Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients compared with on-pump coronary artery bypass grafting: Meta-analysis

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ABSTRACT

Objectives: To assess the benefits and risks of off-pump coronary artery bypass (OPCAB) versus coronary artery bypass grafting (CABG) through a meta-analysis of randomized controlled trials (RCTs), and to investigate the relationship between outcomes and patient risk profile.

Methods: PubMed, Embase, the Cumulative Index of Nursing and Allied Health Literature, Scopus, Web of Science, Cochrane Library, and major conference proceedings databases were searched for RCTs comparing OPCAB and CABG and reporting short-term (≤ 30 days) outcomes. Endpoints assessed were all-cause mortality, myocardial infarction (MI), and cerebral stroke.

Results: The meta-analysis included 100 studies, with a total of 19,192 subjects. There was no difference between the 2 techniques with respect to all-cause mortality and MI (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.71-1.09; $P = .25$; $I^2 = 0\%$ and OR, 0.90; 95% CI, 0.77-1.05; $P = .19$; $I^2 = 0\%$, respectively). OPCAB was associated with a significant 28% reduction in the odds of cerebral stroke (OR, 0.72; 95% CI, 0.56-0.92; $P = .009$; $I^2 = 0\%$). A significant relationship between patient risk profile and benefits from OPCAB was found in terms of all-cause mortality ($P < .01$), MI ($P < .01$), and cerebral stroke ($P < .01$).

Conclusions: OPCAB is associated with a significant reduction in the odds of cerebral stroke compared with conventional CABG. In addition, benefits of OPCAB in terms of death, MI, and cerebral stroke are significantly related to patient risk profile, suggesting that OPCAB should be strongly considered in high-risk patients. (J Thorac Cardiovasc Surg 2016;151:60-77)

Risk profile meta-regression. The benefits of OPCAB are greater in high-risk patients.

Central Message

Benefits of OPCAB in terms of death, MI, and cerebral stroke are significantly related to patient risk profile when compared with CABG.

Perspective

CABG remains the gold standard for surgical coronary revascularization; however, the present meta-analysis clearly demonstrated significantly reduced odds of cerebral stroke with OPCAB. More importantly, benefits of OPCAB in terms of death, MI, and cerebral stroke are significantly related to patient risk profile, suggesting that OPCAB should be strongly considered in high-risk patients.

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Abbreviations and Acronyms

CABG	= Coronary artery bypass grafting
CI	= Confidence interval
CAD	= Coronary artery disease
CORONARY	= CABG Off or On Pump Revascularization Study
ECC	= Extracorporeal circulation
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
MI	= Myocardial infarction
NNT	= Number needed to treat
OPCAB	= Off-pump coronary artery bypass
OR	= Odds ratio
PCI	= Percutaneous coronary intervention
PRISMA	= Preferred Reporting Items for Systematic Reviews and Meta- Analyses
RCT	= Randomized controlled trial
ROOBY	= Veterans Affairs Randomized On/ Off Bypass Trial

Supplemental material is available online.

Coronary artery bypass grafting (CABG) is associated with reduction of mortality and remains a standard of care in patients with extensive coronary artery disease (CAD) as compared to percutaneous coronary intervention (PCI) and medical treatment alone.¹⁻³ CABG with the use of cardiopulmonary bypass (CPB) is recognized as the gold standard technique in terms of safety and effectiveness for surgical myocardial revascularization. A further effort in minimizing the occurrence of some complications related to conventional CABG has led to the development of off-pump (OPCAB) technique in which the anastomoses are performed on the beating heart.⁴ Observational studies have suggested that, by avoiding the negative effects of CBP, OPCAB may substantially reduce the rate of mortality and morbidity when compared with conventional CABG.⁵⁻⁷ These benefits, however, have never been confirmed in a single randomized controlled trial (RCT). First large Veterans Affairs Randomized On/Off Bypass (ROOBY) trial,⁸ found no significant difference between off-pump and on-pump CABG in the rate of the 30-day composite endpoint of death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure (7.0% and 5.6%, respectively; $P = .19$). Similarly, the largest experience to date, the CABG Off or On Pump Revascularization Study (CORONARY),⁹ which randomized more than 4700 patients to OPCAB and conventional CABG, showed no

significant difference between these 2 techniques in terms of 30-day rate of mortality, myocardial infarction (MI), stroke, or renal failure requiring dialysis. Although various analyses have suggested a beneficial effect of the OPCAB technique in selected subsets of high-risk and elderly patients,^{10,11} the evidence is not sufficiently powerful to allow for definite conclusions. Thus, the aim of the present study was to conduct an updated meta-analysis of RCTs of OPCAB versus CABG and to evaluate, by meta-regression analysis, whether the results may be related to patient risk profile.

METHODS**Data Sources and Search Strategy**

Established methods were used in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in health care interventions statement.¹² A PRISMA checklist is available as [Appendix Table 1](#). We conducted a search for relevant RCTs comparing OPCAB with conventional CABG until March 2015 through PubMed ([Appendix Table 2](#)), Embase, the Cumulative Index of Nursing and Allied Health Literature, the Web of Science, the Cochrane Register of Controlled Clinical Trials, and Google Scholar, as well as published proceedings from major cardiac, thoracic and cardiothoracic, and cardiology society meetings. Abstracts were eligible for detailed assessment if available online and reporting outcomes of interest. Search terms included off-pump, on-pump, with/without cardiopulmonary bypass, OPCAB, CABG, extracorporeal circulation (ECC), conventional, beating heart, randomized trial, and trial. No language, publication date, or publication status restriction was imposed. Both blinded and open-label trials were considered eligible. The most updated or inclusive data for each study were used for abstraction. References of original and review articles were cross-checked.

Selection Criteria and Quality Assessment

Citations were screened at the title/abstract level and retrieved as full reports if they fulfilled the inclusion criteria: human study and RCT comparing first-time OPCAB and CABG irrespective of access to the thorax (full or partial median sternotomy/thoracotomy). The exclusion criteria were a prospective cohort and quasi-randomized study, a study with a concomitant surgical procedure other than CABG, a study with a particular medical or invasive treatment in 1 arm (eg, PCI + OPCAB vs CABG), CABG with an on-pump beating heart, miniaturized ECC used in the CABG arm, robot-assisted CABG, and pediatric cardiac surgery.

Two independent reviewers (M.K. and D.P.) selected the studies for inclusion and extracted studies and patient characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with a third reviewer (L.A.). Two authors (K.Z. and M.E.K.) independently assessed the trials' eligibility and risk of bias. The risk of bias for randomized studies was assessed using the components recommended by the Cochrane Collaboration,¹³ including random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Any discrepancies in bias assessment between the assessors were recorded and reported as Cohen's κ .¹⁴

Outcome Measure

The endpoints assessed were all-cause mortality, MI, and cerebral stroke occurring within 30 days after the surgical procedure. Data were extracted in duplicate by 2 investigators (M.K. and D.P.) and independently

FIGURE 1. Flow diagram of the review process according to the PRISMA statement. *RCT*, Randomized controlled trials.

verified by a third investigator (L.A.). Disagreements were resolved by consensus.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as summary statistics. Heterogeneity was assessed using Cochran's Q test.¹⁵ To overcome the low statistical power of Cochran's Q test, the statistical inconsistency test $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom, was used to assess heterogeneity. This determines the percentage of interstudy variation, with values ranging from 0% to 100%. An I^2 value of <40% indicated no obvious heterogeneity, values between 40% and 70% suggested moderate heterogeneity, and values >70% were considered to represent high heterogeneity.

We calculated pooled ORs using the Mantel-Haenszel random-effects model, with weight assigned to each included study adjusted to include a measure of variation (τ^2) in the effects reported between studies. This approach estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result, and is most conservative in case of low between-study heterogeneity.¹⁶ In this model, trials with zero events in both groups were excluded from the pooled analysis, because adding a correction factor of 0.5 to both zero event groups to force these trials into the analysis might have biased the results toward the null hypothesis, owing to the increased number of pseudoevents.¹⁷

In a prespecified sensitivity analysis, we recalculated the results in random-effects models with an inverse variance (DerSimonian-Laird)

method, with natural weighting,¹⁸ in Hartung-Knapp-Sidik Jonkman¹⁹ and Mantel-Haenszel fixed-effect models, and using the Peto method,^{20,21} the preferred approach when intervention effects are small (ie, ORs are close to 1) and events are not particularly common. In addition, we accounted for studies that reported zero events for both investigated arms in a collapsed 4×4 table. To further corroborate the obtained results, we performed analyses for all clinical outcomes expressed as standardized difference in means and after arcsine transformation of risk difference.²² We calculated the number needed to treat (NNT) and number needed to harm as well.

We evaluated potential publication bias for the primary endpoint by constructing a "funnel plot" in which the standard error of the log OR was plotted against the OR. The asymmetry of the plot was estimated both visually and by a linear regression approach.²³ A weighted random-effects risk profile meta-regression analyses for all investigated outcomes were performed by regressing log OR against the odds in the control group, using the inverse of the variance of the log odds as weight.²⁴ Finally, we addressed the influence of each study and potential publication bias by testing whether deleting each study in turn would have resulted in a significant change in the pooled results of the meta-analysis for all endpoints assessed. We checked whether our results were driven by small-sample studies, by deleting studies enrolling <50 and <100 participants and repeating the calculations. Review Manager 5.1 (Nordic Cochrane Center, København, Denmark), Comprehensive Meta-Analysis version 2 (Biostat; Englewood, NJ) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>) with meta package "meta" (<http://CRAN.R-project.org/package/meta>), were used for statistical computations. Results of the weighted

random-effects risk profile meta-regression analyses are reported as β coefficients and 2-sided P values.

RESULTS

A PRISMA flow chart, describing the process of publication screening and the reasons for exclusion, is shown in [Figure 1](#). Among the 351 potentially relevant reports retrieved for scrutiny, 251 were excluded during secondary screening. The remaining 100 studies, which included a total of 19,192 participants, were eventually included for data abstraction and entered the analysis. All published studies were retrieved as full texts. The characteristics of the included studies are listed in [Table 1](#). Patients were evenly randomized to the OPCAB group ($n = 9574$) and the CABG group ($n = 9618$). The estimated mean age was 67.2 years overall, and was slightly higher in the OPCAB group compared with the CABG group (67.4 vs 66.9 years). Internal mammary artery use exceeded 96.3%. Fewer distal anastomoses were performed in the OPCAB group compared with the CABG group (mean, 2.91 vs 3.10; weighted mean difference, -0.19 ; 95% CI, -0.25 to -0.14 ; $P < .01$; $I^2 = 43\%$). The rate of conversion from OPCAB to CABG rates was reported in 81 studies and ranged from 0% to 22.5%. The proportion of patients undergoing “no-touch” anaortic OPCAB was seldom reported (14 studies); the rate of proximal anastomosis device use was reported in only 1 study. Detailed patient baseline characteristics are presented in [Appendix Table 3](#). The risk of bias of the included studies is characterized in [Appendix Table 4](#). Endpoint definitions are provided in [Appendix Table 5](#).

Mortality

Thirty-six studies, with a total of 15,531 subjects, contributed to the analysis of ≤ 30 -day all-cause mortality. No signs of publication bias were demonstrated by visual inspection of the funnel plot ([Appendix Figure 1](#)). The mortality rate was 2.25% overall and ranged from 2.04% (159 of 7779) in the OPCAB group to 2.45% (190 of 7752) in the CABG group. No difference was evident between the 2 techniques (OR, 0.88; 95% CI, 0.71-1.09; $P = .25$; $I^2 = 0\%$) ([Figure 2, A](#)). A significant linear relationship was observed between log OR of all-cause mortality weighted against the odds of mortality ($\beta = -13.124$; $P < .01$; [Figure 2, B](#)) in the control group. The NNT was 246.

Myocardial Infarction

MI's were observed in 43 trials with a total of 15,733 subjects, with an overall incidence of 4.49%. Analysis of a funnel plot did not reveal any signs of publication bias ([Appendix Figure 2](#)). No differences were found between OPCAB and CABG with respect to MI (OR, 0.90; 95% CI, 0.77-1.05; $P = .19$; $I^2 = 0\%$); the event

rate was 4.31% (340 of 7881) for OPCAB and 4.67% (367 of 7852) for CABG ([Figure 3, A](#)). A significant linear relationship was observed between log OR of MI weighted against the odds of MI ($\beta = -5.107$; $P < .01$) in the control group ([Figure 3, B](#)). The NNT was 278.

Cerebral Stroke

The incidence of stroke was reported in 40 RCTs, with a total of 15,829 participants, with an overall rate of 1.67%. No signs of publication bias were observed in a funnel plot ([Appendix Figure 3](#)). OPCAB was associated with a significant (28%) reduction in the odds of stroke compared with CABG (OR, 0.72; 95% CI, 0.56-0.92; $P = .009$; $I^2 = 0\%$); event rates ranged from 1.34% (106 of 7925) in the OPCAB group to 2.00% (158 of 7904) in the CABG group ([Figure 4, A](#)). A significant linear relationship between log OR of stroke and the odds of stroke in the control group ($\beta = -18.876$; $P < .01$) was demonstrated ([Figure 4, B](#)). The NNT was 152.

Sensitivity Analyses

Our results remained consistent after exclusion of studies at high risk of bias. We repeated calculations for all-cause mortality, MI, and stroke using random-effects models with an inverse variance (DerSimonian-Laird) method, by natural weighting, with Hartung-Knapp-Sidik Jonkman and Mantel-Haenszel fixed-effect models, and with the Peto OR method and collapsed 4×4 table, and found no change in either the direction or the magnitude of the estimates ([Figure 5, A-C](#)). Deleting each study at turn and repeating the calculations did not change the results either. Deleting small-sample studies did not affect the final estimates for all outcomes, either after deleting studies enrolling < 50 participants ([Appendix Figures 4-6](#)) or after deleting studies enrolling < 100 participants ([Appendix Figures 7-9](#)). Analyses performed for all clinical outcomes and expressed as standardized difference in means ([Appendix Figures 10-12](#)), and after arcsine transformation of risk differences ([Appendix Figures 13-15](#)), remained consistent with primary estimates.

