Revascularization strategies in patients with multivessel coronary artery disease: a Bayesian network meta-analysis

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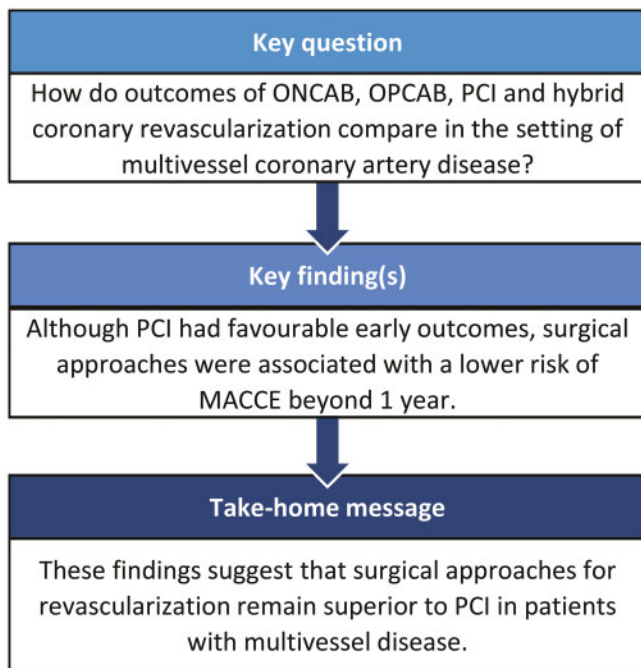[a] Helen B. Taussig Heart Center, The Johns Hopkins Hospital and School of Medicine, Baltimore, MD, USA
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Abstract

Treatment modalities for multivessel disease have rapidly evolved, yet the preferred strategy remains controversial. This meta-analysis compared outcomes after on-pump (ONCAB), off-pump coronary artery bypass grafting (OPCAB), percutaneous coronary intervention (PCI) or hybrid coronary revascularization. A comprehensive search for observational studies and randomized controlled trials published by August 2020 was performed. A Bayesian network meta-analysis was conducted for early (<30 days) and late (>12 months) outcomes. A total of 119 studies were included ($n = 700\ 458$ patients). The main analysis was confined to 31 randomized controlled trials ($n = 24\ 932$ patients). PCI was associated with lower early mortality [odds ratio (OR) 0.50, 95% confidence interval (CI) 0.31–0.79] and stroke (OR 0.22, 95% CI 0.06–0.60) rates compared with ONCAB, whereas a reduced risk of early myocardial infarction was observed with OPCAB compared with ONCAB (OR 0.53, 95% CI 0.32–0.83). Late target vessel revascularization and major adverse cardiac and cerebrovascular events were both increased with PCI compared with ONCAB, OPCAB and hybrid coronary revascularization (by 127–203% and 59–64%,

respectively), and late major adverse cardiac events were increased in PCI compared with ONCAB and OPCAB (by 64% and 59%). However, PCI was associated with a significantly lower risk of late stroke compared with ONCAB (OR 0.70, 95% CI 0.52–0.89). Sensitivity analyses (i) including observational studies and (ii) limiting to studies with recent cohorts confirmed the findings of the main analysis. Surgical approaches for revascularization remain superior to PCI in patients with multivessel disease. Hybrid coronary revascularization might be viable for some patients, although more evidence from randomized controlled trials is warranted.

Keywords: Coronary artery bypass grafting • Hybrid coronary revascularization • Multivessel disease • Network meta-analysis • Percutaneous coronary intervention

ABBREVIATIONS

CABG	Coronary artery bypass grafting
CI	Confidence interval
HCR	Hybrid coronary revascularization
MACCE	Major adverse cardiac and cerebrovascular events
MACE	Major adverse cardiac events
MI	Myocardial infarction
MVD	Multivessel coronary artery disease
ONCAB	On-pump coronary artery bypass grafting
OPCAB	Off-pump coronary artery bypass grafting
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trials
SUCRA	Surface under the cumulative ranking curve
TVR	Target vessel revascularization

INTRODUCTION

Multivessel coronary artery disease (MVD) is defined as luminal stenosis of at least 70% in at least two major coronary arteries or in one coronary artery in addition to a 50% or greater stenosis of the left main trunk [1]. Given that coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) both effectively and safely revascularize the myocardium, both are established modalities in the treatment of patients with MVD. Although ongoing debate about the benefits and risks of each strategy continues, it has become established that PCI offers favourable short-term outcomes related to its minimally invasiveness, while CABG is superior in terms of long-term freedom from target vessel revascularization (TVR) and myocardial infarction (MI) [2, 3]. This is reflected in the 2018 European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) [1] and the 2014 American College of Cardiology and American Heart Association (ACC/AHA) [4] guidelines on myocardial revascularization. However, most data supporting these recommendations are based on observations following on-pump CABG (ONCAB).

In recent years, the use of off-pump CABG (OPCAB) and hybrid coronary revascularization (HCR)—which combines minimally invasive direct coronary artery bypass with PCI—have become increasingly adapted [5]. Despite favourable outcomes in previous observational and randomized studies, the role of these relatively novel strategies for the treatment of patients with MVD remains unclear. In this study, we aimed to conduct a Bayesian network meta-analysis to compare early and late outcomes following ONCAB, OPCAB, PCI or HCR in the setting of MVD.

MATERIALS AND METHODS

Eligibility criteria, databases and search strategy

We followed the internationally recognized PRISMA guidelines [6]. Studies were included if (i) the population consisted of patients with MVD, (ii) patients underwent coronary revascularization by means of ONCAB, OPCAB, PCI or HCR, (iii) outcomes included early (<30 days) and/or late (>12 months) all-cause mortality, MI, TVR, stroke, major adverse cardiac events (MACE) and/or major adverse cardiac and cerebrovascular events (MACCE) and (iv) studies were prospective or retrospective observational studies or randomized controlled trials (RCTs). Multi-arm trials were also included in the study.

PubMed/MEDLINE, Embase, Cochrane Controlled Trials Register (CENTRAL/CCTR) and reference lists of relevant articles were searched for English-language peer-reviewed publications meeting our inclusion criteria and published by 5 August 2020. The detailed search terms that were used for this search are given in Supplementary Material, Methods. The following steps were taken: (i) identification of titles of records through databases searching, (ii) removal of duplicates, (iii) screening and selection of abstracts, (iv) assessment for eligibility through full-text articles and (v) final inclusion in the study. Studies were selected by two independent reviewers (D.N. and X.J.). When concordance was absent, a third reviewer took the decision to include or exclude the study (J.V.D.E.).

Data items

From each study, we extracted first authors' name, year of publication, country of origin, study design, years of enrolment, sample size and baseline characteristics along with the relevant early and late outcomes. Early outcomes were those occurring within 30 days of the procedures. Late outcomes were variable and determined by individual study follow-up periods but were limited to a minimum of 12 months. The key outcomes included all-cause mortality, MI, TVR, stroke, MACE and MACCE. MACE was defined as a composite of all-cause mortality, MI and TVR; whereas MACCE was defined as a composite of all-cause mortality, MI, TVR and stroke. Two independent reviewers extracted the data (X.J. and K.B.). When concordance was absent, a third reviewer checked the data and took the final decision (J.V.D.E.).

