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ORIGINAL ARTICLE

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Safety and efficacy of miniaturized extracorporeal circulation when compared with off-pump and conventional coronary artery bypass grafting: evidence synthesis from a comprehensive Bayesian-framework network meta-analysis of 134 randomized controlled trials involving 22 778 patients

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Abstract

OBJECTIVES: Coronary artery bypass grafting (CABG) remains the standard of care in patients with extensive coronary artery disease. Yet the use of cardiopulmonary bypass (CPB) is believed to be a major determinant of perioperative morbidity. Novel techniques are sought to tackle the shortcomings of CPB, among them off-pump coronary artery bypass (OPCAB) and miniaturized extracorporeal circulation (MECC) systems have been extensively tested in randomized controlled trials (RCTs). To assess perioperative safety and efficacy of MECC and OPCAB when compared with conventional extracorporeal circulation (CECC).

METHODS: Published literature and major congress proceedings were screened for RCTs evaluating the safety and efficacy of MECC, OPCAB and CECC. Selected end-points such as 30-day all-cause mortality, myocardial infarction (MI), cerebral stroke, postoperative atrial fibrillation (POAF) and renal dysfunction were assessed in a Bayesian-framework network meta-analysis.

RESULTS: A total of 134 studies with 22 778 patients were included. When compared with CECC, both OPCAB and MECC significantly reduced 30-day all-cause mortality [odds ratios (95% credible intervals): 0.75 (0.51–0.99) and 0.46 (0.22–0.91)], respectively. No differences in respect to MI were demonstrated with either strategy. OPCAB, when compared with CECC, reduced the odds of cerebral stroke [0.57 (0.34–0.80)]; 60% reduction was observed with MECC when compared with CECC [0.40 (0.19–0.78)]. Both OPCAB and MECC reduced the odds of POAF [0.66 (0.48–0.90) and 0.62 (0.35–0.98), respectively] when compared with CECC. OPCAB conferred over 30% reduction of renal dysfunction when compared with CECC [0.69 (0.46–0.92)]. MECC reduced these odds by more than 50% [0.47 (0.24–0.89)]. Ranking of treatments emerging from the probability analysis (highest to lowest SUCRA values) was MECC followed by OPCAB and CECC.

CONCLUSIONS: MECC and OPCAB both improve perioperative outcomes following coronary bypass surgery when compared with conventional CABG performed with extracorporeal circulation. MECC may represent an attractive compromise between OPCAB and CECC.

Keywords: Coronary artery disease • Coronary artery bypass grafting • Off-pump coronary • Artery bypass • Extracorporeal circulation • Network meta-analysis

INTRODUCTION

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) when compared with 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 coronary artery bypass (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]. On the other hand, it has been claimed that OPCAB does not provide the benefit of complete revascularization, in particular, when distal marginal branches on the lateral and/or posterior wall of the heart are diseased [8, 9].

During the past few years, a substantial number of randomized controlled trials (RCTs) have been made available having compared the effects of miniaturized extracorporeal circulation (MECC) versus conventional extracorporeal circulation (CECC) [10, 11]. These systems provide the advantages of conventional extracorporeal circulation (ECC), however with shorter circuit lines, no cardiotomy suction and no venous reservoir, they avoid air–blood contact. The first results reported lower postoperative blood losses and need for transfusions and inflammatory response markers [12, 13]. No single study was, however, powered for hard clinical outcomes.

Network meta-analyses (NMAs), also known as mixed treatment comparisons, are novel research methods that compare different treatments in a connected network. They allow probability inferences on the best treatment even when direct comparisons are not available, while maintaining the randomization design, integrating data from direct and indirect comparisons. The network framework, in addition to analysing direct within-trial comparisons between two treatments (such as A versus B), incorporates the indirect comparisons from two trials that have one treatment in common (such as A versus C using trials comparing A versus B and B versus C), thereby comparing agents not directly addressed within the individual trials. The role of NMAs in clinical research is well established, as they provide an analytical overview of the available evidence on the largest possible scale [14, 15]. Accordingly, we aimed to perform the first comprehensive NMA of RCTs investigating the clinical impact of different surgical revascularization strategies (MECC, OPCAB and CECC) in patients with CAD undergoing CABG surgery.

METHODS

Data sources and search strategy

Established methods were used in compliance with the PRISMA statement for reporting systematic reviews and meta-analyses in health care interventions [16] (Supplementary Material). Relevant RCTs to be included were searched until May 2015 through MEDLINE, Cochrane, EMBASE and Google Scholar databases and through www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org and www.cardiosource.com websites. Previous meta-analyses as well as abstracts and presentations from major annual meetings of cardiovascular and cardiothoracic surgery societies were screened as well. The following keywords were used: randomized trial, off-pump, on-pump, with/without cardiopulmonary by-pass, OPCAB, CABG, extracorporeal circulation, conventional, beating heart, miniaturized, minimized, closed circuit, minimal, priming, MECC, ECCO, Medtronic resting heart system, CorX, Capiox, Mini Heart Lung Machine, ROCsafe, Jostra Maquet. 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 title/abstract level and retrieved as full reports. The inclusion criteria were (i) human studies; (ii) randomized design; (iii) studies comparing the abovementioned surgical coronary revascularization strategies. The exclusion criteria were: (i) prospective cohort- and quasi-randomized studies; (ii) studies with particular medical or invasive treatment in one arm (e.g. PCI + OPCAB versus CABG); (iii) robot-assisted CABG; (iv) paediatric cardiac surgery. Two independent reviewers (Mariusz Kowalewski and Wojciech Pawliszak) selected the studies for the inclusion, extracted studies and patient characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with a third reviewer (Lech Anisimowicz).

Three authors (Mariusz Kowalewski, Wojciech Pawliszak, Pietro Giorgio Malvindi) assessed the trials' eligibility and risk of bias and extracted the data. Disagreements were resolved by consensus. The bias risk was assessed using the components recommended by the Cochrane Collaboration, such as 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 [17]. Trials with high or unclear risk for bias for any one of the first three components were considered at high risk of bias. Otherwise, they were considered at low risk of bias.

Outcome measure

The end-points assessed were all-cause mortality, myocardial infarction (MI), cerebral stroke, postoperative atrial fibrillation (POAF) and renal dysfunction within 30 days after the surgical procedure. Data were extracted in duplicate by two investigators (Mariusz Kowalewski and Wojciech Pawliszak) and verified by a third investigator (Lech Anisimowicz). Disagreements were resolved by consensus. Clinical end-points are reported as originally defined by the authors.

Statistical analysis

NMA methods on all available networks of treatment comparisons were used to compare the different revascularization strategies. Clinical outcome analyses were compared by odds ratios (ORs) and 95% credible intervals (CrIs) using a Bayesian hierarchical random-effect model taking into account multiarm trials. A random-effect rather than a fixed-effect model was adopted, as this is likely the most appropriate and conservative analysis,

accounting for differences among trials. Model fit was assessed by comparing the posterior mean of the residual deviance with the number of data points [18, 19]. Analysis was based on non-informative prior distributions for effect sizes (Normal(0,100^2)) and between-studies standard deviation (Uniform(0,2)), which yield results that are comparable with those obtained from conventional statistical analysis. Convergence was achieved at 20 000 iterations for all outcomes and lack of autocorrelation was checked and confirmed. A further 40 000 iterations were taken on two chains. In the Bayesian framework, the results for which the 95% CrI of the OR did not include the unit value were regarded as significant. Additionally, to provide a hierarchy of the efficacy and safety of the drugs, we also used the surface under the cumulative ranking (SUCRA) probabilities, which express as a percentage the efficacy or safety of each intervention relative to an imaginary intervention that is always the best without uncertainty. A SUCRA of 90% means that the treatment of interest achieves 90% of the effectiveness or safety of this imaginary intervention. Thus, the larger the SUCRA value, the higher the rank of the treatment, indicating a more effective or safer intervention. Finally, an additional sensitivity analysis was conducted by repeating the main computations after exclusion of trials with high risk of bias and studies available as congress reports. All analyses were performed with WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

RESULTS

Study selection and characteristics

Process of study selection is shown in the analysis flow diagram (Fig. 1). Baseline characteristics of included studies, patient demographics, number of performed grafts and exclusion criteria are listed in Table 1 and Supplementary Table 1. Characteristics of MECC systems (where applicable) used across the trials were extracted from each study and are presented in Table 2. A total of

