International Journal of Surgery 14 (2015) 96–104

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Miniaturized extracorporeal circulation versus off-pump coronary artery bypass grafting: A meta-analysis of randomized controlled trials

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HIGHLIGHTS

- Superiority of OPCAB over MECC in reducing CPB-related side-effects is controversial.
- This controversy is due to current available evidence from limited number of small-sized randomised controlled trials.
- Present meta-analysis confirms that MECC has clinical outcomes comparable to OPCAB.
- MECC should be considered as a valid alternative to OPCAB in order to reduce CPB-related morbidity.

ARTICLE INFO

Article history:
Received 18 July 2014
Received in revised form
17 December 2014
Accepted 21 December 2014
Available online 2 January 2015

Keywords:
Meta-analysis
Off-pump coronary artery bypass grafting
Minimized extracorporeal circulation

ABSTRACT

Background: Controversies exist whether off-pump coronary artery bypass (OPCAB) is superior to miniaturized extracorporeal circulation (MECC) in reducing deleterious effects of cardiopulmonary bypass as only a number of smaller randomized controlled trials (RCT) currently provide a limited evidence base. The main purpose of conducting the present meta-analysis was to overcome the expected low power in RCTs in an attempt to establish whether MECC is comparable to OPCAB.

Methods: A MEDLINE/PubMed search was conducted to identify eligible RCTs. A pooled summary effect estimate was calculated by means of Mantel-Haenszel method.

Results: The search yielded 7 RCTs included in this meta-analysis enrolling 271 patients in the OPCAB group and 279 in the MECC group. The OPCAB and MECC groups were comparable in terms of incidence of in-hospital mortality (Risk Difference [RD] 0.01; 95%CI −0.02, 0.03; P = 0.55; I^2 = 0%), stroke (RD −0.01; 95%CI −0.05, 0.04; P = 0.69; I^2 = 0%), need for renal replacement therapy (RD 0.00; −0.06, 0.06; P = 1; I^2 = 0%), postoperative atrial fibrillation (RD −0.03; −0.17, 0.10; P = 0.64; I^2 = 0%), re-exploration for bleeding (RD −0.01; 95%CI −0.03, 0.02; P = 0.65; I^2 = 0%), transfusion rate (RD −0.01; 95%CI −0.03, 0.02; P = 0.65; I^2 = 0%) and the amount of blood loss (weighted mean difference -25 mL; 95%CI −71, 21; P = 0.28; I^2 = 0%).

Conclusions: Using a meta-analytic approach, MECC achieves clinical results comparable to OPCAB including postoperative blood loss and blood transfusion requirement. On the basis of our findings, MECC should be considered as a valid alternative to OPCAB in order to reduce surgical morbidity of conventional cardiopulmonary bypass.

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http://dx.doi.org/10.1016/j.ijsu.2014.12.021
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1. Introduction

Recognition of the potentially deleterious effects of conventional extracorporeal circulation led to off-pump coronary artery bypass (OPCAB) surgery gaining more popularity worldwide [1]. A number of randomized controlled trials (RCTs) comparing OPCAB to conventional extracorporeal circulation have been completed since then [2]. Although outcomes have been largely comparable [3], the evidence for the benefit of OPCAB has not been as convincing as initially anticipated [4]. Moreover, OPCAB revascularisation can be very demanding, thus leading to the potential for suboptimal revascularization [5]. Therefore, initial enthusiasm for OPCAB became especially tempered by concerns about the completeness of revascularization, the rate of perioperative myocardial infarction and long-term graft patency rates [5].

As an alternative technique, miniaturized extracorporeal circulation (MECC) may provide a more controlled operative field facilitating manipulation of the heart whilst minimizing the inflammatory, coagulopathic and haemodilutional effects of conventional cardiopulmonary bypass [6,7] by reducing foreign surfaces, avoiding blood-air contact and significantly reducing priming volume. However, whether MECC is comparable to OPCAB in terms of operative outcomes still remains unclear. At present, a number of smaller studies provide a limited evidence base.

The main purpose of conducting the present meta-analysis was to overcome the expected low power in most of the individual studies due to the small sample sizes by pooling data in an attempt to establish whether MECC is comparable to OPCAB.

2. Material and methods

2.1. Search strategy

This meta-analysis of RCTs was performed in accordance with the Cochrane Collaboration and PRISMA statements [8]. A reference search was performed through PubMed and Cochrane Library up to June 2014 for RCTs comparing MECC versus OPCAB in adult coronary artery bypass grafting (CABG). Tangential electronic exploration of related articles and hand searches of bibliographies and related journals were also performed. The search was performed using the following keywords: minimal, miniaturised, minimised, priming, cardiopulmonary bypass, extracorporeal, MECC, ECCO. Studies evaluating MECC with conventional extracorporeal circulation procedure were not included in the analysis. Studies were included if they met each of the following criteria: prospective, randomised study with allocation to MECC versus OPCAB; adult