DISCUSSION

The present meta-analysis of RCTs represents the largest ($n = 19,192$ participants) comprehensive source of trial-based evidence on the efficacy of OPCAB compared with conventional CABG, focusing on short-term outcomes. By its unique design, this analysis is the first report to investigate the causal relationship between underlying patient risk profile and the benefits of off-pump coronary revascularization. Our main findings can be summarized as follows. First, OPCAB was associated with a significant (28%) reduction in the odds of ≤ 30 -day cerebral stroke. Second, in the overall analysis, there was no difference between the 2 techniques with

TABLE 1. Characteristics of included studies

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias [†]
Al-Ruzzeh et al ^{E1}	2006	Graft patency at 3 mo, neurocognitive function at 6 wk and 6 mo, and HRQoL	OPCAB (n = 84) CABG (n = 84)	63.1 $\pm$ 11 63.1 $\pm$ 9.6	>50% MV-CAD >50% MV-CAD	48.0 49.1	2.73 2.76	Low
Alwan et al ^{E2}	2004	Myocardial injury markers	OPCAB (n = 35) CABG (n = 35)	61 $\pm$ 11 66 $\pm$ 7	>50% MV-CAD; LM 17.1% >50% MV-CAD; LM 25.7%	100 100	2.3 $\pm$ 1.1 2.5 $\pm$ 0.8	Unclear
Ascione et al ^{E3}	2005	Retinal microvascular damage	OPCAB (n = 10) CABG (n = 10)	63.4 $\pm$ 16.4 61.2 $\pm$ 9.8	>50% MV-CAD >50% MV-CAD	NR	2.4 2.5	Unclear
Ascione et al ^{E4}	2006	Small intestine function	OPCAB (n = 20) CABG (n = 20)	63.2 $\pm$ 8.8 62.4 $\pm$ 9.7	>50% MV-CAD >50% MV-CAD	NR	2.5 3.0	Low
Baker et al ^{E5}	2001	Neuropsychological outcomes and myocardial injury markers	OPCAB (n = 12) CABG (n = 14)	61.7 $\pm$ 11.7 65.9 $\pm$ 8.3	>50% MV-CAD >50% MV-CAD	83.3 100	2.2 $\pm$ 0.6 2.5 $\pm$ 0.5	Unclear
Moller et al [BBS] ^{E6}	2010	MACCE (all-cause mortality, acute MI, cardiac arrest with successful resuscitation, LCOS/cardiogenic shock, stroke, and coronary reintervention)	OPCAB (n = 177) CABG (n = 164)	76.1 $\pm$ 5.2 75.6 $\pm$ 4.9	>50% MV-CAD >50% MV-CAD	95 93	3.22 $\pm$ 0.72 3.34 $\pm$ 0.76	Low
Angelini et al [BHACAS 1] ^{E7,E8}	2002	Short-term morbidity and use of health care resources	OPCAB (n = 100) CABG (n = 100)	62.2 $\pm$ 9.6 61.7 $\pm$ 8.6	NR	93 95	2.23 $\pm$ 0.83 2.31 $\pm$ 0.86	Low
Angelini et al [BHACAS 2] ^{E7}	2002	Short-term morbidity and use of health care resources	OPCAB (n = 100) CABG (n = 101)	61.2 $\pm$ 9.2 63.8 $\pm$ 8.5	NR	99 98	NA NA	Low
Bicer et al ^{E9}	2014	Apoptosis, inflammation, and oxidative stress	OPCAB (n = 25) CABG (n = 25)	57.7 $\pm$ 8.4 56.9 $\pm$ 10.7	NR	100 100	2.53 $\pm$ 1.04 2.57 $\pm$ 0.83	Unclear
Blacher et al ^{E10}	2004	Lymphocyte activation	OPCAB (n = 13) CABG (n = 15)	63 $\pm$ 7 61 $\pm$ 10	NR	100 100	2.6 $\pm$ 0.5 2.7 $\pm$ 1.0	Unclear
Bonacchi et al ^{E11}	2006	Cerebral injury markers	OPCAB (n = 18) CABG (n = 24)	63.7 $\pm$ 5.4 63.5 $\pm$ 7.8	>50% MV-CAD; LM 16.7% >50% MV-CAD; LM 21%	100 100	2.8 $\pm$ 0.7 3.1 $\pm$ 0.6	Unclear
Caputo et al ^{E12}	2002	Inflammatory response and organ function	OPCAB (n = 20) CABG (n = 20)	62.7 $\pm$ 10.6 62.9 $\pm$ 6.9	NR	100 100	2.8 (2.4-3.0) [‡] 2.9 (2.6-3.2) [‡]	Low
Carrier et al ^{E13}	2003	Hospital mortality and morbidity	OPCAB (n = 32) CABG (n = 33)	70 $\pm$ 8 70 $\pm$ 6	>50% MV-CAD; LM 29% >50% MV-CAD; LM 32%	100 100	3 $\pm$ 1 3.4 $\pm$ 1	Unclear
Cavalca et al ^{E14}	2006	Isoprostanes and oxidative stress	OPCAB (n = 25) CABG (n = 25)	68.4 $\pm$ 8.9 63.4 $\pm$ 11.5	NR	100 100	2.5 $\pm$ 0.67 3.1 $\pm$ 0.67	Unclear
Chowdhury et al ^{E15}	2008	Periprocedural inflammatory and myocardial injury marker release	OPCAB (n = 25) CABG (n = 25)	58.8 $\pm$ 7.8 60.2 $\pm$ 6.8	>50% MV-CAD >50% MV-CAD	88.0 76.0	3.1 $\pm$ 0.60 3.2 $\pm$ 0.62	Unclear

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias†
Lamy et al [CORONARY] ^{E16}	2012	Death, nonfatal stroke, nonfatal MI, or new renal failure requiring dialysis at 30 d after randomization	OPCAB (n = 2375)	67.6 $\pm$ 6.7	LM 22.1%; >50% MV-CAD	93.6	3.0 (0.95)‡	Low
			CABG (n = 2377)	67.5 $\pm$ 6.9	LM 20.9% > 50% MV-CAD	93.4	3.2 (0.92)‡	
Covino et al ^{E17}	2001	Length of operation, hematologic and biochemical parameters, hemogas analysis, volume of blood loss, length of stay in ICU	OPCAB (n = 21)	NR	>50% MV-CAD	NR	1.5	Unclear
			CABG (n = 16)		>50% MV-CAD		1.8	
Rogers et al [CRISP] ^{E18}	2014	All-cause death, new-onset renal failure, MI, prolonged initial ventilation, or sternal wound dehiscence	OPCAB (n = 53)	76.4 $\pm$ 5.8	LM 39% > 50% MV-CAD	96.2	2.56	Low
			CABG (n = 53)	75.7 $\pm$ 7.7	LM 27% > 50% MV-CAD	83.0	2.68	
Czerny et al ^{E19}	2000	Periprocedural inflammatory and myocardial injury marker release	OPCAB (n = 15)	63.3 $\pm$ 9.3	>50% MV-CAD	100	2.4 $\pm$ 0.5	Unclear
			CABG (n = 15)	65.1 $\pm$ 11.8	>50% MV-CAD	100	3.4 $\pm$ 0.9	
Czerny et al ^{E20}	2001	Completeness of revascularization	OPCAB (n = 40)	64.7 $\pm$ 10.6	>50% MV-CAD	100	2.6 $\pm$ 0.5	Unclear
			CABG (n = 40)	62.3 $\pm$ 9.9	>50% MV-CAD	100	3.1 $\pm$ 0.8	
Diegeler et al ^{E21}	2000	Periprocedural neurocognitive functioning	OPCAB (n = 20)	65.6 $\pm$ 6.4	>50% MV-CAD	100	1.1 $\pm$ 0.2	Unclear
			CABG (n = 20)	63.8 $\pm$ 7.7	>50% MV-CAD	100	1.1 $\pm$ 0.5	
Dorman et al ^{E22}	2004	Endothelin plasma content	OPCAB (n = 27)	65 $\pm$ 11	NR	NR	3 $\pm$ 1	Unclear
			CABG (n = 25)	61 $\pm$ 3			4 $\pm$ 1	
Houliand et al [DOORS] ^{E23}	2012	Death, stroke, or MI at 30 d	OPCAB (n = 450)	75 (70-88)‡	LM 45.0%; >50% MV-CAD	91.0	2.9 $\pm$ 0.9	Low
			CABG (n = 450)	75 (70-91)‡	LM 48.0%; >50% MV-CAD	93.0	3.1 $\pm$ 1.0	
Fattouch et al ^{E24}	2009	In-hospital death, LCOS, prolonged mechanical and pharmacologic cardiac support, prolonged mechanical ventilation support, and postoperative length of stay in intensive care unit and hospital	OPCAB (n = 63)	63 $\pm$ 16	STEMI 100%; LM 19%	93.6	2.6 $\pm$ 0.5	Low
			CABG (n = 65)	61 $\pm$ 18	STEMI 100%; LM 23%	92	2.8 $\pm$ 0.4	
Formica et al ^{E25}	2013	Periprocedural inflammatory marker release	OPCAB (n = 22)	70.8 $\pm$ 7.0	>50% MV-CAD; LM 25%	100	2.7 $\pm$ 0.5	Unclear
			CABG (n = 20)	68.3 $\pm$ 9.0	>50% MV-CAD; LM 35%	100	2.7 $\pm$ 0.5	
Gasz et al ^{E26}	2004	Periprocedural inflammatory marker release	OPCAB (n = 10)	63.4 $\pm$ 2.8	NR	NR	3.4 $\pm$ 0.31	Unclear
			CABG (n = 10)	63.1 $\pm$ 2.1			3.9 $\pm$ 0.18	
Gasz et al ^{E27}	2005	Periprocedural inflammatory marker release	OPCAB (n = 10)	63.2 $\pm$ 2.5	NR	92	3.0 $\pm$ 0.42	Unclear
			CABG (n = 20)			88	3.21 $\pm$ 0.22	

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias [†]
Gerola et al ^{E28}	2004	Periprocedural all-cause mortality, MI, pulmonary complications, bleeding, wound complications, neurocognitive dysfunction	OPCAB (n = 80) CABG (n = 80)	59.1 $\pm$ 9.7 58.9 $\pm$ 8.9	NR	98.7 97.5	1.77 $\pm$ 0.68 1.81 $\pm$ 0.6	Low
Gu et al ^{E29}	1998	Inflammatory response marker levels	OPCAB (n = 31) CABG (n = 31)	61.0 $\pm$ 10.7 60.0 $\pm$ 8.5	>50% SV-CAD >50% SV-CAD	100 100	1 1	Unclear
Guler et al ^{E30}	2001	Postoperative lung function	OPCAB (n = 40)	57.9 $\pm$ 10.6 52.3 $\pm$ 8.6§	>50% SV-CAD	100	1	High
Gonenc et al ^{E31}	2006	Periprocedural oxidative stress	CABG (n = 18) OPCAB (n = 30) CABG (n = 12)	54.05 $\pm$ 9.03 64.6 $\pm$ 1.2	>50% SV-CAD NR	100 NR	1 NA	High
Diegeler et al [GOPCABE] ^{E32}	2013	Composite of death, stroke, MI, repeat revascularization, or new renal replacement therapy at 30 d and at 12 mo after surgery	OPCAB (n = 1271) CABG (n = 1268)	78.6 $\pm$ 3.0 78.4 $\pm$ 2.9	>50% MV-CAD; LM 28.1% >50% MV-CAD; LM 29.6%	NR NR	2.7 2.8	Low
Gulielmos et al ^{E33}	2000	Periprocedural inflammatory marker and cTn release	OPCAB (n = 20) CABG (n = 20)	65.1 $\pm$ 10.0 62.9 $\pm$ 9.8§ 59.6 $\pm$ 11.0 61.2 $\pm$ 10.0§	>50% MV-CAD >50% MV-CAD	100 100	1 1	Unclear
Hernandez et al ^{E34}	2007	Neurocognitive functioning at discharge	OPCAB (n = 99) CABG (n = 102)	NR	LM 22.2%; >50% MV-CAD LM 28.4%; >50% MV-CAD	97.0 98.0	3.2 $\pm$ 1.0 3.3 $\pm$ 0.9	Low
Hoel et al ^{E35}	2007	Complement activation	OPCAB (n = 22) CABG (n = 22)	NR	NR	100 100	NA	Unclear
Iqbal et al ^{E36}	2014	Neurologic complications	OPCAB (n = 100) CABG (n = 100)	51.6 $\pm$ 10.3 53.5 $\pm$ 10.0	NR	NR	2.96 $\pm$ 0.94 2.99 $\pm$ 0.88	High
Jares et al ^{E37,E104}	2007	Identification of fibrinolysis by rotation thromboelastography	OPCAB (n = 10) CABG (n = 10)	65.5 62.6	NR	NR	2.00 2.60	Unclear
Kobayashi et al [JOCRI] ^{E38}	2005	Cardiac death, MI, CHF, or TVR at 3 y	OPCAB (n = 81) CABG (n = 86)	60 $\pm$ 7 59 $\pm$ 10	>50% MV-CAD >50% MV-CAD	33.6 31.5	3.5 $\pm$ 1.0 3.6 $\pm$ 0.9	Low
Johansson-Synergren et al ^{E39}	2004	Periprocedural inflammatory marker release and endothelial function	OPCAB (n = 26) CABG (n = 26)	62.2 $\pm$ 1.7 62.5 $\pm$ 1.9	NR NR	96.2 96.2	1.8 $\pm$ 0.1 2.2 $\pm$ 0.1	Unclear
Jongman et al ^{E40}	2014	Systemic inflammation markers and endothelial response	OPCAB (n = 30) CABG (n = 30)	63 (47-80)‡ 63 (47-77)‡	NR	NR	3 (2-5)‡ 3 (2-5)‡	Unclear
Khan et al ^{E41}	2004	Graft patency at 3 mo	OPCAB (n = 54) CABG (n = 50)	62.0 $\pm$ 7.9 64.7 $\pm$ 8.4	>50% MV-CAD >50% MV-CAD	96 94	3.1 $\pm$ 0.6 3.4 $\pm$ 0.7	Low
Kochamba et al ^{E42}	2000	Preoperative and postoperative pulmonary gas exchange	OPCAB (n = 29) CABG (n = 29)	55.6 $\pm$ 9.5 61.6 $\pm$ 10.0	NR	97.0 93.0	1.5 1.6	Unclear

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias†
Kok et al ^{E43}	2014	Cerebral tissue oxygenation and postoperative cognitive dysfunction	OPCAB (n = 30) CABG (n = 30)	63.0 $\pm$ 9.0 62.6 $\pm$ 9.9	NR	NR	3.2 $\pm$ 0.9 3.3. $\pm$ 0.8	Unclear
Krejca et al ^{E44}	1999	Periprocedural inflammatory marker release	OPCAB (n = 13) CABG (n = 13)	54.1 $\pm$ 9.6 56.2 $\pm$ 5.3	NR	NR	1.8 (1-2)‡ 1.8 (1-2)‡	Unclear
Kunes et al ^{E45}	2007	Pentraxin 3 release kinetics	OPCAB (n = 17) CABG (n = 17)	66.4 $\pm$ 10.1 70.5 $\pm$ 7.1	NR	NR	2.0 2.0	Unclear
Lee et al ^{E46}	2003	Inhospital all-cause death, stroke, and length of stay, intra-aortic balloon support postoperatively	OPCAB (n = 30) CABG (n = 30)	65.5 $\pm$ 9.6 66.0 $\pm$ 11.2	NR	NR	3.1 $\pm$ 0.7 3.6 $\pm$ 0.9	Unclear
Legare et al ^{E47}	2004	Periprocedural death, MI, stroke, AF, deep sternal wound infection	OPCAB (n = 150) CABG (n = 150)	62.1 $\pm$ 10.1 63.7 $\pm$ 10.0	LM 10.7%; >50% MV-CAD LM 9.3%; >50% MV-CAD	97.3 96.7	2.8 $\pm$ 0.9 3.0 $\pm$ 0.9	Low
Lingaas et al ^{E48,E49}	2004	Graft patency at 12 mo	OPCAB (n = 60) CABG (n = 60)	64 $\pm$ 7.8 65 $\pm$ 8.3	LM 10.0%; >50% MV-CAD LM 5.0%; >50% MV-CAD	100 100	2.6 $\pm$ 0.9 2.8 $\pm$ 1.0	Unclear
Lloyd et al ^{E50}	2000	Serum S-100 protein and neuropsychological outcomes	OPCAB (n = 63) CABG (n = 62)	59 (54-64)‡ 62 (56-69)‡	>50% MV-CAD >50% MV-CAD	NR	2.2 $\pm$ 0.9 2.4 $\pm$ 0.9	Unclear
Lund et al ^{E51,E52}	2003	Intraoperative cerebral embolization	OPCAB (n = 29) CABG (n = 23)	62.0 (52-73)‡ 64.0 (52-79)‡	NR	100 100	2.3 $\pm$ 0.7 2.5 $\pm$ 0.8	Unclear
Malik et al ^{E53}	2006	Periprocedural CPK-MB release	OPCAB (n = 25) CABG (n = 25)	56.4 $\pm$ 8.8 59.8 $\pm$ 6.1	>50% MV-CAD >50% MV-CAD	80 60	3.1 $\pm$ 0.58 3.1 $\pm$ 0.5	Unclear
Mandak J et al ^{E54}	2008	Peripheral tissue metabolism and microvascular blood flow	OPCAB (n = 20) CABG (n = 20)	66.3 $\pm$ 7.0 67.0 $\pm$ 7.3	NR	100 100	2.4 $\pm$ 0.8 2.9 $\pm$ 0.7	Unclear
Matata et al ^{E55}	2000	Periprocedural inflammatory marker release and oxidative stress	OPCAB (n = 10) CABG (n = 10)	59.5 $\pm$ 2.2 59.5 $\pm$ 2.7	NR	NR	1.8 $\pm$ 0.2 1.9 $\pm$ 0.2	Low
Hueb et al [MASS III] ^{E56}	2010	Freedom from overall mortality, stroke, MI, and additional revascularization	OPCAB (n = 156) CABG (n = 155)	61 59	>50% MV-CAD >50% MV-CAD	98 94	2.60 3.18	Low
Medved et al ^{E57}	2008	In-hospital mortality and morbidity	OPCAB (n = 30) CABG (n = 30)	59.3 $\pm$ 7.2 62 $\pm$ 5.4	NR	93.3 90	2.3 $\pm$ 0.34 2.5 $\pm$ 0.58	Unclear
Michaux et al ^{E58,E59}	2011	Right ventricular global and overall systolic function	OPCAB (n = 25) CABG (n = 25)	61 $\pm$ 9 65 $\pm$ 8	>50% MV-CAD >50% MV-CAD	100 100	2.9 $\pm$ 0.6 3.2 $\pm$ 0.7	Low
Modine et al ^{E60}	2009	Renal tubular and glomerular function	OPCAB (n = 35) CABG (n = 36)	66.5 $\pm$ 7.6 62.6 $\pm$ 9.6	NR	100 100	2.4 $\pm$ 0.55 2.8 $\pm$ 0.8	Unclear
Motallebzadeh et al ^{E61}	2004	Periprocedural cerebral injury	OPCAB (n = 15) CABG (n = 20)	65 (53-72)‡ 63 (59-70)‡	>50% MV-CAD >50% MV-CAD	NR	2.2 $\pm$ 0.94 3.2 $\pm$ 0.99	Low
Motallebzadeh et al ^{E62}	2007	Periprocedural neurocognitive function	OPCAB (n = 108) CABG (n = 104)	63.9 $\pm$ 0.9 65.1 $\pm$ 0.9	>50% MV-CAD >50% MV-CAD	NR	NR	Low

