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Minimally Invasive CABG or Hybrid Coronary Revascularization for Multivessel Coronary Diseases: Which Is Best? A Systematic Review and Metaanalysis

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ABSTRACT

Objectives: Minimally invasive coronary revascularization (MICR) involves minimally invasive direct coronary artery bypass grafting (MIDCAB) and robotic-assisted coronary artery bypass grafting (RCABG), and hybrid coronary revascularization (HCR) aims to combine MICR/RCABG on left anterior descending (LAD) and percutaneous coronary interventions (PCI) on non-LAD lesions. We performed a systematic review and metaanalysis to compare clinical outcome after MICR and HCR.

Methods: A metaanalysis was carried out through searching PubMed, EMBASE, Web of Science, and Medline for comparative studies evaluating the primary and secondary clinical end points.

Results: A systematic literature search identified 8 observational studies that satisfied our inclusion criteria, including being suitable for metaanalysis; the studies were between 1990 and 2018 and included 1084 cases of HCR and 2349 cases of MICR. Metaanalysis of these studies showed that HCR was associated with a reduced need for ICU LOS (WMD –11.46 hours, 95% CI, –18.76 ~ –4.25, P = .02), to hospital time (WMD –1.34 hours, 95% CI, –2.42 to 0.26, P < .01), and blood transfusion (OR 0.43, 95% CI, 0.31-0.59, P < .00001) than MICR. Comparisons of individual components showed no significant difference in terms of in-hospital mortality, MACCE, shock, myocardial infarction (MI), long-term survival, total variable cost, and surgical complications (including renal failure, chest drainage, bleeding).

Conclusions: HCR was noninferior to MICR in terms of in-hospital mortality, MACCE, shock, MI, long-term survival, total variable cost, and surgical complications (including renal failure, chest drainage, bleeding), whereas HCR was associated with a reduced need for ICU LOS, hospital time, and blood transfusion than MICR and less infection than MICR. Further randomized studies are warranted to corroborate these observational data.

INTRODUCITON

Coronary artery bypass grafting (CABG) was first introduced in the 1960s [Kolessov 1967]; the application of CABG in coronary disease has expanded to include minimally invasive coronary revascularization (MICR) and hybrid coronary revascularization (HCR) [Barsoum 2015]. MICR involves minimally invasive direct coronary artery

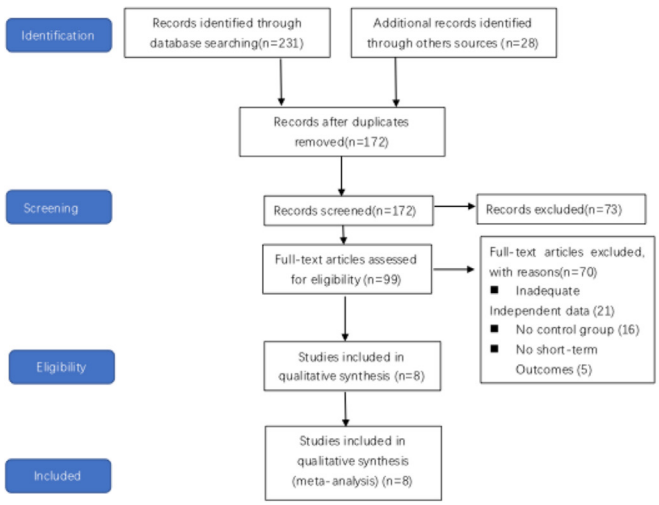

Figure 1. Search strategy.

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Abbreviations: AKI, acute kidney disease; BITA, bilateral internal mammary artery grafts; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; HCR, hybrid coronary revascularization; ICU LOS, length of stay in an intensive care unit; MICR, minimally invasive coronary revascularization; LAD, left anterior descending; LCX, circumflex branch; MACCE, major adverse cerebrovascular events; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass grafting; PCI, percutaneous coronary interventions; RCABG, robotic-assisted coronary artery bypass grafting; WMD, weighted mean difference

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Table 1. Quality Analysis of 8 Studies

