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Minimally Invasive Extracorporeal Circulation Circuit Is Not Inferior to Off-Pump Coronary Artery Bypass Grafting: Meta-Analysis Using the Bayesian Method

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The pathophysiologic side effects of cardiopulmonary bypass have already been identified. Minimally invasive extracorporeal circulation technologies (MiECT) and off-pump coronary artery bypass graft surgery (OPCABG) aim to reduce these problems. This meta-analysis provides a comparison of MiECT and OPCABG in randomized and observational studies. A fully probabilistic, Bayesian approach of primary and secondary endpoints was conducted. MiECT does not give inferior results when compared with OPCABG. However, there is a trend to borderline significantly higher blood loss in this group in randomized controlled trials. The question whether MiECT is equivalent to OPCABG can be answered with the affirmative, but long-term follow-up data are needed to detect any advantage over time.

The technique of off-pump coronary artery bypass grafting (OPCABG) was established more than 3 decades ago with the objective to reduce the unfavorable pathophysiologic side effects of conventional cardiopulmonary bypass circuits on the organ systems triggered by complement system activation through foreign surfaces, priming volume, and negative and positive pressures in the reservoir [1, 2]. To overcome these effects, the concept of minimally invasive extracorporeal circuits evolved over the last 15 years not only as an alternative to the more conventional extracorporeal circulation circuits but also as an alternative to an off-pump strategy in case of coronary artery bypass graft surgery (CABG) [3, 4]. The use of minimally invasive extracorporeal circulation technologies (MiECT) is now expanding; these systems offer several potential advantages because they reduce the systemic inflammatory response and subsequent organ dysfunction [5, 6].

The typical MiECT consists of a closed circuit, which includes the oxygenator and the pump. The circuit has no open venous reservoir. All components of the minimally invasive extracorporeal circuits are coated with heparin, and the tubing system is significantly reduced in length. These characteristics permit a reduction of the priming volume between 200 mL and 650 mL compared with the standard extracorporeal circuit [3, 7]. The OPCABG technique has shown good results as postoperative morbidity and mortality were reduced in various studies compared with CABG with conventional circuits. But the literature also presents some major drawbacks, such as a higher rate of incomplete revascularization, especially in dilated and hypokinetic hearts, due to more difficult exposure of obtuse coronary marginal branches and the lesser quality of the coronary anastomoses. For these reasons, the initial enthusiasm for OPCABG has vanished over the last years [8, 9]. Now, MiECT aims to incorporate the advantages of a traditional cardiopulmonary bypass circuit while overcoming the limitations of OPCABG [10].

With this is in mind, the main questions are these: (1) is MiECT is comparable to OPCABG in terms of operative outcomes; and (2) is the safety of a minimized heart-lung machine (with less systemic inflammatory response) even superior to OPCABG? The aim of the present meta-analysis is to overcome the low power of the limited sample sizes of the existing studies by pooling data of 3,410 patients, and to determine whether MiECT is a valid or superior alternative to OPCABG [11].

To minimize selection bias, we decided to include all studies that compare the two strategies, no matter whether the design was randomized or not. Of course,

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Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass graft surgery
CI = confidence interval
ICU = intensive care unit
MI = myocardial infarction
MiECT = minimally invasive extracorporeal circulation technologies
OPCABG = off-pump coronary artery bypass grafting
OR = odds ratio
RCT = randomized clinical trial
SMD = standardized mean difference

randomized trials are the gold standard in medical research because they provide the strongest evidence of treatment safety and efficacy. With respect to the comparison of MiECT versus OPCABG, randomized trials are not very common, and those trials tend to include only few patients [12]. Observational studies may provide particularly relevant information on the topic; that is the reason we decided to include observational studies. As that might considerably increase heterogeneity, we calculated all pooled estimates stratified by study design: randomized versus observational.

Material and Methods

Studies

The studies reviewed were randomized controlled trials (RCT) and observational studies that compared OPCABG and MiECT for patients undergoing CABG.

Participants

The studies reviewed involved adult patients (aged 18 years or more) who were undergoing cardiac surgery for coronary artery disease with either OPCABG or MiECT.

Search Strategy and Data Source

The search for literature was performed through PubMed, PubMed Central, Web of Science (includes MEDLINE, Conference Proceedings Citation Index, Data Citation Index CAB abstracts, Derwent Innovations Index), OvidSP (includes EMBASE, Ovid MEDLINE, HMIC, Transport Database). For the identification of RCT, the Cochrane Library was accessed. In addition, we searched Google scholar.