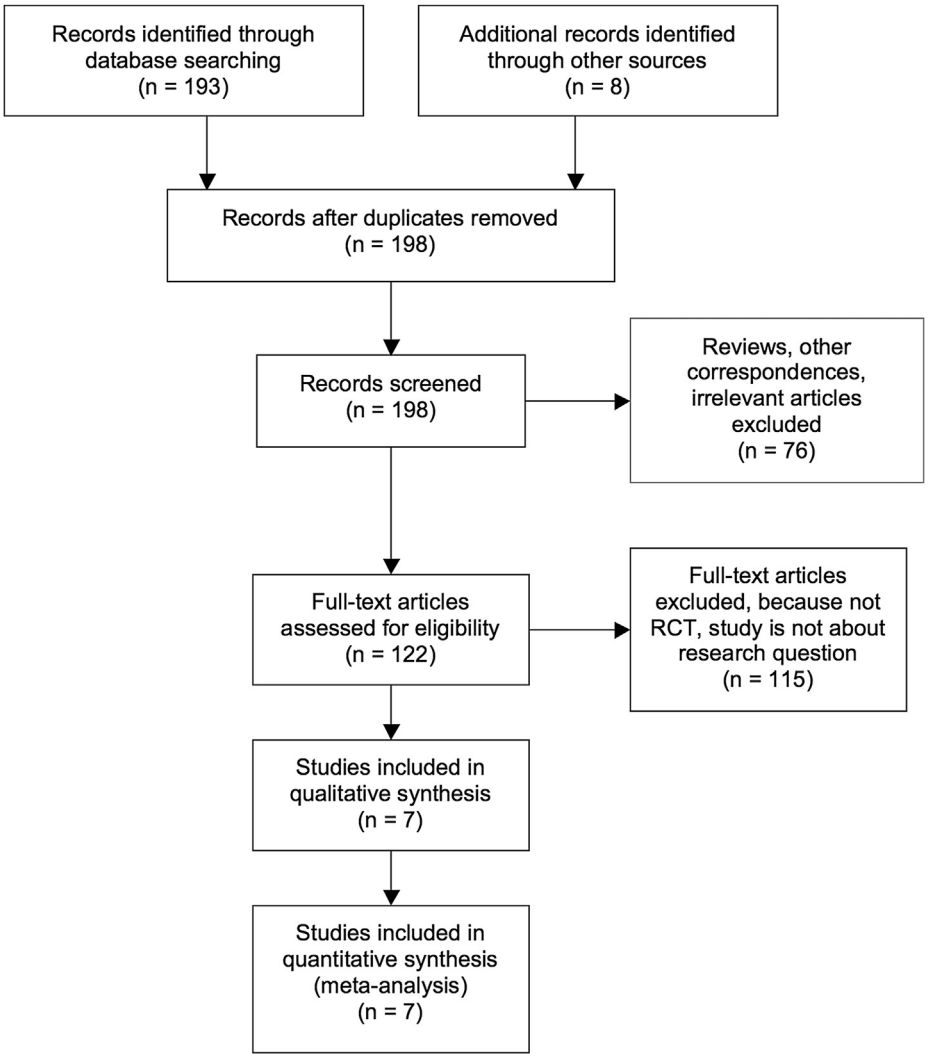

Fig. 1. Study selection flow chart.

Table 1
Study overview.

Study	Sample size	Mean age	% Male	% Diabetics	Number of grafts	Funded by manufacturer	MECC duration (min)	MECC system
Formica 2009 [10]	60	MECC 61 OPCAB 70	MECC 76.6% OPCAB 60%	MECC 23.3% OPCAB 36.6%	MECC 2.7 ± 0.65 OPCAB 2.53 ± 0.61	No	87 ± 19	Jostra MECC system, Maquet-Jostra AG, Hirrlingen, Germany
Formica 2013 [11]	59	MECC 70 OPCAB 71	MECC 78.9% OPCAB 60%	MECC 15.8% OPCAB 45%	MECC 2.8 ± 0.5 OPCAB 2.7 ± 0.5	No	92 ± 27	Jostra MECC system, Maquet-Jostra AG, Hirrlingen, Germany
Mazzei 2007 [12]	300	MECC 66 OPCAB 66	MECC 72% OPCAB 76%	MECC 24% OPCAB 29.7%	MECC 3.25 ± 0.7 OPCAB 3.08 ± 0.9	No	86 ± 21	Jostra MECC system, Maquet-Jostra AG, Hirrlingen, Germany
Murakami 2005 [13]	15	MECC 63 OPCAB 70	MECC 100% OPCAB 100%	MECC 28.5% OPCAB 25%	MECC 2.86 OPCAB 2.25	No	78 ± 23	Jostra MECC system, Maquet-Jostra AG, Hirrlingen, Germany
van Boven 2013 [14]	60	MECC 74 OPCAB 74	MECC 75% OPCAB 75%	MECC 15% OPCAB 35%	MECC 3.8 ± 0.6 OPCAB 3.8 ± 0.8	Yes	76 ± 14	Rotaflow centrifugal pump (Maquet GmbH) and a Quadrox membrane oxygenator (Maquet GmbH)
van Boven 2013 (2) [15]	30	MECC 74 OPCAB 74	MECC 80% OPCAB 80%	MECC 0% OPCAB 40%	MECC 3.7 ± 0.7 OPCAB 3.6 ± 0.8	Yes	82 ± 10	Rotaflow centrifugal pump (Maquet GmbH) and a Quadrox membrane oxygenator (Maquet GmbH)
Wittwer 2011 [16]	76	MECC 66 OPCAB 65	NR	NR	MECC 3.06 ± 0.72 OPCAB 1.89 ± 0.74	No	NR	ROCSafeTM systems (Terumo Medical Corp., Somerset, NJ, USA)

MECC: miniaturized extracorporeal circulation; OPCAB: off-pump coronary artery bypass surgery; NR: not reported.