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias [†]
Muneretto et al ^{E63}	2003	Number of anastomoses, mean mechanical ventilation time, ICU and postoperative stay	OPCAB (n = 88) CABG (n = 88)	67 $\pm$ 8 66 $\pm$ 9	LM 9% >50% MV-CAD LM 11.3% >50% MV-CAD	NR	2.7 $\pm$ 0.5 2.8 $\pm$ 0.8	Unclear
Nesher et al ^{E64}	2006	Periprocedural inflammatory marker and CPK-MB release	OPCAB (n = 61) CABG (n = 64)	67 $\pm$ 1 68 $\pm$ 5	NR	NR	2.3 $\pm$ 0.9 2.9 $\pm$ 1.5	Low
Niranjan et al ^{E65}	2006	Autologous blood transfusion and postoperative complications	OPCAB (n = 40) CABG (n = 40)	67.6 $\pm$ 10.5 66.2 $\pm$ 9.5	>50% MV-CAD >50% MV-CAD	95.0 97.5	3.93 $\pm$ 0.8 3.75 $\pm$ 0.8	Low
Nathoe et al [Octopus] ^{E66}	2003	Freedom from all-cause death, stroke, MI and repeat revascularization	OPCAB (n = 142) CABG (n = 139)	61.7 $\pm$ 9.2 60.8 $\pm$ 8.8	>50% MV-CAD >50% MV-CAD	NR	2.4 2.6	Low
Lemma et al [On-Off] ^{E67}	2012	Operative mortality, MI, stroke, renal failure, reoperation for bleeding and ARDS within 30 d	OPCAB (n = 208) CABG (n = 203)	74 (69-78) [‡] 73 (68-77) [‡]	NR	99 97	3.0 $\pm$ 1.1 3.3 $\pm$ 1.0	Low
Onorati et al ^{E68}	2010	Perioperative changes in MCP-1 and VEGF levels	OPCAB (n = 20) CABG (n = 40)	71.6 $\pm$ 4.8 71.7 $\pm$ 4.4	NR	NR	3.4 $\pm$ 0.5 3.4 $\pm$ 0.6	Unclear
Ozkara et al ^{E69}	2007	Target vessel revascularization at 1 y; periprocedural PAI-1 release	OPCAB (n = 22) CABG (n = 42)	58.9 $\pm$ 10.1 59.5 $\pm$ 9.9	NR	100 100	2.48 $\pm$ 0.52 2.31 $\pm$ 0.60	Unclear
Paparella et al ^{E70}	2006	Activation of the coagulation and fibrinolytic systems	OPCAB (n = 16) CABG (n = 16)	NR NR	NR	NR	2.7 3.25	Unclear
Parolari et al ^{E71}	2003	Periprocedural oxygen metabolism	OPCAB (n = 11) CABG (n = 14)	60 $\pm$ 2.1 62 $\pm$ 2.3	NR	NR	2.3 $\pm$ 0.14 2.9 $\pm$ 0.20	Unclear
Parolari et al ^{E72}	2005	Periprocedural plasma P-selectin and TF levels	OPCAB (n = 15) CABG (n = 15)	65 $\pm$ 1.2 64 $\pm$ 1.4	>50% MV-CAD >50% MV-CAD	NR	2.8 $\pm$ 0.13 2.9 $\pm$ 0.16	Unclear
Penttilä et al ^{E73}	2001	Periprocedural changes in myocardial metabolism	OPCAB (n = 11) CABG (n = 11)	59.5 (53.3-65.8) [‡] 59.2 (53.0-65.4) [‡]	>50% MV-CAD >50% MV-CAD	NR	2.8 (2.3-3.3) [‡] 3.3 (2.4-4.2) [‡]	Unclear
Straka et al [PRAGUE-4] ^{E74}	2004	Death, MI, stroke, renal failure requiring hemodialysis at 30 d	OPCAB (n = 192) CABG (n = 208)	63 62	>50% MV-CAD >50% MV-CAD	97 90	2.3 2.7	Low
Hlavicka et al [PRAGUE-6] ^{E75}	2013	Death, MI, stroke, renal failure requiring hemodialysis at 30 d	OPCAB (n = 98) CABG (n = 108)	74.7 $\pm$ 6.5 73.6 $\pm$ 7.4	NR	NR	2.04 2.66	Low
Bednar et al [PRAGUE 11] ^{E76}	2008	Platelet activity and aspirin efficacy	OPCAB (n = 40) CABG (n = 40)	68 $\pm$ 9 64 $\pm$ 11	NR	NR	1.9 $\pm$ 0.7 2.4 $\pm$ 0.6	Unclear
Sousa Uva et al [PROMISS] ^{E77}	2010	Graft patency at 5 wk	OPCAB (n = 75) CABG (n = 75)	66.1 $\pm$ 9.5 64.6 $\pm$ 9.8	NR	100 100	3.5 $\pm$ 0.6 3.5 $\pm$ 0.6	Low
Rachwalik et al ^{E78}	2006	Periprocedural respiratory function	OPCAB (n = 21) CABG (n = 21)	57.1 $\pm$ 8.9 95.3 $\pm$ 7.9	NR	100 100	NA	Unclear
Rainio et al ^{E79}	2007	Periprocedural retinal microembolism	OPCAB (n = 10) CABG (n = 10)	64.6 $\pm$ 4 58.6 $\pm$ 2.6	NR	100 100	4.1 4.4	Low

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias†
Raja et al ^{E80}	2003	Postoperative gastrointestinal complications	OPCAB (n = 150) CABG (n = 150)	NR	NR	98 98	2 (1-4)‡ 2 (1-4)‡	Unclear
Rasmussen et al ^{E81}	2007	Periprocedural inflammatory marker release	OPCAB (n = 17) CABG (n = 18)	68 $\pm$ 6 67 $\pm$ 4	NR	94 94	3.1 $\pm$ 0.9 3.1 $\pm$ 0.6	Unclear
Rastan et al ^{E82}	2005	Periprocedural inflammatory marker, CPK-MB, and cTn release	OPCAB (n = 20) CABG (n = 20)	63.0 $\pm$ 6.0 65.3 $\pm$ 3.9	NR	100 100	3.0 $\pm$ 0.5 2.9 $\pm$ 0.3	Unclear
Schroyer et al [ROOBY] ^{E83}	2009	All-cause death, reoperation, new mechanical support, coma, stroke, cardiac arrest, renal failure requiring dialysis at 30 d	OPCAB (n = 1104) CABG (n = 1099)	63.0 $\pm$ 8.5 62.5 $\pm$ 8.5	>50% MV-CAD >50% MV-CAD	NR NR	2.9 $\pm$ 0.9 3.0 $\pm$ 1.0	Low
Sahlman et al ^{E84}	2003	Periprocedural inflammatory and CPK-MB release	OPCAB (n = 24) CABG (n = 26)	64.0 $\pm$ 9.0 61.5 $\pm$ 8.1	NR	100 100	3.2 $\pm$ 0.9 3.0 $\pm$ 1.2	Unclear
Sajja et al ^{E85}	2007	Periprocedural renal function	OPCAB (n = 56) CABG (n = 60)	60.0 $\pm$ 8.4 60.5 $\pm$ 7.9	NR	NR	3.11 $\pm$ 0.89 3.85 $\pm$ 0.86	Unclear
Selvanayagam et al ^{E86}	2004	Periprocedural LVEF	OPCAB (n = 30) CABG (n = 30)	60 $\pm$ 9 61 $\pm$ 11	NR	100 97	2.8 $\pm$ 0.9 2.9 $\pm$ 0.8	Low
Puskas et al [SMART] ^{E87}	2003	Completeness of revascularization and graft patency at 30 d	OPCAB (n = 100) CABG (n = 100)	62.2 $\pm$ 11.1 62.5 $\pm$ 9.45	NR	41.3 40.8	3.39 $\pm$ 1.04 3.40 $\pm$ 1.08	Low
Syed et al ^{E88}	2004	Pulmonary gas exchange	OPCAB (n = 37) CABG (n = 38)	56.25 (21-72)‡ 58.78 (43-81)‡	NR	95 87	NR	Unclear
Tang et al ^{E89}	2002	Kidney glomerular and tubular injury	OPCAB (n = 20) CABG (n = 20)	64.8 $\pm$ 6.9 62.1 $\pm$ 9.3	NR	95 90	2.1 $\pm$ 1.0 2.5 $\pm$ 0.7	Unclear
Tatoulis et al ^{E90}	2006	Systemic vascular resistance at 12 h	OPCAB (n = 50) CABG (n = 50)	66 $\pm$ 12 64 $\pm$ 11	LM 8% LM 8%	NR	2.3 $\pm$ 0.8 2.9 $\pm$ 0.9	Low
Tully et al ^{E91}	2008	Neuropsychologic and quality-of-life outcomes at 6 mo	OPCAB (n = 30) CABG (n = 36)	63.6 $\pm$ 10.0	NR	96.7 94.4	2.23 $\pm$ 0.52 2.47 $\pm$ 0.61	Unclear
Van Boven et al ^{E92}	2013	Protein S100 β concentration	OPCAB (n = 10) CABG (n = 10)	73.1 $\pm$ 2.2 73.3 $\pm$ 1.4	>50% MV-CAD >50% MV-CAD	50 50	3.6 $\pm$ 0.8 4.3 $\pm$ 1.4	Unclear
Van Boven et al ^{E93}	2013	Periprocedural inflammatory marker release	OPCAB (n = 20) CABG (n = 20)	73.8 $\pm$ 2.6 74.6 $\pm$ 4.0	>50% MV-CAD >50% MV-CAD	100 100	3.8 $\pm$ 0.8 4.7 $\pm$ 1.2	Unclear
Vedin et al ^{E94}	2006	Neurocognitive function at 6 mo	OPCAB (n = 33) CABG (n = 37)	65 (62-68)‡ 65 (62-68)‡	>50% MV-CAD; LM 0% >50% MV-CAD; LM 5%	100 95	3 (2-4)‡ 3 (2-4)‡	Unclear
Velissaris et al ^{E95}	2003	Gut mucosal oxygenation	OPCAB (n = 27) CABG (n = 27)	61.8 $\pm$ 8.7 63.1 $\pm$ 8.5	NR	88.9 96.3	2.5 $\pm$ 0.8 2.6 $\pm$ 0.9	Unclear
Velissaris et al ^{E96}	2004	Stress response	OPCAB (n = 26) CABG (n = 26)	61.3 $\pm$ 8.5 63.9 $\pm$ 8.0	NR	NR	2.4 $\pm$ 0.9 2.8 $\pm$ 1.0	Unclear
Vural et al ^{E97}	1995	Periprocedural hemodynamic assessment	OPCAB (n = 25) CABG (n = 25)	47.2 $\pm$ 11.3 49.4 $\pm$ 11.3	>50% SV-CAD >50% SV-CAD	NR NR	1.12 1.12	Unclear

(Continued)

TABLE 1. Continued

Study ^{reference}	Year	Primary endpoint	Randomization (ITT)	Age, y, mean $\pm$ SD	Extent of CAD	IMA use, %	No. of grafts*	Risk of bias†
Wan et al ^{E98}	2004	Periprocedural inflammatory marker release	OPCAB (n = 18) CABG (n = 19)	63.61 $\pm$ 10.5 65.37 $\pm$ 9.1	>50% MV-CAD >50% MV-CAD	100 100	2.44 $\pm$ 0.51 2.79 $\pm$ 0.54	Unclear
Wandschneider et al ^{E99}	2000	Periprocedural inflammatory marker release	OPCAB (n = 52) CABG (n = 67)	65 (38-82)‡ 66 (48-78)‡	NR	65.6 65.8	2.34 3.10	Unclear
Wehlin et al ^{E100}	2004	Periprocedural inflammatory marker release	OPCAB (n = 22) CABG (n = 16)	64 (61-68)‡ 66 (61-70)‡	LM 5%; >50% MV-CAD LM 12%; >50% MV-CAD	95.2 100	3 (2-3)‡ 2.5 (2-3)‡	Unclear
Wehlin et al ^{E101}	2005	Peripheral blood monocyte activation	OPCAB (n = 11) CABG (n = 9)	64 (58-70)‡ 67 (59-74)‡	LM 0%; >50% MV-CAD LM 11%; >50% MV-CAD	NR	2 (2-3)‡ 2 (2-3)‡	Unclear
Yu et al ^{E102}	2014	Early clinical outcomes	OPCAB (n = 51) CABG (n = 51)	63.7 $\pm$ 8.6 65.7 $\pm$ 7.6	LM 27.5% LM 31.4%	100 100	3.02 $\pm$ 0.55 3.14 $\pm$ 0.53	Low
Zamvar et al ^{E103}	2002	Neurocognitive function at 10 wk	OPCAB (n = 30) CABG (n = 30)	63.5 $\pm$ 9.1 61.6 $\pm$ 10	LM 13.3%; >50% MV-CAD LM 6.6%; >50% MV-CAD	100 100	2.93 $\pm$ 0.37 2.93 $\pm$ 0.45	Low

ITT, Intention-to-treat; SD, standard deviation; CAD, coronary artery disease; IMA, internal mammary artery; HRQoL, health-related quality of life; OPCAB, off-pump coronary artery bypass; CABG, coronary artery bypass grafting; MV-CAD, multivessel coronary artery disease; LM, left main; NR, not reported; BBS, best bypass surgery trial; MACCE, major adverse cardiac or cerebrovascular accident; MI, myocardial infarction; LCOS, low cardiac output syndrome; BHACAS 1, beating heart against cardioplegic arrest study 1; BHACAS 2, beating heart against cardioplegic arrest study 2; NA, not available; CORONARY, CABG off or on pump revascularization study; ICU, intensive care unit; CRISP, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-pump surgery; DOORS, Danish on-pump versus off-pump randomization study; STEMI, ST-segment elevation MI; SV-CAD, single vessel coronary artery disease; GPCABE, German off-pump coronary artery bypass grafting in elderly patients; cTn, cardiac troponin; JOCRI, Japanese off-pump coronary revascularization investigation study; CHF, chronic heart failure; TVR, target vessel revascularization; AF, atrial fibrillation/flutter; CPK-MB, creatine phosphokinase-muscle brain; MASS III, off-pump and on-pump stable multivessel coronary artery bypass grafting; Octopus, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; ARDS, acute respiratory distress syndrome; MCP-1, monocyte chemo-attractant protein; VEGF, vascular endothelial growth factor; PAI-1, plasminogen activator inhibitor-1; LVEF, left ventricle ejection fraction; TF, tissue factor; PRAGUE-4, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE $\geq$ 6; PRAGUE-11, A randomized comparison between off-pump and on-pump surgery PRAGUE-11; PROMISS, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; ROOBY, veterans affairs randomized on/off bypass study; SMART, surgical management of arterial revascularization therapies. *Reported as in included studies. †Risk of bias according to Cochrane criteria; a study was considered at high risk of bias if $\geq$ 2 of the components were at high risk. ‡Reported as range. §Reported for separate arms.

respect to $\leq$ 30-day all-cause mortality and MI. Finally, a significant linear relationship was found between risk profile and benefits of OPCAB for all endpoints: all-cause mortality, MI, and cerebral stroke. The robustness and stability of the results were confirmed in sensitivity analyses.

