Title: Survival benefits of invasive vs. conservative strategies in heart failure patients with reduced ejection fraction and coronary artery disease

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SURVIVAL BENEFITS OF INVASIVE VS. CONSERVATIVE STRATEGIES IN HEART FAILURE IN PATIENTS WITH REDUCED EJECTION FRACTION AND CORONARY ARTERY DISEASE

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Abstract

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 to medical treatment (MT).

Methods and Results: We performed a meta-analysis of available studies comparing different methods of revascularization (PCI or CABG) against each other or MT in patients with coronary artery disease and left ventricular ejection fraction ≤40%. The primary outcome was all-cause mortality; myocardial infarction, revascularization, stroke were also analyzed. Twenty-one studies involving a total of 16,191 patients were included. Compared to MT there was a significant mortality reduction with CABG (hazard ratio (HR) 0.67 [95% confidence interval (CI) 0.51 to 0.86]; $P < 0.001$) and PCI (HR 0.73, [CI 0.62 to 0.85]; $P < 0.001$). When compared to PCI, CABG still showed a survival benefit (HR 0.82 [CI 0.75 to 0.90]; $P < 0.001$).

Conclusions: The present meta-analysis indicates that revascularization strategies are superior to MT in improving survival in patients with ischemic heart disease and reduced ejection fraction. Between the two revascularization strategies, CABG appears more favourable compared to PCI in this particular clinical setting.

Keywords: CABG, PCI, heart failure, meta-analysis

Commentary:

Previous data have shown improved survival by revascularization with coronary artery bypass grafting (CABG) compared to medical treatment (MT) for patients with coronary artery disease (CAD) but single studies in the setting of CAD with heart failure and reduced ejection fraction (HFrEF) 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. The present meta-analysis indicates that revascularization strategies are superior to MT in improving survival in patients with ischemic heart disease and reduced ejection fraction. Between the two revascularization strategies, CABG appears more favourable compared to PCI in this particular clinical setting. 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.

Introduction

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.

Systolic heart failure, also termed heart failure with reduced ejection fraction (HFrEF), accounts for about 50% of the overall HF burden [1,3,5]. HFrEF is commonly defined as a reduction in left ventricular ejection fraction 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) compared to 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 (PCI) 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.

Materials and Methods

Data sources and search strategy

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

A systematic literature search of articles until 5th July 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 (ACC, AHA Scientific Sessions, ESC Congress). Search terms according to medical subjects headings included revascularization, impaired ejection fraction, left ventricular ejection fraction, severe left ventricular dysfunction, reduced ejection fraction, heart failure, ischemic cardiomyopathy, percutaneous coronary intervention, coronary artery bypass grafting, 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 two of the three 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; 3) single-arm study.

The primary clinical endpoint was mortality; secondary endpoints were myocardial infarction (MI), repeat revascularization (RR), and stroke. Repeat revascularization 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 (DD and GW), who were not personally involved in any of the included trials, abstracted data from each report into pre-specified forms. Data were abstracted according to the intention-to-treat principle, where possible. Internal validity was independently appraised by two investigators (DD and GW); divergences were resolved by discussion with a third investigator (EPN). 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. Hazard ratio (HR) and 95% confidence intervals (CI) were derived from survival parameters in each study and used as summary statistics. Heterogeneity was assessed by the Cochran's Q test, and statistical heterogeneity was summarized by the I^2 statistic, which quantifies the percent of variation in study results that is due to 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, three pre-specified 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 hazard ratios was assumed at a 2-tailed p-value <0.05. Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey) was used for statistical analyses.

Results

Study selection and patient populations

Article screening and selection is described in a PRISMA flow chart (Figure 1). Of 1,108 articles retrieved from the primary searches using pre-specified 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, 15-19, 21, 23-26, 29-35]. For the remaining 5 articles, data were abstracted from the study summaries [8,20,22,27-28]. Patient baseline characteristics are shown in Table 2. Of a total of 16,191 patients (mean age 64 years, 79% male), 7,335 underwent CABG, 4,439 underwent PCI and 4,417 received MT. Three trials involving 1,779 patients had a randomized design, and six observational studies involving 2,611 patients used propensity-score- or case-control-matching, contributing to a total of 4,410 patients in randomized or matched groups. For papers reporting both crude and propensity-score-matched populations (Yang et al. [15] and Velasquez et al. [16]), 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 Supplementary Table 1 and Supplementary Table 2 respectively. Overall, bias was low across RCTs, and moderate in observational studies.

