

Short-term and long-term outcomes of revascularization interventions for patients with severely reduced left ventricular ejection fraction: a meta-analysis

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Abstract

Aims This meta-analysis aimed to determine whether coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) should be preferred in patients with severely reduced left ventricular (LV) ejection fraction.

Methods and results We searched the PubMed, EMBASE, and Cochrane Library databases from the conception of the databases till 1 May 2020 for studies on patients with severely reduced LV ejection fraction undergoing CABG and PCI. The primary clinical endpoints were 30 day and long-term mortalities. The secondary endpoints were 30 day and long-term incidences of myocardial infarction (MI) and stroke, long-term cardiovascular mortality, and repeat revascularization. Eighteen studies involving 11 686 patients were analysed. Compared with PCI, CABG had lower long-term mortality [hazard ratio (HR): 0.70, 95% confidence interval (CI): 0.61–0.80, $P < 0.01$], cardiovascular mortality (HR: 0.60, 95% CI: 0.43–0.85, $P < 0.01$), MI (HR: 0.51, 95% CI: 0.36–0.72, $P < 0.01$), and repeat revascularization (HR: 0.32, 95% CI: 0.23–0.47, $P < 0.01$) risk. Significant differences were not observed for long-term stroke (HR: 1.18, 95% CI: 0.74–1.87, $P = 0.49$), 30 day mortality (HR: 1.18, 95% CI: 0.89–1.56, $P = 0.25$), and MI (HR: 0.42, 95% CI: 0.16–1.11, $P = 0.08$) risk. CABG was associated with a higher risk of stroke within 30 days (HR: 2.88, 95% CI: 1.07–7.77, $P = 0.04$). In a subgroup analysis of propensity score-matched studies, CABG was associated with a higher long-term risk of stroke (HR: 1.61, 95% CI: 1.20–2.16, $P < 0.01$).

Conclusions Among patients with severely reduced LV ejection fraction, CABG resulted in a lower mortality rate and an increased risk of stroke.

Keywords Coronary artery bypass; Coronary artery disease; Heart failure; Meta-analysis; Stroke

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Introduction

Coronary artery disease (CAD) is the leading cause of mortality and severely reduced left ventricular (LV) ejection fraction (LVEF). With an increasing understanding of CAD and changes in treatment methods, the mortality rate has continued to decrease; however, the incidence of LV dysfunction mediated by CAD has been increasing.^{1–4} In the USA alone, >538 000 individuals die of CAD annually, and it is estimated that

CAD-induced LV dysfunction will affect >8 million people by 2030.⁵ As patients with severely reduced LVEF are often excluded from clinical trials, the optimal strategy for revascularization in these patients to date remains controversial.⁶

The main American and European professional bodies currently do not provide precise recommendations for revascularization in patients with severely reduced LVEF.^{7,8} The vagueness of their guidelines reflects the lack of relevant evidence. Several cohort studies have reported that coronary

artery bypass grafting (CABG) is associated with better prognosis compared with percutaneous coronary interventions (PCIs); however, these findings have not been confirmed in clinical trials.^{9–11} Cohort studies are insufficient to confirm the superiority of CABG over PCI. To the best of our knowledge, there is currently no meta-analysis that reports on both the short-term and long-term outcomes of different revascularization strategies for patients with severely reduced LVEF.^{12,13} Thus, we aimed to conduct a systematic review and meta-analysis to identify the optimal revascularization strategy for patients with CAD and severely reduced LVEF.

Methods

This systematic review and meta-analysis were performed according to the established methods recommended by the Cochrane Handbook and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for conducting systematic reviews and meta-analyses in health care interventions.¹⁴

Data sources and search strategy

We comprehensively searched PubMed, EMBASE, and Cochrane Library databases for studies reporting on the use of CABG and PCI for patients with severely reduced ejection fraction from the time of conception of these databases till 1 May 2020. The following search terms and medical subject headings were used: ‘coronary artery bypass grafting’, ‘percutaneous coronary intervention’, ‘revascularization’, ‘reduced ejection fraction’, ‘left ventricular ejection fraction’, ‘LVEF’, ‘severe left ventricular dysfunction’, ‘heart failure’, and ‘ischaemic cardiomyopathy’. In addition, we also checked the reference lists of the identified articles and related reviews to identify other potentially eligible studies.

Selection criteria and outcome measures

The inclusion criteria were as follows: (i) patients who have CAD suitable for revascularization and an LVEF measured by means of contrast magnetic resonance ventriculography, gated SPECT ventriculography, echocardiography, or contrast ventriculography $\leq 35\%$; (ii) randomized registry trials or case-control studies comparing PCI and CABG; (iii) follow-up duration > 12 months; and (iv) reported short-term and long-term outcomes that could be extracted. The exclusion criteria were as follows: (i) publications in languages other than English and (ii) use of the same patient data in more than one study.

J. Y. P. and X. P. W. initially selected the articles. If there was a disagreement regarding the selection of articles, X. Q. H. decided whether the articles met the inclusion

criteria. We did not contact the authors to obtain the original data of the study.