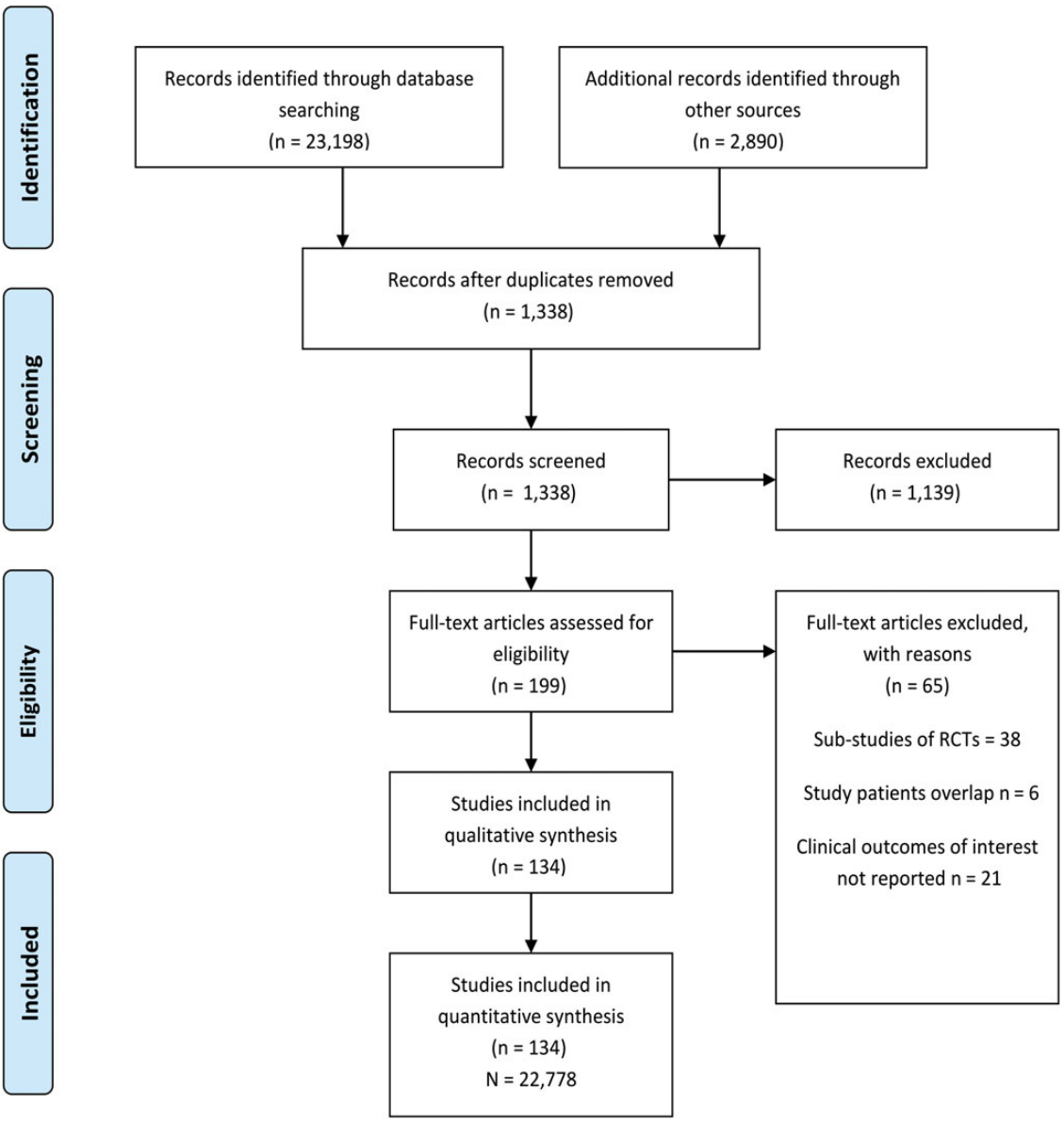

Figure 1: Flow diagram of the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. RCT: randomized controlled trial.

Table 1: Baseline characteristics of included studies

Study [reference]	Primary end-point	Design	*N* of patients	Extent of CAD	IMA use >90%	Mean no. (*n*) of distal anastomoses	Risk of bias[b]
Abdel-Rahman *et al.* [S1]	Inflammatory response lung function and perioperative bleeding	MECC versus CECC	204	NR	NR	3.20 vs 3.10	Unclear
Al-Ruzzeh *et al.* [S2]	Graft patency at 3 months, neurocognitive function at 6 weeks and 6 months and HRQoL	OPCAB versus CECC	168	>50% MV-CAD	No	2.73 vs 2.76	Low
Alwan *et al.* [S3]	Myocardial injury	OPCAB versus CECC	70	>50% MV-CAD	Yes	2.30 vs 2.50	Unclear
Anastasiadis *et al.* [S4]	Haematological parameters	MECC versus CECC	99	>50% MV-CAD	Yes	2.92 vs 2.98	Low
Ascione *et al.* [S5]	Retinal microvascular damage	OPCAB versus CECC	20	>50% MV-CAD	NR	2.40 vs 2.50	Unclear
Ascione *et al.* [S6]	Small intestine function	OPCAB versus CECC	40	>50% MV-CAD	NR	2.50 vs 3.00	Low
Asteriou *et al.* [S7]	MACCE (death, myocardial infarction, stroke or renal failure)	MECC versus CECC	200	>50% MV-CAD	Yes	3.00 vs 3.00	Low
Baker *et al.* [S8]	Neuropsychological outcomes and myocardial injury	OPCAB versus CECC	26	>50% MV-CAD	Yes	2.20 vs 2.50	Unclear
Beghi *et al.* [S9]	Preoperative, intraoperative and postoperative clinical and biological variables	MECC versus CECC	60	>50% MV-CAD	NR	2.75 vs 2.70	Unclear
Moller *et al.* [BBS] [S10]	MACCE (all-cause mortality, acute MI, cardiac arrest with successful resuscitation, LCOS/cardiogenic shock, stroke and coronary reintervention)	OPCAB versus CECC	341	>50% MV-CAD	Yes	3.22 vs 3.34	Low
Angelini *et al.* [BHACAS 1] [S11,S12]	Short-term morbidity and use of health care resources	OPCAB versus CECC	200	NR	Yes	2.23 vs 2.31	Low
Angelini *et al.* [BHACAS 2] [S11]	Short-term morbidity and use of health care resources	OPCAB versus CECC	201	NR	Yes	NA	Low
Bicer *et al.* [S13]	Apoptosis, inflammation and oxidative stress	OPCAB versus CECC	50	NR	Yes	2.53 ± 2.57	Unclear
Blacher *et al.* [S14]	Lymphocyte activation	OPCAB versus CECC	28	NR	Yes	2.60 vs 2.70	Unclear
Bonacchi *et al.* [S15]	Cerebral injury	OPCAB versus CECC	42	>50% MV-CAD	Yes	2.80 vs 3.10	Unclear
Camboni *et al.* [S16]	30-day mortality, postoperative neuropsychological dysfunction, renal dysfunction and hospitalization	MECC versus CECC	93	NR	Yes	NR	Unclear
Caputo *et al.* [S17]	Inflammatory response and organ function	OPCAB versus CECC	40	NR	Yes	2.80 vs 2.90	Low
Carrier *et al.* [S18]	Hospital mortality and morbidity	OPCAB versus CECC	65	>50% MV-CAD	Yes	3.00 vs 3.40	Unclear
Cavalca *et al.* [S19]	Isoprostanes and oxidative stress	OPCAB versus CECC	50	NR	100	2.50 vs 3.10	Unclear
Chowdhury *et al.* [S20]	Inflammatory response and myocardial injury	OPCAB versus CECC	50	>50% MV-CAD	No	3.10 vs 3.20	Unclear
Lamy *et al.* [CORONARY] [S21]	Death, non-fatal stroke, non-fatal MI or new renal failure requiring dialysis at 30 days after randomization	OPCAB versus CECC	4752	>50% MV-CAD	Yes	3.00 vs 3.20	Low
Covino *et al.* [S22]	Length of operation, haematological and biochemical parameters, haemogas analysis, volume of blood loss, length of stay in ICU	OPCAB versus CECC	37	>50% MV-CAD	NR	1.50 vs 1.80	Unclear
Rogers *et al.* [CRISP] [S23,S24]	All-cause death, new onset renal failure, MI, prolonged initial ventilation or sternal wound dehiscence	OPCAB versus CECC	106	>50% MV-CAD	Yes	2.56 vs 2.68	Low
Czerny *et al.* [S25]	Inflammatory response and myocardial injury	OPCAB versus CECC	30	>50% MV-CAD	Yes	2.40 vs 3.40	Unclear
Czerny *et al.* [S26]	Completeness of revascularization	OPCAB versus CECC	80	>50% MV-CAD	Yes	2.60 vs 3.10	Unclear
Diegeler *et al.* [S27]	Periprocedural neurocognitive functioning	OPCAB versus CECC	40	>50% MV-CAD	Yes	1.10 vs 1.10	Unclear
Donndorf *et al.* [S28]	Microvascular perfusion; functional capillary density, blood flow velocity and vessel diameter	MECC versus CECC	40	NR	Yes	NR	Unclear
Dorman *et al.* [S29]	Endothelin plasma content	OPCAB versus CECC	52	NR	NR	3.00 vs 4.00	Unclear
Houlind *et al.* [DOORS] [S30]	Death, stroke or MI at 30 days	OPCAB versus CECC	900	>50% MV-CAD	Yes	2.90 vs 3.10	Low
El-Essawi *et al.* [S31]	Reduction in transfusion requirements	MECC versus CECC	500	NR	NR	NR	Unclear
Farneti *et al.* [S32]	Blood coagulation and monocyte–platelet interaction	MECC versus CECC	20	>50% MV-CAD	NR	2.82 vs 3.00	High
Fattouch *et al.* [S33]	In-hospital death, LCOS, prolonged mechanical and pharmacological cardiac support, prolonged mechanical ventilation support and postoperative length of stay in intensive care unit and hospital	OPCAB versus CECC	128	STEMI 100% >50% MV-CAD	Yes	2.60 vs 2.80	Low
Formica *et al.* [S34]	Systemic and myocardial inflammatory response	MECC versus OPCAB	60	>50% MV-CAD	Yes	2.70 vs 2.53	Low
Formica *et al.* [S35]	Inflammatory response	MECC versus OPCAB versus CECC	61	>50% MV-CAD	Yes	2.80 vs 2.70 vs 2.70	Unclear
Fromes *et al.* [S36]	Inflammatory response	MECC versus CECC	60	>50% MV-CAD	NR	2.80 vs 2.80	High
Gasz *et al.* [S37]	Inflammatory response	OPCAB versus CECC	20	NR	NR	3.40 vs 3.90	Unclear
Gasz *et al.* [S38]	Inflammatory response	OPCAB versus CECC	30	NR	Yes	3.00 vs 3.21	Unclear