The searches were last updated on October 29, 2015. The search terms used for minimal extracorporeal circulation were "MECC" or "mini ECC" or "MiECT" or "minimal extracorporeal circulation" or "minimized extracorporeal circulation" or "mini-extracorporeal circulation" or "miniaturized extracorporeal circulation" or "minimal extracorporeal circulation technique" or "miniaturized extracorporeal circulation technique" or "miniaturized ECC" or "miniaturized extracorporeal circulation circuit" or "minimal extracorporeal circulation circuit."

There are no defined Medical Subject Headings (MeSH) terms for minimal extracorporeal circulation. The MeSH term for off-pump coronary artery bypass grafting was defined as "coronary artery bypass, off-pump," or search terms were used: "off-pump surgery" or "off-pump CABG" or "off-pump coronary artery bypass grafting" or "off-pump technology" or "off-pump coronary revascularization" or "off-pump coronary artery revascularization" or "off-pump coronary artery grafting" or "off-pump revascularization technology" or "off-pump coronary artery revascularization technique" or "off-pump technique" or "off-pump CABG method" or "OPCAB."

No restrictions on publication status, time, or predefined outcome were applied. Reference lists of evaluable studies, systematic reviews, meta-analyses, narrative reviews, and reports were also hand searched for additional studies eligible for inclusion. The search was conducted in compliance with the established Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in health care interventions statement (Appendix 1) [13].

Eligibility Criteria

Two authors independently screened all titles and abstracts of the initial search, and reviewed full-text articles with respect to eligibility for inclusion. Disagreements were resolved by a third reviewer. The final decision was made on the basis of the full texts (Table 1).

Data Extraction and Analyses

Two authors (H.P.P. and B.G.) independently extracted the data into a predefined scheme; disagreement was solved by consensus, and the final decision was made by a third author (B.W.). In addition to the extraction of patient characteristics and operation details, we assessed details of the methodology, the specific study question, and inclusion criteria.

Study Design

Inhouse mortality was defined as the primary endpoint for this analysis; secondary endpoints were stroke, myocardial infarction (MI), postoperative atrial fibrillation (AF), total blood loss in milliliters, length of intensive care unit (ICU) stay in hours and length of hospital stay in days. We treated the number of anastomoses like an endpoint to use the technique of random effects analysis.

Statistical Analysis

We conducted a fully probabilistic, Bayesian analysis when events were rare, with mortality as a primary endpoint and MI and stroke as secondary endpoints. We used a Bayesian method developed for random effects meta-analysis on the odds ratio (OR) scale [14, 15]. Further details can be found in Appendix 2.

The model adequately accounts for situations with sparse event data, including zero cells in one or both treatment group and control group. Monte-Carlo Markov

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Table 1. Study Overview With All Included Studies

Study	Year of Publication	Study Design	Sample Size, n		Mean Age, years		MiECT
			MiECT	OPCABG	MiECT	OPCABG	
Formica	2009	RCT	30	30	61.2 ± 10.4	70 ± 7.7	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
Formica	2013	RCT	20	20	69.9 ± 8.7	70.8 ± 7.0	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
Murakami	2005	RCT	7	8	62.8 ± 6.0	70.2 ± 1.7	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
Mazzei	2007	RCT	150	150	65.7 ± 10.8	66.4 ± 9.8	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
van Boven	2013	RCT	20	20	73.6 ± 3.6	73.8 ± 2.6	Rotaflow centrifugal pump and Quadrox membrane oxygenator; Maquet GmbH
Wittwer	2011	RCT	42	34	65.6 ± 11.2	64.7 ± 10.9	ROCSafe systems; Terumo Medical Corp, Somerset, NJ
Wittwer	2013	RCT	76	44	65.8 ± 11.2	65.2 ± 10.4	ROCSafe systems; Terumo Medical Corp, Somerset, NJ
Reuthebuch	2014	Observational	555	42	65.01 ± 9.5	69.39 ± 9.5	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
Rosato	2012	Observational	50	50	64.1 ± 9.6	65.6 ± 12.3	Rotaflow centrifugal pump and Quadrox membrane oxygenator; Maquet GmbH
Munos	2011	Observational	51	57	74.9 ± 7.5	73.7 ± 9.9	Rotaflow centrifugal pump and Quadrox membrane oxygenator; Maquet GmbH
Panday	2009	Observational	220	109	66 ± 11	64 ± 11	Rotaflow centrifugal pump and Quadrox membrane oxygenator; Maquet GmbH
Puehler	2009	Observational	558	558	67.5 ± 8.8	66.8 ± 9.5	Rotaflow centrifugal pump and Quadrox membrane oxygenator; Maquet GmbH
Gerritsen	2006	Observational	93	95	68.3 ± 8.8	67.5 ± 9.6	Jostra MiECT system; Maquet-Jostra AG, Hirrlingen, Germany
Reber	2010	Observational	117	185	72.1 ± 8	69.3 ± 1	Stöckert; Sorin Group, Munich,Germany, in combination with ECCO perfusion system
Wippermann	2005	Observational	10	10	59.6 ± 8.3	54.3 ± 14.1	CORx; CardioVention, Santa Clara, CA