The primary clinical endpoints were 30 day and long-term mortalities. The secondary endpoints were 30 day and long-term incidences of myocardial infarction (MI), 30 day and long-term incidences of stroke, long-term incidence of cardiovascular mortality (CVD-related mortality), and long-term requirement for repeat revascularization (RR). RR was any revascularization, including target vessel revascularization.

Data extraction and quality assessment

The following data were extracted by two independent researchers (Z. H. X. and K. Y. Z.): study characteristics, patient baseline characteristics, quality indicators, and primary and secondary clinical outcomes. We extracted data according to the intention-to-treat principle. If there was any disagreement, it was resolved through discussion with a third researcher (X. Q. H.). We used the Newcastle-Ottawa Scale criteria to evaluate the quality of the registry studies.¹⁵

Statistical analyses and sensitive analysis

We used hazard ratios (HRs) and 95% confidence intervals (CIs) to present the results. We used Cochran’s *Q* test to assess the potential heterogeneity among studies. Heterogeneity between studies was quantified with I^2 , ranging from 0% to 100%. An $I^2 > 50\%$ was defined as substantial heterogeneity. We used the random-effects model to calculate the pooled HRs for all outcomes owing to differences in the methodology used across the analysed studies.

To assess the reliability of the conclusions drawn, we conducted a sensitivity analysis through two subgroup analyses: one for propensity score-matched studies and the other for studies comparing the outcomes between drug-eluting stent-PCI and CABG. We used the Stata/MP statistical software (version 14.0, StataCorp LP, College Station, TX, USA) to perform the statistical analysis.

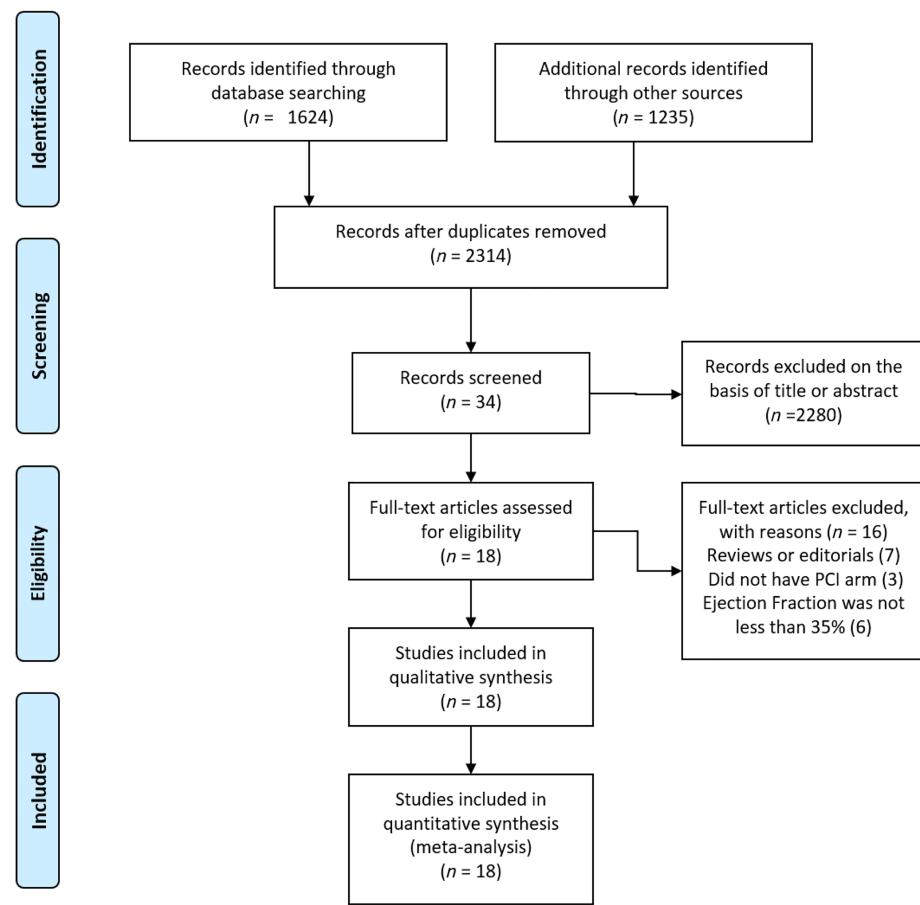
Results

Study selection and patient populations

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart to describe the screening and selection of articles¹⁴ (Figure 1).

After a comprehensive search, we identified 2314 potentially relevant articles. We selected 35 studies for a full review. After applying the inclusion and exclusion criteria, 18 studies published between 2002 and April 2020 were finally

Figure 1 Flow diagram of meta-analysis. PCI, percutaneous coronary intervention.



analysed.^{9–11,16–30} These studies included two randomized controlled trials involving 139 patients,^{26,29} a case–control study involving 107 patients,²⁸ and 16 registry studies involving 16 940 patients.^{9–11,16–25,27,29,30}

The baseline characteristics of the included studies are presented in *Table 1*, and the quality assessment is presented in Supporting Information, *Table S1*. The 18 studies comprised 17 186 patients; of these, 8312 patients underwent PCI, and 8839 patients underwent CABG. The baseline characteristics of the patients are shown in *Table 2*.