Gerola *et al.* [S39a]	Periprocedural all-cause mortality, MI, pulmonary complications, bleeding, wound complications, neurocognitive dysfunction	OPCAB versus CECC	160	NR	Yes	1.77 vs 1.81	Low
Gu *et al.* [S40]	Inflammatory response	OPCAB versus CECC	62	>50% SV-CAD	Yes	1.00 vs 1.00	Unclear
Guler *et al.* [S41]	Postoperative lung functions	OPCAB versus CECC	58	>50% SV-CAD	Yes	1.00 vs 1.00	High
Gonenc *et al.* [S42]	Periprocedural oxidative stress	OPCAB versus CECC	42	NR	NR	NA	High
Diegeler *et al.* [GOPCABE] [S43]	Composite of death, stroke, MI, repeat revascularization or new renal replacement therapy at 30 days and at 12 months after surgery	OPCAB versus CECC	2539	>50% MV-CAD	NR	2.70 vs 2.80	Low
Gulielmos *et al.* [S44]	Periprocedural inflammatory marker and cTn release	OPCAB versus CECC	40	>50% SV-CAD	Yes	1.00 vs 1.00	Unclear
Gunaydin *et al.* [S45]	Gaseous microemboli count and periprocedural inflammatory response	MECC versus CECC	40	NR	Yes	3.25 vs 3.40	Unclear
Hernandez Jr *et al.* [S46]	Neurocognitive functioning at discharge	OPCAB versus CECC	201	>50% MV-CAD	Yes	3.20 vs 3.30	Low
Hoel *et al.* [S47]	Complement activation	OPCAB versus CECC	44	NR	Yes	NA	Unclear
Huybregts *et al.* [S48]	Inflammatory response, proximal renal tubular and intestinal injury	MECC versus CECC	49	>50% MV-CAD	NR	4.30 vs 3.90	Low
Iqbal *et al.* [S49]	Neurological complications	OPCAB versus CECC	200	NR	NR	2.96 vs 2.99	High
Jares *et al.* [S50,S140]	Identification of fibrinolysis using rotation thromboelastography	OPCAB versus CECC	20	NR	NR	2.00 vs 2.60	Unclear
Kobayashi *et al.* [JOCRI] [S51]	Cardiac death, MI, CHF, TVR at 3 years	OPCAB versus CECC	167	>50% MV-CAD	No	3.50 vs 3.60	Low
Johansson-Synnergren *et al.* [S52]	Inflammatory response and endothelial function	OPCAB versus CECC	52	NR	Yes	1.80 vs 2.20	Unclear
Jongman *et al.* [S53]	Inflammatory response and endothelial response	OPCAB versus CECC	60	NR	NR	3.00 vs 3.00	Unclear
Kamiya *et al.* [S54]	Inflammatory response	MECC versus CECC	20	>50% MV-CAD	NR	2.70 vs 2.70	Unclear
Khan *et al.* [S55]	Graft patency at 3 months	OPCAB versus CECC	104	>50% MV-CAD	Yes	3.10 vs 3.40	Low
Kiaii *et al.* [S56]	Inflammatory response	MECC versus CECC	60	>50% MV-CAD	Yes	2.90vs 3.33	Unclear
Kochamba *et al.* [S57]	Preoperative and postoperative pulmonary gas exchange	OPCAB versus CECC	58	NR	Yes	1.50 vs 1.60	Unclear
Kok *et al.* [S58]	Cerebral tissue oxygenation and postoperative cognitive dysfunction	OPCAB versus CECC	60	NR	NR	3.20 vs 3.30	Unclear
Kofidis *et al.* [S59]	Inflammatory response	MECC versus CECC	80	>50% MV-CAD	Yes	2.10 vs 1.90	High
Krejca *et al.* [S60]	Inflammatory response	OPCAB versus CECC	26	NR	NR	1.80 vs 1.80	Unclear
Kunes *et al.* [S61]	Pentraxin 3 release kinetics	OPCAB versus CECC	34	NR	NR	2.00 vs 2.00	Unclear
Lee *et al.* [S62]	In-hospital all-cause death, stroke and length of stay, intra-aortic balloon support postoperatively	OPCAB versus CECC	60	NR	NR	3.10 vs 3.60	Unclear
Legare *et al.* [S63]	Periprocedural death, MI, stroke, AF, deep sternal wound infection	OPCAB versus CECC	300	>50% MV-CAD	Yes	2.80 vs 3.00	Low
Liebold *et al.* [S64]	Cerebral tissue oxygenation and microembolization	MECC versus CECC	40	>50% MV-CAD	Yes	3.70 vs 3.80	Low
Lingaas *et al.* [S65,S66]	Graft patency at 12 months	OPCAB versus CECC	120	>50% MV-CAD	Yes	2.60 vs 2.80	Unclear
Lloyd *et al.* [S67]	Serum S-100 protein and neuropsychological outcomes	OPCAB versus CECC	125	>50% MV-CAD	NR	2.20 vs 2.40	Unclear
Lund *et al.* [S68,S69]	Intraoperative cerebral embolization	OPCAB versus CECC	52	NR	Yes	2.30 vs 2.50	Unclear
Malik *et al.* [S70]	Myocardial injury	OPCAB versus CECC	50	>50% MV-CAD	No	3.10 vs 3.10	Unclear
Mandak *et al.* [S71]	Peripheral tissue metabolism and microvascular blood flow	OPCAB versus CECC	40	NR	Yes	2.40 vs 2.90	Unclear
Matata *et al.* [S72]	Inflammatory response and oxidative stress	OPCAB versus CECC	20	NR	NR	1.80 vs 1.90	Low
Hueb *et al.* [MASS III] [S73]	Freedom from overall mortality, stroke, MI and additional revascularization	OPCAB versus CECC	311	>50% MV-CAD	Yes	2.60 vs 3.18	Low
Mazzei *et al.* [S74]	Inflammatory response and organ injury	MECC versus OPCAB	300	>50% MV-CAD	Yes	3.25 vs 3.08	Low
Medved *et al.* [S75]	In-hospital mortality and morbidity	OPCAB versus CECC	60	NR	Yes	2.30 vs 2.50	Unclear
Michaux *et al.* [S76,S77]	RV global and overall systolic function	OPCAB versus CECC	50	>50% MV-CAD	Yes	2.90 vs 3.20	Low
Modine *et al.* [S78]	Renal tubular and glomerular function	OPCAB versus CECC	71	NR	Yes	2.40 vs 2.80	Unclear
Motallebzadeh *et al.* [S79]	Cerebral injury	OPCAB versus CECC	35	>50% MV-CAD	NR	2.20 vs 3.20	Low
Motallebzadeh *et al.* [S80]	Periprocedural neurocognitive function	OPCAB versus CECC	212	>50% MV-CAD	NR	NR	Low
Muneretto *et al.* [S81]	Number of anastomoses; mean mechanical ventilation time; ICU and postoperative stay	OPCAB versus CECC	176	>50% MV-CAD	NR	2.70 vs 2.80	Unclear
Murakami *et al.* [S82]	Inflammatory response	MECC versus OPCAB	15	>50% MV-CAD	Yes	2.86 vs 2.88	Unclear
Nesher *et al.* [S83]	Inflammatory response and myocardial injury	OPCAB versus CECC	125	NR	NR	2.30 vs 2.90	Low
Ng *et al.* [S84]	Inflammatory response	MECC versus CECC	78	NR	NR	2.00 vs 2.40	Unclear
Nguyen *et al.* [S85,S86]	Inflammatory response and myocardial injury	MECC versus CECC	26	>50% MV-CAD	Yes	3.23 vs 3.23	Low
Niranjan *et al.* [S87]	Autologus blood transfusion and postoperative complications	OPCAB versus CECC	80	>50% MV-CAD	Yes	3.93 vs 3.75	Low
Nollert *et al.* [S88]	Inflammatory response	MECC versus CECC	30	>50% MV-CAD	NR	2.90 vs 2.90	Low
Nathoe *et al.* [Octopus] [S89]	Freedom from all-cause death, stroke, MI and repeat revascularization	OPCAB versus CECC	281	>50% MV-CAD	NR	2.40 vs 2.60	Low

