neither angina nor viable myocardium.[1,40] American guidelines instead take a differing approach, giving a IIb recommendation to CABG, independent of viable myocardium.[3] The present meta-analysis of all available studies on the topic shows a clear survival benefit for revascularization techniques (CABG as well as PCI) compared with MT, largely independent of viability testing. Our results are thus in line with current recommendations from American guidelines with respect to this point and suggest a minor role of viability testing in CAD patients with HFrEF.

In conclusion, this large-scale article emphasizes in patients with HF and CAD the mortality benefits of revascularizations over medical therapy; these findings prompt an update of international guidelines, with higher class and evidence of recommendations assigned to surgical revascularizations to these high-risk patients.

Limitations

The availability of individual patient data would have improved the results of our meta-analysis, especially of potential subgroup analyses. Only few randomized controlled trials were available, with the majority of studies being observational. The observational design has the advantage of adhering to the real world, more appropriately reflecting current practice of unselected higher risk patients versus those derived from randomized trials. Nonetheless, many sensitivity analyses were performed, including those limited to patients randomized or well matched, and were consistent with the main findings, suggesting that the overall effect is justified.

Data on single treatments in the medical therapy group were available only in a minority of studies; therefore, precise description of the adherence to standard guidelines for medical therapy in this patient cohort is not possible. On the other hand, a sensitivity analysis done with the more contemporary studies only confirmed the overall results. Moreover, additional sensitivity analyses in studies using randomization or patient matching have been conducted, generating highly matched patients in terms of allocated MTs; the findings are directionally convergent and have consistent magnitude with the main findings. Caution should be prompted when interpreting subgroup analyses that should be regarded as exploratory, given the degree of variability in patient background characteristics.

Conclusions

This meta-analysis provides evidence that revascularization, irrespective of modality, compared with medical therapy, significantly improves survival and other outcomes in patients with ejection fraction ≤40% and significant CAD. CABG seems to be the most favorable option in this setting, although PCI may have its advantages in special patients and situations. Careful assessment of procedural risk and discussion of the optimal treatment strategy within a heart team is mandatory and recommended by current guidelines. Additional randomized trials will be necessary to further define the most beneficial treatment for these high-risk patients.

Disclosures

None.

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CLINICAL PERSPECTIVE

Previous data have shown improved survival by revascularization with coronary artery bypass grafting compared with medical treatment for patients with coronary artery disease, but single studies in the setting of coronary artery disease with heart failure with reduced ejection fraction have been underpowered to draw definite conclusions, ultimately contributing to the uncertainty of current recommendations on the optimal strategy for patients with coronary artery disease and heart failure with reduced ejection fraction. The present meta-analysis indicates that revascularization strategies are superior to medical treatment in improving survival in patients with ischemic heart disease with reduced ejection fraction. Between the 2 revascularization strategies, coronary artery bypass grafting seems more favorable compared with percutaneous coronary intervention in this particular clinical setting. This large-scale article supports that in patients with HFrEF and coronary artery disease, there is a mortality benefit of revascularizations over medical therapy. These findings may inform an update of international guidelines with higher class and evidence of recommendations assigned to surgical revascularization in these high-risk patients.

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Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis

Georg Wolff, Dimitrios Dimitroulis, Felicita Andreotti, Michalina Kolodziejczak, Christian Jung, Pietro Scicchitano, Fiorella Devito, Annapaola Zito, Michele Occhipinti, Battistina Castiglioni, Giuseppe Calveri, Francesco Maisano, Marco M. Ciccone, Stefano De Servi and Eliano P. Navarese

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Study	Multicenter trial	Adequate sequence generation	Allocation concealment	Blinding			Incomplete Data Outcome Addressed?	Selective Outcome Reporting	Free of Other Bias
				Patient	Physician	Adjudication of Outcomes			
AWESOME RCT	YES	YES	UNCLEAR	YES	YES	YES	YES	NO	YES
Cleland et al.	YES	YES	UNCLEAR	NO	NO	YES	YES	NO	YES
STICH	YES	YES	UNCLEAR	NO	NO	YES	YES	NO	YES

1. **Supplementary Table 1. Bias assessment of randomized controlled trials.**

2. Supplementary Table 2. Bias assessment of observational studies.

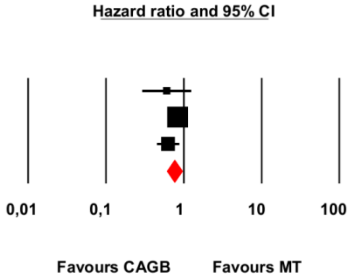
Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Ahn et al.	MODERATE	LOW	NO INFORMATION	NO INFORMATION	NO INFORMATION	LOW	MODERATE
Appoo et al.	MODERATE	LOW	MODERATE	MODERATE	LOW	LOW	LOW
ASAN-MAIN	SERIOUS	NO INFORMATION	NO INFORMATION	NO INFORMATION	NO INFORMATION	LOW	MODERATE
AWESOME	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW
Bangalore et al.	MODERATE	LOW	MODERATE	LOW	LOW	LOW	LOW
Bounous et al.	NO INFORMATION	NO INFORMATION	NO INFORMATION	NO INFORMATION	NO INFORMATION	MODERATE	MODERATE
CASS	MODERATE	LOW	MODERATE	LOW	LOW	LOW	LOW
CREDO-Kyoto	MODERATE	LOW	MODERATE	LOW	MODERATE	LOW	LOW
Gioia et al.	MODERATE	LOW	MODERATE	LOW	LOW	LOW	LOW
Hannan et al.	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW
IRIS-MAIN	NO INFORMATION	NO INFORMATION	NO INFORMATION	NO INFORMATION	NO INFORMATION	LOW	LOW
Kwon et al.	MODERATE	LOW	MODERATE	NO INFORMATION	LOW	LOW	MODERATE
LaBarbera et al.	MODERATE	NO INFORMATION	MODERATE	NO INFORMATION	MODERATE	LOW	LOW
Nagendran et al.	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW
REAL	MODERATE	LOW	LOW	NO INFORMATION	LOW	LOW	LOW
REHEAT	MODERATE	LOW	LOW	NO INFORMATION	LOW	LOW	LOW
Toda et al.	MODERATE	LOW	MODERATE	MODERATE	MODERATE	LOW	LOW
Velazquez et al.	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW
Yang et al.	MODERATE	LOW	MODERATE	NO INFORMATION	LOW	LOW	LOW