The current 2014 European Society of Cardiology guidelines on myocardial revascularization assign class IIa level B recommendations for performing OPCAB in high-risk patients in high-volume off-pump centers.²⁵ The 2011 American College of Cardiology/American Association for Thoracic Surgery guidelines recommend OPCAB in patients with renal impairment, and suggest considering beating heart revascularization to reduce perioperative bleeding and the need for transfusions.²⁶

Various randomized studies have failed to show significant differences in the perioperative stroke rate between surgery with and without ECC,^{27,28} and both European and American guidelines point to conflicting evidence regarding the role of off-pump surgery in

providing a better neurologic outcome. This apparent contradiction with the available registries data^{29,30} reporting a significantly decreased incidence of stroke with OPCAB may be explained by the fact that cerebral stroke represents a relatively rare entity after CABG, and thus even the largest randomized studies are underpowered to prove a possible advantage of one technique over the other. Indeed, the CORONARY trial,⁹ the largest trial to date, found no difference in the incidence of stroke in the 2 groups at 30 days (1.0% for OPCAB vs 1.1% for CABG). Furthermore, although 3 previous meta-analyses of RTCs demonstrated significant (30%-50%) reductions in the risk of stroke,³¹⁻³³ a systematic review of RCTs called these outcomes into question, showing no clear benefit of OPCAB in this regard (OR, 0.76; 95% CI, 0.54-1.06).³⁴

Possible causes of perioperative cerebral stroke include postoperative atrial fibrillation in the hypercoagulable state and thromboembolic events in the setting of cerebral artery disease, particularly in female patients with a previous

FIGURE 2. A, Pooled ORs and 95% CIs for ≤ 30 -day all-cause mortality. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome. B, Weighted random-effects meta-regression analysis regressing the log OR of all-cause mortality against the control group all-cause mortality expressed as odds. Negative values of the log OR (y-axis) mean more benefits in all-cause mortality associated with OPCAB, whereas the mortality rate of the control group, CABG (x-axis), represents the risk profile of the patient population included in each trial. The size of the circle corresponds to the inverse variance of the log-OR, and thus is related to the statistical weight of the individual trial. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *df*, degrees of freedom.

FIGURE 3. A, Pooled ORs and 95% CIs for ≤ 30 -day MI. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome. B, Weighted random-effects meta-regression analysis regressing the log OR of MI against the incidence of MI in the control group expressed as odds. Negative values of the log OR (y-axis) mean more benefits for MI associated with OPCAB, whereas the MI rate in the control group, CABG (x-axis), represents the risk profile of the patient population included in each trial. The size of the circle corresponds to the inverse variance of the log-OR, and thus is related to the statistical weight of the individual trial. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *df*, degrees of freedom.

FIGURE 4. A, Pooled ORs and 95% CIs for ≤ 30 -day cerebral stroke. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome. B, Weighted random-effects meta-regression analysis regressing the log OR of cerebral stroke against the incidence of cerebral stroke in the control group expressed as odds. Negative values of the log OR (y-axis) mean more benefits in cerebral stroke associated with OPCAB, whereas the cerebral stroke rate of the control group, CABG (x-axis), represents the risk profile of the patient population included in each trial. The size of the circle corresponds to the inverse variance of the log-OR, and thus is related to the statistical weight of the individual trial. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *df*, degrees of freedom.

FIGURE 5. Sensitivity analysis of estimated pooled ORs and 95% CIs using 7 different approaches: Mantel-Haenszel random effects (as in the main analysis), inverse variance (DerSimonian-Laird) method, natural weighting, Hartung-Knapp-Sidik Jonkman, Mantel-Haenszel fixed-effect, Peto method, and a collapsed 4×4 table for ≤ 30 -day all-cause mortality (A), MI (B), and cerebral stroke (C). *CI*, Confidence interval; *OPCAB*, off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *OR*, odds ratio

history of cerebral stroke. It is the aortic manipulation and consequent embolization of atherosclerotic material that play crucial roles in the occurrence of cerebral stroke in patients undergoing CABG, however.³⁵ OPCAB confers the benefit of avoiding CPB; it eliminates the need for aortic cannulation and cross-clamping and thereby minimizes the risk of neck and brain vessel embolism. Performing the proximal anastomoses during cross-clamping is a possible strategy for reducing further manipulation of the aorta during conventional CABG; however, the application of a side-biting clamp is usually described, which poses an increased risk of dislodging fragile material from the aortic wall. OPCAB presents the same technical issue in proximal anastomoses; however, especially in the presence of a diffusely diseased aorta, off-pump procedures via complete in situ grafting (no-touch; double internal mammary artery and/or T- or Y-grafting) preclude any type of clamping and may reduce the risk of postoperative neurologic events and cognitive function impairment.^{36,37} In studies included in the current meta-analysis, the proportion of the no-touch technique was seldom reported. The benefits in terms of postoperative stroke are expected to increase with an increasing number of procedures performed without aortic manipulation. Indeed, in a recent meta-analysis of 7 observational studies, clampless OPCAB was associated with significantly reduced risk of stroke compared with conventional CABG (0.38% vs 1.87%; risk ratio, 0.27; 95% CI, 0.14-0.58; $P < .001$) and with OPCAB using a partial clamp (0.31% vs 1.35%; risk ratio, 0.34; 95% CI, 0.18-0.65; $P = .001$).³⁴ Another study comparing clampless OPCAB with conventional CABG found a 56% and 44% significant reduction of mortality and composite endpoint death and stroke, respectively, with the former approach.³⁸ In the present meta-analysis, which included the most recently published RCTs, a significant 28% reduction in the odds of stroke was associated with OPCAB.

Possibly that most important finding of our present analysis is the significant linear relationship between patient risk profile and the beneficial effects of OPCAB with respect to the single endpoints all-cause mortality, MI, and stroke. Observational studies have suggested that OPCAB is particularly beneficial in high-risk patients, including those with left ventricular dysfunction, high calcific load, age >75 years, diabetes, renal failure, left main stem disease, reoperations, chronic pulmonary disease, and an overall European System for Cardiac Operative Risk Evaluation (EuroSCORE) score of >5. In a recent analysis of 14,766 patients,³⁹ OPCAB was associated with mortality benefit in the higher risk quartiles (38% and 55% reduction in the odds of mortality in the 3rd and 4th quartiles, respectively, as defined by the Society of Thoracic Surgeons Predicted Risk of Mortality Score). Of note, there was no difference in operative mortality between

OPCAB and conventional CABG for patients in the lower 2 risk quartiles. Although that analysis was limited by its nonrandomized design, a review of the database revealed that patients receiving OPCAB were older and sicker than those undergoing conventional CABG and had a significantly greater predicted risk of mortality and numerous morbidities. Our results, using solely randomized data, confirm what has long been reported in the large registries.^{40,41}

A common fundamental criticism of the majority of previous randomized studies was that they tend to invariably enroll selected very-low-risk to low-risk patients. In this setting, with adverse events rates of ~1%-2%, demonstration of benefits with either technique in a single trial would require enormous study groups. Through risk profile meta-regression,⁴² combining study-level aggregate data of included studies, we were able to demonstrate a significant relationship between the benefits of OPCAB and baseline patient risk profiles as expressed by the odds of a given outcome in the control group (CABG).

Why high-risk patients are less likely to develop complications after OPCAB than their conventional CABG counterparts remains a subject of ongoing debate. The use of CPB has been associated with a systemic inflammatory response affecting multiple organ systems, including the brain, heart, lungs, kidney, and the gastrointestinal tract. Avoidance of CPB and, in turn, interactions between the inflammatory, coagulation, and fibrinolytic cascades confer complex, organ-specific benefits, especially in high-risk patients. Yokoyama et al⁴³ reported reduced rates of neurologic, renal, coagulopathy, and respiratory complications in OPCAB recipients compared with CABG controls. In particular, 9.3% of the patients with chronic obstructive pulmonary disease undergoing conventional CABG required prolonged postoperative mechanical ventilation, whereas no patient in the OPCAB group experienced delayed extubation. This finding points for the first time to the negative effects of fluid shifts and inflammatory reaction secondary to CPB in a compromised respiratory system and surely merits further research. These organ-specific benefits translated finally in no operative mortality for OPCAB, whereas a postoperative mortality ranging from 2.3% to 8.3% was reported in CPB groups.

The findings on mortality benefit with OPCAB in high risk patients corroborate on a larger scale the hypothesis that beyond an individual patient's risk threshold, OPCAB performs better than CABG. Al-Ruzzeh et al¹⁰ reported that high-risk patients (preoperative EuroSCORE ≥ 5) with multivessel disease showed significant reductions in the incidence of perioperative MI and other major complications ($P = .008$), reduced length of intensive care unit stay, and lower mortality after OPCAB surgery compared with conventional CPB myocardial revascularization.

Since 1999, the EuroSCORE has evolved from “additive” and “logistic” to EuroSCORE II owing to changing clinical pictures of the cardiac surgery patients. In a meta-analysis published in 2009 (8 studies, 24,673 subjects), additive and logistic EuroSCORE algorithms performed similarly, and cumulative evidence suggested comparable performance in CABG and OPCAB procedures (area under the curve, 0.767 for CABG and 0.766 for OPCAB).⁴³ Both risk models significantly overestimated mortality, however. In contrast, EuroSCORE II, which was introduced into clinical practice from initial experience, calculates the risk, which is statistically significantly lower than the risk as assessed by the EuroSCORE, with a reduction of approximately 50%, although definitive data are not yet available.⁴⁴ This decreased calculated risk for a surgical procedure will certainly have clinical consequences for the decision to perform an operation in high-risk patients. The results of the present study may in fact provide guidance for surgeons in performing OPCAB in this patient population or, alternatively, to refer such patients to high-volume centers experienced in off-pump techniques. Although this needs to be confirmed in a large comparative study, surgeons who prefer a selective approach could use EuroSCORE II for the decision making and patient selection for OPCAB.

Several limitations of our meta-analysis should be acknowledged. First, the analysis shares the limitations of original studies included; thus, results were analyzed on the trial level and not on the patient level. Although detailed sensitivity analyses were undertaken, given the heterogeneity of the study protocols, clinically relevant differences could have been missed and might have been better assessed in a meta-analysis of individual patient data. The criteria for patient inclusion were broad across the studies, more closely reflecting current clinical practice, enrolling both high-risk patients and patients undergoing elective surgery. A subtle underlying bias of the trials included remains a possible limitation of this and any systematic review. We accounted for bias by excluding studies at high risk in the sensitivity analysis. Event rates observed in the present analysis, and particularly mortality, were slightly higher than those reported in the available registries (2.25% vs 2.07% as reported in the Society of Thoracic Surgeons database).⁴⁵ In addition, there could be additional confounders not accounted for in the analysis, such as surgeon experience; one influential study included in the present meta-analysis⁸ was indeed criticized because CABG was performed by surgical trainees under the supervision of attending surgeons, who were remarkably inexperienced in the off-pump procedure and much more experienced in the on-pump procedure. The 53 participating surgeons enrolled on average only 8 patients per year over a 5-year period and had unacceptably high rates of conversion to on-pump surgery (12%) and incomplete

revascularization (18%). We acknowledge the need for larger, higher-quality studies addressing training and surgeon experience in OPCAB, proper case selection for OPCAB, timing and effect of conversion to on-pump surgery, and impact of the degree of revascularization (complete vs noncomplete).

On the other hand, because our main analysis was performed using a random-effects model, the present study accounts for baseline between- and within-study variations and is the first to demonstrate, on a comprehensive level, a mortality benefit with OPCAB in patients at higher risk. The findings on significant mortality risk-profile meta-regression are further corroborated in the analysis of MI and stroke.

CONCLUSIONS

OPCAB is associated with a significant (28%) reduction in the odds of ≤ 30 -day stroke compared with conventional CABG, but there is no difference with respect to all-cause mortality and MI between the 2 techniques. A significant linear relationship between benefits in all-cause mortality, MI, and stroke with OPCAB and patient risk profile was shown, suggesting that OPCAB should be seriously considered in high-risk patients.

Conflict of Interest Statement

Dr Navarese has received honoraria for lectures from Eli Lilly. All other authors have nothing to disclose with regard to commercial support.

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Key Words: coronary disease, cardiopulmonary bypass, cerebrovascular disorders

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APPENDIX FIGURE 1. Funnel plot for all-cause mortality. *SE*, Standard error; *OR*, odds ratio.

APPENDIX FIGURE 3. Funnel plot for cerebral stroke. *SE*, Standard error; *OR*, odds ratio.

APPENDIX FIGURE 2. Funnel plot for MI. *SE*, Standard error; *OR*, odds ratio.

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APPENDIX FIGURE 4. Sensitivity analysis of all-cause mortality after exclusion of studies with <50 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 5. Sensitivity analysis of MI after exclusion of studies with <50 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-11*, A randomized comparison between off-pump and on-pump surgery PRAGUE-11; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 6. Sensitivity analysis of cerebral stroke after exclusion of studies with <50 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 7. Sensitivity analysis of all-cause mortality after exclusion of studies with <100 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 8. Sensitivity analysis of MI after exclusion of studies with <100 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimates. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISk patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 9. Sensitivity analysis of cerebral stroke after exclusion of studies with <100 patients. Size of squares is proportional to the statistical weight of each trial. Diamonds represent OR point estimates; horizontal lines represent 95% CIs for given point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests significant outcome. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 10. Sensitivity analysis of all-cause mortality as standardized difference in means. *CI*, Confidence interval; *BBS*, best bypass surgery trial; *BHACAS I*, beating heart against cardioplegic arrest study 1; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump *CORONARY* bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery *PRAGUE-4*; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *OPCAB*, off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting.

APPENDIX FIGURE 11. Sensitivity analysis of MI as standardized difference in means. *CI*, Confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, eating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-Risk patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump *CORONARY* bypass surgery in low-risk patients; *PRAGUE-11*, A randomized comparison between off-pump and on-pump surgery *PRAGUE-11*; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery *PRAGUE-4*; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *OPCAB*, off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting.

APPENDIX FIGURE 12. Sensitivity analysis of cerebral stroke as standardized difference in means. *CI*, Confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump *CORONARY* bypass surgery in low-risk patients; *PRAGUE-11*, A randomized comparison between off-pump and on-pump surgery *PRAGUE-11*; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery *PRAGUE-4*; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *OPCAB*, off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting.