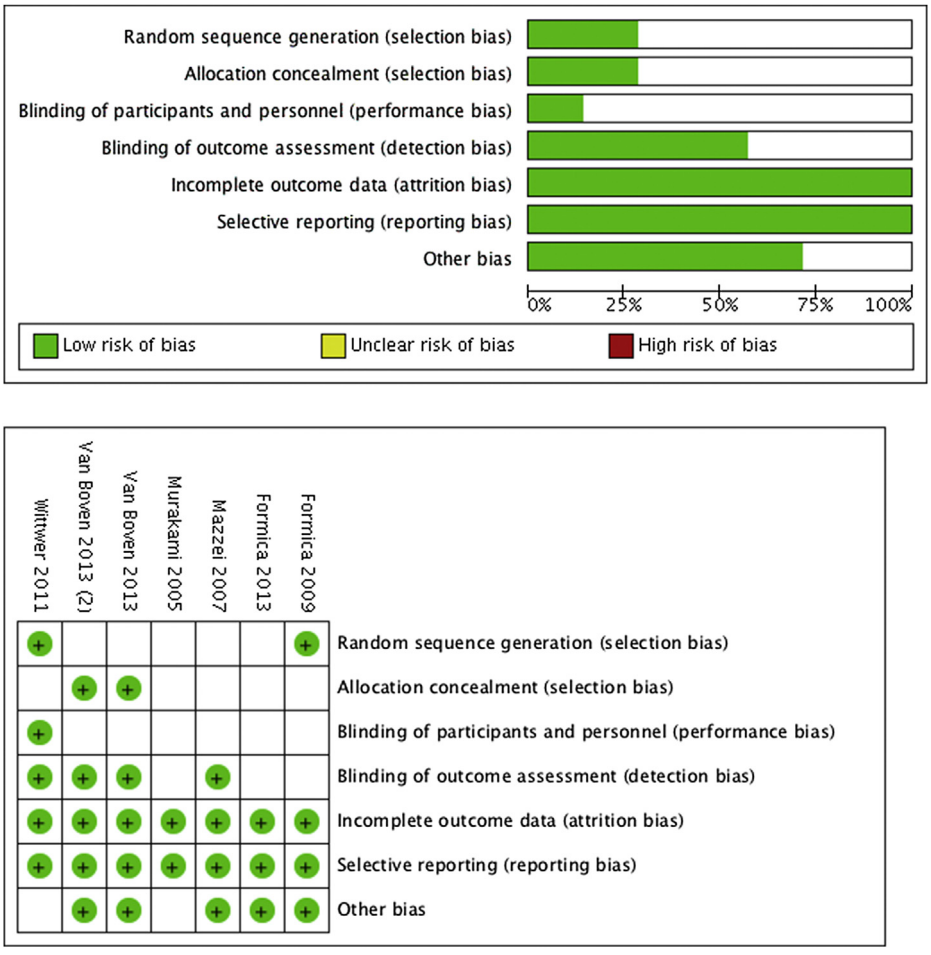

Fig. 2. Risk of bias assessment.

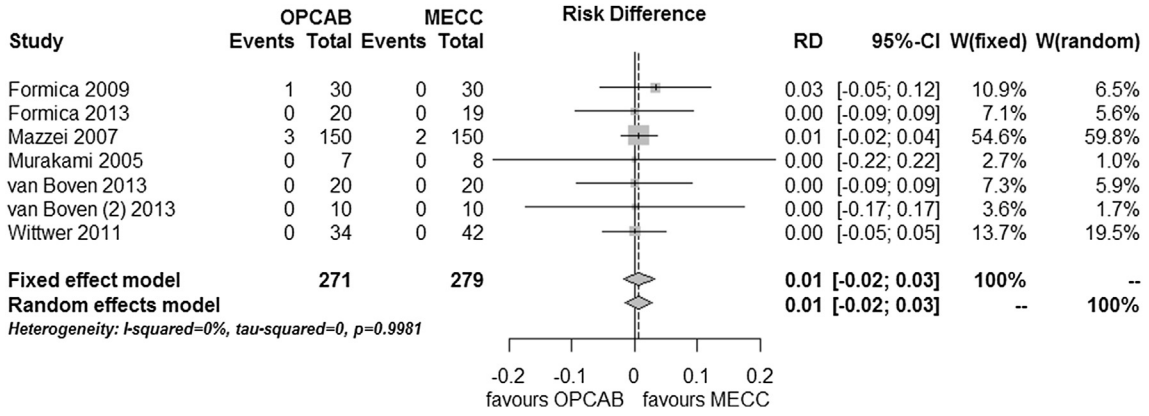

Fig. 3. Forest plot for in-hospital mortality.

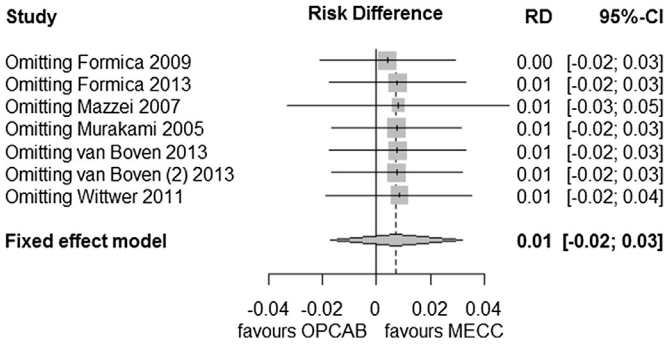

Fig. 4. Forest plot for influence analysis (pooled estimates calculated omitting one study at a time) on in-hospital mortality.

patients undergoing isolated CABG; reporting the primary endpoint: in-hospital death. Secondary endpoints investigated were: stroke, renal replacement therapy, postoperative atrial fibrillation (POAF), rate of transfusion, intensive care unit (ICU) length of stay, in-hospital length of stay, blood loss and/or reoperation for bleeding. Clinical end-points are reported as originally defined by the authors. Study validity was appraised according to the risk of bias tool recommended by the Cochrane Collaboration group [9]. Data abstraction and study appraisal were performed by two independent reviewers (UB, CN), with divergences resolved by consensus.