Mortality with CABG, PCI or MT

Eight studies, of which two had a randomized design [18,21], involved 6,896 patients and reported mortality with CABG compared to contemporary MT (Figure 2A). A statistically significant reduction in mortality was observed with the use of CABG, 31.91% (791 of 2,479 patients), compared to MT, 38.31% (1,692 of 4,417 patients) (HR 0.67 [95% CI 0.51 to 0.86]; $P < 0.001$; heterogeneity $P < 0.001$; $I^2 = 77\%$).

Two studies involved 931 patients and compared PCI vs. MT (Figure 2B). A statistically significant mortality reduction was observed with PCI 34.70% (178 of 513 patients) compared to MT 46.41% (194 of 418 patients) (HR 0.73 [95% CI 0.62 to 0.85]; P < 0.001; heterogeneity P = 0.96; I^2 = 0%).

Sixteen studies involving 8,782 patients and including two RCTs compared CABG vs. 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 4,856 patients) and 24.45% (960 of 3,926 patients) (HR 0.82 [95% CI 0.75 to 0.90]; P < 0.001; heterogeneity P = 0.01; I^2 = 47%).

A sensitivity analysis limited to the randomized or matched cohorts was performed (Supp. Fig. 1). The results of CABG vs. MT were confirmed by three studies [16,18,21] involving 1,779 patients (HR 0.75 [95% CI 0.60 to 0.93]; P= 0.01; Supp. Fig. 1A). Seven studies [15,18,23,28–30,32] involving 2,656 patients confirmed the results on CABG vs. PCI (HR 0.86 [95% CI 0.77 to 0.96]; P = 0.009; Supp. Fig. 1B). Only one small randomized trial was available for the PCI vs. MT comparison (Supp. Fig. 1C).

To account for the procedural and pharmacological progress made over the last years, a sensitivity analysis including only studies published since 2010 was performed (Supp. Fig. 2). The survival benefit seen in the overall analysis for CABG vs. MT was confirmed by five studies [16,18–21] involving 3,366 patients (HR 0.67 [95% CI 0.51 to 0.86]; P = 0.002; Supp. Fig. 2A), and for CABG vs. PCI by ten studies [15,18,20,22,24,27–29,32] involving 5,279 patients (HR 0.79 [95% CI 0.71 to 0.88]; P <0.001; Supp. Fig. 2B).

Secondary endpoints with CABG vs. PCI

Myocardial infarction

Eight studies with a total of 5,122 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 2,938) and 4.26% (93 of 2,184) respectively (HR 0.50 [95% CI 0.36 to 0.68]; P < 0.001; heterogeneity P = 0.51; I^2 = 0%).

Repeat revascularization

Seven studies, involving 3,886 patients, provided data on repeat revascularization [15,24,25,27,28,30–32] (Figure 3B). There was a statistically significant reduction in repeat revascularization with CABG compared with PCI treatment; the respective rates were 5.82% (116 of 1,991 patients) and 20.74% (371 of 1,788 patients) (HR 0.34 [95% CI 0.24 to 0.47], P < 0.001; heterogeneity P = 0.03; I^2 = 57%).

Stroke

Four studies, comprising 2,113 patients, were included in the analysis of stroke (Figure 3C). The rates did not differ significantly between the two groups: 5.21% (58 of 1,112 patients) who underwent CABG and 4.13% (37 of 894 patients) who underwent PCI (HR 0.79 [95% CI 0.52 to 1.18], P = 0.24; heterogeneity P = 0.76; I^2 = 0%).

CABG vs. PCI in patients stratified by disease or treatment characteristics

We investigated whether CABG or PCI favored special patient populations, or patients preferably treated with drug-eluting stents (DES) in the PCI group.