	Study							
	[Bonatti 2012]	[Farid 2018]	[Halkos 2014]	[Khaliel 2017]	[Repossini 2013]	[Rosenblum 2016]	[Yang 2015]	[Zhang 2017]
Selection								
Group A*	1	1	1	1	1	1	1	1
Group B†	1	1	1	0	1	0	1	1
Group C‡	1	1	1	1	1	1	1	1
Comparability								
Group D§	5	5	5	3	5	3	4	4
Group E‖	5	4	4	5	4	5	4	4
Outcome								
Group F¶	1	1	1	1	1	1	1	1
Group G#	0	1	0	0	1	0	1	1
Total	14	14	13	11	14	11	13	13

*Group A. Assignment for treatment—any criteria reported? (If yes, score of 1). <<We have changed to "score of 1 here and throughout the table; is that what you mean?>>

†Group B. How representative was the reference group (MICR) in comparison to the general population for CABG? (If yes, score of 1; no score if the patients were selected or selection of group was not described). << Clarify this part in response to the question you raise.>>

‡Group C. How representative was the treatment group (HCR) in comparison to the general population for CABG? (If drawn from the same community as the reference group, score of 1; no score if drawn from a different source or selection of group was not described.)

§Group D. Groups comparable for 1, 2, 3, 4, 5. (If yes, score of 1 was assigned for each of these. No star was assigned if the 2 groups differed.) Comparability variables: (1) age; (2) sex; (3) hypertension; (4) diabetes; (5) ejection fraction; (6) 3-vessel disease; (7) left main stem disease; (8) urgent/emergency operation; (9) viability studies; (10) surgeon or hospital volume.

‖Group E. Groups comparable for 6, 7, 8, 9, 10. (If yes, 1 star was assigned for each of these. No star was assigned if the 2 groups differed.) Comparability variables: (1) age; (2) sex; (3) hypertension; (4) diabetes; (5) ejection fraction; (6) 3-vessel disease; (7) left main stem disease; (8) urgent/emergency operation; (9) viability studies; (10) surgeon or hospital volume.

¶Group F. Outcome assessment: clearly defined outcome of interest (if yes, 1 star).

#Group G. Outcome assessment: follow-up (score of 1 if described.)

bypass grafting (MIDCAB) and robotic-assisted coronary artery bypass grafting (RCABG). MICR procedures have aimed to further reduce invasiveness through a small incision without cardiopulmonary bypass, and MICR also shows better clinic outcome with fewer complication in terms of bleeding, draining, mediastinitis, and long-term survival [Sim 1999; Thiele 2009; Ruel 2014; Soylu 2016], has lower costs [Ruel 2013], and shows excellent graft patency for patients with multivessel revascularization [Aziz 2007]. HCR aims to combine MICR/RCABG on left anterior descending (LAD) and percutaneous coronary interventions (PCI) on non-LAD lesions, which is the most proven efficacious therapeutic proposal of cardiac surgery and interventional cardiology and has also increasingly been used to treat multivessel coronary artery disease [Aziz 2007; Puskas 2016]; and HCR aims to reduce recovery duration, hospital complications, and surgery trauma [Harskamp 2014; Phan 2015]. However, there is a lack of robust clinical evidence and available data to evaluate the effectiveness of HCR and MICR with multivessel coronary disease. With the aim of filling this knowledge gap, we compared the main clinical outcomes in patients by using HCR and MICR and analyzed which surgery techniques were better in patients with multivessel coronary disease.

METHODS

Search Strategy and Definition

Our strategy was to use a comprehensive search of PubMed, EMBASE, Web of Science, and Medline from January 1990 to January 2018 with MESH search headings, "minimally invasive coronary revascularization," "hybrid coronary revascularization," "minimally invasive direct coronary artery bypass grafting," "robotic-assisted coronary artery bypass grafting," "multivessel coronary disease," "integrated myocardial revascularization." We define 30-days mortality and major adverse cerebrovascular events (MACCE [composite of all-cause mortality, myocardial infarction, and stroke]) as the primary clinical end points and regard reoperation rate, chest drainage, operation time, bleeding, length of stay in an intensive care unit (ICU LOS), hospital time, revascularization, blood transfusion, infection and ventilation times, total variable cost into shock, MI, renal failure, and long-term follow-up of survival as secondary clinical end points.