APPENDIX FIGURE 13. Sensitivity analysis of all-cause mortality after arcsine transformation of risk difference. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *SE*, standard error; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 14. Sensitivity analysis of MI after arcsine transformation of risk difference. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *SE*, standard error; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, beating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-11*, A randomized comparison between off-pump and on-pump surgery PRAGUE-11; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX FIGURE 15. Sensitivity analysis of cerebral stroke after arcsine transformation of risk difference. *OPCAB*, Off-pump coronary artery bypass; *CABG*, coronary artery bypass grafting; *SE*, standard error; *CI*, confidence interval; *BBS*, best bypass surgery trial; *BHACAS 1*, beating heart against cardioplegic arrest study 1; *BHACAS 2*, eating heart against cardioplegic arrest study 2; *CORONARY*, CABG off or on pump revascularization study; *CRISP*, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; *DOORS*, Danish on-pump versus off-pump randomization study; *GOPCABE*, German off-pump coronary artery bypass grafting in elderly patients; *JOCRI*, Japanese off-pump coronary revascularization investigation study; *MASS III*, off-pump and on-pump stable multivessel coronary artery bypass grafting; *Octopus*, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; *PRAGUE-4*, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; *PRAGUE-6*, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; *PROMISS*, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; *ROOBY*, veterans affairs randomized on/off bypass trial; *SMART*, surgical management of arterial revascularization therapies; *df*, degrees of freedom.

APPENDIX TABLE 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	6,7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6,7
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	7,8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	7,8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Table 1, Appendix Table 4
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	7,8
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Table 1 Appendix Table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Table 1, Appendix Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11

(Continued)

APPENDIX TABLE 1. Continued

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Table 1, Appendix Table 4
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	11-17
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	11-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	17, NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(6):e1000097. <http://dx.doi.org/10.1371/journal.pmed1000097>. For more information, visit: www.prisma-statement.org.

APPENDIX TABLE 2. Medline search strategy

Search	Query	Items found
1	OPCAB AND trial	279
2	Beating heart AND trial	307
3	OPCABG AND trial	32
4	Off-Pump AND trial	921
5	Without cardiopulmonary AND trial	8248
6	Without extracorporeal circulation AND trial	3216
7	OPCAB AND study	768
8	Beating heart AND study	3339
9	OPCABG AND study	104
10	Off-Pump AND study	2481
11	Without cardiopulmonary AND study	27,313
12	Without extracorporeal circulation AND study	10,932
13	OPCAB AND random*	261
14	Beating heart AND random*	316
15	OPCABG AND random*	35
16	Off-Pump AND random*	831
17	Without cardiopulmonary AND random*	8057
18	Without extracorporeal circulation AND random*	2417
19	ONCAB AND trial	21
20	CABG AND trial	3043
21	On-pump AND trial	533
22	Cardiopulmonary bypass AND trial	4889
23	Extracorporeal circulation AND trial	6333
24	Conventional bypass AND trial	1038
25	ONCAB AND study	62
26	CABG AND study	8552
27	On-pump AND study	1312
28	Cardiopulmonary bypass AND study	13,316
29	Extracorporeal circulation AND study	19,657
30	Conventional bypass AND study	2615
31	ONCAB AND random*	29
32	CABG AND random*	2780
33	On-pump AND random*	522
34	Cardiopulmonary bypass AND random*	4474
35	Extracorporeal circulation AND random*	4961
36	Conventional bypass AND random*	916

OPCAB, Off-pump coronary artery bypass; OPCABG, off-pump coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass. *Extended search query (randomized, randomised, randomly, random etc.).

APPENDIX TABLE 3. Patients' baseline characteristics

Study ^{reference}	Exclusion criteria	Design	Male, %		Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Al-Ruzzeh S et al ^{E1}	LVEF <30%, renal failure (SCr ≥180 mol or active renal replacement therapy), concomitant cardiac surgery using CPB, emergency surgery after angiographic intervention, inability to communicate in English (for neurocognitive testing), no consent for angiography after surgery, isolated single vessel disease requiring single coronary bypass	OPCAB	83.3	>50%	79%	0	24	62	16			
				30%-49%	21%							
		CABG	80.1	>50%	77%	0	21	55	14	NR	0	NR
				30%-49%	23%							
Alwan et al ^{E2}	Known DM or other endocrinologic disorders, history of heart failure, severely reduced myocardial or kidney function	OPCAB	65.7		0.60 ± 0.1	0	0	NR	37	NR	NR	NR
		CABG	74.3		0.58 ± 0.1	0	0		37			
Ascione et al ^{E3}	Diabetes; history of CVA; significant carotid artery disease; history of ophthalmic, neurologic, or peripheral vascular disease; recent MI (within 1 mo); LVEF <30%	OPCAB	70	>30%	100%	NR	0	70	20	NR	0	NR
		CABG	100	>30%	100%		0	80	40			
Ascione et al ^{E4}	Chronic liver or pancreatic disease, known gastrointestinal disease, LVEF <30%, recent MI (within 1 wk), renal and respiratory impairment, peripheral vascular disease	OPCAB	90	>30%	100%	NR	NR	NR	NR	NR	0	NR
		CABG	85	>30%	100%							

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %		Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Baker et al ^{E5}	LVEF <40%; English not first language; previous cerebrovascular disease, including CVA, reversible ischemic neurologic deficit, and TIA any time before planned surgery; emergency and urgent coronary artery surgery including patients with UA (requiring heparin or glycerine trinitrate before surgery) or recent MI (within 6 wk); previous open heart surgery; >3 distal anastomoses; chronic renal failure (Cr >0.3) or severe COPD	OPCAB	91.6	>40%	100%	NR	11.1	55.6	NR	NR	0	0
		CABG	71.4	>40%	100%		30	70				
Moller et al [BBS] ^{E6}	Previous heart surgery, LVEF <30%, lack of informed consent, unstable preoperative condition (eg, patients receiving continuous infusion of inotropic agents)	OPCAB	65	>50%	51%	4.5	18	48	56	5.1	4.52	NR
		CABG	64	30%-50%	49%	3.1	18	53	58	4.3		
Angelini et al [BHACAS 1] ^{E7,E8}	History of supraventricular arrhythmia, LVEF <30%, recent MI (within 1 mo), elevated SCr (>130 μmol/L), combined valve surgery, respiratory impairment, previous stroke or TIA, coagulopathy, coronary disease involving a	OPCAB	82	>50%	81%	0	19	62	41	NR	2	NR
		CABG	79	30%-50%	79%	0	14	49	30			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Angelini et al [BHACAS 2] ^{E7}	branches of the circumflex artery distal to the first obtuse marginal or posterior branches originating from the left system											
	History of supraventricular arrhythmia, LVEF <30%, recent MI (within 1 mo), elevated SCr (>130 μmol/L), combined valve surgery, respiratory impairment, previous stroke or TIA, coagulopathy	OPCAB	85	<50%	24%	0	32	60	50	NR	0	NR
		CABG	82	<50%	23%	0	30	50	50			
Bicer et al ^{E9}	Infection, redo surgery or emergency surgery, malignancies, immunologic disorders, recent MI (within last mo); steroid use, NYHA class IV heart failure, cardiogenic shock, severe valvular disease, renal failure, and hepatic failure	OPCAB	88	53.76 ± 15.07%	NR	24	68	NR	NR	0	NR	
		CABG	88	52.31 ± 10.8%		12	68					
Blacher et al ^{E10}	Previous heart surgery; acute recent MI (within 3 mo); need for concomitant cardiac procedure (valve replacement, correction of congenital defects, or other surgical procedures); renal failure, defined as SCr >177 μmol/L; immunodeficiency syndrome; chronic or	OPCAB	77	>40%	100%	0	8	77	62	NR	0	NR
		CABG	53	>40%	100%	0	13	68	48			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Bonacchi et al ^{E11}	perioperative corticotherapy; LVEF <40%; active infection; UA requiring intensive care; NYHA class III or IV											
	LVEF <35%, age 70 y, previous MI, redo surgery, presence of valvular heart disease and/or cerebrovascular disease, abnormal preoperative carotid vessel angiography, coronary artery disease involving the distal circumflex artery, renal dysfunction, coagulopathy	OPCAB	66.6	55 ± 8.6%	0	NR	77.8	22.2	33.3	5.55	NR	
		CABG	71	53 ± 7.4%	0		54.2	21	29.2			
Caputo et al ^{E12}	DM, respiratory or renal impairment, coagulopathy, previous CVA											
	LVEF <30%, recent MI (within last mo), type II DM, respiratory or renal impairment, coagulopathy, previous CVA	OPCAB	85	NR	0	0	NR	30	NR	0	NR	
		CABG	95		0	0		35				
Carrier et al ^{E13}	Need for CPB for valve surgery or another reason	OPCAB	67.9	<45%	100%	7	50	82	NR	NR	15.63	NR
		CABG	83.8	<45%	100%	11	46	81				
Cavalca et al ^{E14}	Porcelain aorta, Q-wave MI in the previous 6 wk, UA, LVEF <30%	OPCAB	82	55.8 ± 9.6%	0	23	55	36	NR	4.54	NR	
		CABG	68	56.2 ± 13.4%	14	28	64	48				
Chowdhury et al ^{E15}	Emergency surgery, AMI or recent MI (within 2 wk), treatment with fibrinolytic agents within 48 h, redo surgery, LVEF <30%, concomitant valvular heart disease, UA, renal disease, COPD, steroid therapy, hepatic disease	OPCAB	80	0.54 ± 0.64	0	32	60	44	NR	0	NR	
		CABG	84	0.52 ± 0.60%	0	28	56	40				

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%) [†]	“Clampless” OPCAB (%)
	(as indicated by AST or ALT level >2 times the ULN or bilirubin level >1.5 times the ULN, severe coagulation abnormalities											
Lamy et al [CORONARY] ^{E16}	Planned valve surgery, any contraindication to off-pump CABG or on-pump CABG, surgeon’s decision that 1 of the 2 techniques was not feasible for that patient, life expectancy of <2 y, emergency or repeat CABG surgery, previous enrollment in the trial.	OPCAB	80.0	≥50%	70.5%	1.7	46.5	76.2	33.8	10.0	7.45	NR
				35%-49%	24.0%							
				20%-34%	5.1%							
				<20%	0.3%							
		CABG	81.7	≥50%	70.9%	1.1	47.5	75.5	35.2	9.5		
				35%-49%	23.3%							
				20%-34%	5.4%							
				<20%	0.2%							
Covino et al ^{E17}	LCx stenosis, compulsory treatment with CPB due to presence of stenosis of posterior coronaries	OPCAB CABG	89		NR	NR	14.2 18.7	NR	NR	NR	0	NR
Rogers et al [CRISP] ^{E18}	Additive EuroSCORE of <5, emergency operation (immediate revascularization for hemodynamic instability), concomitant cardiac procedure with CABG, operation scheduled to be done via an incision other than median sternotomy (eg, anterolateral left thoracotomy); known contraindication to ONCABG or OPCABG (eg, calcified aorta, calcified coronary artery, small target vessels)	OPCAB	78	>50%	61%	4	22	84	71	12	2.05	34.7
				30%-50%	35%							
				<30%	4%							
		CABG	76	>50%	55%	2	27	76	69	20		
				30%-50%	36%							
				<30%	5%							

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Czerny et al ^{E19}	Unclear	OPCAB	71.4	66.5 ± 5.8%		NR	NR	NR	NR	NR	NR	NR
		CABG	81.3	67.8 ± 4.8%								
Czerny et al ^{E20}	Unclear	OPCAB	80.0	62.7 ± 11.4%		NR	NR	NR	NR	NR	22.5	0
		CABG	87.5	65.3 ± 8.4%								
Diegeler et al ^{E21}	Carotid artery stenosis; degenerative aortic plaques detected by TEE; cerebrovascular, neurologic, or psychiatric disease; severe functional disturbance of liver or kidney; diabetic neuropathy; carcinoma or malignant melanoma; alcohol or drug addiction; emergency operation	OPCAB	NR	60.8 ± 6.1%		NR	NR	NR	NR	NR	NR	0
		CABG		57.4 ± 6.3%								
Dorman et al ^{E22}	Emergency surgery, unwillingness to participate in the study	OPCAB	44.4	58 ± 10%		NR	26	26	NR	NR	NR	0
		CABG	64	63 ± 4%			48	80				
Houlind et al [DOORS] ^{E23}	Inability to understand given information or reluctance to participate, redo cardiac surgery, infeasibility of both procedures, other logistic reasons that made inclusion impossible	OPCAB	76	≥50%	66%	NR	22	71	27	16	12.66	73‡
				30%-50%	29%							
				<30%	5.4%							
		CABG	78	≥50%	69%		18	71	28	13		
Fattouch et al ^{E24}	Mechanical complications of MI, need for CPR before surgery, life-saving procedures, onset of cardiac shock after >24 h, more than moderate ischemic mitral valve regurgitation,	OPCAB	61	<35%	NR	NR	39	61	39	19	1.59	NR
		CABG	77	<35%	15%		41	68	19	17		

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%) [†]	“Clampless” OPCAB (%)
Formica et al ^{E25}	concomitant cardiac surgical procedures, such as left ventricular aneurysm and mitral valve repair										
	Calcified and intramyocardial coronary arteries, recent or current steroid treatments, emergency or urgency operation, recent MI (within 10 d), UA with intravenous medications, preoperative IABP	OPCAB CABG	60 65	53.9 ± 8.2% 54.7 ± 7.3%	NR	45 35	75 85	15 10	20 5	10	100 [§]
Gasz et al ^{E26}	Recent MI (within 3 mo); acute operation; reoperation; infection; immunologic disease; tumor; acute or chronic renal failure; respiratory impairment; previous stroke; and coagulopathy	OPCAB CABG	30 20	NR	0 0	NR	NR	NR	NR	NR	NR
	Immunologic disease, recent MI (within 3 mo), acute operation, reoperation, previous stroke, infection, coagulopathy, tumor, acute or chronic renal failure, respiratory impairment	OPCAB CABG	76.6	NR	0 0	NR	NR	NR	NR	NR	NR
Gerola et al ^{E28}	Age >70 y, circumflex artery lesions, chronic renal dysfunction (SCr >2.0 mg/dL), ACS after angioplasty failure and/or unstable hemodynamic conditions, LVEF	OPCAB CABG	63.8 67.5	>35% >35%	100% 100%	NR	20.6	50	43.1	NR	NR

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Gu et al ^{E29}	<35%, LV aneurysm, carotid lesions, hepatitis, AIDS, morbid obesity, redo myocardial revascularization	Cardiac		disease, such as a left ventricular aneurysm or valvular disease	OPCAB	70.9		55 ± 9%		NR	9.7	
CABG			19.4	35.5	NR	NR	100	6.5	12.9	29.0		
	61.3			51 ± 9%								
Guler et al ^{E30}	Unclear	OPCAB	NR	NR	NR	NR	NR	NR	NR	NR	100	
		CABG										
Gonenc et al ^{E31}	Captopril or allopurinol therapy, receipt of blood transfusion or blood products during the operation	OPCAB	80.0	NR	NR	NR	NR	NR	NR	0	NR	
		CABG	75.0									
Diegeler et al [GOPCABE] ^{E32}	Additional cardiovascular disease necessitating concomitant surgery, previous pericardiotomy, any condition requiring immediate surgery, planned MIDCAB, patient inability or unwillingness to provide consent	OPCAB	69.2	<30% 30%-50% >50%	2.1% 30.7% 67.1%	2.2	15.1	NR	36.0	22.6	9.05	NR
		CABG	67.8	<30% 30%-50% >50%	3.2% 28.3% 68.5%	2.2	13.8		37.8	21.8		
Gulielmos et al ^{E33}	LVEF <30%; impaired lung and renal function; UA; major calcification of the ascending aorta; BMI >30 kg/m ² ; dipyridamole, anticoagulant, or immunosuppression therapy; previous	OPCAB	80	58.2 ± 21.9% 60.1 ± 12.8%*	0	NR	NR	40	15	0	100	
		CABG	75	71.3 ± 12.6% 76.5 ± 9.1%*	0			55	10			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Hernandez et al ^{E34}	cardiac operations; previous MI (within 2 wk)											
	Concomitant valve or carotid artery procedures, emergency operation, reoperation, heavily calcified ascending aorta, deep intramyocardial left anterior descending coronary artery, preoperative inotropic agent (eg, dobutamine, epinephrine, amrinone, milrinone, dopamine >3 μg/kg/min), cardiac-assist device (IABP) support for hemodynamic instability, inability to obtain written consent	OPCAB	80.8	≥60%	66.7%	2.0	35.4	NR	NR	NR	8.08	0
				50%-59%	15.6%							
				40%-49%	12.2%							
				<40%	5.6%							
		CABG	79.4	≥60%	56.2%	4.9	30.4					
				50%-59%	24.7%							
				40%-49%	9.0%							
Hoel et al ^{E35}				<40%	10.1%							
	LVEF <30%, renal failure (SCr >200 mmol/L)	OPCAB	NR	>30%	100%	0	NR	NR	NR	NR	NR	0
Iqbal et al ^{E36}		CABG		>30%	100%	0						
	Concomitant heart surgery procedure, emergency surgery, cardiogenic shock, preoperative intra-aortic balloon pump, recent MI (within last mo), history of supraventricular tachycardia, atrial fibrillation, renal or respiratory impairment, previous stroke or TIA, coagulopathy	OPCAB	NR		NR	0	42	53	NR	NR	1.00	NR
Jares et al ^{E37,E104}		CABG				1	38	54				
	Previous cardiac surgery, MI within 7 d before surgery, history of	OPCAB	60		NR	NR	NR	NR	NR	NR	0	NR
		CABG	80									