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

Seven studies involving 2,695 patients reported a prevalence of three-vessel-disease >50% in both groups [18,23–25,28,31] (Figure 4B). The overall incidence of all-cause mortality did not differ significantly between the two revascularization strategies: 27.85% (379 of 1,361) among patients undergoing CABG and 30.51% (407 of 1,334) among patients who underwent PCI (HR 0.92 [CI 0.82 to 1.03], P = 0.16; heterogeneity P = 0.66; I^2 = 0%).

Six studies comprising 4,827 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 2,767) and 16.70% (344 of 2,060) (HR 0.82 [CI 0.69 to 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 heart failure patients with reduced ejection fraction and coronary artery disease. The main findings of this analysis are that: a) revascularization with either CABG or PCI carried a significant improvement in long-term survival over MT; b) CABG showed a significantly improved survival compared to PCI, that persisted among patients with left main/proximal LAD disease and in studies conducted after the advent of DES; c) CABG compared to PCI was associated with a significant reduction in the risk of myocardial infarction or need for repeat revascularization, albeit with a numerically higher rate of stroke.

There are potential anatomical 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 coronary artery disease (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 HF and reduced ejection fraction. 2) In HF patients CAD tends to be more complex and diffuse, leading to higher need for repeated revascularisations and myocardial infarction rates after coronary stenting than with CABG[37-38]. 3) CABG revascularizing prolonged epicardial segments vs. PCI only specific stenotic lesion can yield a better vessel patency with a graft vs. a stented native vessel often extensively diseased 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 be related to fewer lethal ventricular arrhythmias or to reverse remodeling. The risk of contrast induced acute nephropathy (CI-AKI) after PCI is also increased in more complex patients with HF and reduced ejection fraction, potentially contributing to higher mortality rates as compared to 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 coronary artery disease patients with heart failure, since this is a specific population that was largely excluded from the early stable angina trials [21]. The only randomized trial specifically addressing heart failure patients is STICH, with its recently published 10-year extended follow-up (STICHES) [33]. For similar reasons, the randomized trials comparing PCI to CABG in CAD patients have failed to provide definite answers regarding patients with comorbid heart failure. Indeed, only approximately 2% of patients enrolled in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial had LVEF <30% [40]. More recently, the NHLBI-sponsored FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial reported similar outcomes with PCI using drug-eluting stents and CABG in patients with LVEF <40%, but only 32 patients (2.5%) were in this pre-specified 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 European Society of Cardiology (ESC) guidelines recommend CABG over PCI for patients with HFrEF and significant CAD in the 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 two/three vessel disease. 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 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 vs. 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 three-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% confidence intervals suggest consistency of the findings that remained statistically significant in the subanalyses of CABG vs. PCI using DES, and of the randomized/matched cohorts. The reduction in mortality, however, was numerically smaller for CABG vs. PCI than for CABG vs. MT, in line with the findings of the present article on the benefits of PCI over MT. In a subanalysis of secondary endpoints, we found significantly reduced risk for myocardial infarction and repeat revascularization in patients treated with CABG vs. PCI.

Although left main and three-vessel disease have long been a domain of CABG rather than PCI for revascularization, due to an established prognostic benefit of CABG, three recent randomized trials, LE MANS [44], SYNTAX [45] and PRECOMBAT [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 repeat revascularization.

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 and/or diabetes mellitus [48,49]. Our findings indicate that surgical revascularization in patients with heart failure and reduced ejection fraction should be regarded as the preferred strategy, with significant survival benefits in patients with left main/proximal LAD disease and a numerical but non-significant mortality reduction in patients with three 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 heart failure with reduced ejection fraction is most often based on clinical symptoms, e.g. 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 [50] 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 to 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 heart failure and associated reduced ejection fraction.

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 RCTs 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 vs. those derived from randomized trials. Nonetheless, a number of 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 medical treatments; 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.