Thirty-day and long-term mortalities

All 18 studies reported the long-term mortality of patients, and eight studies involving 11 686 patients reported 30 day mortality.^{9,11,17,19,22,27,28,30} There was no statistically significant difference in the 30 day mortality between CABG and PCI (HR: 1.18, 95% CI: 0.89–1.56, $P = 0.25$, $I^2: 34.1\%$; *Figure 2*, Supporting Information, *Figure S1*). However, a statistically

significant decrease in the long-term mortality was observed between CABG (8839 of 17 186 patients, 51.4%) and PCI (8312 of 17 186 patients, 48.6%; HR: 0.70, 95% CI: 0.61–0.80, $P < 0.01$, $I^2: 69.6\%$; *Figure 2*, Supporting Information, *Figure S2*).

Secondary endpoints—30 day incidence of myocardial infarction and stroke

Four studies involving 8240 patients reported the 30 day incidence of MI.^{9,17,19,28} There was no statistically significant difference between CABG and PCI with respect to the 30 day incidence of MI (HR: 0.42, 95% CI: 0.16–1.11, $P = 0.08$, $I^2: 70.6\%$; *Figure 2*, Supporting Information, *Figure S3*). The same four studies reported the 30 day stroke incidence. Compared with PCI, CABG significantly increased the risk of stroke within 30 days (HR: 2.88, 95% CI: 1.07–7.77, $P = 0.04$, $I^2: 49.2\%$; *Figure 2*, Supporting Information, *Figure S4*).

Table 1 Characteristics of included studies

Year	Type	Propensity score matched	Patients total			PCI	CABG	Follow-up (months)	DES only	>50% LAD disease	Left main/proximal LAD disease		Complete revascularization (PCI/CABG)	Diabetes (%)	CKD (%)	Short-term outcomes	Long-term outcomes
			117	48	69						Yes	/	42	3			
2002	Observational	No	386	199	187	36	No	No	No	No	/	/	35	/	/	Mortality, survival free of angina, RR	Mortality, survival free of angina, RR
2004	Observational	No	94	47	47	36	No	No	No	No	/	/	28	/	/	Mortality, survival free of angina, RR	Mortality, survival free of angina, RR
2007	Case-control study	/	107	55	52	12	No	No	No	No	/	/	25	/	Mortality, nonfatal, MI, stroke	Mortality, MI, arrhythmia, angina, RR, stroke	
2007	Observational	No	220	128	92	15	Yes	No	No	No	/	/	43	/	Mortality	Mortality, cardiac mortality, MI, stroke	
2010	Observational	No	327	116	176	36	Yes	No	No	No	/	/	/	/	/	Mortality, TVR, NYHA	Mortality, major adverse cardiac or cerebrovascular events
2011	RCT	/	45	15	30	59	No	No	No	No	/	/	/	/	/	Mortality	Mortality
2012	Observational	No	991	498	493	60	No	Yes	Yes	Yes	/	/	/	/	/	Mortality	Mortality
2013	Observational	Yes	296	154	142	60	No	No	No	No	/	/	/	/	/	Mortality	Mortality
2013	Observational	Yes	1436	718	718	180	No	Yes (sub)	Yes	Yes	/	/	34	5	/	Mortality, MI, stroke, RR, TVR	Mortality, MI, stroke, RR, TVR
2013	Observational	Yes	282	141	141	28	Yes	Yes	Yes	Yes	92.5%/95%	/	55	17	/	Mortality, sudden death, readmission for HF, stroke, MI, RR	Mortality, sudden death, readmission for HF, stroke, MI, RR
2014	Observational	Yes	296	158	138	60	Yes	Yes	Yes	Yes	/	/	/	/	/	Mortality, MI, stroke, RR	Mortality, MI, stroke, RR
2016	Observational	Yes	2126	1063	1063	48	Yes	No	No	No	19.8%/19.8%	43	5	Mortality, MI, stroke, RR	Mortality, MI, stroke, RR	Mortality, MI, stroke, RR	
2017	Observational	No	911	469	442	60	Yes	No	Yes	Yes	54%/68.6%	/	52	13	/	Mortality, MI, stroke, RR	Mortality, MI, stroke, RR
2018	Observational	No	1213	452	761	48	No	Yes	Yes	Yes	41	9	Mortality, MI, stroke	Mortality, MI, stroke	Mortality, MI, stroke	Mortality, MI, stroke	
2018	Observational	Yes	1673	718	955	120	Yes (sub)	Yes	Yes	Yes	/	43	6	Mortality	Mortality, AKI, stroke, RR	Mortality, AKI, stroke, RR	
2018	Observational	Yes	1738	869	869	60	Yes	No	No	No	/	100	3	/	Mortality	Mortality, MI, stroke, RR, MACCE	Mortality
2019	Observational	Yes	134	67	67	96	No	No	No	No	48%/48%	31	5	Mortality	Mortality, MI, stroke, RR, MACCE	Mortality	
2020	Observational	Yes	4794	2397	2397	108	No	Yes	Yes	Yes	21.2%/81.4%	/	52	4	Mortality, MI, stroke, RR, MACCE, HF	Mortality, MI, stroke, RR, MACCE, HF	Mortality, MI, stroke, RR, MACCE, HF