MiECT = minimally invasive extracorporeal circulation technologies; OPCABG = off-pump coronary artery bypass graft surgery; RCT = randomized clinical trial.

chain simulation methods were used to obtain posterior distributions of the ORs of outcomes of interest and of random-effects SD (τ). For the control groups (OPCABG) of each study, we set vague priors on the log of the odds of the event risk using normal distribution centered at zero with variance of 100.

For SD of random effects (τ), we set an informative prior, a half-normal distribution with a mean of 0.5 (further details available in Appendix 2). The 95% credibility intervals were obtained from the 2.5th and 97.5th percentile of the posterior distribution, which can be interpreted similarly to a conventional 95% confidence interval (CI). We conducted the analysis separately for randomized trials and observational studies.

All other analyses have been done using STATA 12 software (StataCorp, College Station, TX). For the binary outcomes, we calculated risk ratio and CI with a continuity correction of 0.001 for all outcomes that we observe zero in one arm or in both arms. With respect to the primary outcome mortality, we used these risk ratios as a sensitivity analysis for the Bayesian analysis of rare events outcomes. For continuous outcomes, we calculated standardized mean difference with CI between the treatments. We assessed heterogeneity by calculating the I^2 summary statistics. We follow Higgins and colleagues [16] in quantifying heterogeneity by I^2 into low (25%), moderate (50%), and high (75%).

As an approximation, we calculated SD of SE and calculated the raw numbers of percent when investigators reported only SE.

We calculated hours from days for the ICU stay if days were reported. When only the median was given, we included the median as a mean and approximated the SD by using the mean of all reported SDs. We calculated a separate sensitivity analysis to control for a bias induced by these approximations.

The included papers reported blood loss within different observation periods. We analyzed blood loss in strata for 12 hours, 24 hours, 48 hours, and for the complete postoperative period. For blood loss, we had to construct the SD for one paper, and we constructed it according to the stratum. We assessed publication bias with respect to mortality by visual inspection of the funnel plot and using Harbord's modified test. All p values and 95% CI are two sided.