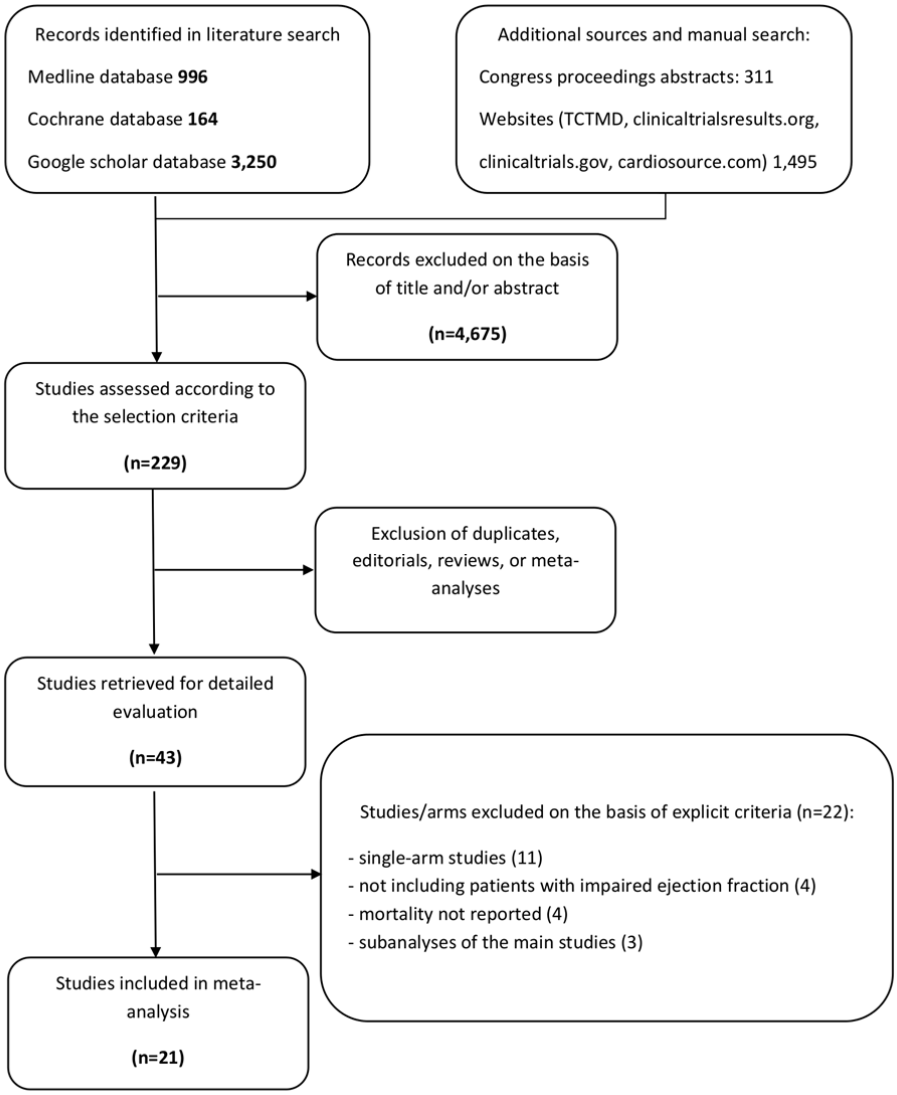
Conclusions

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.

335 **Figure 1 Flow diagram of meta-analysis.**

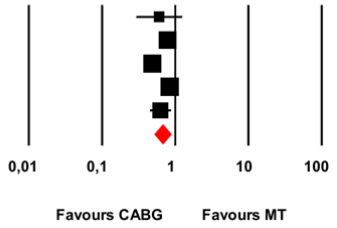


336

Figure 2

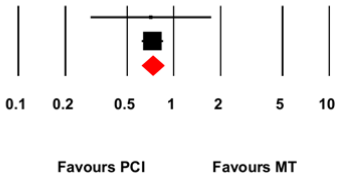
A) Mortality in studies comparing CABG versus MT

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**



B) Mortality in studies comparing PCI versus MT

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
LaBarbera et al., TCT/JACC 2012	0.73	0.619	0.855	-3.858	0.000
OVERALL	**0.73**	**0.620**	**0.852**	**-3.929**	**0.000**