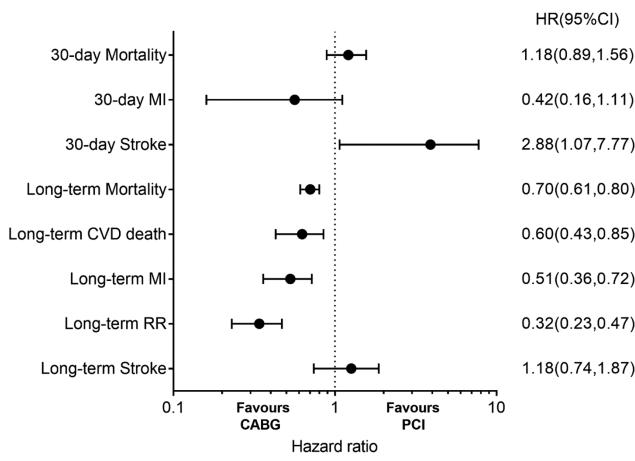
AKI, acute kidney injury; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DES, drug-eluting stent; HF, heart failure; LAD, left anterior descending; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, repeat revascularization; TVR, target vessel revascularization; VT/VF, ventricular tachycardia/ventricular fibrillation.

Table 2 Baseline patient characteristics

Study	Age (years)	Male (%)	Hypertension (%)	Hyperlipoproteinaemia (%)	Previous CABG (%)	Previous PCI (%)	Previous MI (%)
Toda	64	74	NA	NA	20	26	23
Sedlis-Observational (AWESOME)	65	/	66	/	31	20	/
Sedlis-RCT (AWESOME)	64	/	67	/	23	30	/
Buszman	61	77	62	66	/	/	29
Gioia	68	81	69	68	17	20	56
Ahn	/	/	/	/	/	/	/
Cleland (HEART)	/	/	/	/	/	/	/
LaBarbera	/	/	/	/	/	/	/
Fortuna	/	/	/	/	/	/	/
Nagendran	65	81	63	62	6	8	66
Yang	66	75	60	28	5	36	35
Marui (CREDO-Kyoto)	/	/	/	/	/	/	/
Bangalore	66	75	/	/	/	28	65
Kang	67	/	58	34	/	/	19
Hawranek	65	83	/	57	8	47	54
Iribarne	65	74	/	/	/	/	57
Nagendran	65	78	84	81	3	4	50
Shaha	71	88	82	/	/	19	78
Sun	66	80	85	/	/	20	26

AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; CABG, coronary artery bypass grafting; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; HEART, The Heart Failure Revascularisation Trial; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

Figure 2 The primary outcomes and secondary outcomes of this meta-analysis. CABG, coronary artery bypass grafting; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, repeat revascularization.



Long-term secondary outcomes

A total of four studies involving 6118 patients reported the long-term incidence of CVD-related mortality.^{9,18,20,30} A statistically significant decrease in the long-term CVD-related mortality was only observed for CABG (HR: 0.60, 95% CI: 0.43–0.85, $P < 0.01$, I^2 : 59.9%; *Figure 2*, Supporting Information, *Figure S5*). A total of nine studies involving 11 522 patients reported the long-term incidence of MI.^{9,10,17–20,27,28,30} A statistically significant decrease in the reduction in the long-term incidence of MI was only observed for CABG

(HR: 0.51, 95% CI: 0.36–0.72, $P < 0.01$, I^2 : 62.6%; *Figure 2*, Supporting Information, *Figure S6*). A total of 10 studies involving 13 370 patients reported the long-term requirement for RR.^{9–11,17,19–21,27,30} A statistically significant decrease in the long-term requirement of RR was observed with CABG (HR: 0.32, 95% CI: 0.23–0.47, $P < 0.01$, I^2 : 82%; *Figure 2*, Supporting Information, *Figure S7*). A total of seven studies involving 12 751 patients reported the long-term incidence of stroke.^{9–11,17–20} There was no significant difference in the long-term incidence of stroke between CABG and PCI (HR: 1.18, 95% CI: 0.74–1.87, $P = 0.49$, I^2 : 75.5%; *Figure 2*, Supporting Information, *Figure S8*).

Subgroup analysis

Drug-eluting stent percutaneous coronary intervention vs. coronary artery bypass grafting

As only a few studies reported the related outcomes, we only calculated the HR for 30 day mortality among the short-term outcomes (*Figure 3*). Two studies involving 2346 patients reported the 30 day mortality, and there were no statistically significant differences between the two interventions (HR: 2.36, 95% CI: 0.78–7.17, $P = 0.13$, I^2 : 45.7%; *Figure 3*, Supporting Information, *Figure S9*).

With respect to the long-term outcomes, the long-term mortality (HR: 0.69, 95% CI: 0.55–0.87, $P < 0.01$, I^2 : 65%; *Figure 3*, Supporting Information, *Figure S10*), CVD-related mortality (HR: 0.40, 95% CI: 0.20–0.78, $P < 0.01$, I^2 : 42.2%; *Figure 3*, Supporting Information, *Figure S11*), long-term incidence of MI (HR: 0.56, 95% CI: 0.40–0.78, $P < 0.01$, I^2 : 23.1%;

Figure 3 The results of drug-eluting stent percutaneous coronary intervention (PCI) subgroup analysis. CABG, coronary artery bypass grafting; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; RR, repeat revascularization.