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Kobayashi et al [JOCRI] ^{E38}	hematologic or liver disorders, renal insufficiency (sCR >150 μmol/L), preoperative anemia (hemoglobin, <11 g/dL; hematocrit, <32)										
	Age >70 y, indication for additional surgical procedures, documented history of stroke, severe ascending aortic calcification shown by computed tomography scanning, carotid arterial stenosis >75% shown by Duplex scanning, acute Q-wave MI, emergency operation, LVEF <30%, SCr >2.0 mg/dL, liver cirrhosis, COPD, PHT with >25 mm Hg, other morbidities such as anomalous coagulation and cancer, inability to provide written informed consent	OPCAB CABG	86.4 87.2	57 ± 14% 57 ± 14%	0 0	47 58	67 69	52 47	30 21	0	84
Johansson-Synnergren et al ^{E39}	Stenoses in the distal circumflex area, LVEF <30%, preoperative stroke, known peripheral vascular disease, infection or preoperative treatment with anti-inflammatory drugs	OPCAB CABG	69.2 61.5	63.6 ± 2.6% 60.6 ± 2.7%	NR NR	NR NR	NR NR	NR NR	NR NR	0	NR

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Jongman et al ^{E40}	Age <18 y; history of trauma, stroke, or neurosurgery; severe or symptomatic carotid artery disease; concomitant valvular procedure; acute or chronic renal dysfunction; urgent or emergency surgery; difficulties with neurocognitive testing	OPCAB	90%	55%-70%	43.3%	0	27	23	3.3	10.0	0	NR
				40%-55%	50.0%							
				<40%	6.7%							
		CABG	86.6%	55%-70%	58.6%	0	21	35	0	6.9		
				40%-55%	34.5%							
				<40%	6.9%							
Khan et al ^{E41}	Age <30 or >80 y, indication for additional surgical procedures, documented stroke within the preceding 6 mo, carotid artery stenosis >70%, documented MI in the preceding 3 mo, LVEF <20%, pregnancy and breastfeeding, inability to provide written informed consent, history of complications after diagnostic angiography	OPCAB	93.0	>49%	76%	NR	28	NR	39	NR	3.70	NR
				30%-49%	22%							
				<30%	2%							
		CABG	82.0	>49%	73%		26		49			
				30%-49%	27%							
				<30%	0%							
Kochamba et al ^{E42}	Calcified or intramyocardial arteries, lesions in circumflex artery, hemodynamic instability, emergent surgery	OPCAB	76.0	62.7 ± 14.7%		10	41	NR	NR	NR	0	NR
		CABG	79.0	64.3 ± 12.7%		7	41					

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clamless” OPCAB (%)
Kok et al ^{E43}	Difficulty with cognitive testing; problems understanding the Dutch language; impaired function of the dominant hand or arm; history of head trauma, stroke, or neurosurgery; severe or symptomatic carotid artery disease; systemic steroid therapy; preexisting acute or chronic renal impairment (sCR >200 μmol/L)	OPCAB	90%	55%-70%	43%	NR	27%	25%	NR	NR	0	10
				40%-55% <40%	50% 7%							
Krejca et al ^{E44}	Critical lesions in circumflex artery	OPCAB	NR	58.3 ± 9.1%		NR	15.4	53.8	46.2	NR	NR	0
		CABG		54.6 ± 12.4%			23.1	61.5	53.8			
Kunes et al ^{E45}	Anti-inflammatory agents, either steroids or NSAIDs; SCr ≥130 μmol/L; liver failure	OPCAB	70.6	65%		NR	NR	NR	NR	NR	NR	NR
		CABG	82.4	65%								
Lee et al ^{E46}	Unclear, not first-time surgery, nonelective surgery, renal dysfunction (SCr >2.0 mg/dL)	OPCAB	80	53.8 ± 12.9%		0	20	70	10	NR	0	0
		CABG	73	56.6 ± 6.1%		0	37	87	7			
Legare et al ^{E47}	Emergency procedure (requiring immediate surgery), concomitant major cardiac procedure, LVEF <30%, reoperation	OPCAB	81.3	>50%	86.7%	4.7%	29.3	70	44.7	NR	13.33	NR
		CABG	79.3	30%-50% >50% 30%-50%	13.3% 84.7% 15.3%	2.7%	36.0	60	50.7			
Lingaas et al ^{E48,E49}	LVEF <30 %, renal failure (SCr >200 mmol/L), significant lesions of the circumflex in the first 40 cases	OPCAB	86.6	72 ± 12%		0	13.3	41.6	48.3	10.0	11.66	NR
		CABG	70.0	72 ± 10%		0	20	43.3	41.6			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Lloyd et al ^{E50}	LVEF <30%, recent MI (within 1 mo), distal circumflex coronary artery involvement, reoperation or combined valvular surgery, respiratory or renal impairment, coagulopathy; previous psychiatric illness, previous stroke or TIA	OPCAB	86.6	>50%	93.3%	0	10%	NR	NR	NR	0	0
		CABG	90	30%-50% >50% 30%-50%	6.6% 83.3% 16.6%	0	13.3					
Lund et al ^{E51,E52}	Absence of a temporal acoustic window for transcranial Doppler monitoring, malignancy	OPCAB	89.7	>30%	100	NR	13.8	48.3	NR	NR	11.66	0
		CABG	73.9	>30%	100		8.7	39.1				
Malik et al ^{E53}	Aortic incompetence, LVEF <30% concomitant heart valve disease, UA, renal disease, COPD, steroid therapy, reoperation	OPCAB	84	0.52 ± 0.66		0	28	52	32	NR	0	NR
		CABG	84	0.54 ± 0.62		0	24	52	40			
Mandak et al ^{E54}	Unclear	OPCAB	80	56.2 ± 12.7%		NR	40	75	65	NR	0	NR
		CABG	85	57.8 ± 9.8%			20	85	85			
Matata et al ^{E55}	DM, circumflex and LM stem CAD; valvular disease; ventricular aneurysm; heart failure; poor LVEF	OPCAB	80	NR		NR	0	50	NR	NR	0	0
		CABG	90	NR			0	30				
Hueb et al [MASS III] ^{E56}	Emergency or concomitant major surgery, UA requiring emergency revascularization, ventricular aneurysm requiring repair, end LVEF <40%, inability to provide written informed consent	OPCAB	75	70 ± 10%		NR	29	34	34	NR	1.94	NR
		CABG	80	68 ± 10%			27	37	32			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Medved et al ^{E57}	Previous cardiac operations, recent MI (within 7 d), and concomitant heart valve diseases	OPCAB	76.6	45%	NR	NR	93.3	66.6	NR	0	NR
		CABG	66.6	47%							
Michaux et al ^{E58,E59}	Redo or emergency surgery; preoperative hemodynamic instability requiring continuous inotropic medication; lack of sinus rhythm or complete bundle branch block or atrioventricular delay >240 ms on preoperative electrocardiogram; intermittent or permanent ventricular pacing before surgery; moderate or severe mitral or tricuspid valvular disease or atrial septal defect on preoperative transthoracic echocardiogram	OPCAB	84	57 ± 16%	NR	32	52	52	NR	8.00	NR
		CABG	84	58 ± 16%							
Modine et al ^{E60}	Emergency cases, reoperation, combined surgeries	OPCAB	37	>50%	NR	NR	62.9	NR	NR	0	0
		CABG	30.6	>50%							
Motallebzadeh et al ^{E61}	Carotid artery stenosis, previous cerebrovascular or psychiatric disease, absence of a temporal acoustic window for	OPCAB	93	>50% 35%-50% <35%	NR	13	53	67	NR	0	0
		CABG	90	>50% 35%-50% <35%							
				73% 27% 0% 35% 65% 0%		60	75	55			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Motallebzadeh et al ^{E62}	transcranial Doppler monitoring, concomitant surgery, Q-wave MI in the previous 6 wk, very poor LVEF											
	Previous CVA or TIA, right or left internal carotid artery stenosis of ≥50%, previous cardiac surgery, concomitant surgery, previous psychiatric illness, dialysis-dependent renal failure, Q-wave MI in the previous 6 wk, LVEF <20%, illiteracy or nonfluency in English, absence of an acoustic window for transcranial Doppler ultrasound monitoring	OPCAB	87	>50% 35%-50% <35%	46% 48% 6%	2	19	57	52	NR	0	0
		CABG	91	>50% 35%-50% <35%	49% 40% 11%	2	29	66	55			
Muneretto et al ^{E63}	High risk for CPB morbidity, age >75 y, COPD, renal dysfunction (SCr clearance <60 mL/min), carotid disease, severe atherosclerosis of ascending aorta, history of CVA	OPCAB	62.5	<30%	12.5%	3.4	42	NR	38.6	NR	9.09	100
		CABG	59.1	<30%	7.9%	2.2	39.7		40.9			
Nesher et al ^{E64}	Heavily calcified, atherosclerotic coronary arteries; heavily calcified ascending aorta; debilitating noncardiac disease; severe peripheral vascular disease; uncontrolled	OPCAB	73.3	NR	0.2	20	40	NR	NR	0	NR	
		CABG	76.6		0.5	21	34					

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Niranjan et al ^{E65}	type 2 DM (FPG >250 g%); history of infection; recent steroidal or antifibrinolytic therapy; SCr ≥2.0 mg %; total bilirubin ≥1.5 mg%; hemoglobin ≤10.0 g%; platelet count ≤100,000 cells/mL; clotting abnormality or white blood cell count <3000 or >14,000 cells/mL ³											
	Known inflammatory disease, existing infection, emergent surgery, use of long-term corticosteroids and nonsteroidal anti-inflammatory drugs, antiplatelet agents in the week before surgery, known coagulopathy/long-term anticoagulation with warfarin or heparin, severe preexisting renal dysfunction (SCr >200 μmol/L), lung dysfunction (FVC or FEV ₁ <80% of predicted), LVEF <40%	OPCAB	85.0	40%-50% >50%	20% 80%	10	10.0	65.0	NR	NR	0	NR
		CABG	80.0	40%-50% >50%	12.5% 87.5%	2.5	80.0	75.0				
Nathoe et al [Octopus] ^{E66}	Emergency or concomitant major surgery, Q-wave MI in the previous 6 wk, poor LVEF	OPCAB	66.0	<40% >40%	23% 77%	NR	9	40	34	17	7.04	NR
		CABG	71.0	<40% >40%	21% 79%		17	44	26	20		

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Lemma et al [On-Off] ^{E67}	Age <18 y, cardiogenic shock requiring emergency surgery and/or preoperative IABP, concomitant cardiac or noncardiac surgical procedures, radiographic evidence of a diseased (porcelain) ascending aorta, inability or unwillingness to provide consent.	OPCAB	70.2	>50% 30%-50% <30%	43.3% 51.0% 5.8%	20.2	42.8	83.7	69.2	3.84	33.2
		CABG	68.5	>50% 30%-50% <30%	41.4% 56.7% 2.0%	13.8	43.3	82.2	78.3		
Onorati et al ^{E68}	Chronic renal insufficiency/failure, liver failure, COPD, abdominal aortic aneurysm with abdominal arteriopathy, autoimmune disease, severe anemia (hemoglobin <8 g/dL), known coagulation disorder or UA	OPCAB	80	43.0 ± 5.9%	0	30	65	60	NR	0	NR
		CABG	80	43.2 ± 4.5%	0	32.5	65	70			
Ozkara et al ^{E69}	Concomitant carotid or peripheral artery surgery, MI in the previous 6 mo, concomitant heart valve disease, LVEF <35%	OPCAB	77	55 ± 13%	NR	54.5	36.3	22.7	NR	0	0
		CABG	73	56 ± 11%		63.6	45.4	18.1			
Paparella et al ^{E70}	Preexisting hemolytic or coagulative disorders, oral or intravenous anticoagulant treatment, antiplatelet treatment within 5 d before surgery, surgically inaccessible coronary arteries, complete revascularization unfeasible	OPCAB CABG	NR	NR	NR	NR	NR	NR	NR	6.25	NR

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Parolari et al ^{E71}	Emergency or concomitant major surgery, Q-wave MI in the previous 6 wk, UA, poor LVEF	OPCAB CABG	73 79	60 ± 1.8% 61 ± 2.4%	NR	NR	NR	64 50	NR	0	NR
Parolari et al ^{E72}	Age >80 y, renal or liver disease, intake of drugs affecting platelet function or coagulation, fibrinolysis within 10 d before surgery, excessive (1000 mL/24 h) postoperative bleeding or reexploration for bleeding, perioperative MI, stroke, renal failure requiring dialysis	OPCAB CABG	60 67	58 ± 1.8% 56 ± 1.5%	NR	33 27	67 87	40 60	NR	0	NR
Penttilä et al ^{E73}	Ongoing ischemia, AMI within previous month, poorly controlled diabetes, SCr >150 mmol/L, chronic AF, aortic or mitral valvular diseases	OPCAB CABG	NR	<50% >50% <50% >50%	9.1% 90.9% 0% 100%	NR	NR	NR	NR	NR	0
Straka et al [PRAGUE-4] ^{E74}	Emergency or concomitant major surgery	OPCAB CABG	77 86	>50% 30%-50% <30% >50% 30%-50% <30%	78% 18% 4% 84% 11% 5%	1 2	28 29	56 59	58 61	18 17	9.61 0
Hlavicka et al [PRAGUE-6] ^{E75}	NA	OPCAB CABG	59.2 57.4	<30% <30%	11.2% 11.1%	NR	NR	NR	59.2 67.6	NR	8.16 NR
Bednar et al [PRAGUE-11] ^{E76}	Unstable angina, AMI within previous 30 d, PCI within previous 30 d, history of stroke (6 mo), concomitant operation (valvular or Maze procedure),	OPCAB CABG	77 82	NR	NR	28 35	63 65	50 40	NR	0	NR

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %		Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
	renal insufficiency (SCr >120 μmol/L), liver disorder, platelet count <150,000, INR >1.2, APTT test/control >1.2, antithrombin III level <80% or >120%, fibrinogen level <2 or >6 g/L											
Sousa Uva et al [PROMISS] ^{E77}	Intravenous inotropes,	OPCAB	82.2	>49%	93%	0	35.6	83.6	49.3	9.6	1.33	NR
	IABP or ventilation	CABG	85.1	>49%	74%	0	36.5	78.4	55.4	18.9		
	before surgery, associated surgical procedure, SCr.1.5 times the ULN, atrial fibrillation, allergy to contrast material, premenopausal status, and inability to give informed consent											
Rachwalik et al ^{E78}	LVEF<40%, age >85 y, chronic lung disease (eg, COPD)	OPCAB CABG	NR		62.2 ± 10.6% 64.3 ± 11.4%	NR	NR	NR	NR	NR	NR	0
Rainio et al ^{E79}	NR	OPCAB	60		<40% 0%	NR	20	20	0	NR	NR	0
		CABG	90		>40% <40% >40% 80%		0	60	20			
Raja et al ^{E80}	Previous abdominal surgery, distal lesions in marginal branch/ circumflex artery on angiography, atherosclerotic arteries <2 mm Ø, especially PD artery	OPCAB CABG	NR		NR	NR	NR	NR	NR	NR	NR	NR
Rasmussen et al ^{E81}	LVEF <40%, ACS,	OPCAB	77.7	67 ± 11%		NR	27.8	44.4	NR	NR	5.88	NR
	previous cardiac surgery, concomitant valve disease,	CABG	76.5	67 ± 12%			35.3	23.5				