C) Mortality in studies comparing CABG versus 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
AWESOME-RCT, Am J Cardiol 2004	0,88	0,471	1,626	-0,422	0,673
AWESOME-Registry, Am J Cardiol 2004	1,08	0,804	1,451	0,510	0,610
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
Gioia et al., Cath Cardiovasc Int 2007	1,38	0,602	3,142	0,755	0,450
Hannan et al., NEJM 2008	0,77	0,591	1,002	-1,942	0,052
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
REHEAT, Am J Cardiol 2007	2,00	0,205	19,541	0,596	0,551
Toda et al., Ann Thorac Surg 2002	0,85	0,488	1,475	-0,582	0,560
Yang et al., Am J Cardiol 2013	0,86	0,621	1,191	-0,907	0,365
OVERALL	**0,82**	**0,752**	**0,900**	**-4,265**	**0,000**

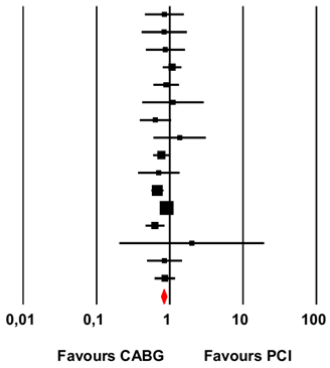
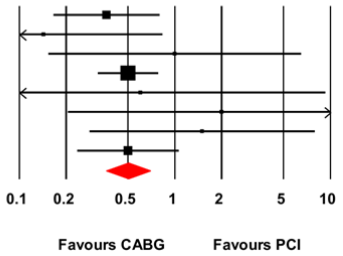


Figure 2: Individual and summary hazard ratios for mortality of studies stratified by treatment comparison: A) CABG vs. MT; B) PCI vs. MT; C) CABG vs. PCI.

Figure 3

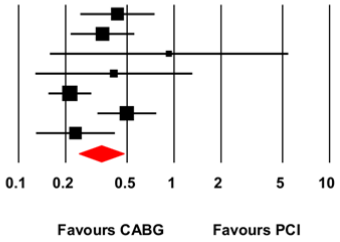
A) Myocardial infarction in studies comparing CABG versus PCI

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Bangalore et al., NEJM 2015	0.36	0.165	0.800	-2.513	0.012
CREDO-Kyoto, Am J Cardiol 2014	0.14	0.024	0.836	-2.159	0.031
Gioia et al.,Cath Cardiovasc Int 2007	1.00	0.153	6.523	0.000	1.000
Hannan et al., NEJM 2008	0.50	0.318	0.785	-3.010	0.003
IRIS-MAIN, TCT/JACC 2015	0.60	0.039	9.343	-0.365	0.715
REHEAT, Am J Cardiol 2007	2.00	0.205	19.541	0.596	0.551
Toda et al., Ann Thorac Surg 2002	1.50	0.282	7.978	0.476	0.634
Yang et al., Am J Cardiol 2013	0.50	0.235	1.064	-1.798	0.072
OVERALL	**0.50**	**0.361**	**0.689**	**-4.219**	**0.000**



B) Repeat revascularization in studies comparing CABG versus PCI

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Bangalore et al., NEJM 2015	0.43	0.249	0.751	-2.975	0.003
CREDO-Kyoto, Am J Cardiol 2014	0.35	0.216	0.556	-4.384	0.000
Gioia et al., Cath Cardiovasc Int 2007	0.93	0.158	5.440	-0.083	0.934
IRIS-MAIN, TCT/JACC 2015	0.41	0.128	1.316	-1.498	0.134
Nagendran et al., Ann Thorac Surg 2013	0.21	0.155	0.294	-9.429	0.000
Toda et al., Ann Thorac Surg 2002	0.50	0.320	0.772	-3.116	0.002
Yang et al., Am J Cardiol 2013	0.23	0.129	0.418	-4.872	0.000
OVERALL	**0.34**	**0.243**	**0.471**	**-6.426**	**0.000**



C) Stroke in studies comparing CABG versus PCI

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Bangalore et al., NEJM 2015	0.44	0.139	1.419	-1.369	0.171
CREDO-Kyoto, Am J Cardiol 2014	0.94	0.430	2.076	-0.141	0.888
IRIS-MAIN, TCT/JACC 2015	0.83	0.160	4.292	-0.224	0.823
Yang et al., Am J Cardiol 2013	0.81	0.473	1.402	-0.743	0.458
OVERALL	**0.79**	**0.525**	**1.180**	**-1.157**	**0.247**