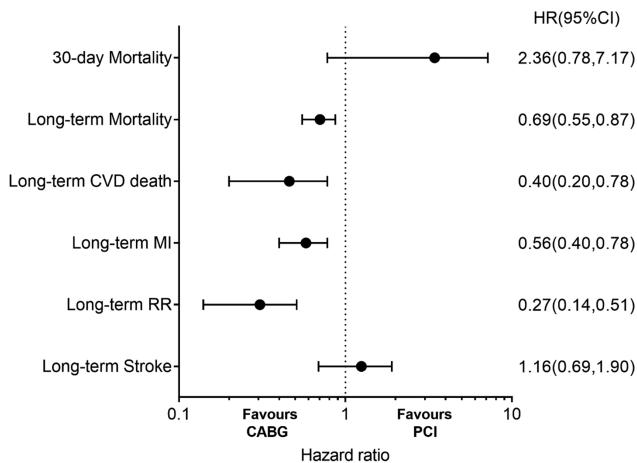


Figure 3, Supporting Information, Figure S12), long-term requirement for RR (HR: 0.27, 95% CI: 0.14–0.51, $P < 0.01$, I^2 : 76.9%; Figure 3, Supporting Information, Figure S13), and the long-term incidence of stroke (HR: 1.15, 95% CI: 0.69–1.90, $P = 0.59$, I^2 : 35.7%; Figure 3, Supporting Information, Figure S14) were similar compared with the overall results.

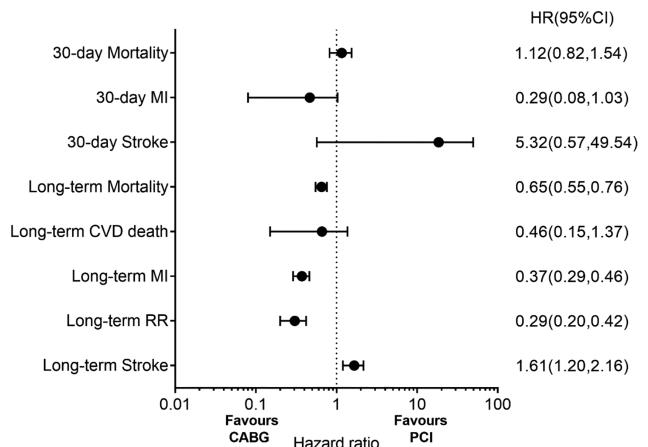
Propensity score-matched studies

A total of nine propensity score-matched studies involving 12 775 patients were analysed. The short-term outcomes were not significantly different between the PCI and CABG groups for mortality (HR: 1.12, 95% CI: 0.82–1.54, $P = 0.48$, I^2 : 49.9%), MI incidence (HR: 0.29, 95% CI: 0.08–1.03, $P = 0.06$, I^2 : 78.8%), and stroke (HR: 5.32, 95% CI: 0.57–49.54, $P = 0.14$, I^2 : 82%) as shown in Figure 4. Additionally, significant statistical differences between the two groups were observed for long-term outcomes, mortality (HR: 0.65, 95% CI: 0.55–0.76, $P < 0.01$, I^2 : 73.6%), incidence of MI (HR: 0.37, 95% CI: 0.29–0.46, $P < 0.01$, I^2 : 23.1%), and need for RR (HR: 0.29, 95% CI: 0.20–0.42, $P < 0.01$, I^2 : 71%), and therefore, CABG still shows a clear advantage. The incidence of CVD-related mortality was not different between the two propensity score-matched groups (HR: 0.46, 95% CI: 0.15–1.37, $P = 0.17$, I^2 : 71%). The long-term risk of stroke was significantly higher in the CABG group than in the PCI group after propensity score matching (HR: 1.61, 95% CI: 1.20–2.16, $P < 0.01$, I^2 : 24.8%; Figure 4, Supporting Information, Figures S15–S22).

Discussion

The results of this systematic review and meta-analysis show that the short-term outcomes are similar among patients

Figure 4 The results of propensity score-matched study subgroup analysis. CABG, coronary artery bypass grafting; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, repeat revascularization.



with severely reduced LVEF treated with PCI or CABG, except for the higher risk of stroke in patients who received CABG. In the long term, patients undergoing PCI showed a worse prognosis than those receiving CABG. However, a propensity score matching analysis revealed a higher long-term risk of stroke after CABG.

To the best of our knowledge, there are currently only two randomized controlled studies on revascularization that include patients with severely reduced LVEF. The Heart Failure Revascularization Trial (HEART) included only 138 patients and did not compare PCI with CABG.²⁶ This study did not conclude that revascularization is better than conservative treatment and due to the early termination of the experiment, the conclusion of the experiment may not be reliable. The Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES) compared CABG and optimal medical therapy and showed that CABG could reduce absolute mortality by 7% during a 10 year follow-up and was associated with fewer CVD-related hospitalizations.³¹

Most clinical studies exclude patients with severely reduced LVEF. Many large clinical randomized controlled studies comparing PCI and CABG included only a small number of these patients. For example, the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX trial) only enrolled approximately 2% patients with LVEF <30%,³² while the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial only enrolled 32 (2.5%) patients with LVEF <30%.³³ High-quality evidence from randomized controlled studies for revascularization strategies for patients with severely reduced LVEF is insufficient.

