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 CPB, 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 |
|-----------------|-----------------------------------------------------------------------------------|----------------------------------------|---------------|---------------|--------------|------------------------------------|--------------|
| Abdel-Rahman et al. | Inflammatory response lung function and perioperative bleeding                    | MECC versus CECC                      | 204           | NR            | No           | 3.20 vs 3.10                       | Unclear      |
| Al-Ruzzeh et al. | 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.     | Myocardial injury                                                                  | OPCAB versus CECC                     | 70            | >50% MV-CAD   | Yes          | 2.30 vs 2.50                       | Unclear      |
| Anastasiadis et al. | Haematomatological parameters                                                       | MECC versus CECC                      | 99            | >50% MV-CAD   | Yes          | 2.92 vs 2.98                       | Low          |
| Asione et al.    | Retinal microvascular damage                                                         | OPCAB versus CECC                     | 20            | >50% MV-CAD   | No           | 2.40 vs 2.50                       | Unclear      |
| Asione et al.    | Small intestine function                                                            | OPCAB versus CECC                     | 40            | >50% MV-CAD   | No           | 2.50 vs 3.00                       | Low          |
| Asteriou et al.  | 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.     | Neurpsychological outcomes and myocardial injury                                    | OPCAB versus CECC                     | 26            | >50% MV-CAD   | Yes          | 2.20 vs 2.50                       | Unclear      |
| Beghi et al.     | Perioperative, intraoperative and postoperative clinical and biological variables  | MECC versus CECC                      | 60            | >50% MV-CAD   | No           | 2.75 vs 2.70                       | Unclear      |
| M. Kowalewski et al. | 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.  | Short-term morbidity and use of health care resources                               | OPCAB versus CECC                     | 200           | NR            | Yes          | 2.30 vs 2.50                       | Low          |
| Angelini et al.  | Short-term morbidity and use of health care resources                               | OPCAB versus CECC                     | 201           | NR            | Yes          | 2.30 vs 2.50                       | Low          |
| Blacher et al.   | Lymphocyte activation                                                              | OPCAB versus CECC                     | 50            | NR            | Yes          | 2.53 ± 2.57                        | Unclear      |
| Bonacchi et al.  | Cerebral injury                                                                     | OPCAB versus CECC                     | 42            | >50% MV-CAD   | Yes          | 2.80 vs 3.10                       | Unclear      |
| Camboni et al.   | 30-day mortality, postoperative neurpsychological dysfunction, renal dysfunction and hospitalization | MECC versus CECC                     | 93            | NR            | Yes          | NR                                  | Unclear      |
| Caputo et al.    | Inflammatory response and organ function                                            | OPCAB versus CECC                     | 40            | NR            | Yes          | 2.80 vs 2.90                       | Low          |
| Carrier et al.   | Hospital mortality and morbidity                                                     | OPCAB versus CECC                     | 65            | >50% MV-CAD   | Yes          | 3.00 vs 3.40                       | Low          |
| Cavalcà et al.   | Isoprostanes and oxidative stress                                                   | OPCAB versus CECC                     | 50            | NR            | Yes          | 2.50 vs 3.00                       | Unclear      |