Although inclusion was limited to patient cohorts with MVD, a proportion of <5% of patients with non-MVD was tolerated for studies reporting outcomes of mixed populations. If studies reported only the outcomes of a CABG group, consisting of both ONCAB and OPCAB, it was checked if outcomes were stratified in a related publication. If this was not the case, the proportion of OPCAB was determined: studies reporting ≥80% OPCAB were

included in the OPCAB group in our analyses, whereas other studies were included in the ONCAB group. Where multiple studies were reported on the same patient cohort, only the population with the largest sample size and longest follow-up was included.

The level of evidence for each outcome in the main analysis was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach [7].

Statistical analysis

Continuous demographical data were pooled using the 'meta-mean' function in R for continuous variables and are presented as mean [95% confidence interval (CI)], while binary demographical data were pooled using the 'metaprop' function in R and are presented as proportion (95% CI). Subgroup analysis was performed to check for baseline differences between the 4 treatment groups. *P*-values were adjusted for multiple comparison using Bonferroni *post-hoc* correction.

The network meta-analysis was conducted using a random-effects model and a Bayesian method using the 'BUGSnet' package of R software as reported by Béliveau *et al.* [8]. The main analysis included only RCTs. We specified a burn-in period of 50 000 iterations followed by 100 000 iterations with 10 000 adaptations in the nma.run() function. Higher event rate was defined to imply a worse treatment. Outcomes are reported as odds ratios (OR) with 95% CI, and statistical significance was considered when the CIs did not cross the line of neutral effect. Heterogeneity was assumed to be similar for all comparisons, and the distribution of effect modifiers was assessed using the data.plot() function. Loop inconsistency was explored using the nma.fit() and nma.compare() function to ensure that the assumption of transitivity was valid, as recommended by the NICE DSU Technical Support Document [9]. In addition, we used Bayesian Markov Chain Monte Carlo modelling to rank the treatments according to the surface under the cumulative ranking curve (SUCRA) probabilities. Ranking is performed based on the point estimates and standard errors of the network estimates. They measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. Rank 1 is considered as the best and leads to the greatest reduction in the relevant outcome, whereas rank N the worst and is associated with higher rates of the outcome. League plots and forest plots were constructed to demonstrate the estimated relative effect sizes for all treatments.

As a sensitivity analysis, all comparisons were repeated (i) including data from both observational studies and RCTs and (ii) including only studies with a period of enrolment after the year 2005 in order to evaluate potential differences using contemporary standards for all the included treatments. All analyses were performed using R Statistical Software (version 4.0.5, Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection and characteristics

A total of 5551 citations were identified, of which 243 studies were potentially relevant and retrieved as full text (Fig. 1). One hundred and nineteen studies fulfilled our eligibility criteria (Supplementary Material, Table S1). A total of 700 458 patients (ONCAB: 438 743 patients; OPCAB: 44 980 patients; PCI: 213 536 patients; HCR: 3199 patients) were included from studies published from 2000 to 2020. Of the included studies, 31 were RCTs, 21 were prospective observational studies and 67 were retrospective observational studies. Among the latter, 24 studies used propensity-matching. Thirty-eight of the studies were multicentre studies. Six were multi-arm trials.

When focusing on the 31 RCTs that constitute the main analysis, the number of patients in the individual studies ranged from 50 to 4752. The median follow-up duration was 2.8 years (interquartile range 1–5 years). Baseline characteristics for all 4 treatment arms were largely comparable, suggesting adequate balance of effect modifiers (Table 1). However, the proportion of patients with peripheral arterial disease was higher in HCR (30.8%) when compared with ONCAB (12.0%, *P* = 0.026) and PCI (6.0%, *P* = 0.007), and proportion of patients with stable angina in HCR (85.1%) was higher than that in ONCAB (65.4%, *P* = 0.031) and OPCAB (69.2%, *P* = 0.020). Finally, reflecting an overall higher risk profile in ONCAB and OPCAB, the EuroSCORE in these groups were significantly higher than those in PCI and HCR (all *P* < 0.05). Characteristics for the complete set of all 119 studies are given in Supplementary Material, Table S2.

Main analysis

The main analysis consisted of the 31 RCTs. The evidence network is shown in Fig. 2. League plots summarizing the results of the network meta-analysis are given in Figs 3 and 5, and corresponding forest plots are given in Supplementary Material, Figs S1 and S2. SUCRA curves for all outcomes are presented in Figs 4 and 6. A GRADE assessment of the main analysis is provided in Supplementary Material, Tables S2 and S3.

Early outcomes. Early mortality was significantly reduced with PCI compared with ONCAB (OR 0.50, 95% CI 0.31–0.79). Early mortality also tended to be lower with OPCAB compared with ONCAB (OR 0.80, 95% CI 0.50–1.04), although this was not significant (Fig. 3). Bayesian Markov Chain Monte Carlo modelling demonstrated that PCI had the lowest probability of early mortality (SUCRA 94.8%), followed by OPCAB (SUCRA 61.4%), ONCAB (SUCRA 27.4%) and HCR (SUCRA 16.3%; Fig. 4A).

Demonstrating a similar pattern, early stroke was significantly reduced with PCI compared with ONCAB (OR 0.22, 95% CI 0.06–0.60). Here as well, early stroke also tended to be lower with OPCAB compared with ONCAB (OR 0.65, 95% CI 0.22–1.07), although this was not significant (Fig. 3). Bayesian Markov Chain Monte Carlo modelling demonstrated that PCI had the lowest probability of early stroke (SUCRA 92.5%), followed by OPCAB (SUCRA 55.1%), HCR (SUCRA 35.3%) and ONCAB (SUCRA 17.1%; Fig. 4D).

The network meta-analysis furthermore revealed that OPCAB reduced the risk of early MI by 47% compared with ONCAB (OR 0.53, 95% CI 0.32–0.85; Fig. 3). Bayesian Markov Chain Monte Carlo modelling demonstrated that OPCAB had the lowest probability of early MI (SUCRA 92.7%), followed by PCI (SUCRA 46.2%), HCR (SUCRA 32.5%) and ONCAB (SUCRA 28.6%; Fig. 4B).