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Table 2. The Baseline of Patients' Characteristics

Study	Type	Study period	Number of patients		Patient type		Follow-up
			HCR	RCABG/ MIDCAB	HCR	RCABG/ MIDCAB	
[Bonatti 2012]	RCS	2001 Jun to 2011 Jun	140	64	Simultaneous 28 PCI before surgery 38; surgery before PCI74	RCABG 64	5 years
[Farid 2018]	RCS	2001 Feb to 2015 Oct	82	100	Simultaneous	MIDCAB100	10.9 years
[Halkos 2014]	RCS	2010 to 2011	26	28	Simultaneous	MIDCAB	83.6 ± 11.1 months
[Khaliel 2017]	RCS	2003 Oct to 2015 Oct	147	336	Simultaneous	RCABG	12 years
[Repossini 2013]	RCS	1997 May to 2011 Feb	166	810	2 Stage	MIDCAB	4.5 ± 2.3 years
[Rosenblum 2016]	RCS	2003 Oct to 2013 Dec	306	873	2 Stage	RCABG	5 years
[Yang 2015]	RCS	2007 Feb to 2014 Oct	100	140	Simultaneous	RCABG	3 years
[Zhang 2017]	RCS	2014 Aug to 2017 Feb	40	30	2 Stage	MIDCAB	NS

Eligibility Criteria

The inclusion of studies was done according to the following: observational studies and randomized controlled trials (RCTs) comparing HCR and MICR in multivessel coronary disease, with at least 10 patients included in each cohort (Figure 1). Animal studies and review papers were excluded. Studies that did not have any of the desired outcome measures or had participants who were treated by other modalities such as percutaneous coronary intervention and emergency or salvage conditions were excluded. Studies with incomplete data were excluded.

Data Extraction and Critical Appraisal

We reviewed all abstracts, studies, and citations irrespective of the language in which the study was written. Three authors (Z. G., K. G., J. L.) reviewed independently by extracting the following data from each study: first author, year of publication, trial characteristics, study design, inclusion and exclusion criteria, graft type, clinic outcome (Figure 1). The modified Newcastle–Ottawa scale was carried out in our metaanalysis with a quality assessment score. The modified Newcastle–Ottawa scale checklist has been summarized in Table 1, and we also define the studies' scores higher than 7 as indicating high-quality studies Table 1. The quality of all studies has been evaluated by 2 authors, considered as independent researchers (W. Z., J. L.).

Statistical Analysis

Group statistics are expressed as mean ± standard deviation. The odds ratios (ORs) were used as the common measure for dichotomous data. Random effect models are mostly used in studies with large differences, mainly because patients undergoing operations in different centers have varying risk profiles and selection criteria for each surgical technique. All analyses were conducted using Review Manager version 5.3 software for Windows (The Nordic Cochrane Centre, The Version 5.3, Cochrane Collaboration, Copenhagen, Denmark; 2014). We evaluated heterogeneity by focusing on patients with left ventricular dysfunctions and a quality score greater than 7. We also used a funnel plot to assess publication bias and defined 5% as the level of significance with a 95% confidence interval.

RESULTS

Study Characteristics

We identified 8 observational studies that satisfied our inclusion criteria, including being suitable for metaanalysis; the studies were between 1990 and 2018 and included 1084 cases of HCR and 2349 cases of MICR. The date extraction was done by 2 authors, and Table 1 presents the baseline characteristics of the metaanalysis. Four studies used a single-stage approach for HCR, and 4 other studies used a staged approach for HCR. Four studies used MICR, and 4 other studies used HCR. Mean age of the patients ranged from 58 to 73 years; the male population varied from 27% to 84%, whereas duration of follow-up ranged from in-hospital to 10.3 years (Tables 2 and 3).

Outcomes of Metaanalysis

See Figures 2-5 [Bonatti 2012; Repossini 2013; Halkos 2014; Rosenblum 2015; Yang 2015; Khaliel 2017; Lufeng 2017; Farid 2018].

Primary clinical end point: in-hospital mortality. For in-hospital mortality in HCR (0.626%) and MICR (0.563%) in 4 studies, the results showed significant difference (OR 0.91; 95% CI, 0.22-3.77; $P = .9$). However, in subgroup analysis, HCRs are similar to MICRs (OR 0.73; 95% CI, 0.10-5.36; $Z = 0.31$; $P = .75$) and RCABGs (OR 1.18; 95% CI, 0.42-3.33; $Z = 0.32$; $P = .75$).