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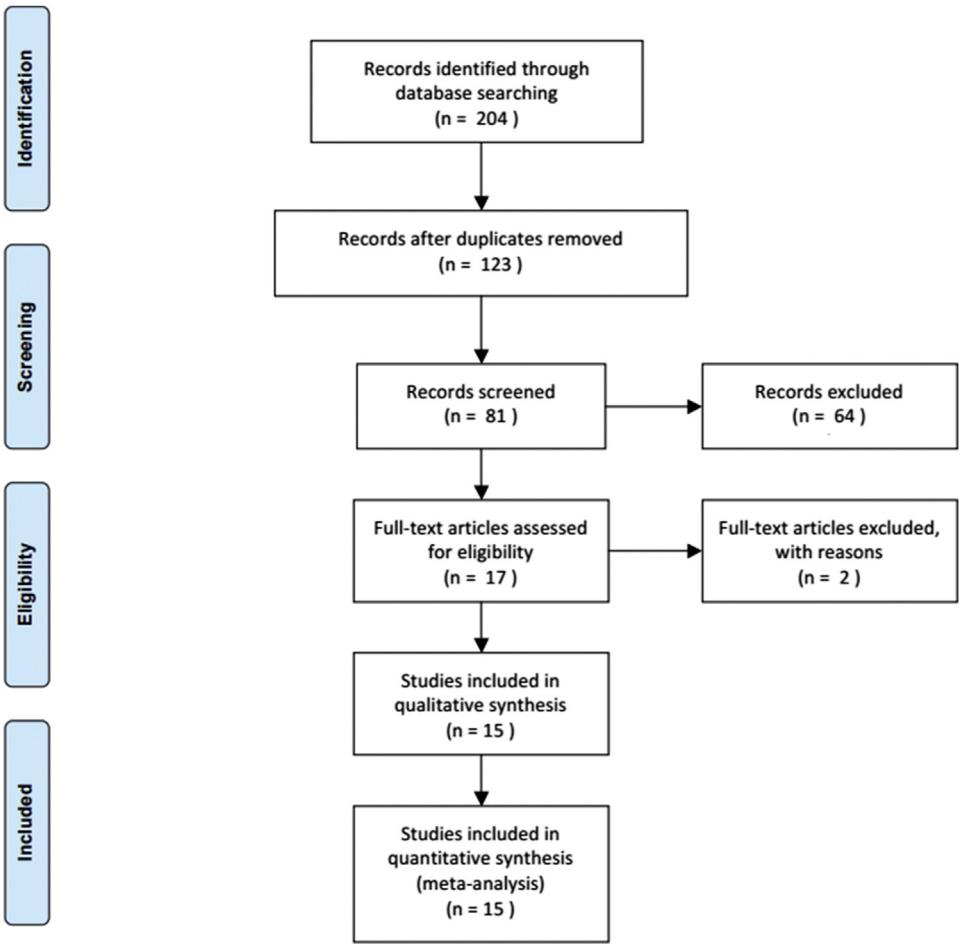

Fig 1. Study selection overview.

Results

Results of Search

ELIGIBLE PAPERS. Overall, 204 publications were found that potentially addressed the study question, of which 17 articles described a comparison of MiECT versus OPCABG (Fig 1). Overall seven randomized controlled (RCT) and eight observational studies were found [5, 17–31]. After thorough review process, three publications were identified that were possibly based on the same patient cohort. Therefore, two publications were excluded [32, 33]. Furthermore, the quality of the included studies were analyzed with respect to the comparability and reported endpoints (Supplemental Table 1).

PUBLICATION BIAS. The funnel plot indicates that there is no publication bias with respect to the primary endpoint, which is confirmed by the Harbord test that yields overall $p = 0.331$, in randomized trials $p = 0.669$, and in observational studies $p = 0.496$ (Fig 2).

Estimates of Endpoints

ALL-CAUSE MORTALITY. Inhospital death is a rare outcome: 5 of 7 studies (71%) report zero events in both arms; therefore, was analyzed using the Bayesian approach (Table 2). In the RCTs, the Bayesian OR is 0.64 with credibility interval of 0.16 to 2.48; the corresponding frequentist analysis yields an OR of 0.66 with CI 0.11 to 3.90. In observational studies, the Bayesian OR is 0.76 with credibility interval of 0.39 to 1.41; the frequentist OR is

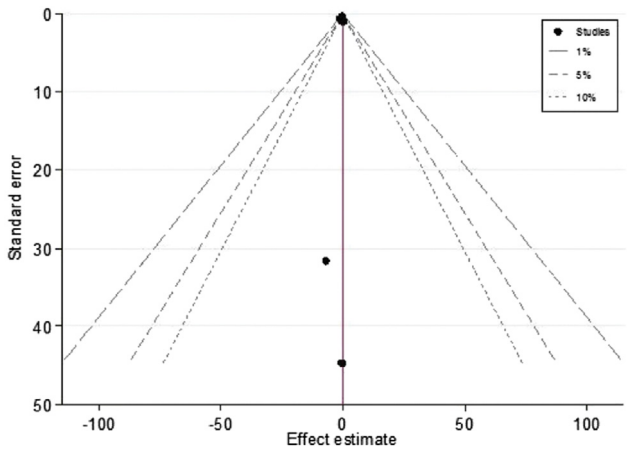

Fig 2. Funnel plot showing no publication bias. (Black dots = studies; long-dash line = 1%; medium-dash line = 5%; short-dash line = 10%.)

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Table 2. Combined Effect Sizes of Binary Endpoints

Variable	OR of MiECT Compared With OPCABG	
	Randomized	Observational
Mortality	0.64 (0.16–2.48)[a]	0.76 (0.39–1.41)[a]
Myocardial infarction	…	1.15 (0.30–4.37)[a]
Stroke	2.1 (0.42–11.19)[a]	1.55 (0.68–3.37)[a]
Renal failure	…	0.72 (0.38–1.38)
Postoperative AF	0.95 (0.71–1.26)	0.56 (0.45–0.69)

[a] Calculated using the Bayesian approach.