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)	
Rastan et al ^{E82}	supraventricular arrhythmia, pulmonary dysfunction (medical treatment or FEV ₁ <1.5 L/min), chronic dialysis											
	Age >75 y, combined cardiac procedures, cardiac reoperation, emergency surgery, LM stenosis >70%, LVEF >50%	OPCAB CABG	80 80	66.1 ± 6.7% 63.0 ± 14.2%	NR	65 60	100 90	45 40	NR	5.00	NR	
Shroyer et al [ROOBY] ^{E83}	Clinically significant valve disease, need for immediate surgery, small target vessels (<1.1 mm Ø) or diffuse coronary disease, clinical reservations of the surgical team regarding patients with risk factor profiles predisposing to extremely high risk of an adverse event, inability or unwillingness to provide consent	OPCAB	99.4	>54% 45%-54% 35%-44% <35%	59.4% 23.4% 11.5% 5.7%	8.5	42.6	85.9	NR	NR	12.41	NR
		CABG	99.5	>54% 45%-54% 35%-44% <35%	58.0% 23.8% 12.4% 5.7%	7.2	44.7	86.6				
Sahlman et al ^{E84}	Not reported	OPCAB	87.5	54.4 ± 9.9%	NR	20.8	58.3	37.5	NR	NR	NR	62.5
		CABG	76.9	57.7 ± 11.9%		3.9	38.5	26.9				
Sajja et al ^{E85}	GFR >60 mL/min/m ²	OPCAB	87.5	<50%	42.9%	100	58.9	66.1	NR	NR	0	NR
		CABG	90.0	<50%	41.7%	100	53.3	76.7		NR		
Selvanayagam et al ^{E86}	Age >75 y, LVEF <20%, involvement in other clinical trials, typical MRI contraindications, baseline SCr 200 μmol/L.	OPCAB	90	>57%	60%	0	23	80	NR	NR	3.33	100
		CABG	83	>57%	60%	0	27	63		NR		

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*		Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Puskas et al [SMART] ^{E87}	Cardiogenic shock and IABP; chronic renal insufficiency with SCr >2.5 mg/dL were exempt from postoperative cardiac angiography.	OPCAB	78	>54%	52%	4	33	65	35	9	1.00	41
				45%-54%	22%							
				35%-44%	16%							
				25%-34%	6%							
				<25%	5%							
		CABG	77	>54%	52%	2	30	60	31	6		
				45%-54%	22%							
				35%-44%	12%							
				25%-34%	5%							
				<25%	7%							
Syed et al ^{E88}	None	OPCAB	81	43% (25%-65%)		NR	48	NR	NR	NR	NR	0
		CABG	76	46% (25%-65%)			55					
Tang et al ^{E89}	Age >80 y, preexisting renal disease SCr >135 μmol/L, LVEF <40%, chronic uncontrolled hypertension, DM, UA, nephrotoxic drug use, inotrope dependency	OPCAB	75	NR		0	0	NR	NR	NR	0	0
		CABG	85			0	0					
Tatoulis et al ^{E90}	Calcification or atheroma of the ascending aorta, extensive diffuse coronary artery, deep intramyocardial course of coronary arteries. Patients operated on urgently (ie, same day as angiography) were excluded, because informed consent was not uniformly possible.	OPCAB	76	>60%	56%	4	36	80	36	6	NR	96
				46%-59%	32%							
				30%-46%	12%							
				<30%	0%							
				>60%	58%	4	28	78	42	10		
		CABG	80	46%-59%	32%							
				30%-46%	10%							
				<30%	0%							
Tully et al ^{E91}	LVEF <40%; chronic renal failure (SCr <0.3 mmol/L); COPD; >3 distal anastomoses; emergency surgery; preoperative UA; recent MI (within 6 wk); participation in another	OPCAB	81.2	>40%	100%	NR	13.3	56.7	NR	NR	0	0
		CABG		>40%	100%		22.2	58.3				

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Van Boven et al ^{E92}	study; previous cardiac surgery; history of cerebrovascular disease, stroke, or TIA, head injury resulting in loss of consciousness; epilepsy; Alzheimer’s disease; current use of psychoactive drugs; hearing difficulties; history of substance abuse; residency outside South Australia, English not first language										
	LVEF <30%, use of acetylsalicylic acid and/or clopidogrel, carotid disease, <3 distal anastomoses	OPCAB	80	Good: Moderate: Poor: 60% 40% 0%	NR	40	50	NR	NR	0	NR
Van Boven et al ^{E93}	Use of acetylsalicylic acid and/or clopidogrel, <3 distal anastomoses	OPCAB	75	50%-65% 30%-50% 60% 40%	NR	35	NR	NR	NR	0	NR
		CABG	40	50%-65% 30%-50% 50% 50%		10					
Vedin et al ^{E94}	Age <50 or >80 y, LVEF <30%, SCr >150 μmol/L, tight main stem stenosis (>70%), redo operation, diffuse distal coronary artery disease, UA	OPCAB	78	>50% 30%-50% 76% 24%	NR	18	52	30	NR	0	0
		CABG	84	>50% 30%-50% 73% 27%	NR	19	46	38	NR		
Velissaris et al ^{E95}	Age >75 y, LVEF <50%, recent (<3 mo) MI, intravenous therapy for UA, DM, renal insufficiency, liver failure, gastrointestinal disease, peripheral vascular disease, previous CVA	OPCAB	77.8	>50% 100%	0	0	48.1	18.5	NR	0	0
		CABG	81.5	>50% 100%	0	0	40.7	33.3			

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %		Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Velissaris et al ^{E96}	Age >75 y, LVEF <50%, recent (<3 mo) MI,	OPCAB	76.9	>50%	100%	0	0	50	19.2	NR	0	0
	intravenous therapy for UA, DM, renal insufficiency, endocrine disease, steroid therapy, previous CVA	CABG	80.1	>50%	100%	0	0	50	34.6			
Vural et al ^{E97}	NA	OPCAB CABG	NR	NR		NR	NR	NR	NR	NR	0	NR
Wan et al ^{E98}	Recent MI, UA, steroid treatment, age >75 y,	OPCAB	83.3		52.93 ± 13.58%	NR	38.9	72.2	22.2	NR	0	0
	SCr >200 μmol/L, single-vessel disease, previous open cardiac procedure, LVEF <30%	CABG	57.9		50.42 ± 12.04%		31.6	78.9	15.8			
Wandschneider et al ^{E99}	Valve operations, combined procedures, or emergency operations; renal insufficiency or any kind of neurologic symptoms	OPCAB CABG	78.0 79.1	NR		NR	NR	NR	NR	NR	21.15¶	NR
Wehlin et al ^{E100}	Age <50 or >80 y, LVEF <30%, SCr >150 μmol/L, LM stenosis, redo operation, peripheral CAD, UA, history of cerebrovascular disease	OPCAB	81	>50%	80%	NR	14	NR	NR	NR	4.54	0
		CABG	81	30%-50%	19%		19					
Wehlin et al ^{E101}	Age <50 or >80 y, LVEF <30%, SCr >150 μmol/L, LM stenosis, redo operation, peripheral CAD, UA, history of cerebrovascular disease	OPCAB	100	>50%	73%	NR	18	NR	NR	NR	0	0
		CABG	89	30%-50%	27%		11					
Yu et al ^{E103}	Emergency or urgent operation, combined valve surgery,	OPCAB	78.4	43.39 ± 9.53%		NR	49	60.9	70.6	17.6	3.92	0
		CABG	74.5	41.9 ± 8.8%			41.2	68.6	76.5	15.6		

(Continued)

APPENDIX TABLE 3. Continued

Study ^{reference}	Exclusion criteria	Design	Male, %	Baseline LVEF*	Kidney disease, %	Diabetes, %	Hypertension, %	History of MI, %	History of PCI, %	Conversion rate (%)†	“Clampless” OPCAB (%)
Zamvar et al ^{E102}	dyskinetic ventricles (LV aneurysms), history of renal insufficiency (SCr >2 mg/dL), stroke or TIA within 1 mo, continuous infusion of inotropics on the day of the operation										
	Carotid artery stenosis >50%, recent MI (within 1 mo), previous TIA or CVA, previous psychiatric illness, renal failure, emergency operation, reoperation, combined valvular surgery	OPCAB	83.3	>50%	76.6%	NR	NR	NR	NR	0	0
				30%-50%	20%						
				<30%	3.3%						
		CABG	90	>50%	76.6%						
				30%-50%	16.6%						
				<30%	6.6%						

LVEF, Left ventricle ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; OPCAB, off-pump coronary artery bypass graft; SCr, serum creatinine; CPB, cardiopulmonary bypass; NR, not reported; CABG, coronary artery bypass graft; DM, diabetes mellitus; CVA, cerebrovascular accident; TIA, transient ischemic attack; UA, unstable angina; Cr, creatinine; COPD, chronic pulmonary obstructive disease; BBS, Best Bypass Surgery Trial; BHACAS 1, Beating Heart Against Cardioplegic Arrest Study 1; BHACAS 2, Beating Heart Against Cardioplegic Arrest Study 2; NYHA, New York Heart Association; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; CORONARY, CABG off or on pump revascularization study; CPR, cardiopulmonary resuscitation; LCx, Left circumflex artery; CRISP, The Coronary artery bypass grafting in high-RISK patients randomised to off- or on-Pump surgery; EuroSCORE, European system for cardiac operative risk evaluation; ONCABG, on-pump coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting; TEE, transesophageal echocardiography; DOORS, Danish on-pump versus off-pump randomization study; IABP, intra-aortic balloon pump; ACS, acute coronary syndrome; LV, left ventricle; GOPCABE, German off-pump coronary artery bypass grafting in elderly patients; AIDS, acquired immunodeficiency syndrome; MIDCAB, minimally invasive direct coronary artery bypass; BMI, body mass index; JOCRI, Japanese Off-Pump Coronary Revascularization Investigation study; PHT, pulmonary hypertension; NSAID, nonsteroidal anti-inflammatory drug; DM, diabetes mellitus; LM, left main; MASS III, off-pump and on-pump stable multivessel coronary artery bypass graft study; CAD, Coronary artery disease; FPG, fasting plasma glucose; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; AMI, acute myocardial infarction; AF, atrial fibrillation/flutter; PRAGUE-4, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; PRAGUE-11, A randomized comparison between off-pump and on-pump surgery PRAGUE-11; NA, not available; INR, International normalized ratio; APTT, activated partial thromboplastin time; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multivessel Coronary Artery Bypass Surgery; PD, posterior descending; ROOBY, veterans affairs randomized on/off bypass study; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; SMART, surgical management of arterial revascularization therapies. *Reported as in included studies. †Conversion OPCAB to CABG. ‡27% of OPCAB operations were performed with a side-biting clamp. §In all patients, the proximal anastomosis in the aortic root was done with the HeartString II Proximal Seal System device (Maquet AG, Hirrlingen, Germany). ¶Data not available.

APPENDIX TABLE 4. Potential sources of bias in included studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Al-Ruzzeh et al ^{E1}							
Alwan et al ^{E2}							
Ascione et al ^{E3}							
Ascione et al ^{E4}							
Baker et al ^{E5}							
Moller et al [BBS] ^{E6}							
Angelini et al [BHACAS 1] ^{E7,E8}							
Angelini et al [BHACAS 2] ^{E7}							
Bicer et al ^{E9}							
Blacher et al ^{E10}							
Bonacchi et al ^{E11}							

(Continued)

APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Caputo et al ^{E12}	+	+	±	+	+	+	±
Carrier et al ^{E13}	+	+	-	+	+	+	±
Cavalca et al ^{E14}	±	±	-	±	+	+	±
Chowdhury et al ^{E15}	+	±	-	+	+	+	±
Lamy et al [CORONARY] ^{E16}	+	+	±	+	+	+	+
Covino et al ^{E17}	±	+	-	±	+	-	+
Rogers et al [CRISP] ^{E18}	+	+	±	+	+	+	+
Czerny et al ^{E19}	+	±	-	+	+	+	±
Czerny et al ^{E20}	+	±	-	+	+	+	±
Diegeler et al ^{E21}	±	+	-	±	±	+	+
Dorman et al ^{E22}	±	±	-	±	±	+	+

(Continued)

APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Houlind et al [DOORS] ^{E23}	+	+	+	+	+	+	±
Fattouch et al ^{E24}	+	+	±	+	+	+	±
Formica et al ^{E25}	+	±	-	+	±	+	+
Gasz et al ^{E26}	±	±	-	±	±	+	+
Gasz et al ^{E27}	+	±	-	±	±	+	±
Gerola et al ^{E28}	+	+	±	+	±	+	+
Gu et al ^{E29}	+	+	±	+	±	±	±
Guler et al ^{E30}	±	±	-	±	±	-	+
Gonenc et al ^{E31}	±	±	-	±	+	±	-
Diegeler et al [GOPCABE] ^{E32}	+	+	±	+	+	+	+
Gulielmos et al ^{E33}	±	+	-	±	±	±	±

(Continued)

APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hernandez et al ^{E34}							
Hoel et al ^{E35}							
Iqbal et al ^{E36}							
Jares et al ^{E37,E104}							
Kobayashi et al [JOCRI] ^{E38}							
Johansson-Synnergren et al ^{E39}							
Jongman et al ^{E40}							
Khan et al ^{E41}							
Kochamba et al ^{E42}							
Kok et al ^{E43}							
Krejca et al ^{E44}							

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kunes et al ^{E45}							
Lee et al ^{E46}							
Legare et al ^{E47}							
Lingaas et al ^{E48,E49}							
Lloyd et al ^{E50}							
Lund et al ^{E51,E52}							
Malik et al ^{E53}							
Mandak et al ^{E54}							
Matata et al ^{E55}							
Hueb et al [MASS III] ^{E56}							
Medved et al ^{E57}							

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Michaux et al ^{E58,E59}							
Modine et al ^{E60}							
Motallebzadeh et al ^{E61}							
Motallebzadeh et al ^{E62}							
Muneretto et al ^{E63}							
Nesher et al ^{E64}							
Niranjan et al ^{E65}							
Nathoe et al [Octopus] ^{E66}							
Lemma et al [On-Off] ^{E67}							
Onorati et al ^{E8}							
Ozkara et al ^{E69}							

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Paparella et al ^{E70}
Parolari et al ^{E71}
Parolari et al ^{E72}
Penttilä et al ^{E73}
Straka et al [PRAGUE-4] ^{E74}
Hlavicka et al [PRAGUE-6] ^{E75}
Bednar et al [PRAGUE 11] ^{E76}
Sousa Uva et al [PROMISS] ^{E77}
Rachwalik et al ^{E78}
Rainio et al ^{E79}
Raja et al ^{E80}

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Rasmussen et al ^{E81}							
Rastan et al ^{E82}							
Schroyer et al [ROOBY] ^{E83}							
Sahlman et al ^{E84}							
Sajja LR et al ^{E85}							
Selvanayagam et al ^{E86}							
Puskas et al [SMART] ^{E87}							
Syed et al ^{E88}							
Tang et al ^{E89}							
Tatoulis et al ^{E90}							
Tully et al ^{E91}							

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Van Boven et al ^{E92}							
Van Boven et al ^{E93}							
Vedin et al ^{E94}							
Velissaris et al ^{E95}							
Velissaris et al ^{E96}							
Vural et al ^{E97}							
Wan et al ^{E98}							
Wandschneider et al ^{E99}							
Wehlin et al ^{E100}							
Wehlin et al ^{E101}							
Yu et al ^{E103}							

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APPENDIX TABLE 4. Continued

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Zamvar et al ^{E102}
Cohen's kappa	0.78	0.81	0.76	0.76	0.80	0.65	0.74