In view of MACCE in HCR (1.59%) and MICR (1.69%) in 4 studies, the results showed that MACCE

Table 3. The Baseline of Patients' Characteristics

Study	Group	N	Age, y ± SD	Male, n (%)	Diabetes, n (%)	Hyper-tension, n (%)	Previous MI, n (%)	Smoking, n (%)	COPD	LVEF	Euro SCORE	BMI
[Bonatti 2012]	HCR	140	61	111 (79.3%)	40 (28.6%)	118 (84.3%)	61 (43.6%)	40 (28.6%)	16 (11.4%)	0.60 (0.20-0.79)	2 (0-13)	29 (19-90)
	MIDCAB/ RCABG	64	62	50 (78.1%)	19 (29.7%)	53 (82.8%)	20 (31.3%)	22 (34.4%)	6 (9.4%)	0.55 (0.30-0.85)	2 (0-11)	27 (14-40)
[Farid 2018]	HCR	82	64 ± 9.82	64	86	NS	NS	NS	6		2.63 ± 2.90	NS
	MIDCAB/ RCABG	100	61 ± 10.1	86	13	NS	NS	NS	10		2.03 ± 1.92	NS
[Halkos 2014]	HCR	26	73.0 ± 5.9	18	5 (19.2)	22 (84.6)	27 (96.4)	NS	NS	0.543 ± 0.089	NS	26.8 ± 3.6
	MIDCAB/ RCABG	28	72.9 ± 5.2	20	17 (60.7)	27 (96.4)	13 (46.4)	NS	NS	0.514 ± 0.146	NS	28.1 ± 4.8
[Khaliel 2017]	HCR	147	61.2 ± 11.0	113 (76.9)	21	NS	NS	NS	4.7	NS	NS	NS
	MIDCAB/ RCABG	336	61.2 ± 10.5	250 (74.4)	12	NS	NS	NS	6.3	NS	NS	NS
[Repossini 2013]	HCR	166	65.8 ± 10.3	150	40	130	NS	45	24	NS	NS	NS
	MIDCAB/ RCABG	810	64.6 ± 12.0	0.838	NS	NS	NS	NS	NS	NS	NS	NS
[Rosen-blum 2016]	HCR	306	64.4 ± 11.9	215	113 (36.9)	280 (91.5)	NS	63 (20.6)	NS	NS	NS	28.3 ± 5.3
	MIDCAB/ RCABG	873	59.0 ± 10.1	738	241 (27.6)	728 (83.4)	NS	262 (30.0)	NS	NS	NS	29.8 ± 13.5
[Yang 2015]	HCR	100	58.7 ± 8.6	84 (84.0%)	26 (26.0%)	50 (50.0%)	20 (20.0%)	46 (46.0%)	NS	0.628 ± 0.051	1.1± 1.3	25.2 ± 2.6
	MIDCAB/ RCABG	140	59.3 ± 9.7	103 (73.6%)	34 (24.3%)	73 (52.1%)	34 (24.3%)	57 (40.7%)	NS	0.63 ± 0.057	1.4 ± 1.2	25.9 ± 2.1
[Zhang 2017]	HCR	40	65.6 ± 8.4	28	22	11	8	NS	NS	66.95 ± 7.14	NS	NS
	MIDCAB/ RCABG	30	65.8 ± 10.4	23	17	9	7	NS	NS	68.00 ± 11.08	NS	NS

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<<Should the LVEF, EuroSCORE, and BMI columns have unit information in the heads? Also, the range and perhaps SD may need to be indicated. A footnote might be best for these.>>

between HCR and MICR have a significant difference (OR 0.72; 95% CI, 0.26-2.00; *P* = .53). In subgroup analysis, HCRs are similar with MICRs (OR 0.51; 95% CI, 0.11-2.25; Z = 0.89; *P* = .37) and RCABGs (OR 1.07; 95% CI, 0.52-2.20; Z = 0.17; *P* = .86). MI (OR 0.62; 95% CI, 0.18-2.22; Z = 0.73; P = .47), shock (OR 1.02; 95% CI, 0.35-2.94; *P* = .98), renal failure (OR 0.57; 95% CI, 0.23-1.40; *P* = .22), long-term follow-up survival (OR 0.70; 95% CI, 0.35-1.40; *P* = .31) had no difference between HCRs and MICRs.