Several studies have clarified that CABG improves the clinical outcome of patients with reduced LVEF compared with PCI.^{9,10,13,19} The meta-analysis by Wolff *et al.* also reported

that the prognosis of patients who underwent CABG was better than that of those who underwent PCI; however, they did not specify that CABG may increase the risk of stroke.¹² After Wolff *et al.* published their work in 2017, many important studies were published; for example, Sun *et al.* published the largest propensity score-matched cohort study to date.⁹ This study reported that CABG was associated with a higher stroke risk than that observed with PCI for patients with severely reduced ejection fraction. The current guidelines recommend that CABG should be selected as the revascularization strategy for patients with severely reduced ejection fraction; however, the European Society of Cardiology guidelines state that CABG is better than PCI, while the US guidelines only recommend CABG but do not comment on PCI.^{7,8} Owing to the feasibility of PCI and the choice of the patients, PCI is still widely performed. To the best of our knowledge, this is the first study to assess the relevant short-term outcomes for patients who underwent CABG and PCI, providing more solid evidence for clinical decision-making with respect to the selection of the revascularization strategy.

Both functional and anatomical factors may account for the difference in mortality between patients who underwent CABG and PCI. Complete revascularization is achieved more frequently with CABG than with PCI.³⁴ Complete revascularization reduces the burden of myocardial ischaemia more effectively, and consequently, the risk of sudden and cardiac mortality. Moreover, the blood supply to the distal vascular bed is better with CABG.³⁵ In patients with ischaemic heart failure after MI, the LV systolic function decreases mainly owing to the loss of myocardial tissue and its replacement with fibrous tissue.³⁶ However, in recent decades, myocardial stunning and hibernating myocardium have gradually received more attention. Myocardial stunning and hibernating myocardium will gradually restore function after the coronary blood supply is restored.^{37,38} This may account for the complete revascularization observed after CABG, which, in turn, leads to better patient prognosis.

A study published by Head *et al.* in 2018 showed that CABG has a higher risk of stroke than PCI in a randomized controlled study.³⁹ In the subgroup analysis, the stroke risk of CABG was not higher than that of PCI in patients with LVEF <50%. This may be due to the small number of patients. As mentioned earlier, the number of patients with severely reduced ejection fraction included in randomized controlled studies is particularly rare. In another meta-analysis published in 2018, it reported that CABG did not increase the risk of stroke.⁴⁰ The inclusion criteria of this study were patients with ischaemic heart failure. Although most of the patients in the study had LVEF <35%, not all patients in the study had ejection fractions less than 35%. Furthermore, that study did not include the study published by Sun *et al.* in 2020, which is the largest propensity score-matched study so far,⁹ or a comparison of the short-term outcomes of CABG and PCI. Therefore, for these reasons, that study could not

conclude whether CABG increased the risk of stroke in patients with severely reduced ejection fraction compared with PCI.

There may be many factors responsible for the increased risk of long-term stroke in CABG compared with patients after PCI. First, CABG surgery is performed on the pump, while intubation and aortic clamping are performed. Even if it is performed without extracorporeal circulation, it is often necessary to manipulate the aorta to construct a proximal anastomosis.^{41–43} The data of the cohort study showed that the limitation of (even if not completely avoiding) aortic operations by performing CABG surgery without extracorporeal circulation can significantly reduce the incidence of stroke.⁴⁴ Second, strategies to reduce post-operative bleeding (such as the use of tranexamic acid) that are usually required after CABG surgery (rather than after PCI) can lead to excessive blood clotting, which increases the risk of stroke.⁴⁵ Third, atrial fibrillation often occurs after CABG and increases the risk of stroke in the early post-operative period.^{46,47} Fourth, hypoperfusion during surgery and early post-operative low cardiac output syndrome may impair cerebral perfusion, leading to ischaemia and watershed strokes.⁴⁸ Another study suggested that the routine use of dual antiplatelet therapy after stent implantation may have led to lower incidences of stroke after PCI.⁴⁹

There are some limitations of this study. All data assessed in this study were extracted from published studies. If individual patient data are obtained, more reliable conclusions can be drawn, and more robust and subgroup analyses can be conducted. Furthermore, most of the studies included in this meta-analysis were observational studies. Observational research better reflects real-world data. However, the making of relevant medical decisions is often determined by many factors. The patient's choice between CABG and PCI may also be determined by the number of co-morbidities and physical conditions of the patient. Sometimes CABG is more suitable for some patients, but due to its higher surgical risk, the patient chooses PCI. Circumstances may also cause some bias. This factor may also be one of the reasons why CABG has a better prognosis than PCI in real-world data. We performed a subgroup analysis of propensity score-matched studies but could not control for the confounding factors as effectively as that in the randomized controlled studies.

In conclusion, CABG decreases the risk of mortality, MI, and revascularization than PCI in patients with severely reduced ejection fraction but may increase the short-term and long-term risk of stroke.