Continued

Table 1: Continued

Study [reference]	Primary end-point	Design	*N* of patients	Extent of CAD	IMA use >90%	Mean no. (*n*) of distal anastomoses	Risk of bias[b]
Ohata *et al.* [S90]	Inflammatory response, haemodilution during CPB, blood loss during and after surgery	MECC versus CECC	98	>50% MV-CAD	NR	3.60 vs 3.10	Unclear
Lemma *et al.* [On-Off] [S91]	Operative mortality, MI, stroke, renal failure, reoperation for bleeding and ARDS within 30	OPCAB versus CECC	411	NR	Yes	3.00 vs 3.30	Low
Onorati *et al.* [S92]	Perioperative changes in MCP-1 and VEGF levels	OPCAB versus CECC	60	NR	NR	3.40 vs 3.40	Unclear
Ovcina *et al.* [S93]	Perioperative clinical parameters	MECC versus CECC	288	>50% MV-CAD	NR	NR	High
Ozkara *et al.* [S94]	Target vessel revascularization at 1 year; periprocedural PAI-1 release	OPCAB versus CECC	64	NR	Yes	2.48 vs 2.31	Unclear
Paparella *et al.* [S95]	Activation of the coagulation and fibrinolytic systems	OPCAB versus CECC	32	NR	NR	2.70 vs 3.25	Unclear
Parolari *et al.* [S96]	Periprocedural oxygen metabolism	OPCAB versus CECC	25	NR	NR	2.30 vs 2.90	Unclear
Parolari *et al.* [S97]	Periprocedural plasma P-selectin and TF levels	OPCAB versus CECC	29	>50% MV-CAD	NR	2.80 vs 2.90	Unclear
Penttilä *et al.* [S98]	Periprocedural changes in myocardial metabolism	OPCAB versus CECC	22	>50% MV-CAD	NR	2.80 vs 3.30	Unclear
Straka *et al.* [PRAGUE-4] [S99]	Death, MI, stroke, renal failure requiring haemodialysis at 30 days	OPCAB versus CECC	400	>50% MV-CAD	Yes	2.30 vs 2.70	Low
Hlavicka *et al* [PRAGUE-6] [S100]	Death, MI, stroke, renal failure requiring haemodialysis at 30 days	OPCAB versus CECC	206	NR	NR	2.04 vs 2.66	Low
Bednar *et al.* [PRAGUE 11] [S101]	Platelet activity and aspirin efficacy	OPCAB versus CECC	80	NR	NR	1.90 vs 2.40	Unclear
Sousa Uva *et al.* [PROMISS] [S102]	Graft patency at 5 weeks	OPCAB versus CECC	150	NR	Yes	3.50 vs 3.50	Low
Rachwalik *et al.* [S103]	Periprocedural respiratory function	OPCAB versus CECC	42	NR	Yes	NA	Unclear
Rainio *et al.* [S104]	Periprocedural retinal microembolism	OPCAB versus CECC	20	NR	Yes	4.10 vs 4.40	Low
Raja *et al.* [S105]	Postoperative gastrointestinal complications	OPCAB versus CECC	300	NR	Yes	2.00 vs 2.00	Unclear
Rasmussen *et al.* [S106]	Inflammatory response	OPCAB versus CECC	35	NR	Yes	3.10 vs 3.10	Unclear
Rastan *et al.* [S107]	Inflammatory response and myocardial injury	OPCAB versus CECC	40	NR	Yes	3.00 vs 2.90	Unclear
Remadi *et al.* [S108]	The operative mortality rate (<30 days)	MECC versus CECC	400	>50% MV-CAD	NR	2.80 vs 2.70	Low
Rimpiläinen *et al.* [S109]	Retinal microembolization; inflammatory, coagulation and endothelial markers	MECC versus CECC	40	>50% MV-CAD	NR	4.40 vs 4.30	Low
Schroyer *et al.* [ROOBY] [S110]	All-cause death, reoperation, new mechanical support, coma, stroke, cardiac arrest, reanal failure requiring dialysis at 30 days	OPCAB versus CECC	2203	>50% MV-CAD	NR	2.90 vs 3.00	Low
Sahlman *et al.* [S111]	Inflammatory response and myocardial injury	OPCAB versus CECC	50	NR	Yes	3.20 vs 3.00	Unclear
Sajja *et al.* [S112]	Periprocedural renal function	OPCAB versus CECC	116	NR	NR	3.11 vs 3.85	Unclear
Sakwa *et al.* [S113]	Laboratory perimeters: haemoglobin and platelet count	MECC versus CECC	199	>50% MV-CAD	Yes	3.52 vs 3.38	Low
Sch□ttler *et al.* [S114]	Intrathoracic blood volume- and extravascular lung water indices	MECC versus CECC	60	>50% MV-CAD	NR	3.30 vs 3.30	Unclear
Selvanayagam *et al.* [S115]	Periprocedural LVEF	OPCAB versus CECC	60	NR	Yes	2.80 vs 2.90	Low
Skrabal *et al.* [S116]	Circulating endothelial cells count	MECC versus CECC	20	>50% MV-CAD	NR	3.50 vs 3.80	Low
Skrabal *et al.* [S117]	Myocardial injury	MECC versus CECC	60	NR	NR	3.60 vs 3.80	Unclear
Puskas *et al.* [SMART] [S118]	Completeness of revascularization and graft patency at 30 days	OPCAB versus CECC	200	NR	No	3.39 vs 3.40	Low
Svitek *et al.* [S119]	Inflammatory response	MECC versus CECC	54	>50% MV-CAD	NR	2.30 vs 2.60	Low
Syed *et al.* [S120]	Pulmonary gas exchange	OPCAB versus CECC	75	NR	Yes	NR	Unclear
Tang *et al.* [S121]	Kidney glomerular and tubular injury	OPCAB versus CECC	40	NR	Yes	2.10 vs 2.50	Unclear
Tatoulis *et al.* [S122]	Systemic vascular resistance at 12 h	OPCAB versus CECC	100	LM 8%	NR	2.30 vs 2.90	Low
Tully *et al.* [S123]	Neuropsychological and QoL Outcomes at 6 months	OPCAB versus CECC	66	NR	Yes	2.23 vs 2.47	Unclear
Van Boven *et al.* [S124]	Myocardial injury	MECC versus OPCAB versus CECC	30	>50% MV-CAD	Yes	3.90 vs 3.90 vs 4.50	Unclear
Van Boven *et al.* [S125]	Protein S100β concentrations	MECC versus OPCAB versus CECC	30	>50% MV-CAD	Yes	3.70 vs 3.60 vs 4.30	Unclear
Van Boven *et al.* [S126]	Inflammatory response	MECC versus OPCAB versus CECC	60	>50% MV-CAD	Yes	3.80 vs 3.80 vs 4.70	Unclear
Vedin *et al.* [S127]	Neurocognitive function at 6 months	OPCAB versus CECC	70	>50% MV-CAD	Yes	3.00 vs 3.00	Unclear
Velissaris *et al.* [S128]	Gut mucosal oxygenation	OPCAB versus CECC	54	NR	Yes	2.50 vs 2.60	Unclear
Velissaris *et al.* [S129]	Stress response	OPCAB versus CECC	52	NR	NR	2.40 vs 2.80	Unclear
Vural *et al.* [S130]	Periprocedural haemodynamic assessment	OPCAB versus CECC	50	>50% SV-CAD	NR	1.12 vs 1.12	Unclear
Wan *et al.* [S131]	Inflammatory response	OPCAB versus CECC	37	>50% MV-CAD	100	2.44 vs 2.79	Unclear
Wandschneider *et al.* [S132]	Inflammatory response	OPCAB versus CECC	119	NR	No	2.34 vs 3.10	Unclear

Wehlin *et al.* [S133]	Inflammatory response	OPCAB versus CECC	38	>50% MV-CAD	Yes	3.00 vs 2.50	Unclear
Wehlin *et al.* [S134]	Peripheral blood monocyte activation	OPCAB versus CECC	20	>50% MV-CAD	NR	2.00 vs 2.00	Unclear
Wippermann *et al.* [S135]	Parameters of coagulation and inflammatory marker release	MECC versus CECC	20	>50% MV-CAD	Yes	3.50 vs 3.70	Unclear
Wittwer *et al.* [S136]	Circulating endothelial cells release and parameters of endothelial function	MECC versus OPCAB	76	>50% MV-CAD	Yes	3.06 vs 1.89	High
Wittwer *et al.* [S137]	In-hospital mortality	MECC versus OPCAB	120	>50% MV-CAD	Yes	3.11 vs 1.78	Unclear
Yu *et al.* [S138]	Early clinical outcomes	OPCAB versus CECC	102	LM 29.5%	Yes	3.02 vs 3.14	Low
Zamvar *et al.* [S139]	Neurocognitive function at 10 weeks	OPCAB versus CECC	60	>50% MV-CAD	Yes	2.93 vs 2.93	Low

ITT: intention-to-treat; 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; LM: left main; BBS: The 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; CORONARY: CABG Off- or On-Pump Revascularization Study; ICU: intensive care unit; DOORS: Danish On-Pump Versus Off-Pump Randomization Study; STEMI: ST-segment elevation myocardial infarction; GOPCABE: 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; RV: right ventricle; Octopus: A 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; TF: tissue factor; PROMISS: The Prospective Randomized Comparison of Off-Pump and On-Pump Multi-vessel Coronary Artery BypasS Surgery; ROOBY: Veterans Affairs Randomized On/Off Bypass Study; LVEF: left ventricle ejection fraction; SMART: Surgical Management of Arterial Revascularization Therapies; NR: not reported.

[a]Reported as in included studies.

[b]Risk of bias according to Cochrane Criteria; study was considered at high risk of bias if ≥2 of the components were at high risk.

134 RCTs [s1–s140] comprising 22 778 patients met the inclusion criteria and entered the final analysis. Figure 2 shows the evidence network of direct comparisons. When compared directly in a random-effect model, significantly fewer distal anastomoses were performed in the OPCAB when compared with CECC [weighted mean difference: (95% CI): −0.19 (−0.25 to −0.14); $P < 0.01$; $I^2 = 43\%$]. No significant differences in the number of distal anastomoses were observed for MECC when compared with CECC [−0.06 (−0.14 to 0.02); $P = 0.16$; $I^2 = 35\%$] and for MECC when compared with OPCAB [0.26 (−0.14 to 0.66); $P = 0.20$; $I^2 = 90\%$].