| Chowdhury et al. | Inflammatory response and myocardial injury                                         | OPCAB versus CECC                     | 50            | >50% MV-CAD   | No           | 3.10 vs 3.20                       | Unclear      |
| Lamy et al. [CORONARY] | 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.    | Length of operation, haematomatological 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] | 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.    | Inflammatory response and myocardial injury                                         | OPCAB versus CECC                     | 30            | >50% MV-CAD   | Yes          | 2.40 vs 3.40                       | Unclear      |
| Czerny et al.    | Completenss of revascularization                                                    | OPCAB versus CECC                     | 80            | >50% MV-CAD   | Yes          | 2.60 vs 3.10                       | Unclear      |
| Diegeler et al.  | Periprocedural neurocognitive functioning                                           | OPCAB versus CECC                     | 40            | >50% MV-CAD   | Yes          | 1.10 vs 1.10                       | Unclear      |
| Donndorf et al.  | Microvascular perfusion; functional capillary density, blood flow velocity and vessel diameter | MECC versus CECC                     | 40            | NR            | Yes          | NR                                  | Unclear      |
| Dorman et al.    | Endothelin plasma content                                                           | OPCAB versus CECC                     | 52            | NR            | NR           | 3.00 vs 4.00                       | Unclear      |
| Fouilhier et al. | 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. | Reduction in transfusion requirements                                              | MECC versus CECC                      | 500           | NR            | NR           | NR                                  | Unclear      |
| Farneti et al.   | Blood coagulation and monocyte–platelet interaction                                 | MECC versus CECC                      | 20            | >50% MV-CAD   | NR           | 2.82 vs 3.00                       | High         |
| Fattouch et al.  | 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 | 2.60 vs 2.80                       | Low          |
| Formica et al.   | Systemic and myocardial inflammatory response                                      | MECC versus OPCAB                    | 60            | >50% MV-CAD   | Yes          | 2.70 vs 2.53                       | Low          |
| Formica et al.   | Inflammatory response                                                              | MECC versus OPCAB                     | 61            | >50% MV-CAD   | Yes          | 2.80 vs 2.70 vs 2.70               | Unclear      |
| Fromes et al.    | Inflammatory response                                                              | MECC versus CECC                      | 60            | >50% MV-CAD   | NR           | 2.80 vs 2.80                       | High         |
| Gaz et al.       | Inflammatory response                                                              | OPCAB versus CECC                     | 20            | NR            | NR           | 3.40 vs 3.90                       | Unclear      |
| Gaz et al.       | Inflammatory response                                                              | OPCAB versus CECC                     | 30            | NR            | Yes          | 3.00 vs 3.21                       | Unclear      |
| Study Authors | Study Details | Outcome | Comparator | Follow-up | Reference | Outcome Description |
|---------------|---------------|---------|------------|-----------|-----------|---------------------|
| Gerola et al. | 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. | Inflammatory response | OPCAB versus CECC | 62 | >50% SV-CAD | Yes | 1.00 vs 1.00 | Unclear |
| Guler et al. | Postoperative lung functions | OPCAB versus CECC | 58 | >50% SV-CAD | Yes | 1.00 vs 1.00 | High |
| Gonenc et al. | Periprocedural oxidative stress | OPCAB versus CECC | 42 | NR | NA | High |
| Diegeler et al. | 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 |
| Gulieinos et al. | Periprocedural inflammatory marker and cTn release | OPCAB versus CECC | 40 | >50% SV-CAD | Yes | 1.00 vs 1.00 | Unclear |