2.2. Statistical analysis

The outcome endpoints were analysed as dichotomous and continuous variables. Continuous outcome end-points were expressed as the weighted mean difference (WMD, <0 favors OPCAB and >0 favors MECC) with 95% confidence interval (CI). Due to no events frequently observed for outcomes investigated, dichotomous outcome endpoints were expressed as the risk difference (RD, <0 favors OPCAB and >0 favors MECC) with 95%CI. Heterogeneity was explored by calculating the I^2 statistic to quantify the degree of heterogeneity across the trials that could not be attributed to chance alone. A pooled summary effect estimate was calculated by means of Mantel-Haenszel method. If there was a significant heterogeneity ($I^2 \geq 50\%$), a random effect model was chosen; otherwise a fixed effect model was used. Sensitivity analysis was performed for the primary endpoint (in-hospital death) by

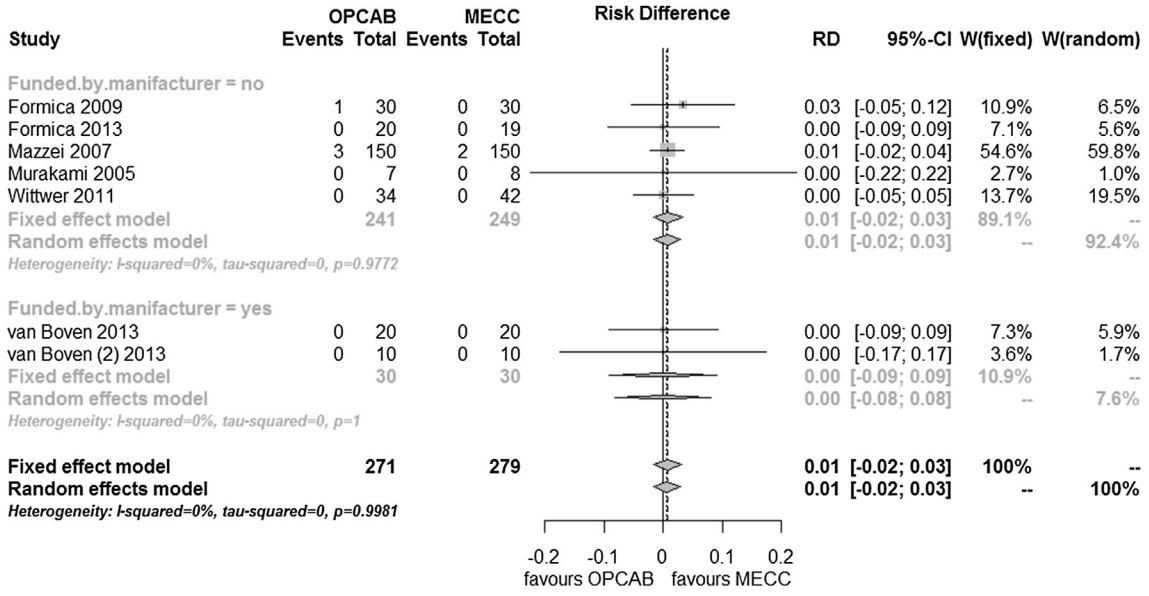

Fig. 5. Forest plot for subgroup analysis for study funded by the manufacturer.

means of influence analysis (pooled estimates calculated omitting one study at a time) and subgroup analysis for studies funded by the manufacturer. Meta-regression analysis for in-hospital death on the following MECC group characteristics was performed: mean age, percentage of male subjects, percentage of diabetics and mean MECC duration. Publication bias for the primary endpoint was visually inspected using the funnel plot method and assessed by means of Begg & Mazumdar and Egger's tests. A p value less than 0.05 was used as the level of significance.

R version 3.1.0 (R Core Team 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and **meta** package (Guido Schwarzer (2014). meta: Meta-Analysis with R. R package version 3.6-0. http://CRAN.R-project.org/package=meta) were used for statistical analysis.

3. Results

The flow chart in Fig. 1 summarises the results of a literature search and process of study inclusion and exclusion. The searches yielded 198 potentially relevant studies, of which 122 potentially eligible articles were reviewed after duplicates were removed. After screening the remaining articles and selecting those that met our criteria, the search yielded 7 RCTs [10–16] to be included in this meta-analysis with their study characteristics summarised in Table 1. Risk of bias is presented in Fig. 2. There were 271 patients in

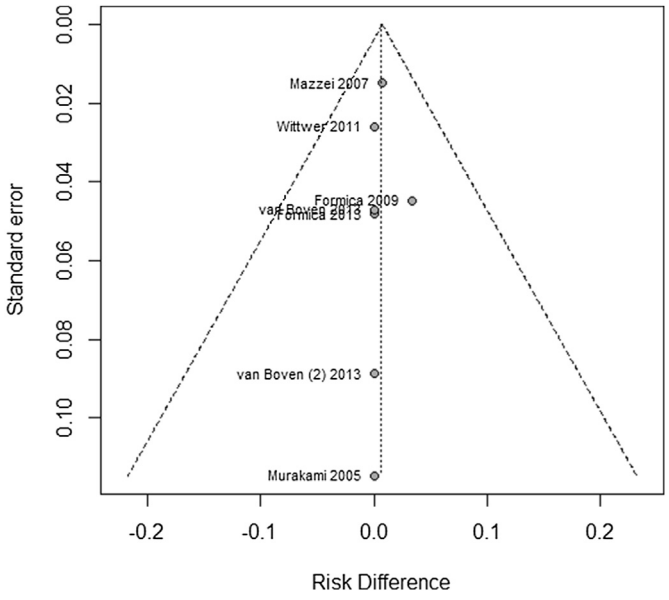

Fig. 7. Funnel plot for in-hospital mortality.