All-cause mortality

After exclusion of trials reporting zero events and studies not reporting the incidence of death, a total of 50 RCTs (17 638 patients) contributed to the analysis. When compared with CECC, both OPCAB and MECC significantly reduced all-cause mortality by 25 and 54%, respectively [OR (95% CrI): 0.75 (0.51–0.99) and 0.46 (0.22–0.91)]; Fig. 3A. No significant differences were demonstrated between OPCAB and MECC [OR (95% CrI): 0.62 (0.29–1.30)]. CECC was associated with highest posterior median rates of ≤30-day all-cause mortality [2.59 (2.10–3.16)] whereas MECC displayed lowest rates [1.20 (0.55–2.48); Table 3]. The hierarchy of treatments was confirmed in the probability analysis (highest to lowest SUCRA values): MECC followed by OPCAB and CECC; Fig. 4.

Myocardial infarction

Forty-six studies enrolling 16 428 patients remained after exclusion of studies not reporting the incidence of MI; there was no significant improvement in the incidence of MI with any of the investigated strategies when compared with each other (Fig. 3B), with comparable posterior median ≤30-day rates (Table 3). The treatment hierarchy for MI in the probability analysis (highest to lowest SUCRA value) was MECC, OPCAB and CECC (Fig. 4).

Cerebral stroke

Data on the occurrence of cerebral stroke were available in 49 RCTs (17 563 patients). OPCAB, when compared with CECC was associated with a significant 43% reduction in the odds of cerebral stroke [OR (95% CrI): 0.57 (0.34–0.80)]. Similar 60% significant reduction of the odds of cerebral stroke was observed with MECC when compared with CECC [OR (95% CrI): 0.40 (0.19–0.78)]; Fig. 3C. No apparent differences were seen between MECC and OPCAB. CECC was associated with the highest, and MECC with the lowest posterior median ≤30-day rates of stroke [0.65 (0.30–1.33) and 1.24 (1.16–2.05), respectively]; Table 3. The hierarchy of treatments was confirmed in the probability analysis (highest to lowest SUCRA values): MECC >OPCAB >CECC.

Postoperative atrial fibrillation

After exclusion of studies with zero events in both arms, 46 RCTs with 10 980 patients contributed to the analysis of POAF. When compared with CECC, both OPCAB and MECC, to similar extent, significantly reduced the odds of POAF [OR (95% CrI): 0.66 (0.48–0.90) and OR (95% CrI): 0.62 (0.35–0.98), respectively]; Fig. 3D.

Table 2: Characteristics of miniaturized extracorporeal circulation systems used in included studies

Study	MECC system manufacturer and location	Minimal priming volume (ml)	MECC circuits	Minimal ACT (s)	Total heparin dose	MECC duration	X-clamp duration	Cell saver
Abdel-Rahman *et al.* [S1]	CorX system CardioVention, Inc., Santa Clara, CA, USA	500	Heparin-coated	400	350 IU/kg + 5000 IU	78 ± 22	44 ± 14	Yes
Anastasiadis *et al.* [S4]	Maquet Cardiopulmonary Hirlingen, Germany	500	Heparin-coated	300	150 IU/kg	103 ± 24.8	65.3 ± 17.0	Yes
Asteriou *et al.* [S8]	Maquet Cardiopulmonary Hirlingen, Germany	500	Heparin-coated	300	150 IU/kg	113 ± 37.9	69.7 ± 20.2	Yes
Beghi *et al.* [S10]	Jostra AG, Hirlingen, Germany	450	Heparin-coated	NR	1.5 mg/kg	99 ± 28	59 ± 20	Yes
Camboni *et al.* [S17]	Maquet Cardiopulmonary, Hirlingen, Germany	500	Heparin-coated	NR	NR	96 ± 24	61 ± 20	Yes
	PRECiSe Medos Medizintechnik AG, Stolberg, Germany	500	Heparin-coated			85 ± 26	47 ± 16	
	Resting Heart Medtronic GmbH, Düsseldorf, Germany	1400	Heparin-coated			79 ± 20	46 ± 14	
Donndorf *et al.* [S29]	Maquet Cardiopulmonary, Rastatt, Germany	800	Heparin-coated	250	200 IU/kg	96 ± 27	54 ± 16	Yes
El-Essawi *et al.* [S31]	ROCsafeRX MPC Terumo Cardiovascular Systems, Ann Arbor, MI, USA	600	Polymethoxyethylacrylate-coated	480	NR	74.9 ± 26.7	48.2 ± 20.5	Yes
Farneti *et al.* [S32]	Synergy, Cobe Cardiovascular. Arvada, CO, USA	680	Phosphorylcholine-coated	NR	300 IU/kg	NR	60.0 ± 11.2	Yes
Formica *et al.* [S34]	Maquet-Jostra AG, Hirlingen, Germany	650	Heparin-coated	350–400	3 mg/kg	87.1 ± 19	67.15 ± 15.21	Yes
Formica *et al.* [S35]	Maquet-Jostra AG, Hirlingen, Germany	650	Heparin-coated	350–400	NR	92.5 ± 27.8	71.4 ± 20.8	Yes
Fromes *et al.* [S36]	Jostra, France	NR	Heparin-coated	NR	300 IU/kg	91 ± 20	63 ± 17	Yes
Gunaydin *et al.* [S45]	ROCsafe MPC, Terumo, Ann Arbor, MI, USA	1050	Polymethoxyethylacrylate-coated	480	300 IU/kg	98.7 ± 4.2	76.8 ± 3	Yes
Huybregts *et al.* [S48]	Synergy, Cobe Cardiovascular. Arvada, CO, USA	800	Phosphorylcholine-coated	480	400 IU/kg	95 ± 4	71 ± 3	Yes
Kamiya *et al.* [S54]	Resting Heart System; Medtronic, Inc., Minneapolis, MN, USA	990	Heparin-coated	NR	150 IU/kg	68 ± 25	32 ± 11	Yes
Kiaii *et al.* [S56]	Resting Heart System; Medtronic, Inc., Minneapolis, MN, USA	750	Heparin-coated	450	400 IU/kg	101 ± 24.1	56.2 ± 18	Yes
Kofidis *et al.* [S59]	Jostra Medizintechnik AG, Hirlingen, Germany	500	Heparin-coated	NR	NR	74 ± 17	42 ± 12	Yes
Liebold *et al.* [S64]	Maquet Cardiopulmonary Hirlingen, Germany	500	Heparin-coated	250	150 IU/kg	83 ± 16	52 ± 12	Yes
Mazzei *et al.* [S74]	Jostra MECC system, Jostra, Inc., Hirlingen, Germany	500	Heparin-coated	250–300	150 IU/kg	86.5 ± 21	NR	Yes
Murakami *et al.* [S82]	Jostra MECC system, Jostra Inc., Hirlingen, Germany	500	Heparin-coated	>250	5000 IU	78.4 ± 23.9	NR	Yes
Ng *et al.* [S84]	Synergy Sorin®, Sorin Group, Italy	800–900	Phosphorylcholine-coated	NR	NR	103.4 ± 31.9	57.7 ± 25.3	Yes
Nguyen *et al.* [S85,S86]	ECCO system, Dideco, Sorin, Italy	300	NR	>400	3 mg/kg	72.5 ± 4.5	29.5 ± 2.3	Yes
Nollert *et al.* [S88]	Carmeda Medtronic, Minneapolis, MN, USA	800	Heparin-coated	250	150 IU/kg	96.9 ± 6.7	71.3 ± 5.8	Yes
Ohata *et al.* [S90]	Capiox RX25, Terumo, Tokyo, Japan	750	Polymethoxyethylacrylate-coated	NR	300 IU/kg	146 ± 35	93 ± 28	Yes
Ovcina *et al.* [S93]	NR	NR	NR	NR	NR	111 ± 28.1	65 ± 19.2	NR
Remadi *et al.* [S108]	Bioline-Jostra, Gretz, France	450	Non-coated	400	3 mg/kg	63.4 ± 19.5	31.4 ± 11.7	Yes
Rimpiläinen *et al.* [S109]	ROCSafe; Terumo Europe NV, Leuven, Belgium	300	Polymethoxyethylacrylate-coated	400	3 mg/kg	117 ± 20	89 ± 19	Yes
Sakwa *et al.* [S113]	Medtronic Resting Heart, Medtronic, Inc., Minneapolis, MN, USA	300	Heparin-coated	400	350 IU/kg	75 ± 20	NR	Yes
Sch□ttler *et al.* [S114]	Maquet Cardiopulmonary AG (Hirlingen, Germany)	900	Heparin-coated	NR	5000 IU	103.3 ± 26.6	61.1 ± 18.7	Yes
Skrabal *et al.* [S116]	Jostra Maquet Cardiopulmonary AG	NR	Heparin-coated	350–400	300 IU/kg	90.2 ± 35.4	NR	Yes
Skrabal *et al.* [S117]	Jostra Maquet Cardiopulmonary AG	500	Heparin-coated	250	200–350 IU/kg	85.5 ± 3.4	52.3 ± 2.6	Yes
Svitek *et al.* [S119]	The Minisystem Synergy Sorin® (Sorin Group, Mirandola, Italy)	1100	Phosphorylcholine-coated	480	300 IU/kg	66 ± 21	35 ± 13	No
Van Boven *et al.* [S124]	Maquet Gmbh, Rastatt, Germany	500	Heparin-coated	NR	300 IU/kg	85.1 ± 17.6	61.5 ± 13.0	Yes
Van Boven *et al.* [S125]	Maquet Gmbh, Rastatt, Germany	500	Heparin-coated	>300	150 IU/kg	82.8 ± 10.3	54.0 ± 14.1	Yes
Van Boven *et al.* [S126]	Maquet Gmbh, Rastatt, Germany	500	Heparin-coated	>300	150 IU/kg	78 ± 14	58 ± 12	Yes
Wippermann *et al.* [S135]	Jostra AG, Hirlingen, Germany	820	Non-coated	>450	400 IU/kg	87 ± 28	51 ± 22	Yes
Wittwer *et al.* [S136]	ROCSafe™ (Terumo Medical Corp., Somerset, NJ, USA)	NR	NR	NR	NR	NR	NR	NR
Wittwer *et al.* [S137]	ROCSafe™ (Terumo Medical Corp., Somerset, NJ, USA)	500	Heparin-coated	NR	NR	75.9 ± 18.6	41.1 ± 11.6	NR

MECC: miniaturized extracorporeal circulation; ACT: activated clotting time; X-clamp: cross-clamp; NR: not reported.