| Gunaydin et al. | Gaseous microemboli count and periprocedural inflammatory response | MECC versus OPCAB | 40 | NR | Yes | 3.25 vs 3.40 | Unclear |
| Hernandez Jr et al. | Neurocognitive functioning at discharge | OPCAB versus CECC | 201 | >50% MV-CAD | Yes | 3.20 vs 3.30 | Low |
| Hoel et al. | Complement activation | OPCAB versus CECC | 44 | NR | Yes | NA | Unclear |
| Huybregts et al. | Inflammatory response, proximal renal tubular and intestinal injury | MECC versus OPCAB | 49 | >50% MV-CAD | NR | 4.30 vs 3.90 | Low |
| Jares et al. | Neurological complications | OPCAB versus CECC | 200 | NR | NR | 2.96 vs 2.99 | High |
| Kobayashi et al. | Identification of fibrinolysis using rotation thromboelastography | OPCAB versus CECC | 20 | NR | NR | 2.00 vs 2.60 | Unclear |
| Johansson-Synnergren et al. | Cardiac death, MI, CHF, TVR at 30 days and at 12 months after surgery | OPCAB versus CECC | 167 | >50% MV-CAD | No | 3.50 vs 3.60 | Low |
| Jolhans et al. | Periprocedural inflammatory and endothelial response | OPCAB versus CECC | 60 | NR | NR | 3.00 vs 3.00 | Unclear |
| Komaiya et al. | Inflammatory response | OPCAB versus CECC | 20 | >50% MV-CAD | NR | 2.70 vs 2.70 | Unclear |
| Khan et al. | Graft patency at 3 months | OPCAB versus CECC | 104 | >50% MV-CAD | Yes | 3.10 vs 3.40 | Low |
| Kauai et al. | Inflammatory response | MECC versus OPCAB | 60 | NR | NR | 3.00 vs 3.00 | Unclear |
| Kobayashi et al. | Preoperative and postoperative pulmonary gas exchange | OPCAB versus CECC | 58 | NR | Yes | 1.50 vs 1.60 | Un unclear |
| Kok et al. | Cerebral tissue oxygenation and postoperative cognitive dysfunction | OPCAB versus CECC | 60 | NR | NR | 3.20 vs 3.30 | Unclear |
| Kofidis et al. | Inflammatory response | MECC versus OPCAB | 80 | >50% MV-CAD | Yes | 2.10 vs 1.90 | High |
| Krejca et al. | Inflammatory response | OPCAB versus CECC | 26 | NR | NR | 1.80 vs 1.80 | Unclear |
| Kunes et al. | Pentraxin 3 release kinetics | OPCAB versus CECC | 34 | NR | NR | 2.00 vs 2.00 | Unclear |
| Lee et al. | 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. | Perioperative 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. | Cerebral tissue oxygenation and microembolization | MECC versus OPCAB | 40 | >50% MV-CAD | Yes | 3.70 vs 3.80 | Low |
| Lingas et al. | Graft patency at 12 months | OPCAB versus CECC | 120 | >50% MV-CAD | Yes | 2.60 vs 2.80 | Unclear |
| Lloyd et al. | Serum S-100 protein and neuropsychological outcomes | OPCAB versus CECC | 125 | >50% MV-CAD | NR | 2.20 vs 2.40 | Unclear |
| Lund et al. | Intraoperative cerebral embolization | OPCAB versus CECC | 52 | NR | NR | 2.30 vs 2.50 | Unclear |
| Malik et al. | Myocardial injury | OPCAB versus CECC | 50 | >50% MV-CAD | Yes | 3.10 vs 3.30 | Unclear |
| Mandak et al. | Peripheral tissue metabolism and microvascular blood flow | OPCAB versus CECC | 40 | NR | Yes | 2.40 vs 2.90 | Unclear |
| Matata et al. | Inflammatory response and oxidative stress | OPCAB versus CECC | 20 | NR | NR | 1.80 vs 1.90 | Low |
| Hueb et al. [MASS III] | 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. | Inflammatory response and organ injury | MECC versus OPCAB | 300 | >50% MV-CAD | Yes | 3.25 vs 3.08 | Low |
| Medved et al. | In-hospital mortality and morbidity | OPCAB versus CECC | 60 | NR | Yes | 2.30 vs 2.50 | Unclear |
| Michaux et al. | RV global and overall systolic function | OPCAB versus CECC | 50 | >50% MV-CAD | Yes | 2.90 vs 3.20 | Low |
| Modine et al. | Renal tubular and glomerular function | OPCAB versus CECC | 71 | NR | Yes | 2.40 vs 2.80 | Unclear |
| Moltenbezdah et al. | Cerebral injury | OPCAB versus CECC | 35 | >50% MV-CAD | NR | 2.20 vs 2.30 | Low |
| Motallebzadeh et al. | Periprocedural neurocognitive function | OPCAB versus CECC | 212 | >50% MV-CAD | NR | Low |
| Munretto et al. | 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. | Inflammatory response | MECC versus OPCAB | 15 | >50% MV-CAD | Yes | 2.86 vs 2.88 | Unclear |
| Nesher et al. | Inflammatory response and myocardial injury | OPCAB versus CECC | 125 | NR | NR | 2.30 vs 2.90 | Low |
| Ng et al. | Inflammatory response | MECC versus OPCAB | 78 | NR | NR | 2.00 vs 2.40 | Unclear |
| Nguyen et al. | Inflammatory response and myocardial injury | MECC versus OPCAB | 26 | >50% MV-CAD | Yes | 3.23 vs 3.23 | Low |