No differences were observed with regard to early TVR, MACE or MACCE (Fig. 3). Bayesian Markov Chain Monte Carlo modelling demonstrated that ONCAB had the lowest probability of early TVR (SUCRA 80.4%), followed by HCR (SUCRA 47.8%), PCI
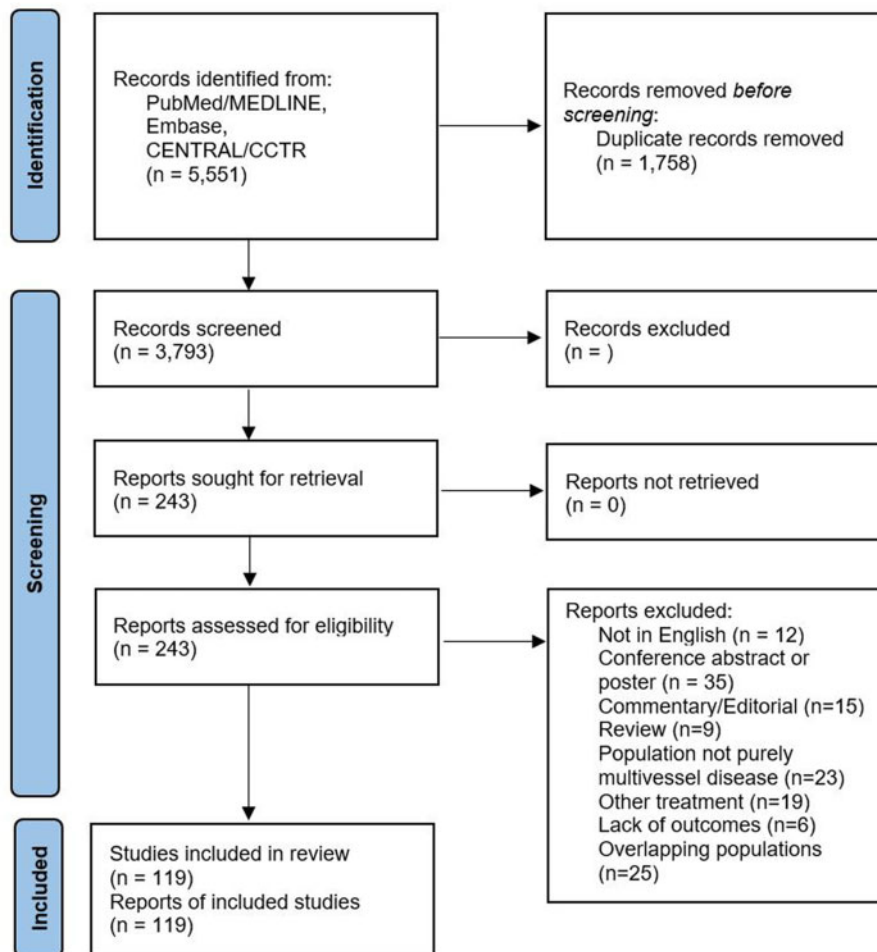
Figure 1: PRISMA flow diagram of studies included in data search.

(SUCRA 36.8%) and OPCAB (SUCRA 35.1%), although with important overlap (Fig. 4C). In terms of MACE, OPCAB had the lowest probability (SUCRA 79.8%), followed by ONCAB (SUCRA 54.8%), PCI (SUCRA 36.6%) and HCR (SUCRA 28.8%; Fig. 4E). Finally, early MACCE was lowest in OPCAB (SUCRA 76.7%), followed by PCI (SUCRA 73.7%), ONCAB (SUCRA 26.4%) and HCR (SUCRA 23.3%; Fig. 4F).

Late outcomes. The network meta-analysis found no significant differences in late mortality between treatment groups (Fig. 5). Bayesian Markov Chain Monte Carlo modelling demonstrated that ONCAB had the lowest probability of late mortality (SUCRA 74.1%), followed by HCR (SUCRA 53.8%), OPCAB (SUCRA 47.4%) and PCI (SUCRA 25.8%; Fig. 6A).

Similarly, no differences in late MI were observed between treatment groups (Fig. 5). Bayesian Markov Chain Monte Carlo modelling demonstrated that HCR had the lowest probability of late MI (SUCRA 69.0%), followed by OPCAB (SUCRA 62.6%), ONCAB (SUCRA 49.7%) and PCI (SUCRA 18.7%; Fig. 6B).

PCI was associated with significantly higher rates of late TVR, with a 203% increased risk compared with ONCAB (OR 3.03, 95% CI 2.33–4.00), 156% compared with OPCAB (OR 2.56, 95% CI 1.64–4.00) and 127% compared with HCR (OR 2.27, 95% CI 1.06–4.55; Fig. 5). Bayesian Markov Chain Monte Carlo modelling

demonstrated that ONCAB had the lowest probability of late TVR (SUCRA 88.5%), followed by OPCAB (SUCRA 59.1%), HCR (SUCRA 51.8%) and PCI (SUCRA 0.7%; Fig. 6C).

The network meta-analysis revealed that PCI reduced the risk of late stroke by 30% compared with ONCAB (OR 0.70, 95% CI 0.52–0.89; Fig. 5). Bayesian Markov chain Monte Carlo modelling demonstrated that PCI had the lowest probability of late stroke (SUCRA 84.6%), followed by HCR (SUCRA 51.4%), OPCAB (SUCRA 43.8%) and ONCAB (SUCRA 20.3%; Fig. 6D).

The risk of late MACE was significantly increased with PCI, with a 79% increase compared with ONCAB (OR 1.79, 95% CI 1.56–2.08) and a 67% increase compared with OPCAB (OR 1.67, 95% CI 1.33–2.08). The risk with PCI also tended to be higher compared with HCR (1.54, 95% CI 0.97–2.33; Fig. 5). Bayesian Markov Chain Monte Carlo modelling demonstrated that ONCAB had the lowest probability of late MACE (SUCRA 85.1%), followed by OPCAB (SUCRA 59.4%), HCR (SUCRA 54.6%) and PCI (SUCRA 0.9%; Fig. 6E).

Similarly, the risk of late MACCE was significantly increased with PCI, with a 64% increase compared with ONCAB (OR 1.64, 95% CI 1.43–1.85), a 59% increase compared with OPCAB (OR 1.59, 95% CI 1.27–1.96), and a 64% increase compared with HCR (OR 1.64, 95% CI 1.04–2.44; Fig. 5). Bayesian Markov Chain Monte Carlo modelling demonstrated that ONCAB had the lowest probability of late MACE (SUCRA 71.0%), followed by HCR