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Table 4. Results of Metaanalysis of Clinical Outcome

Primary Clinical Outcome	No.	HCR/MICR	I2 (%)	Analysis Model	Statistics Method*	OR/WMD	95% CI	*P*
In-hospital mortality	4	959/1954	34	Random	M-H	0.91	0.22-3.77	.9
MI	3	679/1890	0	Random	M-H	0.63	0.18-2.23	.47
Shock	4	959/1954	0	Random	M-H	1.02	0.35-2.94	.98
MACCE	4	819/1954	33	Random	M-H	0.72	0.26-2.00	.53
RF	2	513/1080	0	Random	M-H	0.57	0.23-1.40	.22
Mortality in the long term	3	613/595	70	Random	M-H	0.7	0.35-1.40	.31
Second Clinical Outcome	**No.**	**HCR/MICR**	**I2 (%)**	**Analysis Model**	**Statistics Method**	**OR/WMD**	**95% CI**	**P**
Reoperation	5	1066/2366	77	Random	M-H	1.06	0.41-2.72	.9
Infection	3	653/1144	7	Random	M-H	0.28	0.08-0.97	.04
Bleeding	5	931/1982	92	Random	M-H	1.14	0.3-4.26	.85
Revascularization	2	200/222	0	Random	M-H	1.11	0.58-2.14	.75
Blood transfusion	4	579/1138	17	Random	M-H	0.43	0.31-0.59	.00001
ICU LOS	3	166/198	30	Random	M-H	−11.46	−18.76 to −4.25	.02
Operation time	3	352/232	92	Random	M-H	−33.55	−72.87~5.78	.09
Hospital stay	5	1351/565	97	Random	M-H	−1.34	−2.42 to 0.26	.01
Ventilator time	4	392/262	89	Random	M-H	−2.66	−4.95 to −0.38	.02
Chest drainage	2	140/170	94	Random	M-H	−170.78	−612.17 to 270.62	.45
Cost	2	233/235	22	Random	M-H	0.01	−0.25 to 0.27	.92

*M-H, Mantel–Haenszel. <<Confirm this footnote added.>>
<<What is RF? Radiofrequency? Rheumatoid factor?>>

Second clinical end points. Five studies reported on reoperation. Three studies reported on infection. HCR was associated with less ICU LOS (WMD –11.46 hours; 95% CI, –18.76 to –4.25; *P* = .02), hospital time (WMD –1.34 hours; 95% CI, –2.42 to –0.26; *P* = .01), blood transfusion (OR 0.43; 95% CI, 0.31 to 0.59; *P* <.00001), ventilator time (WMD –2.66d; 95% CI –4.95 to 0.38; *P* = .02). However, there was no significant difference in terms of bleeding (OR 1.14; 95% CI, 0.08 to 0.97; *P* = .85).

Bias Assessment

A funnel plot with a proximal standard error between HCR and MICR is shown in Figure 6 and indicates no significant statistical bias.

DISCUSSION

In this metaanalysis, HCR was noninferior to MICR in terms of in-hospital mortality, MACCE, shock, MI, long-term survival, total variable cost, and some surgical complications (including renal failure, chest drainage, bleeding), whereas HCR was associated with a reduced need for reoperation, ICU LOS, hospital time, ventilator time, and blood transfusion in comparison with MICR and had less infection than MICR. Our study was the first metaanalysis on clinical outcomes of HCR compared with MICR, and our findings suggests HCR is a safe and durable alternative to MICR.

The common advantages of HCR and MICR compared with traditional CABG are the avoidance of cardiopulmonary bypass, aortic clamping, and complete sternotomy when one uses minimally invasive surgical techniques. The difference between HCR and MICR is the durability and survival advantage of LIMA-LAD and PCI for non-LAD in HCR for patients with multivessel CAD, but for patients with MICR, non-LAD has been treated by MIDCAB or RCABG, whereas LIMA-LAD is the same with HCR. Our studies found that in-hospital mortality, MACCE, shock, MI, long-term survival, and total variable cost have no significant difference between HCR and MICR. It means that PCI for non-LAD offer similar major clinical outcomes compared with MIDCAB/RCABG for non-LAD in the complexity of the coronary lesion. With using newer generation stents, the clinical outcome has improved after PCI in HCR, and the early restenosis rate of non-LAD vessels after PCI with drug-eluting stent seems to be significantly less than saphenous vein graft.