AF = atrial fibrillation; MiECT = minimally invasive extracorporeal circulation technologies; OPCABG = off-pump coronary artery bypass graft surgery; OR = odds ratio.

0.77 with CI 0.48 to 1.25. In general, observational studies report a higher mortality rate, but this difference does not substantially affect the ORs, indicating that the difference is the same in both treatment groups. No heterogeneity is observed with respect to mortality ($I^2 = 0$), neither in the RCTs nor in the observational studies, nor when both types are considered together.

MYOCARDIAL INFARCTION. Myocardial infarction is a rare event, it was not reported in any RCT; therefore, no effect size can be calculated (Table 2). In observational studies, MI is equally frequent after MiECT and OPCABG; the Bayesian OR is 1.15 with credibility interval 0.3 to 4.37, and the frequentist OR in observational studies is 2.22 with CI 0.43 to 11.61 with no heterogeneity ($I^2 = 0$).

STROKE. Stroke is a rare event: 36% of the studies report zero events (Table 2). The stroke rate might be higher after MiECT in RCTs, but the difference does not reach significance. The Bayesian OR is 2.1 with credibility interval 0.42 to 11.19. The corresponding frequentist OR cannot be calculated (CI: 0 to ∞). In observational studies, the Bayesian OR is 1.55 with credibility interval 0.68 to 3.37, which is close to the frequentist OR of 1.66, CI 0.83 to 3.33. No heterogeneity is observed in any group ($I^2 = 0$).

POSTOPERATIVE ATRIAL FIBRILLATION. With respect to AF, there was no study reporting a rate of zero, so AF cannot be considered as a rare event (Supplemental Fig 1). For this reason, we analyzed it using the frequentist approach (Table 2). Atrial fibrillation is equally frequent after MiECT and after OPCABG, OR 0.87 (CI: 0.56 to 1.36) with a high heterogeneity (81.1%), when all studies are considered. In RCTs, the OR is 0.95 (CI: 0.71 to 1.26) with no heterogeneity, whereas in observational studies, the OR decreases to 0.56 (CI: 0.45 to 0.69) with high heterogeneity (90.3%).

RENAL DYSFUNCTION. Not a single case of acute kidney injury was reported after MiECT in RCTs, so no effect size can be calculated (Table 2). In observational studies, renal failure is no rare event; the frequentist OR is 0.86, CI 0.34 to 2.16 with moderate heterogeneity (44.5%).

NUMBER OF ANASTOMOSES. The standardized mean difference (SMD) of the number of anastomoses is 0.82, CI 0.44 to 1.20 (the crude difference between the groups is 0.61, CI: 0.56 to 0.66), but the heterogeneity between the trials is very high ($I^2 = 95\%$). In the RCTs alone, this difference is smaller (0.56, CI: 0.39 to 0.72); and in the observational studies, the difference is larger (1.12, CI: 1.03 to 1.21). In both subgroups, heterogeneity is very high: $I^2 = 91\%$ within the randomized trials; $I^2 = 96\%$ within the observational studies (Fig 3).

BLOOD LOSS. The SMD of blood loss is overall 0.16 (CI: −0.05 to 0.37), but with a high heterogeneity of 62%; that comes exclusively from the observational studies ($I^2 = 0\%$ within the RCTs and $I^2 = 83.4\%$ in observational studies; Fig 4). In RCTs, the SMD is 0.23 (CI: 0.00 to 0.45), whereas in observational studies, the SMD is 0.14 (CI: −0.21 to 0.50).