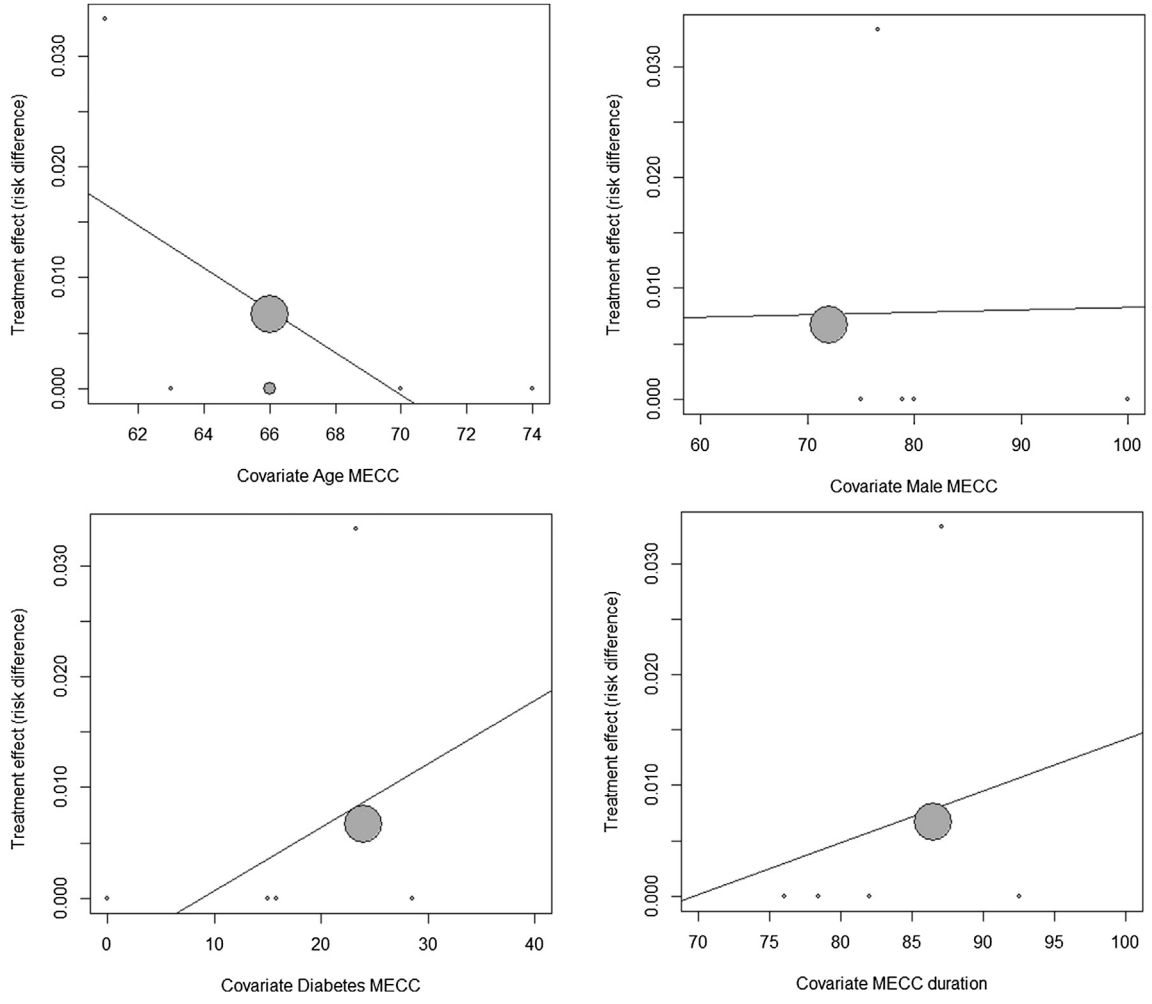

Fig. 6. Bubble plot displaying the result of meta-regression for in-hospital mortality.

the OPCAB group and 279 in the MECC group undergoing CABG. OPCAB was associated with non-significantly lower number of grafts per patients (WMD -0.30 grafts/pt; 95%CI −0.64, 0.05; P = 0.09; I^2 = 85%).

3.1. Primary endpoint

The cumulative in-hospital mortality was 1.5% in OPCAB group and 0.7% in the MECC group without significant difference between the two groups (RD 0.01; 95%CI −0.02, 0.03; P = 0.55; I^2 = 0%, Fig. 3). Pooled estimates calculated omitting one study at a time did not show any significant impact from individual studies (P ranging from 0.54 to 0.74, Fig. 4). Subgroup analysis for studies funded by the manufacturer (Fig. 5), did not show significant difference between the two subgroups (Test for subgroup differences, P = 0.86).

No significant effect on in-hospital mortality was demonstrated using meta-regression (Fig. 6) of MECC group characteristics: mean age (P = 0.65), percentage of male subjects (P = 0.99), percentage of diabetic subjects (P = 0.84) and mean MECC duration (P = 0.90).

Visual assessment of funnel plot for in-hospital mortality did not show outliers (Fig. 7). Begg & Mazumdar and Egger's tests excluded significant risk of publication bias (P = 0.65 and P = 0.96, respectively).