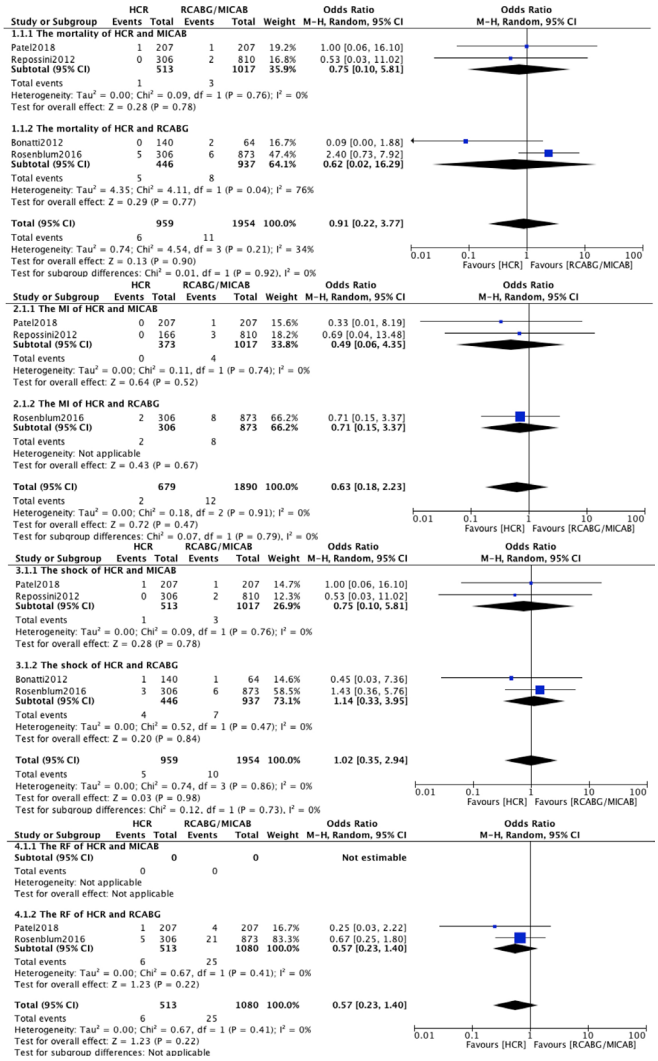

Figure 2. Clinical outcome of metaanalysis between HCR and MICR. M-H, Mantel-Haenszel; Favours, favors, _____.

Mohr and associated reported LITA to LAD with MIDCAB and PCI to non-LAD had better clinical outcome than others with surgery choice [Mohr 2013]. However, with the development of surgery technique in MICR, especially with bilateral internal mammary artery grafts (BITA) and others arteries bridge (for example radial artery, gastro-epiploic artery), performed minimally invasively, new stabilizers, and video-assisted thoracoscopic surgery, the MICR evolved as a new surgical stagey that was not only minimally invasive but also improved the survival rate and long-term patency and had fewer surgery complications compared with the HCR.

The cost of HCR were combines costly less invasive hardware and surgical disposables, catheter-based coronary intervention and very expensive coronary implants device. However, these costs may be share out by long hospital stay costs and improved surgery complications cost compared with conventional CABG. But for MICR, the lower surgery complications may lead to a decrease in total cost similar to HCR [Wu 2017].