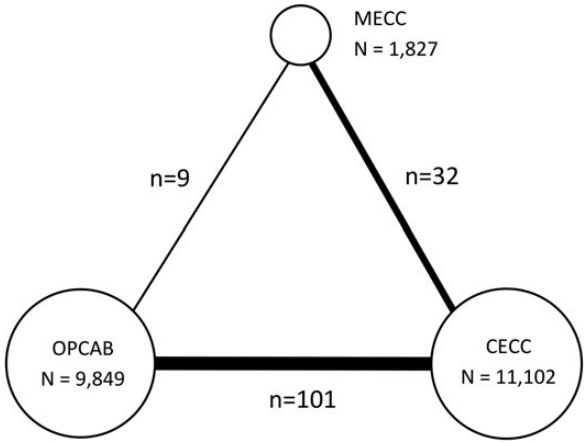

Figure 2: Evidence network of treatment comparisons for surgical coronary revascularization. The size of the nodes corresponds to the number of trials for the given treatment. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. Numbers next to every line joining two treatments correspond to the number of studies that compared the treatments. Total number of comparisons is higher than total number of studies accounting for three-arm trials. MECC: miniaturized extracorporeal circulation; OPCAB: off-pump coronary artery bypass graft; CECC: conventional extracorporeal circulation.

There was no significant difference in the odds of POAF between OPCAB and MECC. POAF posterior median ≤30-day rates were lowest with MECC [12.82 (7.63–20.62)] and highest with CECC [17.66 (16.16–20.71)]; Table 3. In the probability analysis, the hierarchy of treatments was MECC followed by OPCAB and CECC; Fig. 4.

Renal dysfunction

Twenty-nine studies (n = 13 791 patients) were included in the analysis of renal dysfunction after exclusion of studies with zero events or not mentioning this end-point. A significant, over 30% reduction of the odds of renal dysfunction was demonstrated with OPCAB when compared with CECC [OR (95% CrI): 0.69 (0.46–0.92)]. MECC reduced these odds by more than 50% when compared with CECC [OR (95% CrI): 0.47 (0.24–0.89)]; Fig. 3E. No significant effect of either intervention was seen in comparison with OPCAB versus MECC. CECC displayed highest posterior median rates of renal dysfunction [1.75 (1.35–2.21)] whereas MECC was associated with lowest rates [0.83 (0.40–1.64)]; Table 3. The ranking of treatments was later confirmed in the probability analysis (highest to lowest SUCRA values): MECC >OPCAB >CECC; Fig. 4.

Sensitivity analysis

Sensitivity analysis performed after exclusion of studies with high risk of bias and those available as congress proceedings only, and repeating all calculations, did not alter the direction nor the magnitude of the estimates.

DISCUSSION

Despite technological improvements, and innovations in cardiovascular anaesthesia, CABG performed 'on-pump' with the use of extracorporeal circulation is still associated with a substantial risk of postoperative morbidity in patients undergoing surgical coronary revascularization. In the present large-scale meta-analysis (n = 134; n = 22 778), two promising techniques, OPCAB and MECC that were demonstrated to partially abolish CPB-related adverse effects were investigated. The main findings of the current study are: (i) MECC and OPCAB were associated with a significant reduction of the odds of ≤30-day all-cause mortality and cerebral stroke when compared with CECC; (ii) MECC and OPCAB offered significantly higher protection against postoperative AF and renal dysfunction when compared with CECC; (iii) no significant differences between three strategies were seen in regard to MI; (iv) the hierarchy of numerical treatments' emerging from the probability inference analyses was MECC >OPCAB >CECC.

The key finding of the current meta-analysis is a significant ≤30-day mortality reduction with both MECC and OPCAB when compared with CECC. Previous observational studies and meta-analyses reported increased long-term mortality with OPCAB. In a recent pooled analysis of 22 studies, both randomized and observational, OPCAB was associated with a statistically significant 7% increase in long-term all-cause mortality relative to on-pump CABG [HR (95% CI): 1.07 (1.03–1.11); P = 0.003] [20]; on the other hand, no differences however were seen when RCTs were analysed separately [HR (95% CI): 1.14 (0.84–1.56); P = 0.39]. Selection bias seems to be the obvious explanation for the discrepancies between observational and randomized strata. Patients included in the OPCAB group were more likely to be at higher baseline risk, when compared with their CECC counterparts, not only because there were more diabetics and women in that subgroup, but also because they could have been disqualified from CECC by the surgeon due to atherosclerotic aorta, kidney disease or other comorbidities that are known to worsen the clinical course after CECC. Potentially, other factors might have contributed to increased mortality with OPCAB found in other studies, such as learning curve; in a recently available large Korean National Registry [21], patients who underwent elective isolated CABG (off-pump: n = 2333; on-pump: n = 2870) were evaluated; summary analysis (years 1989–2012) revealed almost 30% increase of the HR [1.29 (1.11–1.50)] for all-cause mortality in the OPCAB cohort (P = 0.0012); this benefit of on-pump was however mainly driven during the years 1989–99 (n of patients = 1040) when 97.9% surgeries were performed with CPB. With increasing number of surgeries performed off-pump (82.4% in years 2008–12), in a stratified analysis, the direction of the estimates was no longer conclusive, if not indeed favouring OPCAB [0.88 (0.50–1.53)]. One influential RCT included in the present meta-analysis [8] was 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 [22, 23]. One of the first meta-analyses assessing mid-term mortality after OPCAB demonstrated a statistically significant increase by a factor of 1.37 with off-pump relative to on-pump CABG (risk ratio, 1.373; 95% CI: 1.043–1.808) [24]; however, after exclusion of ROOBY trial [8] from the meta-analysis, no differences were seen between the two strategies any longer. Those results remain in line with two well-conducted largest studies to date [25, s141] that showed somewhat reduced or comparable mortality rates with OPCAB at both short- and mid-term follow-up [s142] but were underpowered for this outcome. This current meta-analysis by integrating data from 134 RCTs is the first to suggest reduced odds of all-cause mortality with OPCAB when compared with CECC. It also puts in a wider perspective, findings of another recently available, well