3.2. Secondary endpoints

The OPCAB and MECC groups were comparable in terms of incidence of stroke [10,11,13,15,16] (0% versus 0.9% respectively RD −0.01; 95%CI −0.05, 0.04; P = 0.69; I^2 = 0%), need for renal replacement therapy [10,11,15] (0% versus 0% respectively, RD 0.00; −0.06, 0.06; P = 1; I^2 = 0%) and incidence of POAF [10,11,13,16] (33% versus 36% respectively, RD −0.03; −0.17, 0.10; P = 0.64; I^2 = 0%) (Fig. 8).

No difference were found between the OPCAB group and the

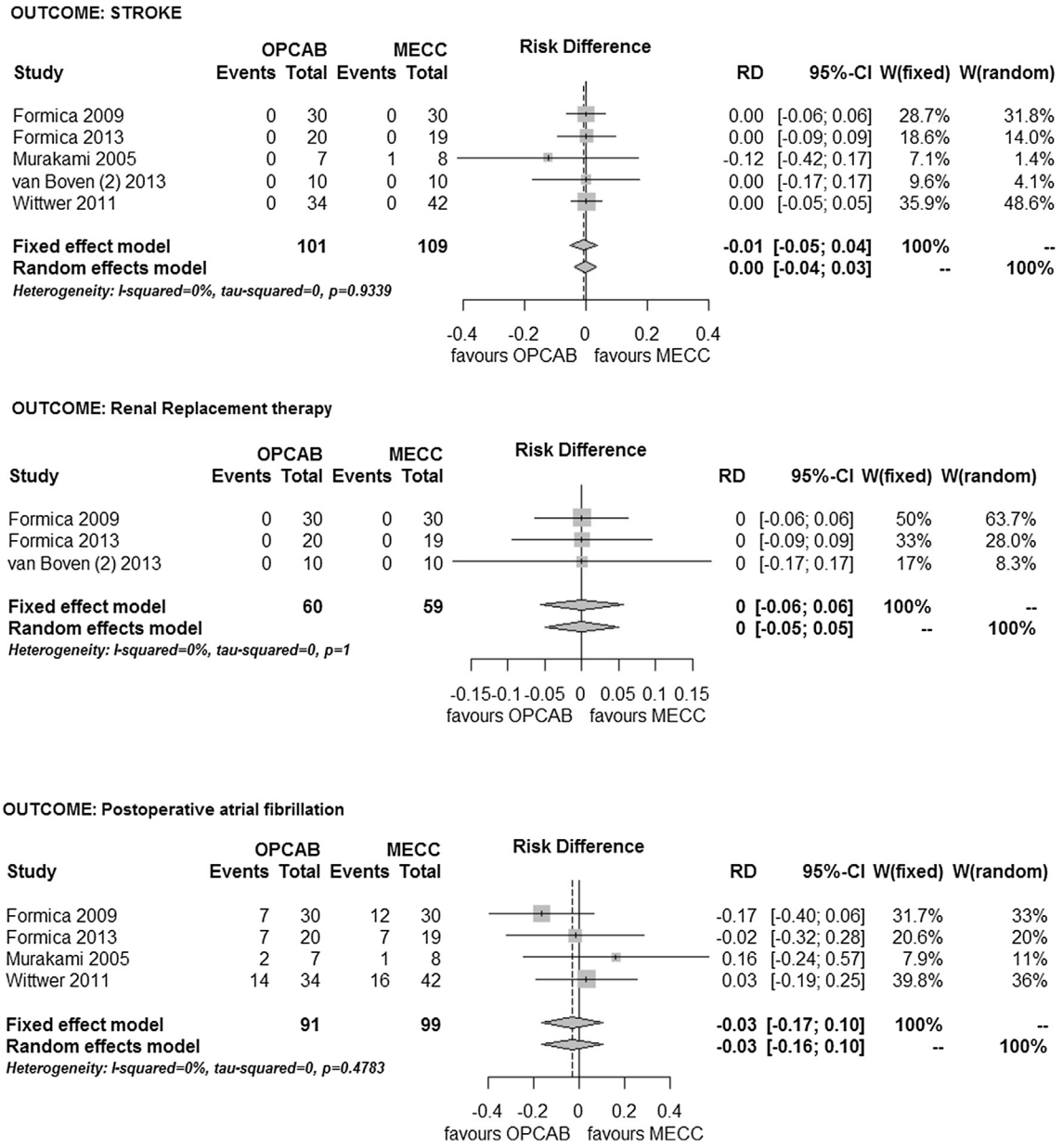

Fig. 8. Forest plot for stroke, renal replacement therapy and postoperative atrial fibrillation.

MECC group in terms of incidence of re-exploration for bleeding [10–12] (0.5% versus 1.0% respectively; RD −0.01; 95%CI −0.03, 0.02; P = 0.65; I^2 = 0%), transfusion rate [10–14] (18% versus 15% respectively; RD −0.01; 95%CI −0.03, 0.02; P = 0.65; I^2 = 0%) and the amount of blood loss [10,11,13,15,16] (WMD -25 mL; 95%CI −71, 21; P = 0.28; I^2 = 0%) (Fig. 9).

OPCAB was associated with a minimal reduction of ICU length of stay [10–14,16] (WMD -1.50 h; 95%CI −2.3, −0.67; P = 0.0004, I^2 = 0%) but no difference was found between the two groups with regard to in-hospital length of stay [10–13] (WMD 0.40 days; 95%CI -0.06, 0.87; P = 0.08 I^2 = 49%) (Fig. 10).