ADULT CARDIAC

Table 1: Main analysis including randomized controlled trials

Variable	Procedure				P-value[a]					
	ONCAB	OPCAB	PCI	HCR	PCI versus ONCAB	OPCAB versus ONCAB	HCR versus ONCAB	PCI versus OPCAB	HCR versus PCI	HCR versus OPCAB
Age, years	64.5 (61.2–67.8)	65.8 (61.9–69.7)	62.6 (61.7–63.5)	61.9 (60.7–63.0)	0.274	1.000	0.799	0.733	1.000	0.353
Male sex, %	80.1 (72.2–86.3)	80.8 (73.1–86.7)	73.0 (51.3–87.4)	75.3 (68.6–80.9)	0.454	1.000	1.000	1.000	1.000	1.000
Diabetes mellitus, %	51.6 (26.6–75.8)	29.1 (24.2–34.5)	94.5 (23.5–99.9)	28.2 (20.4–37.5)	1.000	0.545	0.547	0.416	0.402	1.000
Smoking, %	28.6 (20.3–38.6)	34.1 (22.8–47.5)	23.6 (13.9–37.2)	37.6 (31.0–44.8)	1.000	1.000	0.813	1.000	0.403	1.000
AHT, %	58.2 (44.6–70.6)	57.8 (42.2–72.0)	63.4 (41.5–81.3)	86.6 (52.4–97.4)	1.000	1.000	0.624	1.000	1.000	0.635
Dyslipidaemia, %	69.5 (53.7–81.7)	73.2 (61.1–82.6)	60.1 (28.9–84.8)	60.6 (50.5–70.0)	1.000	1.000	1.000	1.000	1.000	0.630
BMI, kg/m²	27.6 (26.8–28.4)	27.5 (26.6–28.4)	28.4 (26.2–30.6)	28.3 (27.7–28.9)	1.000	1.000	0.986	1.000	1.000	1.000
COPD	8.0 (5.3–12.0)	11.3 (7.3–17.0)	5.6 (2.8–10.8)	7.7 (2.9–18.8)	1.000	1.000	1.000	0.477	1.000	1.000
CKD, %	3.8 (1.4–10.0)	3.9 (1.5–9.9)	6.5 (2.3–16.7)	1.9 (0.3–12.4)	1.000	1.000	1.000	1.000	1.000	1.000
eGFR, ml/min/1.73m²	78.1 (66.6–89.6)	ND	ND	77.9 (70.6–85.2)	ND	ND	1.000	ND	ND	ND
Prior MI, %	38.8 (30.5–47.8)	43.9 (38.9–49.1)	31.9 (17.4–51.1)	53.4 (45.3–61.4)	1.000	1.000	0.106	1.000	0.257	0.315
Prior CABG, %	0.3 (0.0–2.2)	ND	0.5 (0.0–14.2)	ND	1.000	ND	ND	ND	ND	ND
Prior PCI, %	11.3 (6.3–19.4)	13.2 (8.2–20.7)	5.7 (0.6–39.0)	ND	1.000	1.000	ND	1.000	ND	ND
CHF, %	15.8 (5.4–38.2)	32.2 (14.8–56.5)	4.6 (1.2–16.3)	5.8 (1.9–16.4)	0.874	1.000	1.000	0.055	1.000	0.055
EF, %	52.9 (29.6–76.2)	43.3 (14.1–72.4)	60.9 (57.8–64.0)	57.9 (54.4–61.4)	1.000	1.000	1.000	1.000	1.000	1.000
PAD, %	12.0 (7.2–19.3)	17.1 (11.4–24.8)	6.0 (2.3–15.0)	30.8 (19.8–44.5)	1.000	1.000	**0.026**	0.249	**0.007**	0.274
CVA, %	8.3 (6.0–11.3)	7.7 (5.0–11.8)	6.6 (4.6–9.4)	5.5 (2.8–10.6)	1.000	1.000	1.000	1.000	1.000	1.000
Stable angina, %	65.4 (50.6–77.7)	69.2 (60.1–77.0)	40.9 (11.4–78.9)	85.1 (78.0–90.2)	1.000	1.000	**0.031**	1.000	0.109	**0.020**
Left main disease, %	7.9 (2.3–23.5)	19.3 (14.1–25.8)	0.1 (0.0–55.3)	ND	1.000	0.787	ND	0.828	ND	ND
Number of vessels treated	3.2 (2.9–3.4)	2.8 (2.5–3.1)	2.9 (2.8–3.0)	ND	0.227	0.305	ND	1.000	ND	ND
SYNTAX score	24.5 (21.1–27.9)	22.9 (21.8–24.0)	23.3 (19.4–27.2)	24.0 (18.4–29.5)	1.000	1.000	1.000	1.000	1.000	1.000
EuroSCORE	4.7 (3.2–6.2)	6.1 (4.7–7.4)	2.4 (1.8–3.1)	1.7 (1.5–1.9)	**0.041**	1.000	**0.001**	**<0.001**	0.208	**<0.001**

Baseline characteristics. Data are presented as mean (95% confidence interval) or proportion (95% confidence interval). P < 0.05 (bold P-values) was deemed statistically significant.

[a]P-values after Bonferroni *post hoc* correction for multiple comparison.

AHT: arterial hypertension; BMI: body mass index; CABG: coronary artery bypass grafting; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HCR: hybrid coronary revascularization; MI: myocardial infarction; ND: not determined; ONCAB: on-pump coronary artery bypass grafting; OPCAB: off-pump coronary artery bypass grafting; PAD: peripheral arterial disease; PCI: percutaneous coronary invention.
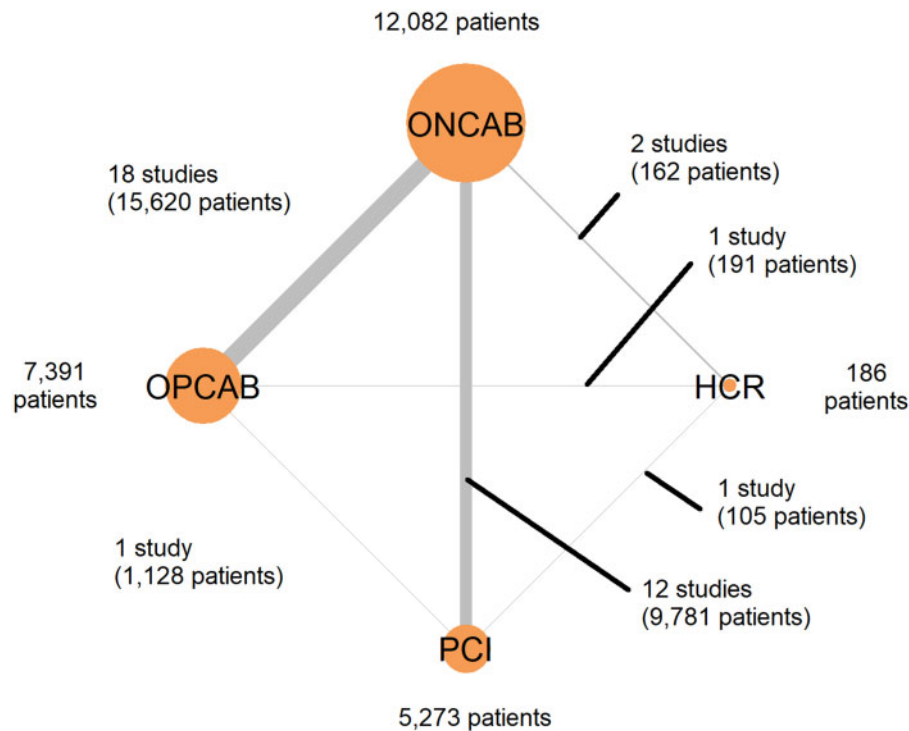
Figure 2: Main analysis including randomized controlled trials. Network plot of eligible comparisons among the different treatment modalities. Lines represent direct comparisons and the thickness of the lines indicates the number of studies comparing treatment pairs. The size of the nodes is proportional to the number of patients within each treatment modality. HCR: hybrid coronary revascularization; ONCAB: on-pump coronary artery bypass grafting; OPCAB: off-pump coronary artery bypass grafting; PCI: percutaneous coronary intervention.

(SUCRA 69.8%), OPCAB (SUCRA 58.6%) and PCI (SUCRA 0.7%; Fig. 6F).