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Conflict of interest

The paper has no financial interest in any individual or organization; it does not infringe on the intellectual property rights of others.

Supporting information

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

Data S1 Supporting Information

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References

- Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, Sadowski Z, Golba KS, Prior DL, Rouleau JL, Bonow RO. Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006; **114**: 1202–1213.
- Bourassa MG, Gurné O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and patterns of current practice in heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. *J Am Coll Cardiol* 1993; **22**: 14A–19A.
- Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; **93**: 1137–1146.
- Briceno N, Schuster A, Lumley M, Perera D. Ischaemic cardiomyopathy: pathophysiology, assessment and the role of revascularisation. *Heart* 2016; **102**: 397–406.
- Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, De Ferranti S, Després JP, Fullerton HJ. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation* 2016; **133**: e38–e360.
- Sun LY, Tu JV, Bader Eddeen A, Liu PP. Prevalence and long-term survival after coronary artery bypass grafting in women and men with heart failure and preserved versus reduced ejection fraction. *J Am Heart Assoc* 2018; **7**: e008902.
- Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; **40**: 87–165.
- Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; **60**: e44–e164.
- Sun LY, Gaudino M, Chen RJ, Bader Eddeen A, Ruel M. Long-term outcomes in patients with severely reduced left ventricular ejection fraction undergoing percutaneous coronary intervention vs coronary artery bypass grafting. *JAMA Cardiol* 2020; **5**: 631–641.
- Nagendran J, Bozso SJ, Norris CM, McAlister F, Appoo JJ, Moon MC, Freed DH, Nagendran J. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. *J Am Coll Cardiol* 2018; **71**: 819–827.
- Iribarne A, DiScipio AW, Leavitt BJ, Baribeau YR, McCullough JN, Weldner PW, Huang YL, Robich MP, Clough RA, Sardella GL, Olmstead EM. Comparative effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in a real-world Surgical Treatment for Ischemic Heart Failure trial population. *J Thorac Cardiovasc Surg* 2018; **156**: 1410–1421.e2.
- Wolff G, Dimitroulis D, Andreotti F, Kołodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail* 2017; **10**: e003255.
- Cui K, Zhang D, Lyu S, Song X, Yuan F, Xu F, Zhang M. Meta-analysis comparing percutaneous coronary revascularization using drug-eluting stent versus coronary artery bypass grafting in patients with left ventricular systolic dysfunction. *Am J Cardiol* 2018; **122**: 1670–1676.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **b2700**: 339.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603–605.
- Shah S, Benedetto U, Caputo M, Angelini GD, Vohra HA. Comparison of the survival between coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with poor left ventricular function (ejection fraction <30%): a propensity-matched analysis. *Eur J Cardiothorac Surg* 2019; **55**: 238–246.
- Hawranek M, Zembala MO, Gasior M, Hrapkowicz T, Pyka Ł, Cieśla D, Zembala M. Comparison of coronary artery bypass grafting and percutaneous coronary intervention in patients with heart failure with reduced ejection fraction and multivessel coronary artery disease. *Oncotarget* 2018; **9**: 21201–21210.
- Kang SH, Lee CW, Baek S, Lee PH, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Park SJ. Comparison of outcomes of coronary artery bypass grafting versus drug-eluting stent implantation in patients with severe left ventricular dysfunction. *Am J Cardiol* 2017; **120**: 69–74.
- Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: everolimus-eluting stents versus coronary artery bypass graft surgery. *Circulation* 2016; **133**: 2132–2140.
- Marui A, Kimura T, Nishiwaki N, Mitsudo K, Komiya T, Hanyu M, Shiomi H, Tanaka S, Sakata R, CREDO-Kyoto PCI/CABG Registry Cohort-2