INTUBATION TIME, LENGTH OF ICU STAY, LENGTH OF HOSPITAL STAY. Intubation time, length of ICU stay, and length of hospital stay were similar in the two treatment groups when considering all studies (0.07, CI: −0.21 to 0.35; 0.08, CI: −0.04 to 0.21; and 0.04, CI: −0.25 to 0.32, respectively); the RCTs (0.01, CI: −0.34 to 0.37; 0.11, CI: −0.11 to 0.32, and −0.04, CI: -0.24 to 0.15, respectively); and in observational studies (0.22, CI: −0.16 to 0.6). However, only Munos and associates [30] reported intubation time, 0.02 (CI: −0.08 to 0.12) and 0.69 (CI: −0.17 to 1.56). Heterogeneity is moderate for intubation time ($I^2 = 51.1\%$, 59.6% in RCTs and I^2 not calculated in observational studies), low for ICU stay ($I^2 = 27.1\%$, with $I^2 = 32.5\%$ in RCTs and $I^2 = 0\%$ in observational studies [Supplemental Fig 2]), and high for hospital stay (overall $I^2 = 77.6\%$, in RCTs $I^2 = 10.5\%$ and in observational studies $I^2 = 91.8\%$ [Supplemental Fig 3]).

Comment

The concepts of MiECT and OPCABG have been introduced in the field of CABG to eliminate or at least mitigate the disadvantages of standard extracorporeal circulation [11, 34, 35]. Both methods have strengths and benefits—for instance, the safety of a heart-lung machine during the procedure but also the advantage of a "no touch method" in OPCABG where the aorta is untouched during cannulation and avoided for proximal anastomoses [36–38]. These positive aspects compared favorably with those after full extracorporeal circulation and have been investigated in various studies over the past decade [21, 39–41]. Nevertheless, different independent and systematic concerns have been raised with regard to both applications [11]. The principal points of discussion are perioperative outcome, safety of MiECT, and related aspects, for example, aortic cannulation, filled heart, impaired luxation, and volume shift, and conversely, the known issues of OPCABG in terms of blood-free field with related anastomosis quality, long-term patency, and hemodynamic instability, as well as learning curve of the surgeon and the anesthesiologist concerning intraoperative management.

In this analysis, we were able that to demonstrate that there is no disadvantage for MiECT when compared with OPCABG, with respect to inhouse mortality, even though blood loss is higher in MiECT patients, which we would

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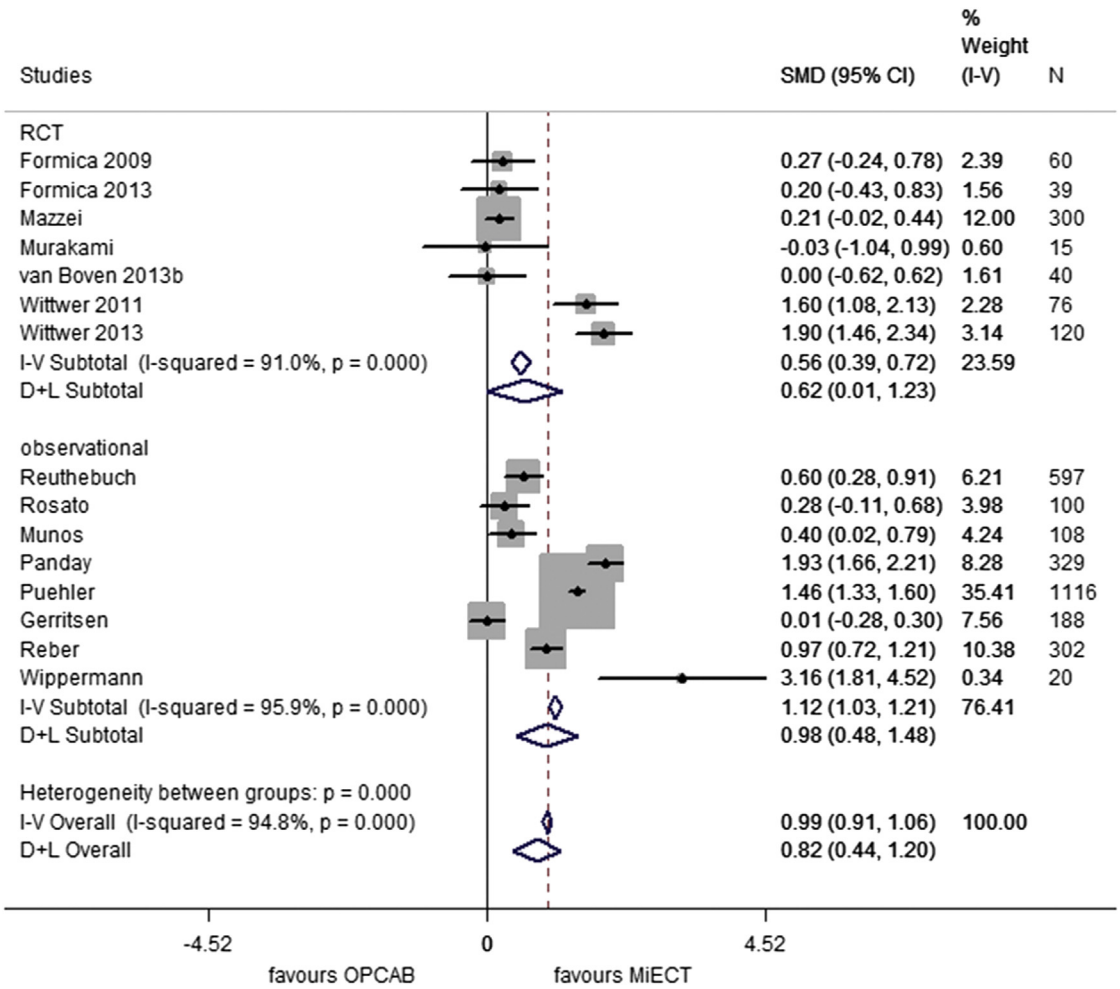