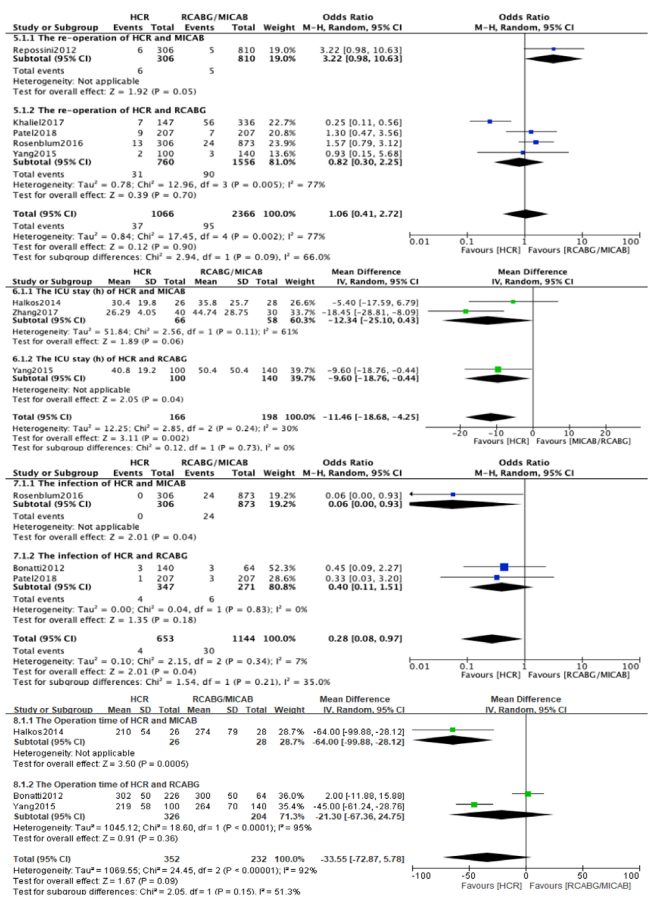

Figure 3. Clinical outcome of metaanalysis between HCR and MICR. M-H, Mantel-Haenszel; IV, inverse variance; Favours, favors, _____.

In this analysis, the significantly low requirement of blood transfusion in HCR was attributed to the short time of MIDCAB compared with MICR despite the use of aspirin and clopidogrel [Nenna 2016]. The ICU LOS, hospital time, and ventilator time were significantly shorter in HCR mean that HCR had a quick recovery which were contributed to lower blood transfusion and reduced systemic inflammation with improved postoperative recovery. And what is more, the better myocardial protection and advances in the catheter interventions are also other mechanisms for quickly recovery. Some factors influenced the quick recovery, including the surgeon's experience, learning-curve effect, cooperation of physician and surgeon, and postoperative management [Hart 1999]. The RCABG was blunted compared with the conventional CABG due to the inflammatory response, for example, the cytokine and C-reactive protein release [Stastny 2018]. A similar clinical outcome [Misumida 2018] showed no significant difference between conventional CABG and RCABG and fewer blood products, shorter ICU stay, hospital stay, and less pain compared with conventional CABG [Messerli 2018].

Despite the potential benefits of MICR, the technique has not been perfected. This can be attributed to a number of

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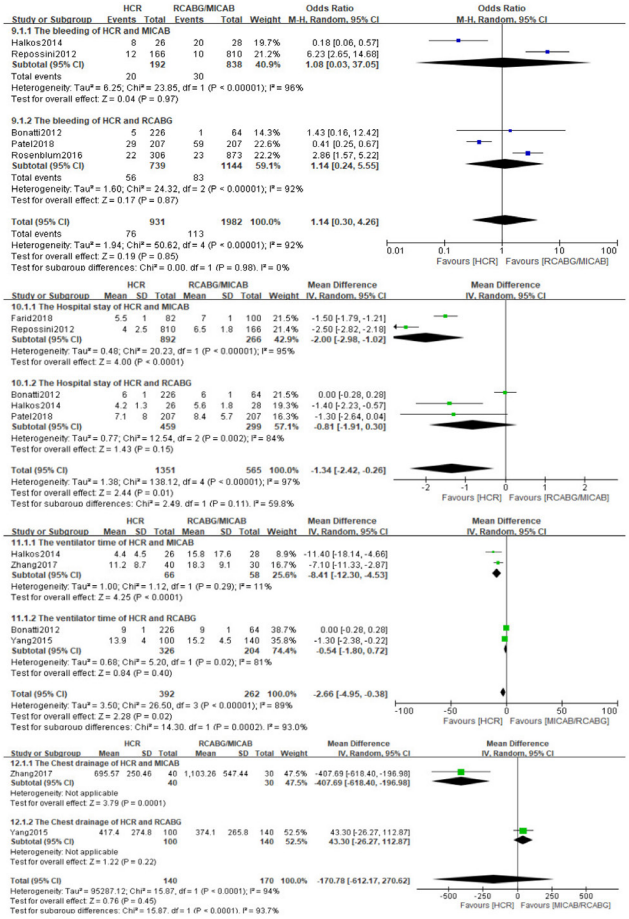

Figure 4. Clinical outcome of metaanalysis between HCR and MICR. M-H, Mantel-Haenszel; IV, inverse variance; Favours, favors, _____.