| Niranjan et al. | Autologous blood transfusion and postoperative complications | OPCAB versus CECC | 80 | >50% MV-CAD | Yes | 3.93 vs 3.75 | Low |
| Nollert et al. | Inflammatory response | MECC versus OPCAB | 30 | >50% MV-CAD | NR | 2.90 vs 2.90 | Low |
| Natho et al. [Octopus] | 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 |
|-----------------|-------------------|--------|---------------|--------------|-------------|-----------------------------------|-------------|
| Ohata et al. [90] | 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] [91] | Operative mortality, MI, stroke, renal failure, reoperation for bleeding and ARDS within 30 days | OPCAB versus CECC | 411 | NR | Yes | 3.00 vs 3.30 | Low |
| Onorati et al. [92] | Perioperative changes in MCP-1 and VEGF levels | OPCAB versus CECC | 60 | NR | NR | 3.40 vs 3.40 | Low |
| Ovčina et al. [93] | Perioperative clinical parameters | OPCAB versus CECC | 288 | >50% MV-CAD | NR | NR | High |
| Ozkara et al. [94] | Target vessel revascularization at 1 year, perioperative PAI-1 release | OPCAB versus CECC | 64 | NR | Yes | 2.48 vs 2.31 | Unclear |
| Paparella et al. [95] | Activation of the coagulation and fibrinolytic systems | OPCAB versus CECC | 32 | NR | NR | 2.70 to 3.25 | Unclear |
| Parolari et al. [96] | Perioperative oxygen metabolism | OPCAB versus CECC | 25 | NR | NR | 2.30 to 2.90 | Unclear |
| Paroti et al. [97] | Perioperative changes in myocardial metabolism | OPCAB versus CECC | 22 | >50% MV-CAD | NR | 2.80 vs 3.00 | Unclear |
| Penta et al. [98] | Death, MI, stroke, renal failure requiring haemodialysis at 30 days | OPCAB versus CECC | 400 | >50% MV-CAD | Yes | 2.30 to 2.70 | Low |
| Straka et al. [PRAGUE-4] [99] | Death, MI, stroke, renal failure requiring haemodialysis at 30 days | OPCAB versus CECC | 206 | NR | Yes | 2.04 vs 2.66 | Low |
| Hlavicka et al. [PRAGUE 11] [100] | Platelet activity and aspirin efficacy | OPCAB versus CECC | 80 | NR | NR | 1.90 to 2.40 | Unclear |
| Bednar et al. [PROMISS] [101] | Graft patency at 5 weeks | OPCAB versus CECC | 150 | NR | Yes | 3.50 to 3.50 | Low |
| Sousa Uva et al. [102] | Postoperative gastrointestinal complications | OPCAB versus CECC | 300 | NR | Yes | NA | Unclear |
| Raja et al. [103] | Retinal microembolism, inflammatory, coagulation and endothelial markers | OPCAB versus CECC | 42 | NR | Yes | 4.10 vs 4.40 | Low |
| Rasmussen et al. [104] | Inflammatory response and myocardial injury | OPCAB versus CECC | 40 | NR | Yes | 3.00 vs 2.90 | Unclear |
| Rastan et al. [105] | The operative mortality rate (<30 days) | OPCAB versus CECC | 400 | >50% MV-CAD | NR | 2.80 to 2.70 | Low |
| Remadi et al. [106] | Inflammatory response | OPCAB versus CECC | 20 | NR | Yes | 3.00 vs 2.80 | Unclear |
| Rimplainen et al. [107] | Retinal microembolization, inflammatory, coagulation and endothelial markers | OPCAB versus CECC | 40 | >50% MV-CAD | NR | 4.40 vs 4.30 | Low |
| Schroyer et al. [ROOBY] [108] | All-cause death, reoperation, new mechanical support, coma, stroke, cardiac arrest, renal failure requiring dialysis at 30 days | OPCAB versus CECC | 2203 | >50% MV-CAD | NR | 2.90 vs 3.00 | Low |
| Sahlman et al. [109] | Inflammatory response and myocardial injury | OPCAB versus CECC | 50 | NR | Yes | 3.20 vs 3.00 | Unclear |
| Saha et al. [110] | Perioperative renal function | OPCAB versus CECC | 116 | NR | Yes | 3.11 vs 3.85 | Unclear |
| Saka et al. [111] | Laboratory parameters: haemoglobin and platelet count | MECC versus CECC | 199 | >50% MV-CAD | Yes | 3.52 vs 3.38 | Low |
| Schöttler et al. [112] | 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. [113] | Perioperative LVEF | OPCAB versus CECC | 60 | NR | Yes | 2.80 to 2.90 | Low |
| Skrabal et al. [114] | Circulating endothelial cells count | MECC versus CECC | 20 | >50% MV-CAD | NR | 3.50 to 3.80 | Unclear |
| Skrabal et al. [115] | Myocardial injury | MECC versus CECC | 60 | NR | Yes | 3.60 vs 3.80 | Unclear |
| Puskas et al. [SMART] [116] | Complete revascularization and graft patency at 30 days | OPCAB versus CECC | 200 | NR | Yes | 3.39 vs 3.40 | Low |
| Svitik et al. [117] | Inflammatory response | MECC versus CECC | 54 | >50% MV-CAD | NR | 2.30 to 2.60 | Unclear |
| Syed et al. [118] | Pulmonary gas exchange | OPCAB versus CECC | 75 | NR | Yes | NR | Unclear |