Fig 3. Number of anastomoses. (CI = confidence interval; D+L Subtotal/Overall = random effect meta-analysis; I-V Subtotal/Overall = fixed effects meta-analysis; MiECT = minimally invasive extracorporeal circulation technologies; OPCAB = off-pump coronary artery bypass; RCT = randomized clinical trial; SMD = standardized mean difference.)

expect to increase mortality in the short term. There was no evidence that AF—a well-known factor for several related comorbidities, for example, stroke, thromboembolisms [42]—is more frequent after MiECT than after OPCABG, neither in randomized nor in observational studies. The number of anastomoses varies greatly between the studies but is generally higher when MiECT is used, not only on average but also for each of the included papers. The difference is smaller in RCTs, which could indicate that in a randomized trial, surgeons tend to do an equal number of grafts with MiECT and OPCABG (Fig 3).

One paper reported a follow-up longer than discharge [28], but no paper reported long-term survival estimates or hazard ratios for the two treatments. Long-term mortality would be the most important outcome to reliably compare the two strategies, because it is only in the long term that advantages and disadvantages might or might not compensate.

In randomized trials [5, 18–21, 31], the mortality rate is biased: 2,760 of the 3,410 patients and 72 of the 78 inhouse deaths were extracted from observational studies. This bias, fortunately, does not induce a bias of the ORs.

The risk of stroke is a significant issue for MiECT and result (most frequently) from the cannulation of the ascending aorta, especially when compared with the no-touch technique of OBCABG [43]. Except for AF and renal dysfunction, all binary endpoints are rare, so some of the CIs are huge. Larger cohorts would increase the reliability to the results. Blood loss is slightly more pronounced in MiECT operations; the difference is larger in randomized trials, indicating that in similar patients, bleeding is more likely when MiECT is used.

The Bayesian method was chosen for the analysis of rare endpoints (the primary endpoint mortality and the secondary endpoints MI and stroke) because many studies reported no event in one or both study arms owing to small study sizes and rare endpoints. The usual frequentist type of analysis cannot deal with zero cells when calculating risk ratios; therefore, studies with empty cells are omitted from the analysis or zero events are replaced by partial events, the standard is 0.5. We