Sensitivity analysis

The sensitivity analysis including both observational studies and RCTs confirmed the results of the main analysis, although some additional effects were observed (Supplementary Material, Figs S3–S9). In particular, OPCAB was found to reduce early MI not only compared with ONCAB but also compared with HCR and PCI. Similarly, PCI was found to reduce early stroke not only compared with ONCAB but also compared with OPCAB and HCR. Furthermore, in this sensitivity analysis, HCR increased the risk of early TVR compared with ONCAB, while PCI reduced the risk of early MACCE compared with ONCAB. In terms of late outcomes, the sensitivity analysis found significantly higher risk of late MI but lower risk of late stroke in PCI compared with OPCAB and ONCAB. Finally, these analyses found that HCR was associated with a higher risk of late TVR compared with ONCAB and OPCAB, and a higher risk of late MACE compared with ONCAB.
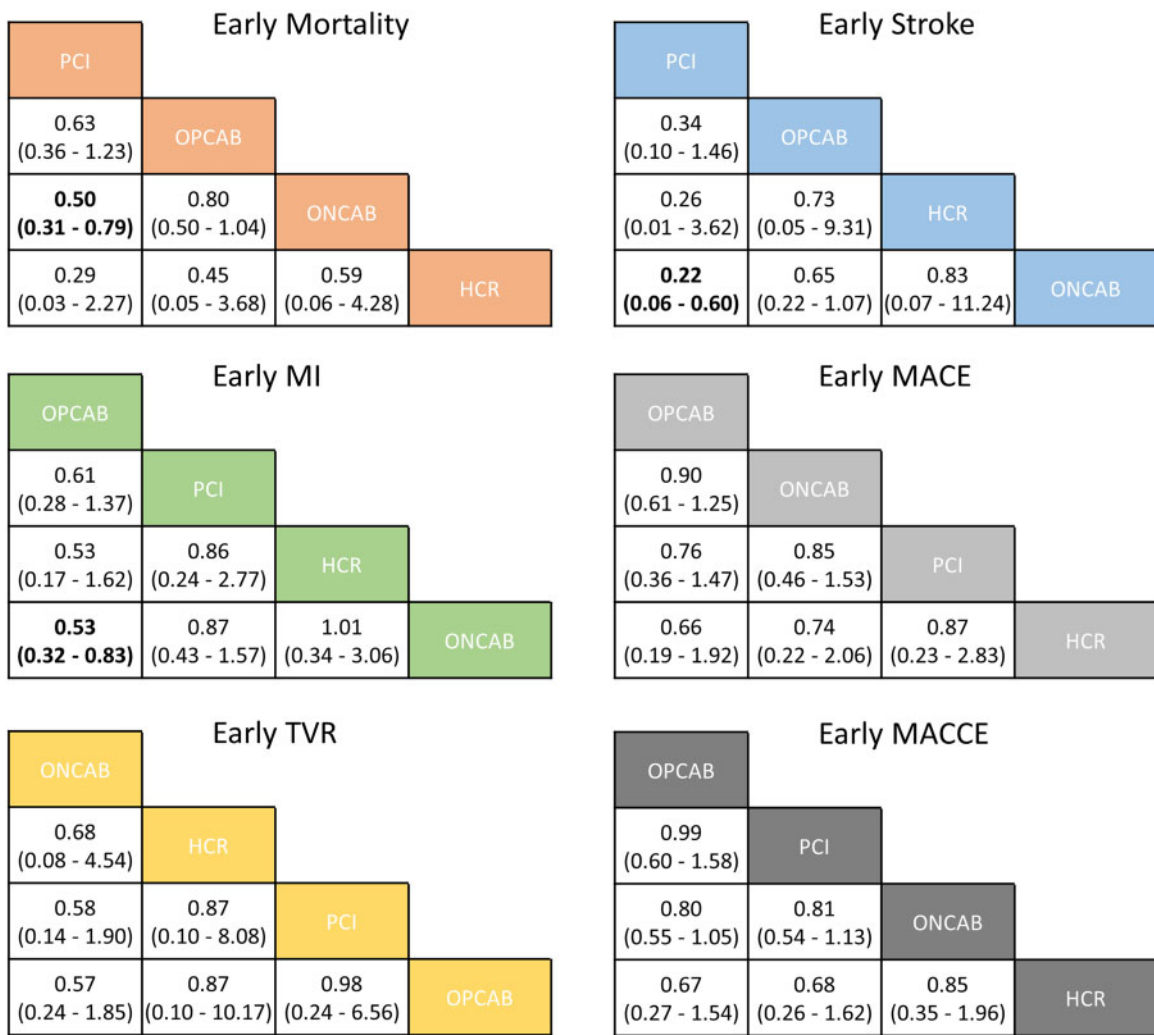
The sensitivity analysis including only studies with a period of enrolment after the year 2005 was roughly in line with those of the main analysis and the first sensitivity analysis (Supplementary Material, Figs S10–S15). Briefly, PCI was associated with lower early mortality and stroke rates when compared with ONCAB and HCR. Interestingly, this analysis found a significant effect with regard to late mortality: a significantly higher risk was observed with PCI compared with ONCAB and OPCAB. Furthermore, PCI was associated with increased risk of late TVR, MACE and MACCE compared with ONCAB, OPCAB and HCR.

The risk of MI was higher in PCI compared with ONCAB and OPCAB, while PCI and HCR both reduced the risk of late stroke compared with ONCAB and OPCAB.

DISCUSSION

Summary of evidence

While the arduous 'CABG versus PCI' debate is ongoing, alternative options for myocardial revascularization in patients with MVD such as OPCAB and HCR are increasingly becoming adapted in multiple centres. The present network meta-analysis compared the 4 main modalities (ONCAB, OPCAB, PCI and HCR) for the treatment of MVD based on 119 studies with 700 458 patients, including 31 RCTs with 24 932 patients that contributed to the main analysis. The key findings are as follows: (i) PCI was associated with lower early mortality and stroke rates compared with ONCAB; (ii) OPCAB reduced early MI compared with ONCAB; (iii) in terms of late outcomes, TVR, MACE and MACCE were increased with PCI compared with ONCAB, OPCAB and HCR; (iv) on the other hand, PCI had a lower risk of late stroke compared with ONCAB; and (v) these findings were confirmed in sensitivity analyses including both observational studies and RCTs or including only studies with a period of enrolment after the year 2005. These findings suggest that surgical approaches for revascularization remain superior to PCI in patients with MVD in the long term. OPCAB might further improve short-term outcomes in these patients. Furthermore, HCR might be a viable approach for some patients.

Early Mortality

PCI			
0.63 (0.36 - 1.23)	OPCAB		
0.50 (0.31 - 0.79)	0.80 (0.50 - 1.04)	ONCAB	
0.29 (0.03 - 2.27)	0.45 (0.05 - 3.68)	0.59 (0.06 - 4.28)	HCR

Early Stroke

PCI			
0.34 (0.10 - 1.46)	OPCAB		
0.26 (0.01 - 3.62)	0.73 (0.05 - 9.31)	HCR	
0.22 (0.06 - 0.60)	0.65 (0.22 - 1.07)	0.83 (0.07 - 11.24)	ONCAB

Early MI

OPCAB			
0.61 (0.28 - 1.37)	PCI		
0.53 (0.17 - 1.62)	0.86 (0.24 - 2.77)	HCR	
0.53 (0.32 - 0.83)	0.87 (0.43 - 1.57)	1.01 (0.34 - 3.06)	ONCAB

Early MACE

OPCAB			
0.90 (0.61 - 1.25)	ONCAB		
0.76 (0.36 - 1.47)	0.85 (0.46 - 1.53)	PCI	
0.66 (0.19 - 1.92)	0.74 (0.22 - 2.06)	0.87 (0.23 - 2.83)	HCR

Early TVR

ONCAB			
0.68 (0.08 - 4.54)	HCR		
0.58 (0.14 - 1.90)	0.87 (0.10 - 8.08)	PCI	
0.57 (0.24 - 1.85)	0.87 (0.10 - 10.17)	0.98 (0.24 - 6.56)	OPCAB

Early MACCE

OPCAB			
0.99 (0.60 - 1.58)	PCI		
0.80 (0.55 - 1.05)	0.81 (0.54 - 1.13)	ONCAB	
0.67 (0.27 - 1.54)	0.68 (0.26 - 1.62)	0.85 (0.35 - 1.96)	HCR

Figure 3: Main analysis including randomized controlled trials. League plots representing the results of the network meta-analyses comparing the effects of all interventions: early outcomes (cumulative events through <30 days follow-up after procedure). Odds ratios (OR) and 95% confidence intervals are presented for each comparison. An OR > 1 favours the row-defining treatment, and OR < 1 favours the column-defining treatment. HCR: hybrid coronary revascularization; MACCE: major adverse cardiac and cerebrovascular accidents; MACE: major adverse cardiac events; MI: myocardial infarction; ONCAB: on-pump coronary artery bypass grafting; OPCAB: off-pump coronary artery bypass grafting; PCI: percutaneous coronary intervention; TVR: target vessel revascularization.