4. Discussion

OPCAB and MECC have been proposed to avoid harmful effects of cardiopulmonary bypass in patients undergoing CABG [2,3,6,7]. Since the advent of MECC several concerns have been raised about safety due to poor air-handling capacity. It has also been suggested that MECC is subject to certain flow limitations that can affect outcomes [17,18].

However, recent meta-analyses [19,20] have confirmed that the use of MECC is as safe as conventional extracorporeal circulation and have resulted in a clear trend towards reduced blood product use in CABG patients.

Controversies exist whether OPCAB is still superior to MECC in perioperative outcome. Only a number of smaller studies currently provide a limited evidence base. At the present time, there are no multi-centre RCTs comparing OPCAB and MECC and, although there is a suggestion from several smaller studies that MECC and OPCAB can achieve comparable operative outcomes over standard extra-corporeal techniques [10–16], further evidence is needed to guide its use in daily cardiac surgical practice.

The main purpose of conducting the present meta-analysis was to overcome the expected low power in most of the individual

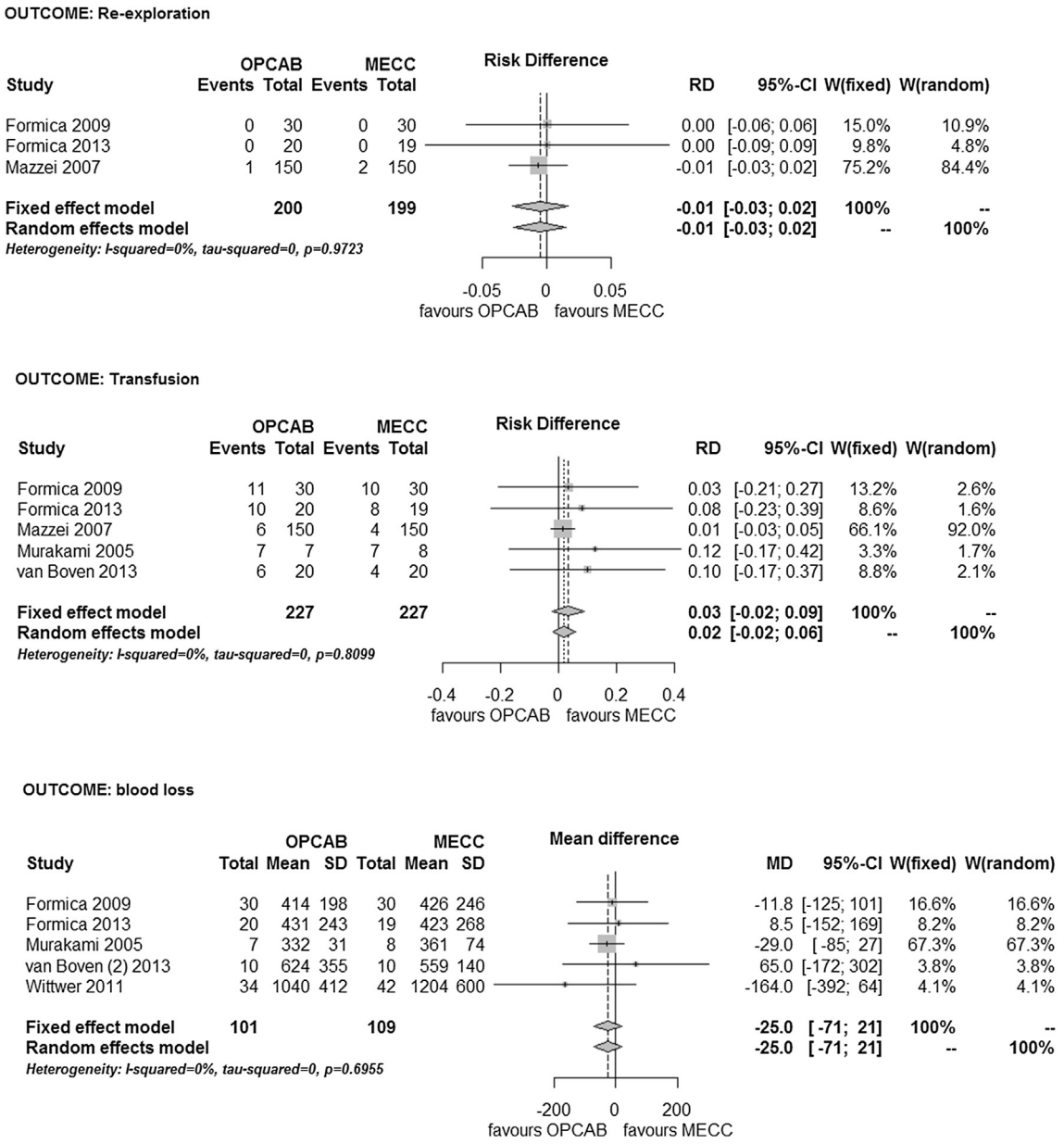

Fig. 9. Forest plot for re-exploration for bleeding, transfusion rate and total amount of postoperative blood loss.