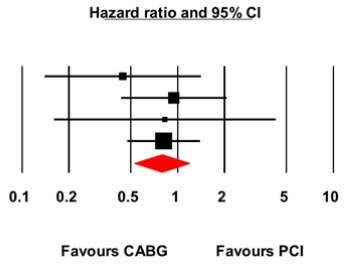
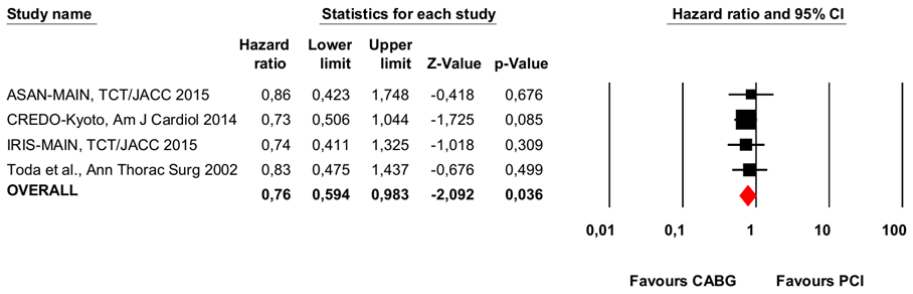


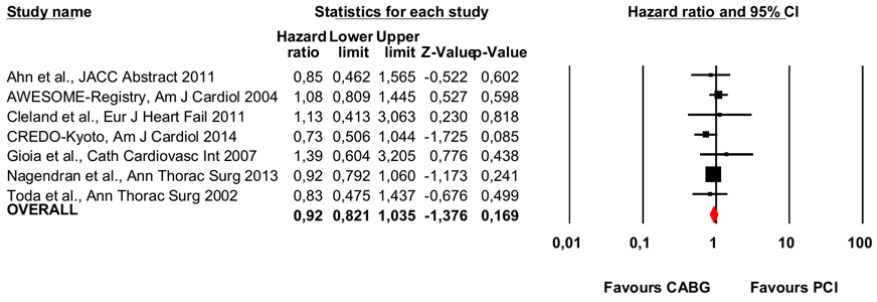
Figure 3: Individual and summary hazard ratios for secondary endpoints of studies comparing CABG versus PCI: A) Myocardial infarction; B) Repeat revascularization; C) Stroke.

Figure 4

A) Mortality in studies comparing CABG versus PCI in patients with left main/proximal LAD disease



B) Mortality in studies comparing CABG versus PCI in patients with three-vessel-disease



C) Mortality in studies comparing CABG versus PCI, with drug-eluting stents in the PCI group

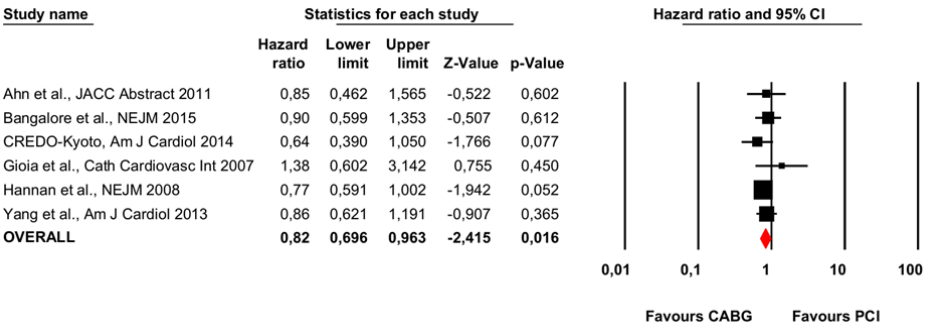


Figure 4: Individual and summary hazard ratios for mortality in studies comparing CABG versus PCI stratified by patient characteristics or treatment: A) in patients with left main/proximal LAD disease; B) in patients with three-vessel-disease; C) in studies using drug-eluting stents in the PCI group.