APPENDIX TABLE 5. Endpoint definitions

Study	Endpoint definitions	
	Cerebral stroke	Myocardial infarction
Al-Ruzzeh et al ^{E1}	Focal neurologic signs and symptoms persisting for >24 h, confirmed by CT	New Q-waves on ECG, CK-MB concentration >50 ng/mL with ECG changes or >70 ng/mL without ECG changes
Alwan et al ^{E2}	Not defined	New Q-waves >0.04 ms and a reduction in R-waves of >25% in at least 2 leads. cTnI diagnostic criteria for MI: cTnI peak concentration >3.7 µg/L and cTnI concentration >3.1 µg/L at 12 h or >2.5 µg/L at 24 h
Ascione et al ^{E3}	Not defined	Not defined
Ascione et al ^{E4}	Not defined	Not defined
Baker et al ^{E5}	Not defined	Not defined
Moller et al [BBS] ^{E6}	Global or focal neurologic deficits persisting for >24 h and verified by a neurologist or brain CT scan	CK-MB increase >80 µg/L or TnT >3.0 µg/L the first 48 h after surgery; thereafter, the definition was enzymatic elevation of CK-MB >10 µg/L or TnT >0.1 µg/L along with at least 1 of the following findings: classic angina symptoms, ECG signs of necrosis or ischemia, or coronary reintervention
Angelini et al [BHACAS 1] ^{E7,E8}	Adjudicated by a CEC	New Q-waves of >0.04 ms and/or a reduction in R-waves of >25% in ≥2 leads
Angelini et al [BHACAS 2] ^{E7}	Adjudicated by a CEC	New Q-waves of >0.04 ms and/or a reduction in R-waves of >25% in ≥2 leads
Bicer et al ^{E9}	Not defined	Not defined
Blacher et al ^{E10}	Not defined	New Q-waves, reduction of >25% in R-wave amplitude in ≥2 contiguous leads, CK-MB level ≥5% of the creatine phosphate kinase value for >18 h
Bonacchi et al ^{E11}	Evidence in the postoperative period of a new central neurologic deficit persisting for >72 h	Not defined
Caputo et al ^{E12}	Adjudicated by a CEC	New Q-waves of >0.04 ms, or a reduction in R-waves of >25% in at least 2 leads
Carrier et al ^{E13}	Adjudicated by a CEC	Serial CK-MB level >100 U or new Q-wave on postoperative ECG
Cavalca et al ^{E14}	Not defined	Not defined
Chowdhury et al ^{E15}	Not defined	One of the following criteria: (1) appearance of a new and persistent Q-wave with a duration of >40 ms in at least 2 adjacent leads; (2) disappearance of an R-wave or a 25% reduction of R-waves in 2 leads; (3) appearance of ST-segment deviations at the J-point in 2 or more contiguous leads with cutoff points >0.2 mV in leads V1, V2, and V3 and >0.1 mV in other leads or T-wave abnormalities in 2 or more continuous leads; (4) appearance of a new-onset LBBB; (5) new and persistent wall-motion abnormalities on TEE; and (6) requirement of inotropic support to maintain stable hemodynamics as stated in the absence of mechanical external compression
Lamy et al [CORONARY] ^{E16}	Acute focal neurologic deficit thought to be of vascular origin persisting for >24 h and confirmed by a neurologist	Perioperative MI (within 72 h of surgery): CK-MB measurement ≥5 times the 99th percentile upper reference limit without new pathological Q-waves or new LBBB (non-Q-wave MI) or with new pathological Q-waves or new LBBB (Q-wave MI); angiographic evidence of new graft or native

(Continued)

APPENDIX TABLE 5. Continued

Study	Endpoint definitions	
	Cerebral stroke	Myocardial infarction
		coronary artery occlusion; or imaging evidence of new loss of viable myocardium
		Nonperioperative MI (later than 72 h after surgery): detection of a rise and/or fall of cardiac biomarkers with at least 1 value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathological Q-waves on the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Covino et al ^{E17}	Not defined	Not defined
Rogers et al [CRISP] ^{E18}	New acute focal neurologic deficit thought to be of vascular origin, with signs or symptoms persisting >24 h and confirmed by a neurologist	TnI level of >0.5 µg/L or TnT level of >0.2 µg/L and new pathological Q-waves with documented new wall motion abnormalities except in the septum; CK-MB level ≥10 times the ULN (non-Q MI); or ECG changes consistent with infarction (new significant Q-waves ≥0.04 cm or a reduction in R-waves of >25%, in at least 2 contiguous leads).
Czerny et al ^{E19}	Adjudicated by a CEC	Adjudicated by a CEC
Czerny et al ^{E20}	Adjudicated by a CEC	Adjudicated by a CEC
Diegeler et al ^{E21}	Not defined	Not defined
Dorman et al ^{E22}	Not defined	Not defined
Houliind et al [DOORS] ^{E23}	Acute focal or global neurologic deficit lasting >24 h or leading to death of presumed vascular origin	Postoperative acute MI: peak CK-MB of at least 75 ng/mL by day 3; new Q-wave evidence of MI, along with CK-MB of at least 50 ng/mL by day 3; new Q-wave evidence of MI by day 30 that was not present at day 3; MI (Q-wave or non-Q-wave) as defined according to World Health Organization criteria
Fattouch et al ^{E24}	Not defined	ECG signs (Q-waves and ST-segment elevation) and increased serum myocardial enzyme levels (creatinine phosphokinase and cardiac troponin I)
Formica et al ^{E25}	Not defined	New Q-waves of >0.05 mV and a reduction in R-waves of >25% in at least 2 ECG leads, as well as new echocardiographic akinetic or hypokinetic areas
Gasz et al ^{E26}	Not defined	Not defined
Gasz et al ^{E27}	Not defined	Not defined
Gerola et al ^{E28}	Neurologic dysfunction, including all alterations of behavior, mental confusion, and psychomotor agitation up to stroke and coma	CK-MB level increase ≥5 times the ULN.
Gu et al ^{E29}	Not defined	Not defined
Guler et al ^{E30}	Not defined	Not defined
Gonenc et al ^{E31}	Adjudicated by a CEC	Adjudicated by a CEC
Diegeler et al [GOPCABE] ^{E32}	New acute focal neurologic deficit thought to be of vascular origin with signs or symptoms lasting >24 h; stroke needs to be confirmed by a neurologist; imaging is encouraged to distinguish ischemic and hemorrhagic stroke.	Within 72 h, at least 1 of the following: measured CK-MB ≥5 times the 99th percentile upper reference limit; angiographic evidence of new graft or native coronary artery occlusion; imaging evidence of new loss of viable myocardium later than 72 h; and at least 1 of the following:

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APPENDIX TABLE 5. Continued

Study	Endpoint definitions	
	Cerebral stroke	Myocardial infarction
		symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB, development of pathological Q waves in the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Gulielmos et al ^{E33}	Adjudicated by a CEC	Adjudicated by a CEC
Hernandez et al ^{E34}	Cerebrovascular accident documented by a physician and defined by the following: new focal neurologic deficit that appears and is still at least partially evident for >24 h after its onset, occurring during or after the CABG procedure, and established before discharge	Not defined
Hoel et al ^{E35}	Not defined	Not defined
Iqbal et al ^{E36}	Any neurologic deficit persisting for >30 min	Not defined
Jares et al ^{E37,E104}	Not defined	Not defined
Kobayashi et al [JOCRI] ^{E38}	Not defined	Maximum CK-MB >100 IU/L with ECG change (new Q-wave or T-wave inversion by Minnesota criteria code)
Johansson-Synnergren et al ^{E39}	Adjudicated by a CEC	Adjudicated by a CEC
Jongman et al ^{E40}	Not defined	Not defined
Khan et al ^{E41}	Adjudicated by a CEC	Adjudicated by a CEC
Kochamba et al ^{E42}	Adjudicated by a CEC	Adjudicated by a CEC
Kok et al ^{E43}	Not defined	Not defined
Krejca et al ^{E44}	Not defined	Not defined
Kunes et al ^{E45}	Not defined	Not defined
Lee et al ^{E46}	Adjudicated by a neurologist according to the modified National Institutes of Health Stroke Scale	Adjudicated by a CEC
Legare et al ^{E47}	Adjudicated by a CEC	New Q-wave (0.04 ms) in at least 2 leads or ST changes on ECG in association with significant CK-MB enzyme release
Lingaas et al ^{E48,E49}	Adjudicated by a CEC	Adjudicated by a CEC
Lloyd et al ^{E50}	Not defined	Not defined
Lund et al ^{E51,E52}	Neurologic deficit confirmed by MRI and neurologist examination	Not defined
Malik et al ^{E53}	Adjudicated by a CEC	ECG criteria or in-hospital death
Mandak et al ^{E54}	Adjudicated by a CEC	Adjudicated by a CEC
Matata et al ^{E55}	Not defined	Not defined
Hueb et al [MASS III] ^{E56}	Focal brain injury persisting for 24 h, combined with an increase in disability of at least 1 grade on the Rankin Scale	Elevation of CK-MB ≥ 5 times the ULN (>30 ng/mL) or TnI values >5 ng/mL associated or not with the appearance of new pathological Q-waves, defined as new QS in 2 associated leads in the absence of LBBB, Wolf-Parkinson white syndrome; or new QS in 2 associated leads, defined as ≥ 0.04 s broad and/or Q/R ratio $\geq 1/4$
Medved et al ^{E57}	Not defined	Not defined
Michaux et al ^{E58,E59}	Not defined	Not defined
Modine et al ^{E60}	Adjudicated by a CEC	Adjudicated by a CEC
Motallebzadeh et al ^{E61}	Adjudicated by a CEC	Adjudicated by a CEC
Motallebzadeh et al ^{E62}	Adjudicated by a CEC	Adjudicated by a CEC
Muneretto et al ^{E63}	Not defined	Not defined
Nesher et al ^{E64}	Adjudicated by a CEC	Adjudicated by a CEC

(Continued)

APPENDIX TABLE 5. Continued

Study	Endpoint definitions	
	Cerebral stroke	Myocardial infarction
Niranjan et al ^{E65} Nathoe et al [Octopus] ^{E66}	Adjudicated by a CEC Focal neurologic deficit, lasting >24 h, combined with an increase in disability of at least 1 grade on the Rankin Scale	Adjudicated by a CEC Within 7 d after surgery: Non-Q-wave MI was diagnosed if the serum CK-MB isoenzyme level was >5 times the ULN value, and a Q-wave MI was diagnosed if pathological Q-waves appeared concomitantly. At 7 d or more after surgery: non-Q-wave MI was diagnosed if the ratio of CK-MB isoenzyme to total CK exceeded 0.1, and Q-wave MI was diagnosed if pathological Q-waves appeared.
Lemma et al [On-Off] ^{E67}	Neurologic deficit lasting >24 h with positive CT findings	New Q-wave on the ECG with CK-MB isoenzyme fraction increase >100 UI/L and/or >10% of the total CK level and/or with documented new wall motion abnormalities other than septal on echocardiography.
Onorati et al ^{E68}	Not defined	Perioperative acute MI, defined by any of the following: new Q-waves >0.04 ms with a peak TnI level >3.7 µg/L or TnI concentration >3.1 µg/L at 12 h following surgery; >25% reduction in R-waves in 2 or more ECG leads associated with the same troponin I peaks; or new akinetic or dyskinetic segments on echocardiography
Ozkara et al ^{E69}	Not defined	Not defined
Paparella et al ^{E70}	Not defined	Not defined
Parolari et al ^{E71}	Not defined	Not defined
Parolari et al ^{E72}	Not defined	Not defined
Penttilä et al ^{E73}	Not defined	Not defined
Straka Z et al [PRAGUE-4] ^{E74}	Global or focal neurologic deficit, lasting <24 h or >24 h	Q-wave MI, defined as ECG sign of necrosis, CK and CK-MB elevation, or new akinetic segment on echocardiography
Hlavicka et al [PRAGUE-6] ^{E75}	Not defined	Not defined
Bednar et al [PRAGUE 11] ^{E76}	Not defined	Not defined
Sousa Uva et al [PROMISS] ^{E77}	Not defined	Not defined
Rachwalik et al ^{E78}	Not defined	Not defined
Rainio et al ^{E79}	Not defined	Not defined
Raja et al ^{E80}	Not defined	Not defined
Rasmussen et al ^{E81}	Not defined	Not defined
Rastan et al ^{E82}	Not defined	Not defined
Shroyer et al [ROOBY] ^{E83}	Adjudicated by a CEC	Adjudicated by a CEC
Sahlman et al ^{E84}	Adjudicated by a CEC	CK-MB fraction release >100 U and new Q-wave
Sajja et al ^{E85}	Focal neurologic deficit lasting >24 h	Not defined
Selvanayagam et al ^{E86}	Not defined	Not defined
Puskas et al [SMART] ^{E87}	Focal neurologic deficit lasting >24 h, confirmed by CT scan and neurologist examination	Not defined
Syed et al ^{E88}	Not defined	Not defined
Tang et al ^{E89}	Not defined	Not defined
Tatoulis et al ^{E90}	Defined according to Society of Thoracic Surgeons database definitions	Defined according to Society of Thoracic Surgeons database definitions
Tully et al ^{E91}	Not defined	Two or more episodes of prolonged typical chest pain (>20 min) not relieved by rest and/or nitrates, enzyme level elevation, new wall motion abnormality, or new Q-wave in 2 leads on serial ECG

(Continued)

APPENDIX TABLE 5. Continued

Study	Endpoint definitions	
	Cerebral stroke	Myocardial infarction
Van Boven et al ^{E92}	Adjudicated by a CEC	Adjudicated by a CEC
Van Boven et al ^{E93}	Adjudicated by a CEC	Adjudicated by a CEC
Vedin et al ^{E94}	Adjudicated by a CEC	Adjudicated by a CEC
Velissaris et al ^{E95}	Not defined	Not defined
Velissaris et al ^{E96}	Not defined	Not defined
Vural et al ^{E97}	Not defined	Not defined
Wan et al ^{E98}	Not defined	Not defined
Wandschneider et al ^{E99}	Not defined	Not defined
Wehlin et al ^{E100}	Not defined	Not defined
Wehlin et al ^{E101}	Not defined	Not defined
Yu et al ^{E103}	New acute focal neurologic deficit with signs and symptoms lasting >24 h	CK-MB release >80 IU/mL regardless of concomitant changes on ECG or impaired hemodynamics
Zamvar et al ^{E102}	Not defined	Not defined

CT, Computed tomography; ECG, echocardiography; CK-MB, creatine kinase muscle brain; cTnI, cardiac troponin I; MI, myocardial infarction; BBS, best bypass surgery trial; TnT, troponin T; BHACAS 1, beating heart against cardioplegic arrest study 1; CEC, Clinical Events Committee; BHACAS 2, beating Heart Against Cardioplegic Arrest Study 2; LBBB, left bundle branch block; TEE, transesophageal echocardiography; CORONARY, CABG off or on pump revascularization study; ST-T, ST-T wave; CRISP, The Coronary artery bypass grafting in high-RISK patients randomized to off- or on-Pump surgery; TnI, troponin I; ULN, upper limit of normal; DOORS, Danish on-pump versus off-pump randomization study; GOPCABE, German off-pump coronary artery bypass grafting in elderly patients; JOCRI, Japanese off-pump coronary revascularization investigation study; MRI, magnetic resonance imaging; MASS III, off-pump and on-pump stable multivessel coronary artery bypass grafting; QS, QS complex; Octopus, comparison of on-pump and off-pump CORONARY bypass surgery in low-risk patients; PRAGUE-4, A randomized comparison between off-pump and on-pump surgery PRAGUE-4; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥ 6 ; PRAGUE-11, A randomized comparison between off-pump and on-pump surgery PRAGUE-11; PROMISS, The prospective randomized comparison of off-pump and on-pump multivessel coronary artery bypass surgery; ROOBY, veterans affairs randomized on/off bypass study; SMART, surgical management of arterial revascularization therapies.