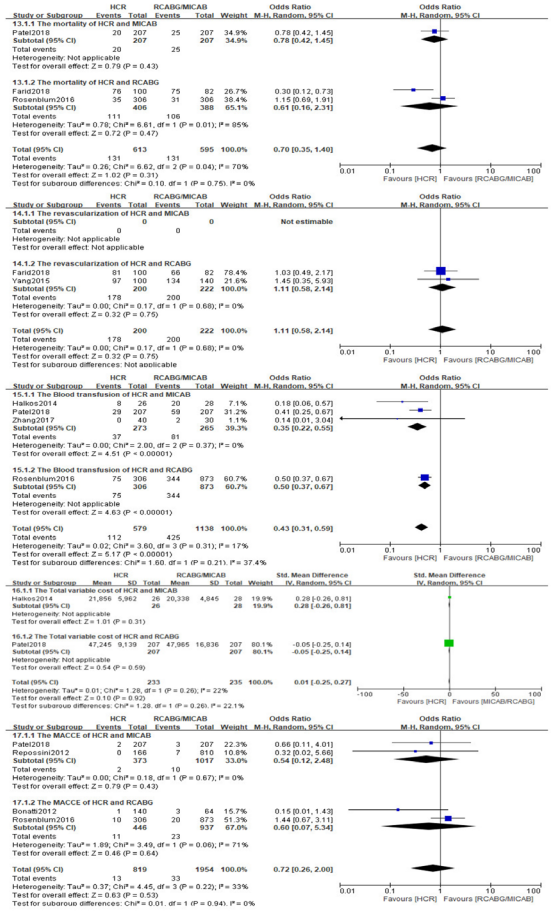

Figure 5. Clinical outcome of metaanalysis between HCR and MICR. M-H, Mantel-Haenszel; IV, inverse variance; Favours, favors, _____.

factors, including long-learning curing and operation time with increased difficulty surgery, the difficulties for older patients with serval left dysfunction, the use of vascular bridge which were suitable operation and better long-term patency. The surgical expose of MICR for multivessel disease is made more laterally which lead to rib injury and costochondral .what's more, hand-sewn proximal and distal anastomose. In general, the ideal candidate for HCR has LAD to LIMA and proximal lesions in the right coronary artery and circumflex branch (LCX) with PCI. But for MICR, the lesions in the right coronary artery and LCX may increasing the difficulty though left thoracic approach [Saran 2018] and a 92% overall graft patency and 100% LIMA patency at 6 months [Ruel 2014]. Therefore, the suitable patients for MICR should be performed on stable patients with preserved ventricular function and with no severe chest deformities or pulmonary comorbidities.

Limitations

This study has several limitations that should be acknowledged. First, the main drawback of our metaanalysis was the retrospective nature of the available data. The limited observational studies subject to section bias and we only included studies with similar baseline characteristic in order to limit this bias. Second, the results of the included studies are from MIDCAB/RCABG compared with HCR. But the subgroup analysis has obvious heterogeneity and a small sample size, which reduces the statistical power. The multi-institutional RCT trials were require in order to further validation and comprehensive evaluation index also need to require. Finally, the different definitions of major clinical outcome and secondary clinical outcome varied to some degree, which also have weakened the evidence in our analysis.

CONCLUSION

This metaanalysis found that HCR was noninferior to MICR in terms of in-hospital mortality, MACCE, shock, MI, long-term survival, total variable cost, and surgical complications (including renal failure, chest drainage, bleeding), whereas HCR was associated with a reduced need for ICU LOS, hospital time, and blood transfusion in comparison to MICR and had less infection than MICR. This warrants

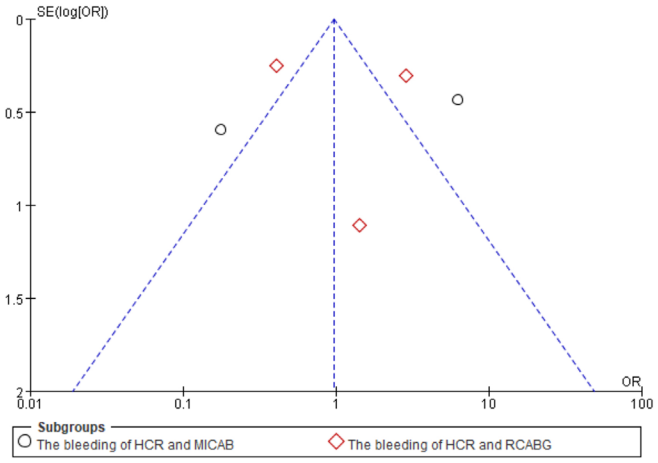

Figure 6. A funnel plot of bleed between HCR and MICR.

further validation in multicentric RCT trials to definitively assess the benefits and risks in these 2 surgery techniques.

ACKNOWLEDGMENTS

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