Table 1. Characteristics of included studies

Study	Year	Type	Patients (total)	Comparison	FU (months)	Reported outcomes
Ahn et al. [34]	2011	Registry	327	CABG vs PCI	36	Mortality, major adverse cardiac or cerebrovascular events
Appoo et al. [17]	2004	Registry	2169	CABG vs MT	12	Mortality
ASAN-MAIN [22]	2015	Registry	213	CABG vs PCI	24	Mortality
AWESOME [23,35]	2004	RCT/Registry	386	CABG vs PCI	36	Mortality, survival free of angina, RR
Bangalore et al. [32]	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. [18]	2011	RCT	109	CABG vs PCI vs MT	59	Mortality
CREDO-Kyoto [24]	2014	Registry	293	CABG vs PCI	60	Mortality, cardiac mortality, sudden death, readmission for HF, stroke, MI, RR
Gioia et al. [25]	2007	Registry	220	CABG vs PCI	15	Mortality, cardiac mortality, MI, TVR, NYHA
Hannan et al. [26]	2008	Registry	2673	CABG vs PCI	18	Mortality, MI
IRIS-MAIN [27]	2015	Registry	364	CABG vs PCI	12	Mortality, cardiac mortality, MI, RR, TVR, stroke
Kwon et al. [19]	2012	Registry	450	CABG vs MT	70	Mortality
LaBarbera et al. [20]	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 [21,33]	2011/2016	RCT	1212	CABG vs MT	118	Mortality, cardiovascular mortality
Toda et al. [31]	2002	Registry	117	CABG vs PCI	36	Mortality, MI, TVR, heart failure
Velazquez et al. [16]	2012	Registry	763	CABG vs MT	120	Mortality
Yang et al. [15]	2013	Registry	953	CABG vs PCI	28	Mortality, MI, stroke, RR, TVR

Table 1: Characteristics of included studies. MT=medical therapy, PCI=percutaneous coronary intervention, RCT=randomized controlled trial, FU=follow-up, MI=myocardial infarction, RR=repeat revascularization, TVR=target vessel revascularization, CABG=coronary artery bypass graft.

Table 2. Baseline patient characteristics

Study	Age (y)	Male (%)	HTN (%)	DM (%)	HLP (%)	CKD (%)	Prior CABG (%)	Prior PCI (%)	Prior MI (%)	DES use >50%	Left main/prox. LAD >50%	3-vessel disease >50%	Viability test >50%
Ahn et al. [34]	-	-	-	-	-	-	-	-	-	yes	no	yes	no
Appoo et al. [17]	64	85	50	26	39	4	12	8	61	no	no	no	no
ASAN-MAIN [22]	-	-	-	-	-	-	-	-	-	no	yes	no	no
AWESOME [23,35]	65	-	66	33	-	-	29	23	-	no	no	yes	no
Bangalore et al. [32]	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. [18]	67	93	50	36	59	-	8	8	73	no	no	yes	yes
CREDO-Kyoto [24]	69	77	87	57	-	11	-	-	44	yes	yes	yes	no
Gioia et al. [25]	68	81	69	43	68	-	17	20	56	yes	no	yes	no
Hannan et al. [26]	66	70	-	-	36	4	-	-	42	yes	no	no	no
IRIS-MAIN [27]	66	79	-	-	-	-	-	-	-	no	yes	no	no
Kwon et al. [19]	63	74	51	37	49	-	20	-	-	no	no	no	yes
LaBarbera et al. [20]	-	-	-	-	-	-	-	-	-	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 [21,33]	60	88	60	40	60	8	3	-	77	no	yes	yes	no
Toda et al. [31]	64	74	-	42	-	3	20	26	23	no	yes	yes	no
Velazquez et al. [16]	64	75	-	34	-	4	30	21	39	no	no	no	no
Yang et al. [15]	66	76	60	50	27	13	5	25	29	yes	no	no	no

Table 2: Baseline patient characteristics of all included studies. HTN=hypertension, DM=diabetes mellitus, HLP=hyperlipoproteinemia, CKD=chronic kidney disease, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, MI=myocardial infarction, DES=drug-eluting stent, LAD=left anterior descending artery.

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