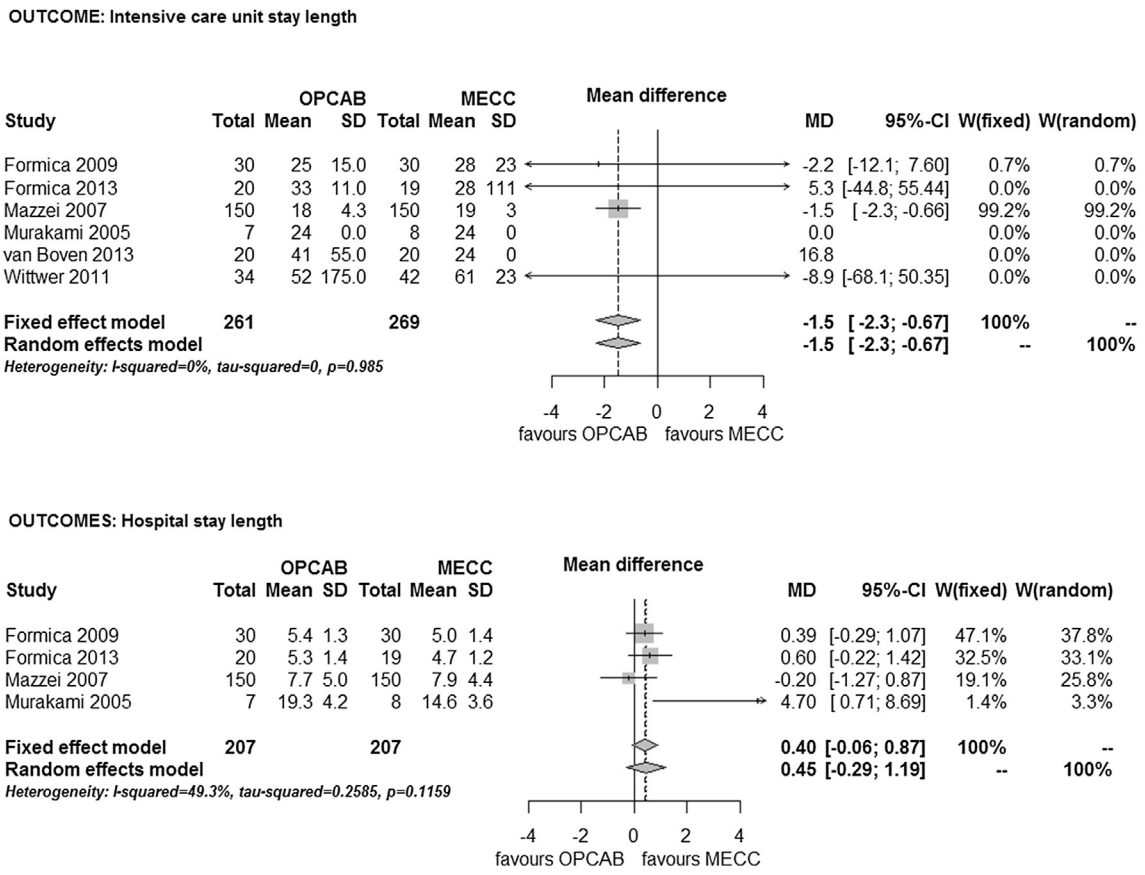

Fig. 10. Forest plot for intensive care unit and in-hospital stay length.

studies due to the small sample sizes, and at least improve the power of detecting association by pooling data from available RCTs. We found that MECC achieves clinical results comparable to OPCAB including postoperative blood loss and blood transfusion requirement. Moreover, MECC was associated with a trend towards a higher number of grafts performed.

Despite concerns regarding long term graft patency [5], OPCAB remains the most preferred alternative to conventional extracorporeal circulation technique in order to reduce operative morbidity after CABG especially in high risk cases [21]. A recently published report from The Society of Thoracic Surgeons National Cardiac Database on 876,081 patients [21] found that OPCAB was associated with reduced adverse events compared with on-pump coronary artery bypass after adjustment for 30 patient risk factors and center and surgeon identity. Moreover patients with higher predicted risk of mortality had the largest apparent benefit.

However, MECC combines OPCAB-benefits with less morbidity in high risk patients while facilitating more complete revascularization in patients with complex lesions [12]. Advantages from MECC over conventional cardiopulmonary bypass CPB have been consistently demonstrated in a recent systematic review and meta-analysis of randomized controlled trials by Anastasiadis et al. [22]. They found that MECC was associated with a significant decrease in operative mortality (0.5% vs. 1.7%, P = 0.02), in the risk of post-operative myocardial infarction (1.0% vs. 3.8%, P = 0.03) and reduced rate of adverse neurologic events (2.3% vs. 4.0%, P = 0.08). Additionally, MECC was associated with reduced systemic inflammatory response as measured by polymorphonuclear elastase, hemodilution as calculated by hematocrit drop after procedure, need for red blood cell transfusion, reduced levels of peak troponin release, incidence of low cardiac output syndrome, need for inotropic support, peak creatinine level, occurrence of post-operative atrial fibrillation, duration of mechanical ventilation and intensive care unit stay.

Preliminary results have suggested that MECC might be associated with better long term outcomes following CABG [12]; this might be explained by the achievement of a still and bloodless operating field as in traditional on-pump revascularization.

On the basis of our findings, MECC should be considered as a valid alternative to OPCAB in order to reduce surgical morbidity of conventional cardiopulmonary bypass whilst ensuring complete revascularization without affecting anastomotic quality.

Several potential study limitations should be considered. Most trials included in our analysis did not report adequate information about randomisation and allocation concealment, and this might undermine the validity of overall findings. Finally, the small size of the randomised studies performed so far and their methodological heterogeneity still prevent conclusive results. Larger trials with long term follow-up involving high-risk patients along with more homogeneous methods are needed to obtain further data on a possible superiority of MECC over OPCAB.

Ethical approval

None required.

Source of funding

None.

Author contribution

Umberto Benedetto study design, data analysis, writing.
Colin Ng data collections.
Giacomo Frati writing.
Giuseppe Biondi-Zoccai writing.
Piergiusto Vitulli data collection.
Mohamed Zeinah data collection.
Shahzad G. Raja writing.

Conflict of interest statement

None.

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