Some comments

Overall, the findings of this comprehensive network meta-analysis support current recommendations by the 2018 ESC/ EACTS guidelines that CABG should be the favoured revascularization modality in patients with MVD with or without diabetes (both class I recommendations) [1]. The findings also concur with previous meta-analyses [2, 10–13]. In a meta-analysis of 6 RCTs involving 6055 patients, Sipahi *et al.* [2] demonstrated that CABG was associated with a 27% reduction in mortality compared with PCI, a 42% reduction in MI and a 71% reduction in TVR. They also observed a trend towards excess stroke rates with CABG, although this was not statistically significant ($P = 0.06$). Furthermore, a recent collaborative individual patient pooled analysis of 11 RCTs involving 11 518 patients found that 5-year all-cause mortality was 11.2% after PCI and 9.2% with CABG (hazard ratio 1.20, 95% CI 1.06–1.37) [14]. In subanalyses, this difference remained significant for patients with MVD but not for those with left main disease, regardless of diabetes status. While significant differences in terms of late mortality and

MI were only observed in our sensitivity analyses, our present meta-analysis could consistently demonstrate an increased risk of late TVR after PCI compared with all surgical modalities. In addition, we could also confirm the trend observed by Sipahi *et al.* [2], showing a 30% increased risk of stroke in the long term with CABG compared with PCI.

Altogether, surgical revascularization in the setting of MVD certainly appears more favourable than PCI. However, we acknowledge that there might be particular factors that favour PCI over CABG which could not be addressed in our aggregate analysis. For example, Head *et al.* [14] demonstrated that outcomes after CABG and PCI were more comparable in patients with lower SYNTAX scores. This is reflected in current ESC/EACTS guidelines [1], where a class I recommendation was assigned to PCI in patients without diabetes and with low anatomical complexity (SYNTAX score 0–22).

In contrast to previous studies, our network meta-analysis divided CABG into its 3 main types (ONCAB, OPCAB and HCR), thus providing a unique opportunity to investigate the relative treatment effects of these treatment strategies compared with
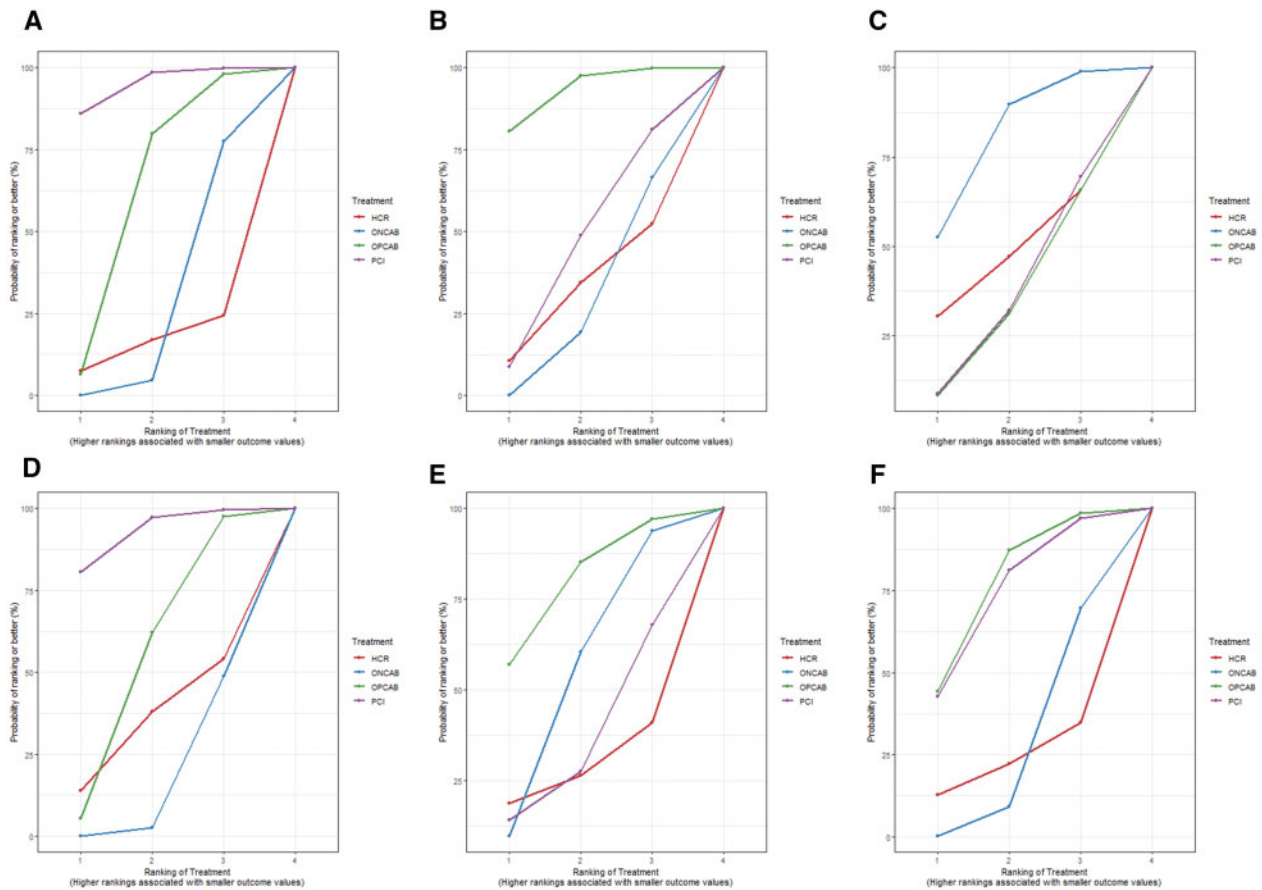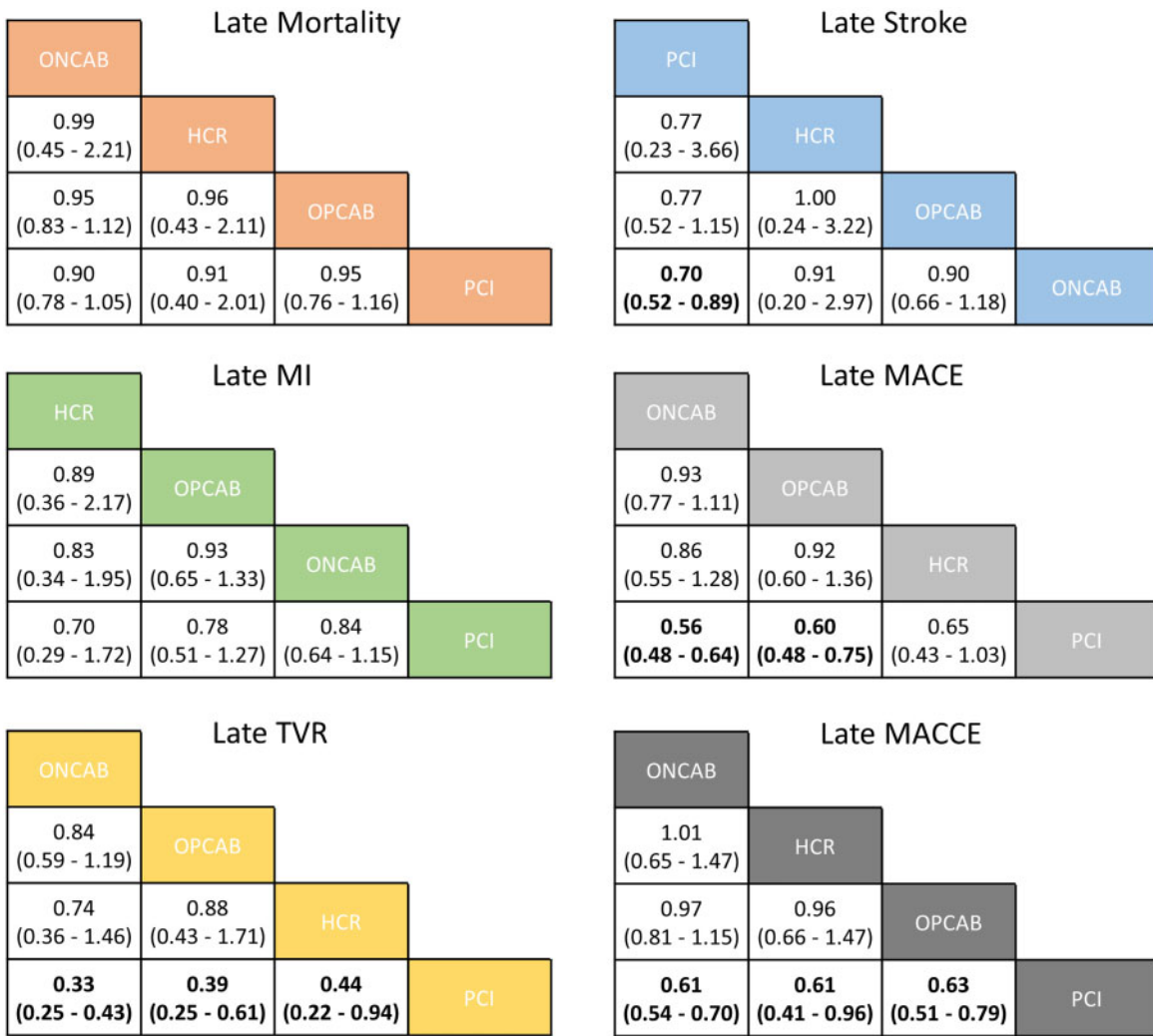
Figure 4: Main analysis including randomized controlled trials. Surface under the cumulative ranking curve plot displaying the probabilities of each treatment to be ranked first through fourth: early outcomes (cumulative events through <30 days follow-up after procedure). (**A**) early mortality, (**B**) early MI, (**C**) early TVR, (**D**) early stroke, (**E**) early MACE, (**F**) early MACCE. HCR, hybrid coronary revascularization; MACCE, major adverse cardiac and cerebrovascular accidents; MACE, major adverse cardiac events; MI, myocardial infarction; ONCAB, on-pump coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass grafting; PCI, percutaneous coronary intervention, TVR, target vessel revascularization.