| Tang et al. [119] | Kidney glomerular and tubular injury | OPCAB versus CECC | 40 | NR | Yes | 2.10 to 2.50 | Unclear |
| Tatoulis et al. [120] | Systemic vascular resistance at 12 h | OPCAB versus CECC | 100 | LM 8% | NR | 2.30 to 2.90 | Low |
| Tully et al. [121] | Neuropsychological and QoL Outcomes at 6 months | OPCAB versus CECC | 66 | NR | Yes | 2.23 vs 2.47 | Unclear |
| Van Boven et al. [122] | 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. [123] | 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. [124] | Inflammatory response | MECC versus OPCAB versus CECC | 60 | >50% MV-CAD | Yes | 3.80 vs 3.80 vs 4.70 | Unclear |
| Van Boven et al. [125] | Neurocognitive function at 6 months | OPCAB versus CECC | 70 | >50% MV-CAD | Yes | 3.00 vs 3.00 | Unclear |
| Velissaris et al. [126] | Gut mucosal oxygenation | OPCAB versus CECC | 54 | NR | Yes | 2.50 vs 2.60 | Unclear |
| Velissaris et al. [127] | Stress response | OPCAB versus CECC | 52 | NR | Yes | 2.40 vs 2.80 | Unclear |
| Vural et al. [128] | Perioperative haemodynamic assessment | OPCAB versus CECC | 50 | >50% SY-CAD | NR | 1.12 vs 1.12 | Unclear |
| Wan et al. [129] | Inflammatory response | OPCAB versus CECC | 37 | >50% MV-CAD | 100 | 2.44 vs 2.79 | Unclear |
| Wandschneider et al. [130] | Inflammatory response | OPCAB versus CECC | 119 | NR | No | 2.34 vs 3.10 | Unclear |
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; I² = 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; I² = 35%] and for MECC when compared with OPCAB [0.26 (−0.14 to 0.66); P = 0.20; I² = 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% CI): 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% CI): 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% CI): 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% CI): 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% CI): 0.66 (0.48–0.90) and OR (95% CI): 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.          | CorV system CardioVention, Inc., Santa Clara, CA, USA                         | 500                           | Heparin-coated                     | 400            | 350 IU/kg + 5000 IU | 78 ± 22       | 44 ± 14         | Yes        |
| Anastasiadis et al.          | Maquet Cardiopulmonary Hirlingen, Germany                                    | 500                           | Heparin-coated                     | 300            | 150 IU/kg          | 103 ± 24.8    | 65.3 ± 17.0    | Yes        |
| Asteriou et al.              | Maquet Cardiopulmonary Hirlingen, Germany                                    | 500                           | Heparin-coated                     | 300            | 150 IU/kg          | 113 ± 37.9    | 69.7 ± 20.2    | Yes        |
| Beghi et al.                 | Jostra AG, Hirlingen, Germany                                                | 450                           | Heparin-coated                     | NR             | 1.5 mg/kg          | 99 ± 28       | 59 ± 20         | Yes        |
| Camboni et al.               | Maquet Cardiopulmonary, Hirlingen, Germany                                   | 500                           | Heparin-coated                     | NR             | NR                | 96 ± 24       | 61 ± 20         | Yes        |
| PRECiSe Medos Medizintechnik AG, Stolberg, Germany | RESTING Heart Medtronic GmbH, Dusseldorf, Germany | 1400                          | Heparin-coated                     | 250            | 200 IU/kg          | 96 ± 27       | 85 ± 26         | 47 ± 16    |
| Abdel-Rahman et al.          | Maquet Cardiopulmonary, Rastatt, Germany                                    | 400                           | Heparin-coated                     | 250            | 200 IU/kg          | 79 ± 20       | 46 ± 14         | Yes        |
| El-Essawi et al.             | ROCsafe MPC, Terumo, Ann Arbor, MI, USA                                     | 600                           | Polymethoxyethylacrylate-coated    | NR             | NR                | 74.9 ± 26.7   | 48.2 ± 20.5    | Yes        |