- Investigators. Comparison of five-year outcomes of coronary artery bypass grafting versus percutaneous coronary intervention in patients with left ventricular ejection fractions $\leq 50\%$ versus $> 50\%$ (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol* 2014; **114**: 988–996.
21. Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Jeong DS, Sung K, Kim WS, Lee YT, Gwon HC. Long-term outcomes of drug-eluting stent implantation versus coronary artery bypass grafting for patients with coronary artery disease and chronic left ventricular systolic dysfunction. *Am J Cardiol* 2013; **112**: 623–629.
 22. Nagendran J, Norris CM, Graham MM, Ross DB, Macarthur RG, Kieser TM, Maitland AM, Southern D, Meyer SR, APPROACH Investigators. Coronary revascularization for patients with severe left ventricular dysfunction. *Ann Thorac Surg* 2013; **96**: 2038–2044.
 23. Fortuna D, Nicolini F, Guastaroba P, De Palma R, Di Bartolomeo S, Saia F, Pacini D, Grilli R, RERIC (Regional Registry of Cardiac Surgery), REAL (Regional Registry of Coronary Angioplasties) Investigators. Coronary artery bypass grafting vs percutaneous coronary intervention in a ‘real-world’ setting: a comparative effectiveness study based on propensity score-matched cohorts. *Eur J Cardiothorac Surg* 2013; **44**: e16–e24.
 24. Ahn JM, Oh JH, Sun BJ, Cho SW, Kim YR, Lee CH, Hwang KW, Song H, Kim WJ, Lee JY, Kang SJ. AS-230 comparisons of drug-eluting stents vs. coronary-artery bypass grafting for patients with multi-vessel disease and severely compromised ventricular dysfunction. *Am J Cardiol* 2011; **107**: 87–80.
 25. LaBarbera M, Hui P, Shaw R. TCT-372 Coronary artery disease in patients with reduced left ventricular systolic function treated with medicine, surgery, or percutaneous coronary intervention: a retrospective review of outcomes within a multicenter healthcare system. *J Am Coll Cardiol* 2012; **60**: B107.
 26. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011; **13**: 227–233.
 27. Gioia G, Matthai W, Gillin K, Dralle J, Benassi A, Gioia MF, White J. Revascularization in severe left ventricular dysfunction: outcome comparison of drug-eluting stent implantation versus coronary artery by-pass grafting. *Catheter Cardiovasc Interv* 2007; **70**: 26–33.
 28. Buszman P, Szkrobka I, Gruszka A, Parma R, Tendera Z, Leśko B, Wilczyński M, Bochenek T, Wojakowski W, Bochenek A, Tendera M. Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. *Am J Cardiol* 2007; **99**: 36–41.
 29. Sedlis SP, Ramanathan KB, Morrison DA, Sethi G, Sacks J, Henderson W, Department of Veterans Affairs Cooperative Study #385, Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) Investigators. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). *Am J Cardiol* 2004; **94**: 118–120.
 30. Toda K, Mackenzie K, Mehra MR, DiCorte C, Davis JE, McFadden P, Ochsner JL, White C, Van Meter CH Jr. Revascularization in severe ventricular dysfunction ($15\% \leq \text{LVEF} \leq 30\%$): a comparison of bypass grafting and percutaneous intervention. *Ann Thorac Surg* 2002; **74**: 2082–2087 discussion 2087.
 31. Velazquez EJ, Lee KL, Jones RH, al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL, STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016; **374**: 1511–1520.
 32. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stähle E, Feldman TE, Van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**: 961–972.
 33. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V, FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367**: 2375–2384.
 34. Schwann TA, Engoren M, Bonnell M, Clancy C, Habib RH. Comparison of late coronary artery bypass graft survival effects of radial artery versus saphenous vein grafting in male and female patients. *Ann Thorac Surg* 2012; **94**: 1485–1491.
 35. Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, Velazquez E, Diegeler A, Sigusch H. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol* 2019; **73**: 964–976.
 36. Cantly JM Jr, Suzuki G. Myocardial perfusion and contraction in acute ischemia and chronic ischemic heart disease. *J Mol Cell Cardiol* 2012; **52**: 822–831.
 37. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. *N Engl J Med* 1998; **339**: 173–181.
 38. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation* 2008; **117**: 103–114.
 39. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Mäkikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Stroke rates following surgical versus percutaneous coronary revascularization. *J Am Coll Cardiol* 2018; **72**: 386–398.
 40. Sá M, Perazzo ÁM, Saragiotti F, Cavalcanti LRP, Almeida ACE Neto, Campos JCS, Braga PGB, Rayol SDC, Diniz RGS, Sá FBKA, Lima RC. Coronary artery bypass graft surgery improves survival without increasing the risk of stroke in patients with ischemic heart failure in comparison to percutaneous coronary intervention: a meta-analysis with 54,173 patients. *Braz J Cardiovasc Surg* 2019; **34**: 396–405.
 41. Head SJ, Börgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass grafting: part 2—optimizing outcomes and future prospects. *Eur Heart J* 2013; **34**: 2873–2886.
 42. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Rieß FC, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M, GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med* 2013; **368**: 1189–1198.
 43. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegoeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med* 2012; **366**: 1489–1497.
 44. Börgermann J, Hakim K, Renner A, Parsa A, Aboud A, Becker T, Masshoff M, Zittermann A, Gummert JF, Kuss O. Clampless off-pump versus conventional coronary artery revascularization: a propensity score analysis of 788 patients. *Circulation* 2012; **126**: S176–S182.
 45. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, Cooper DJ, Marasco S, McNeil J, Bussières JS, Wallace S, ATACAS Investigators of the ANZCA Clinical Trials Network. Stopping vs. continuing aspirin before

- coronary artery surgery. *N Engl J Med* 2016; **374**: 728–737.
46. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol* 2004; **43**: 742–748.
47. Kosmidou I, Chen S, Kappetein AP, Serruys PW, Gersh BJ, Puskas JD, Kandzari DE, Taggart DP, Morice MC, Buszman PE, Bochenek A, Schampaert E, Pagé P, Sabik JF 3rd, McAndrew T, Redfors B, Ben-Yehuda O, Stone GW. New-onset atrial fibrillation after PCI or CABG for left main disease: the EXCEL trial. *J Am Coll Cardiol* 2018; **71**: 739–748.
48. Hogue CW Jr, Murphy SF, Schechtman KB, Dávila-Román VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999; **100**: 642–647.
49. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP, Feldman T, Stahle E, Escaned J, Banning AP, Gunn JP, Colombo A, Steyerberg EW, Mohr FW, Serruys PW. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation* 2015; **131**: 1269–1277.