1. Supplementary Figure 1

A) Mortality in studies comparing CABG and OMT in randomized/matched patients only

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Cleland et al., Eur J Heart Fail 2011	0,61	0,293	1,251	-1,356	0,175
STICH, NEJM 2016	0,84	0,729	0,968	-2,404	0,016
Velazquez et al., AnnThoracSurg 2012	0,63	0,451	0,881	-2,700	0,007
OVERALL	**0,75**	**0,608**	**0,936**	**-2,559**	**0,011**

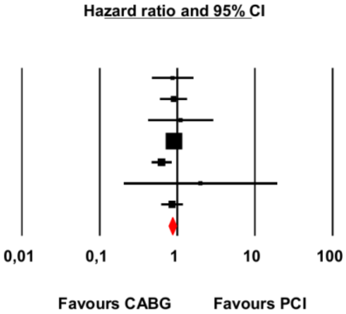
Statistics for each study



B) Mortality in studies comparing CABG and PCI in randomized/matched patients only

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
AWESOME-RCT, Am J Cardiol 2004	0,88	0,471	1,626	-0,422	0,673
Bangalore et al., NEJM 2015	0,90	0,599	1,353	-0,507	0,612
Cleland et al., Eur J Heart Fail 2011	1,11	0,421	2,935	0,213	0,832
Nagendran et al., Ann Thorac Surg 2013	0,91	0,789	1,049	-1,299	0,194
REAL, Eur J Cardiothorac Surg 2013	0,63	0,466	0,852	-2,998	0,003
REHEAT, Am J Cardiol 2007	2,00	0,205	19,541	0,596	0,551
Yang et al., Am J Cardiol 2013	0,86	0,621	1,191	-0,907	0,365
OVERALL	**0,86**	**0,770**	**0,964**	**-2,609**	**0,009**

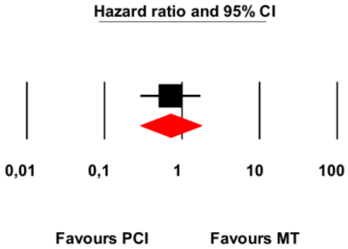
Statistics for each study



C) Mortality in studies comparing PCI and OMT in randomized/matched patients only

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Cleland et al., Eur J Heart Fail 2011	0,71	0,290	1,744	-0,745	0,456
OVERALL	**0,71**	**0,290**	**1,744**	**-0,745**	**0,456**

Statistics for each study

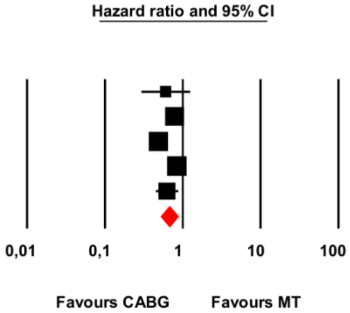


2. Supplementary Figure 2

A) Mortality in studies published 2010 or later comparing CABG and OMT

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Cleland et al., Eur J Heart Fail 2011	0,61	0,293	1,251	-1,356	0,175
Kwon et al., Circulation 2012	0,79	0,633	0,980	-2,144	0,032
LaBarbera et al., TCT/JACC 2012	0,49	0,405	0,592	-7,376	0,000
STICH, NEJM 2016	0,84	0,729	0,968	-2,404	0,016
Velazquez et al., AnnThoracSurg 2012	0,63	0,451	0,881	-2,700	0,007
OVERALL	**0,67**	**0,519**	**0,864**	**-3,077**	**0,002**

Statistics for each study



B) Mortality in studies published 2010 or later comparing CABG and PCI

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Ahn et al., JACC Abstract 2011	0,85	0,462	1,565	-0,522	0,602
ASAN-MAIN, TCT/JACC 2015	0,84	0,412	1,712	-0,480	0,631
Bangalore et al., NEJM 2015	0,90	0,599	1,353	-0,507	0,612
Cleland et al., Eur J Heart Fail 2011	1,11	0,421	2,935	0,213	0,832
CREDO-Kyoto, Am J Cardiol 2014	0,64	0,390	1,050	-1,766	0,077
IRIS-MAIN, TCT/JACC 2015	0,71	0,368	1,371	-1,020	0,308
LaBarbera et al., TCT/JACC 2012	0,68	0,559	0,828	-3,842	0,000
Nagendran et al., Ann Thorac Surg 2013	0,91	0,789	1,049	-1,299	0,194
REAL, Eur J Cardiothorac Surg 2013	0,63	0,466	0,852	-2,998	0,003
Yang et al., Am J Cardiol 2013	0,86	0,621	1,191	-0,907	0,365
OVERALL	**0,79**	**0,711**	**0,883**	**-4,204**	**0,000**

Statistics for each study