one another and compared with PCI. OPCAB was developed to achieve revascularization without the use of cardiopulmonary bypass and aortic manipulation, thus theoretically reducing early complications that have been traditionally associated with ONCAB [15]. Initial observational studies have indeed shown benefits including reduced transfusion [16], renal dysfunction [17], postoperative atrial fibrillation [18] and risk of stroke [19]. However, a benefit of OPCAB has not been consistently shown in RCTs [20, 21], possibly due to the large variations in centre and surgeon volume as well as higher frequencies of incomplete revascularization with OPCAB [21]. In accordance with this, only an association of OPCAB with lower risk of early MI could be demonstrated in our main analyses, whereas OPCAB was shown to reduce early mortality, MI and stroke compared with ONCAB if observational studies were also considered. It seems that reduced early MI might be the most well-established benefit of OPCAB, as its rates of MI were also lower than PCI and HCR in our sensitivity analysis and OPCAB was ranked first in the SUCRA plots for early MI in all of our analyses. Regarding this outcome, however, we should note the emerging concern that rates of periprocedural MI after PCI and CABG might vary greatly with different definitions [22, 23]. Furthermore, retrospective studies, as in the majority of the studies included in this meta-analysis, might underestimate the rate of MI as they are less likely to include serial troponin measurement. Therefore, caution should be taken when

interpreting this body of evidence, and future studies will be needed to determine which definition has the highest diagnostic accuracy and greatest prognostic utility. Beyond 1 year after the procedure, outcomes of OPCAB tended to be comparable to ONCAB, although previous studies have suggested that the long-term benefits of OPCAB might only become apparent in high-volume institutions, with good patient selection and when anaortic techniques are used [24, 25].