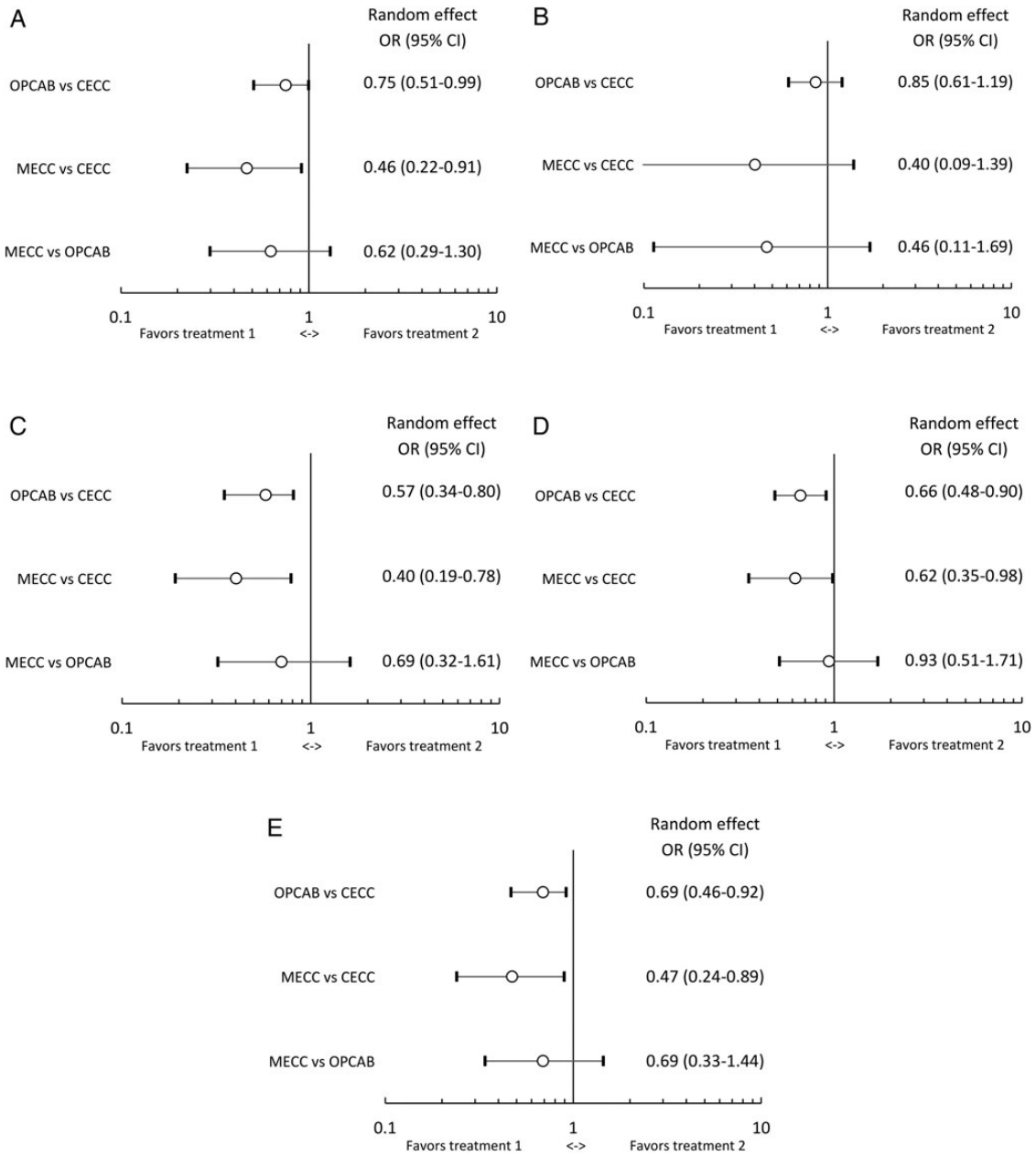

Figure 3: Pooled odds ratios and 95% credible intervals determined by random-effects network meta-analysis for 30-day all-cause mortality (**A**), myocardial infarction (**B**), cerebral stroke (**C**), postoperative atrial fibrillation (**D**) and renal dysfunction (**E**). MECC: miniaturized extracorporeal circulation; OPCAB: off-pump coronary artery bypass graft; CECC: conventional extracorporeal circulation.

Table 3: Event rates for different strategies of surgical coronary revascularization

Outcome	MECC	OPCAB	CECC
All-cause mortality	1.20 (0.55–2.48)	1.94 (1.25–2.75)	2.59 (2.10–3.16)
Myocardial infarction	2.16 (0.54–7.27)	4.56 (3.18–6.42)	5.29 (4.59–6.05)
Cerebral stroke	0.65 (0.30–1.33)	0.92 (0.53–1.42)	1.24 (1.16–2.05)
Postoperative AF	12.82 (7.63–20.62)	13.55 (10.14–17.89)	17.66 (16.16–20.71)
Renal dysfunction	0.83 (0.40–1.64)	1.21 (0.76–1.76)	1.75 (1.35–2.21)

Numbers are reported as rates (% with 95% credible intervals).
AF: atrial fibrillation; MECC: miniaturized extracorporeal circulation; OPCAB: off-pump coronary artery bypass; CECC: conventional extracorporeal circulation.

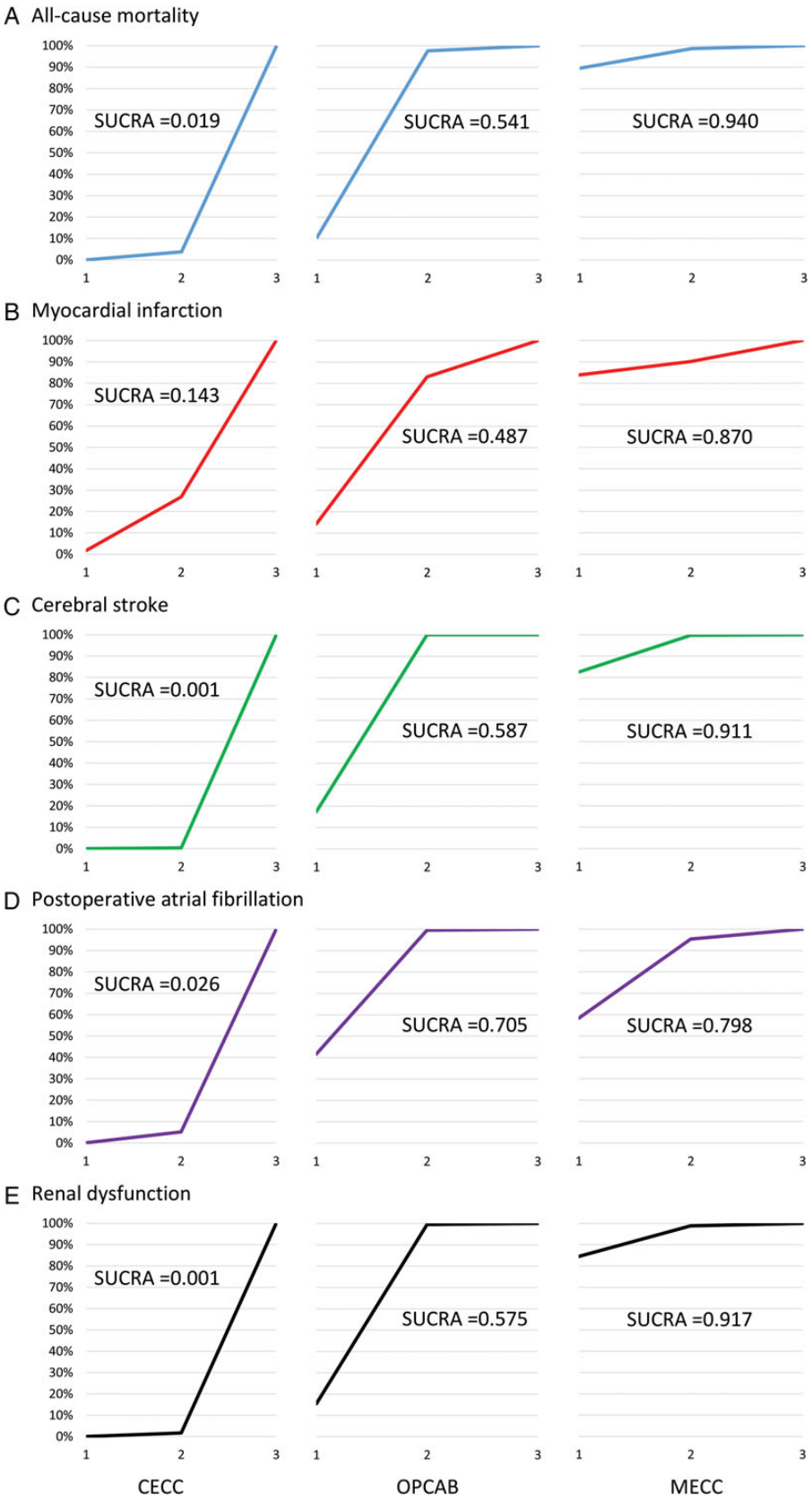

Figure 4: Hierarchy of treatments for 30-day all-cause mortality (**A**), myocardial infarction (**B**), cerebral stroke (**C**), postoperative atrial fibrillation (**D**) and renal dysfunction (**E**) using SUCRA. The higher the SUCRA value the higher the treatment rank. MECC: miniaturized extracorporeal circulation; OPCAB: off-pump coronary artery bypass graft; CECC: conventional extracorporeal circulation; SUCRA: surface under cumulative ranking curves.

conducted meta-analysis that found reduced all-cause mortality with OPCAB [s143] OR (95% CI): 0.86 (0.69–1.06) however not reaching statistical significance ($P = 0.16$). Differently from a study by Deppe *et al.*, we did not include in quantitative analysis studies reporting '0 events' in both arms, thus reducing the risk of deflating the magnitude of the pooled treatment effect by widening the confidence intervals; also in contrast, our current estimates are derived from both direct and indirect comparisons thus higher quantities of information and concordantly resulting in lower estimates of opportunity loss due to uncertainty.

Another potentially breakthrough finding is the reduction of all-cause mortality with MECC when compared with CECC. Miniaturized circuits provide the advantages of conventional ECC; however, with shorter lines, no cardiotomy suction and no venous reservoir, they avoid air–blood contact that was shown to cause the systemic inflammatory response and myocardial damage. From the initial experience, MECC was demonstrated to be safe, feasible and superior to CECC in terms of postoperative complications; numerous studies report reduced need for transfusions due to lower haemodilution [s144], less myocardial damage as evidenced by diminished release of CK-MB [s145] and positive impact on postoperative neurocognitive outcome [s146] when compared with standard CPB. None of the single RCTs was capable though of detecting any difference in hard clinical outcomes [11]. None of the three previously published meta-analyses were able to detect difference in mortality between these two techniques as well, most probably due to small sample sizes of individual studies included. Current meta-analysis, by incorporating most recent reports, with the number of patients roughly twice as high when compared with previous meta-analyses on MECC versus CECC, for the first time demonstrated survival benefit with the former and is in line with another recently published report focusing on direct comparisons of MECC versus CECC [s147]. This finding once again highlights the unmet need for restricting the CPB exposure, and in particular in patients at high risk.