| Synergy, Cobe Cardiovascular, Arvada, CO, USA | RESTING Heart Medtronic, Inc., Minneapolis, MN, USA | 750                           | Heparin-coated                     | 450            | 400 IU/kg          | 102 ± 24.1    | 56.3 ± 18.2    | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 800                           | Polymethoxyethylacrylate-coated    | NR             | NR                | 103.4 ± 31.9  | 57.7 ± 25.3    | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 300                           | Heparin-coated                     | NR             | NR                | 72.5 ± 4.5    | 29.5 ± 2.3     | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 750                           | Heparin-coated                     | NR             | NR                | 100 ± 20      | 61 ± 18.7      | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 300                           | Heparin-coated                     | NR             | NR                | 111 ± 28.3    | 65 ± 19.2      | NR         |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 450                           | Non-coated                        | 400            | 3 mg/kg            | 63.4 ± 19.5   | 31.4 ± 11.7    | Yes        |
| Synergy, Cobe Cardiovascular, Arvada, CO, USA | Resting Heart System, Medtronic, Inc., Minneapolis, MN, USA | 300                           | Non-coated                        | 400            | 3 mg/kg            | 117 ± 20      | 89 ± 19         | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Ecco System, Diedo, Sorin, Italy                                            | 300                           | Polymethoxyethylacrylate-coated    | NR             | NR                | 75 ± 20       | NR              | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 820                           | Non-coated                        | NR             | NR                | 103.3 ± 26.6  | 61.1 ± 18.7    | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 800                           | Heparin-coated                     | 250            | 150 IU/kg          | 86 ± 5        | NR              | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 500                           | Heparin-coated                     | 250            | 150 IU/kg          | 93 ± 28       | 93 ± 28         | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 500                           | Heparin-coated                     | 250            | 150 IU/kg          | 85.5 ± 3.4    | 52.3 ± 2.6     | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 1100                          | Polymethoxyethylacrylate-coated    | 480            | 300 IU/kg          | 66 ± 21       | 35 ± 13         | No         |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 500                           | Heparin-coated                     | 300            | 150 IU/kg          | 85.1 ± 17.6   | 61.5 ± 13.0    | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 500                           | Heparin-coated                     | 300            | 150 IU/kg          | 82.8 ± 10.3   | 54.0 ± 14.1    | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 500                           | Heparin-coated                     | 300            | 150 IU/kg          | 78 ± 14       | 58 ± 12         | Yes        |
| Synergy Sorin® (Sorin Group, Italy) | Resting Heart Medtronic GmbH, Dusseldorf, Germany | 820                           | Non-coated                        | 400            | 400 IU/kg          | 87 ± 28       | 51 ± 22         | Yes        |
| El-Essawi et al.             | ROCsafe* (Terumo Medical Corp., Somerset, NJ, USA) | 250                           | Heparin-coated                     | NR             | NR                | 75.9 ± 18.6   | 41.1 ± 11.6    | NR         |
| El-Essawi et al.             | 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.
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, which 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

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% CI): 0.69 (0.46–0.92)]; MECC reduced these odds by more than 50% when compared with CECC [OR (95% CI): 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
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 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; I² = 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 micro-emboli 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 CPB 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.

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