HCR is an emerging approach for myocardial revascularization [5]. It combines the excellent patency of the left internal mammary artery and the possibility to avoid a full sternotomy during minimally invasive direct coronary artery bypass with the early recovery and reduced short-term complications of PCI [26]. Previous reports have demonstrated favourable outcomes, including lower need for blood transfusion, shorter length of stay and faster recovery, while maintaining similar rates of MACCE compared with conventional CABG [20, 27, 28]. In the present study, such benefits were suggested by the sensitivity analyses but could not be confirmed in the main analysis. Even though this could merely be the result from the low number of patients enrolled in the 3 RCTs that have compared HCR to either ONCAB or OPCAB to date [28–30], it should be concluded that for now there remains a lack of high-quality evidence supporting the benefits of HCR. On the other hand, our analysis of both observational and randomized evidence suggested that HCR was
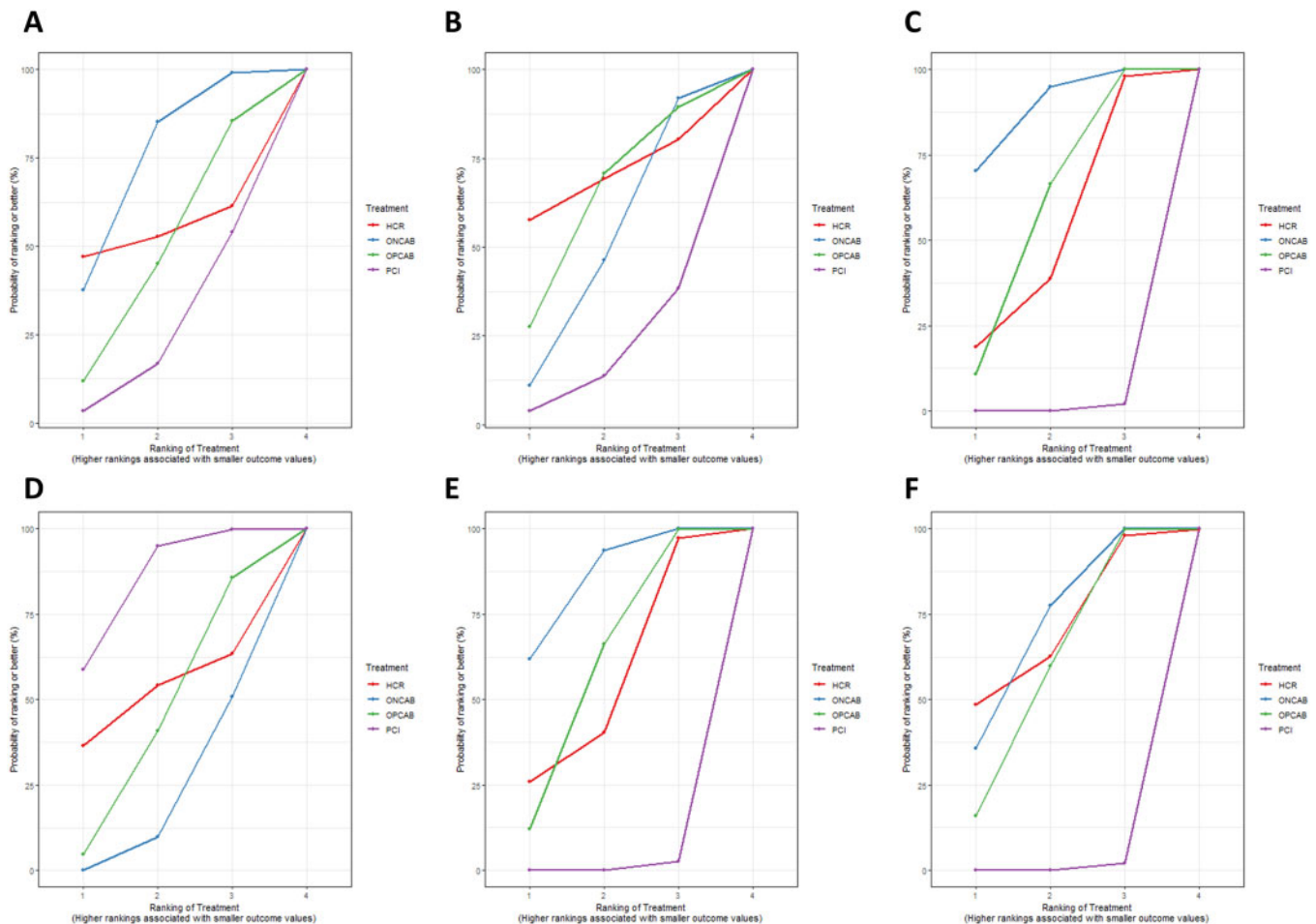
Figure 5: Main analysis including randomized controlled trials. League plots representing the results of the network meta-analyses comparing the effects of all interventions: late outcomes (cumulative events through >12 months follow-up after procedure). Odds ratios and 95% confidence intervals are presented for each comparison. An OR > 1 favours the row-defining treatment, and OR < 1 favours the column-defining treatment. HCR: hybrid coronary revascularization; MACCE: major adverse cardiac and cerebrovascular accidents; MACE: major adverse cardiac events; MI: myocardial infarction; ONCAB: on-pump coronary artery bypass grafting; OPCAB: off-pump coronary artery bypass grafting; PCI: percutaneous coronary intervention; TVR: target vessel revascularization.

associated with a significantly higher risk of both early and late TVR compared with ONCAB and OPCAB. Harskamp *et al.* [20] previously demonstrated that this effect was driven both by a greater need for left anterior descending revascularization and by revascularization for non-target lesion-related progression of native coronary artery disease. On another note, the average age in the studies was 63.4 years old and patients had lower surgical risk (as reflected by a lower EuroSCORE) than those in the ONCAB and OPCAB groups. Outcomes in a real-world setting where candidates for HCR usually include 70- to 80-year-old frail patients with comorbidities and at high risk for conventional surgery, might be different from these observed in published data and thus remain to be determined.

Limitations

There are some limitations that certainly merit consideration. First, while RCT data provide the highest quality of evidence, these constituted only 26.1% of all available data. Especially, RCTs comparing HCR with other revascularization were scarce, potentially blunting the ability to demonstrate statistically significant effects of this strategy. On the other hand, although several of the observational studies corrected for potential confounders using either propensity score matching or multivariable regression models, residual confounding cannot be excluded in the sensitivity analysis. Nonetheless, there were a number of findings that were consistent in all analyses. Second, as highlighted earlier, we included studies on the condition that >95% of the patients had MVD; therefore, a limited number of patients with single-vessel disease might have been included in our network meta-analysis. Similarly, not all studies reported outcomes for ONCAB and OPCAB separately. Studies were assigned to either of the two treatment arms in our network meta-analysis based on whether or not they contained ≥80% OPCAB cases, such that a number of OPCAB patients might have been included in the ONCAB arm and vice versa. Nonetheless, our results confirmed that this did not affect our ability to observe the individual treatment effects of both strategies. Third, revascularization strategies have

Figure 6: Main analysis including randomized controlled trials. Surface under the cumulative ranking curve plot displaying the probabilities of each treatment to be ranked first through fourth: late outcomes (cumulative events through >12 months follow-up after procedure). (**A**) late mortality, (**B**) late MI, (**C**) late TVR, (**D**) late stroke, (**E**) late MACE, (**F**) late MACCE. HCR: hybrid coronary revascularization; MACCE: major adverse cardiac and cerebrovascular accidents; MACE: major adverse cardiac events; MI: myocardial infarction; ONCAB: on-pump coronary artery bypass grafting; OPCAB: off-pump coronary artery bypass grafting; PCI: percutaneous coronary intervention; TVR: target vessel revascularization.

advanced in recent years, with improvements in overall outcomes for patients. Although most findings in our sensitivity analysis including only studies with a period of enrolment after the year 2005 revealed similar results, a mortality benefit became clear with surgical revascularization compared with PCI, which was not present in the main analysis. Fourth, while heterogeneity exists within the 4 main revascularization strategies, the current analysis allows for better generalization. Lastly, although minimally invasive surgical approaches such as multivessel (robotic-assisted) minimally invasive direct coronary artery bypass have also entered the stage for the treatment of MVD in recent years, the number of studies comparing these with approaches was too limited to be included in the present study.

CONCLUSIONS

This comprehensive network meta-analysis provides evidence that surgical revascularization remains superior to PCI in patients with MVD. OPCAB might further improve short-term outcomes in these patients. Furthermore, HCR might be a viable approach for some patients, although more evidence from RCTs is warranted to support its benefits.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Data Availability Statement

Databases and code will be made available from the corresponding author upon reasonable request.

Author contribution

Jef Van den Eynde: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Katrien Bomhals:** Data curation; Investigation; Writing—review & editing. **Dries Noé:** Data curation; Investigation; Writing—review & editing. **Xander Jacquemyn:** Data curation; Investigation; Writing—review & editing. **Keir McCutcheon:** Conceptualization; Investigation; Supervision; Validation; Writing—review & editing. **Johan Bennett:** Conceptualization; Investigation; Supervision; Validation; Writing—review & editing. **John D. Puskas:** Conceptualization; Investigation; Supervision; Validation; Writing—review & editing. **Wouter Oosterlinck:** Conceptualization; Investigation; Software; Supervision; Writing—review & editing.

Reviewer information

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