We observed marked reductions in the incidence of POAF and stroke after both MECC and OPCAB when compared with conventional CPB. The finding on stroke reduction is not new with regard to OPCAB; as the degree of aortic manipulation is well established and the predominant cause of neurological injury. Recent meta-analysis of 100 RCTs [s148], encompassing over 19 000 patients, showed a significant, nearly 30% reduction in the occurrence of postoperative stroke with OPCAB (OR, 0.72; 95% CI: 0.56–0.92; $P = .009$; $I^2 = 0\%$). OPCAB confers the benefit of CPB avoidance eliminating the need for inserting a large-bore cannula into the aorta, more importantly, however, OPCAB does not require cross-clamping of the aorta and therefore minimizes the risk of neck and brain vessel embolism with dislodged fragile atheromatous material from the aortic wall. Explanation for lower incidence of stroke among MECC-treated patients is yet more complex: the maintenance of cerebral perfusion during CPB along with acid–base balance maintenance seems to play a crucial role; on the other hand, extensive haemodilution (often seen with CECC due to high required priming volume), hypotension, cerebral microemboli and compromised permeability of blood-brain barrier resulting from systemic inflammatory response, substantially reduce the cerebral perfusion and might account for neurological damage seen in patients' postoperative course [s149]. In general, MECCs use heparin-coated tubing systems which resemble the endothelium, preventing both gaseous and thrombotic emboli formation; another factor is the absence of cardiotomy suction together with venous reservoir and, in turn, recirculating of shed blood with cellular debris, lipids and macrophages. Finally, MECCs maintain much higher mean perfusion pressure during CBP when compared with standard devices. Although none of single studies was powered for stroke, current analysis, by pooling together the available literature evidence, indeed, sheds a new light onto the potential role of MECC in preventing neurological complications, which needs to be addressed in adequately powered randomized study.

Perioperative renal dysfunction after coronary revascularization is associated with significantly increased hospital length of stay, infections, risk of permanent renal replacement therapy and mortality [s150]. Studies available so far did not define the benefit of either revascularization strategy in terms of improved renal outcomes. Indeed, both OPCAB and CECC entail the risk of renal failure: CECC comprises the contact of blood components with the artificial surface of the bypass circuit, endotoxaemia and reduced haemoglobin levels due to haemodilution; by systemic immune response, complement, adhesion molecules and oxygen-free radicals are activated leading to leucocytes extravasation, peroxidation of the lipids, cellular oedema and, in turn, tubular necrosis. This renal ischaemia and cellular injury could either initiate acute kidney injury (AKI) or extend pre-existing renal injury. On the other hand, OPCAB still is technically more demanding and kidneys are prone to impaired perfusion in instances when lateral and posterior heart wall are revascularized. Forced contortion of the heart with the stabilizer device and secondary ventricular compression lead to outflow tract obstruction, lowering of cardiac output and haemodynamic instability in some cases. Findings of the present meta-analysis that demonstrated a significant 30% reduction of the odds of renal dysfunction are in line with a recent, well-conducted meta-analysis of randomized and observational studies addressing AKI after CABG that demonstrated a protective effect of the OPCAB technique over CECC: (OR, 0.57; 95% CI: 0.43–0.76; P for effect <0.001) [s151]. Considerable heterogeneity found in the previous meta-analysis (67%) was attributed to non-unified definitions of AKI. Rather than AKI definitions, we used the term renal dysfunction that included not only AKI requiring renal replacement therapy but also in some instances asymptomatic increases by 50% of the serum creatinine levels. With different definitions between-studies, but maintained in a single study, we could assess the whole pooled spectrum of renoprotective effects of OPCAB varying from mild to severe kidney injury. Surgery performed with the use of MECC demonstrated reduction of the odds of renal dysfunction as well, by roughly halving the odds when compared with CECC. In the earlier studies, non-pulsatile flow was considered the main limitation of extracorporeal circulation devices, hindering the perfusion of vital organs such as brain, kidney and liver. Often, the paradigm that organ function is dependent on pulsatile blood flow has led surgeons to use an intra-aortic balloon pump in patients with reduced perfusion to maintain pulsatile blood flow while on ECC. By reflecting the recent findings from RCTs of left ventricular assist devices that indeed found no differences or better outcomes with continuous when compared with pulsatile flow devices [s152], current study corroborates in a wider perspective that, improved biocompatibility of the devices, tubing and centrifugal pump as offered by MECC, plays a much more important role in organ perfusion than preservation of the pulsatile flow itself.

LIMITATIONS

Several limitations to the current analysis need to be acknowledged. Firstly, we did not have access to the individual patient

data; therefore, we could not adjust for baseline characteristics of included patients; these were however largely balanced within particular studies. There could be additional confounders not accounted for in the analysis such as surgeon's experience; indeed, OPCAB poses a challenge for unexperienced surgeons, especially when distal marginal branches on the lateral and/or posterior wall of the heart need to be addressed. This is reflected by a significantly lower number of distal anastomoses performed in OPCAB when compared with CECC in the current analysis. We could not, however, adjust the estimates for completeness of revascularization as 'planned versus performed' number of anastomoses were rarely reported across the studies and reasons for incomplete revascularization in OPCAB and not-revascularized vessels were not available. On the other hand, randomization to OPCAB and CABG across trials was mostly performed at the time of admission and later unblinded so that the surgeon experienced in CABG would not operate a patient assigned to OPCAB. We acknowledge that the recurrence of angina end-point could substantially add to evaluation of the efficacy of the treatment. While mid- and long-term evaluation was indeed not objective of this study, short-term incidence of recurrent angina and reasons for repeat revascularization were seldom reported, thus precluding assessment in meta-analysis. Finally, number of events was small as mortality, MI, cerebral stroke and renal dysfunction represent a relatively rare entity after coronary revascularization. Although in such cases, large and adequately powered randomized trials are needed to determine the true treatment effect, and before long-term follow-up data are available no firm conclusions can be drawn, the stability of the results in the network, as confirmed in the probability inference analysis, justifies the robustness of the estimates and with high dose of certainty rejects the play of chance.

CONCLUSIONS

MECC and OPCAB graft are both associated with improved perioperative outcomes following coronary bypass surgery when compared with CABG performed with CECC. MECC may represent an attractive compromise between OPCAB and CECC.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

[2] Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY *et al*. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015;372:1204–12.

[3] Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A *et al*. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607–16.

[4] de Jaegere PP, Suyker WJ. Off-pump coronary artery bypass surgery. Heart 2002;88:313–8.

[5] Meharwal ZS, Mishra YK, Kohli V, Bapna R, Singh S, Trehan N. Off-pump multivessel coronary artery surgery in high-risk patients. Ann Thorac Surg 2002;74:S1353–1357.

[6] Marui A, Okabayashi H, Komiya T, Tanaka S, Furukawa Y, Kita T *et al*. Benefits of off-pump coronary artery bypass grafting in high-risk patients. Circulation 2012;126:S151–7.

[7] Sharony R, Bizekis CS, Kanchuger M, Galloway AC, Saunders PC, Applebaum R *et al*. Off-pump coronary artery bypass grafting reduces mortality and stroke in patients with atheromatous aortas: a case control study. Circulation 2003;108():II15–20.

[8] Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E *et al*. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361:1827–37.

[9] Robertson MW, Buth KJ, Stewart KM, Wood JR, Sullivan JA, Hirsch GM *et al*. Complete revascularization is compromised in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2013;145:992–8.

[10] Biancari F, Rimpilainen R. Meta-analysis of randomised trials comparing the effectiveness of miniaturised versus conventional cardiopulmonary bypass in adult cardiac surgery. Heart 2009;95:964–9.

[11] Harling L, Warren OJ, Martin A, Kemp PR, Evans PC, Darzi A *et al*. Do miniaturized extracorporeal circuits confer significant clinical benefit without compromising safety? A meta-analysis of randomized controlled trials. ASAIO J 2011;57:141–51.

[12] Remadi JP, Rakotoarivelo Z, Marticho P, Benamar A. Prospective randomized study comparing coronary artery bypass grafting with the new mini-extracorporeal circulation Jostra System or with a standard cardiopulmonary bypass. Am Heart J 2006;151:198.

[13] Asteriou C, Antonitsis P, Argiriadou H, Deliopoulos A, Konstantinou D, Foroulis C *et al*. Minimal extracorporeal circulation reduces the incidence of postoperative major adverse events after elective coronary artery bypass grafting in high-risk patients. A single-institutional prospective randomized study. Perfusion 2013;28:350–6.

[14] Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G *et al*. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015;385:2047–56.

[15] Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE *et al*. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ 2013;347:f6530.

[16] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.

[17] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[18] Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–17.

[19] Welton NJ, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. Evidence Synthesis for Decision Making in Healthcare, 2012.

[20] Takagi H, Umemoto T, All-Literature Investigation of Cardiovascular Evidence G. Worse long-term survival after off-pump than on-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014;148:1820–9.

[21] Kim JB, Yun SC, Lim JW, Hwang SK, Jung SH, Song H *et al*. Long-term survival following coronary artery bypass grafting: off-pump versus on-pump strategies. J Am Coll Cardiol 2014;63:2280–8.

[22] Taggart DP. On-pump versus off-pump CABG. N Engl J Med 2010;362:852; author reply 853–854.

[23] Puskas JD, Mack MJ, Smith CR. On-pump versus off-pump CABG. N Engl J Med 2010;362:851; author reply 853–854.

[24] Takagi H, Matsui M, Umemoto T. Off-pump coronary artery bypass may increase late mortality: a meta-analysis of randomized trials. Ann Thorac Surg 2010;89:1881–8.

[25] Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E *et al*. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012;366:1489–97.