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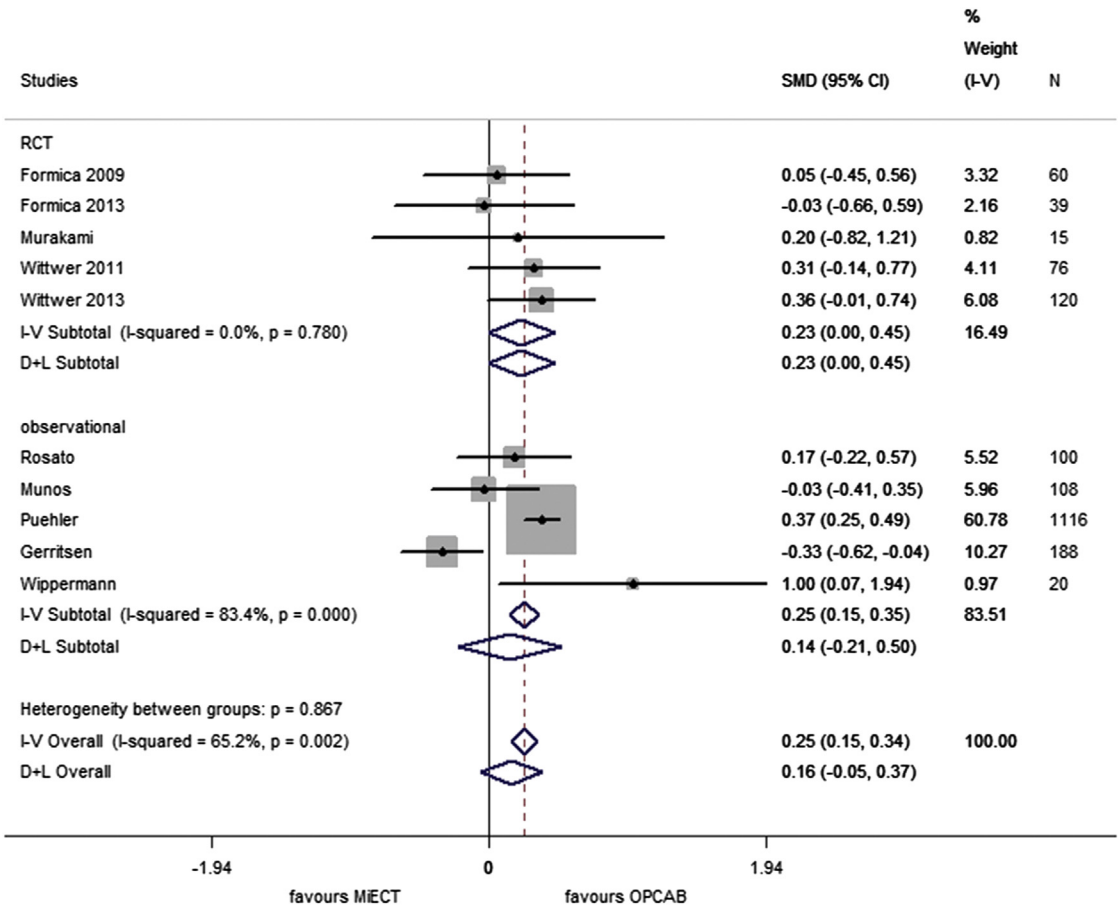

Fig 4. Blood loss. (CI = confidence interval; D+L Subtotal/Overall = random effect meta-analysis; I-V Subtotal/Overall = fixed effects meta-analysis; MiECT = minimally invasive extracorporeal circulation technologies; OPCAB = off-pump coronary artery bypass; RCT = randomized clinical trial; SMD = standardized mean difference.)

considered the risk of biased results that is associated with either usual analysis strategy to be too high and so decided to use the Bayesian method, which can handle zero cells.

There are several limitations to this study. Most important, to validly answer the question whether MiECT might indeed be superior to OPCABG would need long-term follow-up data. The advantages of either treatment might prevail over time. Our study shares this limitation with all other papers in the field. Most studies do not report troponin, creatine kinase, and creatine kinase–myocardial band, or not in a way that would be comparable (time interval after surgery, measurement regimen), which could be an excellent marker of cell damage in the myocardium shortly after the operation [44, 45]. A further limitation is that the included studies do not give explicit definitions of MI or renal failure. Furthermore, the differences among the techniques used in MiECT or OPCABG are not reported for the included studies, especially no separate event rates for different MiECT or OPCABG strategies are provided in the studies. Meta-analysis techniques have been developed for RCTs, and inclusion of observational studies increases the heterogeneity and widens the CIs of all estimates. Even so, we consider the analysis of observational studies justified by our results because, in this case, far more statistical power was generated and predictions significantly enabled as stated above for each endpoint. Future research should report long-term follow-up and hazard ratios for the treatments with respect to mortality.

In conclusion, using a meta-analytic approach including randomized and observational studies, the question whether MiECT is superior to OPCABG can only be answered by long-term follow-up data. Including all eligible studies, there is no short-term disadvantage of MiECT compared with OPCABG in terms of MI, stroke, AF, renal dysfunction, intubation time, length of ICU stay, and inhouse mortality, even though blood loss is significantly higher in the MiECT group in the RCTs. The number of anastomoses is higher when MiECT is used, not only on average but also for each of the included papers. Minimally invasive extracorporeal circulation technology can be considered a valid alternative to OPCABG, especially when the support of a heart-lung machine is mandatory. As advantages of MiECT might prevail over time, however, long-term follow-up data and large cohort studies are needed.

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