

# On-pump beating heart versus conventional on-pump coronary artery bypass grafting on clinical outcomes: a meta-analysis

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**Background:** A hybrid surgery method, on-pump beating heart coronary artery bypass graft (ON-BH CABG), is supposed to be a promising technology for coronary artery revascularization. Here, we conducted a comprehensive meta-analysis of the data derived from published studies on ON-BH CABG and conventional on-pump coronary artery bypass graft (C-CABG) to compare their short-term and long-term clinical outcomes.

**Methods:** We searched major electronic databases and 24 studies incorporating 6,862 patients (1,847 ON-BH CABG and 5,015 C-CABG) were included eventually, and 9 studies of them were focusing on high-risk patients.

**Results:** Compared with ON-BH CABG, C-CABG was associated with a higher risk in early mortality [odds ratio (OR), 1.45; 95% confidence interval (CI), 1.09 to 1.93; P=0.01], myocardial infarction (MI) (OR, 2.60; 95% CI, 1.41 to 4.78; P<0.01), low output syndrome (LOS) (OR, 2.56; 95% CI, 1.55 to 4.23; P<0.01), renal failure (OR, 1.84; 95% CI, 1.38 to 2.44; P<0.01). In contrast, there was no significant difference in long-term survival [hazard ratio (HR), 1.08; 95% CI, 0.81 to 1.43; P=0.60]. In systematic analysis of the studies in high-risk patients, ON-BH CABG showed a lower risk in terms of early mortality, intra-aortic balloon pump (IABP) usage, renal failure, hemodialysis, MI and pulmonary complication. No significant difference was observed in the long-term survival between ON-BH CABG and C-CABG.

**Conclusions:** With experienced and adept surgical team and mature ON-BH technology, ON-BH CABG may reduce the risk of postoperative death and complications in some patients. It might be an attractive alternative for high-risk patient populations.

Keywords: Coronary artery bypass graft (CABG); on-pump; beating heart; meta-analysis

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# Introduction

Conventional on-pump coronary artery bypass graft (C-CABG) was first introduced in the mid-1960s and developed rapidly as standard treatment for coronary revascularization. However, it may increase the risk of physiological disorders such as systemic inflammatory response, nervous system disorders, and renal failure due to the use of cardiopulmonary bypass (CPB), cardioplegic arrest and aortic cross-clamping (1-3). Offpump CABG (OPCAB) has been considered to be a

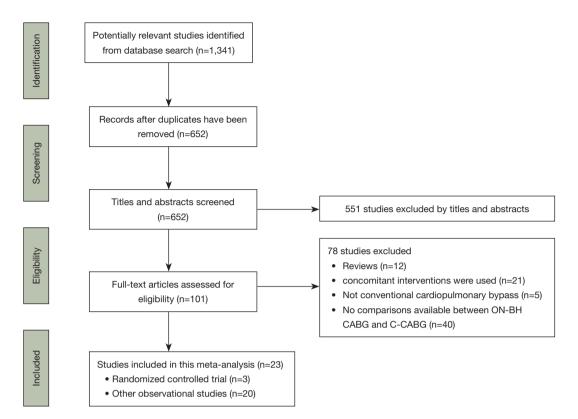


Figure 1 Flow diagram of search strategy. ON-BH CABG, on-pump beating heart coronary artery bypass graft; C-CABG, conventional on-pump coronary artery bypass graft.

potentially ideal strategy to avoid serious complications of C-CABG, by obviating the use of CPB and cardioplegic arrest. However, there are studies increasingly reporting high incidence of incomplete revascularization and potentially inferior long-term survival with OPCAB (4-6). Therefore, a hybrid surgery method, on-pump beating heart coronary artery bypass graft (ON-BH CABG) has been developed, which seems to be a promising technology for coronary artery revascularization. It allows performance of surgical operations while maintaining hemodynamic stability and providing adequate exposure to the target coronary artery, but without cardioplegic arrest and aortic cross-clamping (7). However, the clinical benefits of ON-BH CABG have not been clearly proven yet. The purpose of this study is to summarize the relevant published literature and conduct a systematic review, so as to evaluate whether ON-BH CABG has the potential to become an effective surgical method for coronary revascularization through short-term and longterm clinical outcomes compared with C-CABG.

We present the following article in accordance with the

PRISMA reporting checklist (available at https://dx.doi. org/10.21037/jtd-21-568) (8).

#### **Methods**

### Search strategy

Literature searches were conducted through PubMed, EBSCO, Embase, Cochrane database and Web of Science up to 1 April, 2020. The following key terms were used either alone or in combination: "on pump", "cardiopulmonary bypass", "coronary artery bypass", "beating heart". The reference list of relevant articles and review were manually scrutinized to find additional studies. The included search was limited to human coronary artery bypass graft surgery research published in any country after 1990. A summary of our strategy is described in *Figure 1*.

### Eligibility criteria

The inclusion criteria were as follows: (I) direct

comparation of ON-BH CABG versus conventional onpump CABG; (II) provided at least one of the following major clinical outcomes: early mortality, long-term survival, myocardial infarction (MI), low output symptoms, incidence of incomplete revascularization, renal failure; (III) isolated CABG surgery.

The exclusion criteria were as follows: (I) concomitant interventions were used; (II) unconventional CPB was used; (III) the data provided was inaccurate and effective data extraction cannot be performed; (IV) repeated reporting of the same group of people research, in this case more credible and recently published data was selected. A study with a Newcastle-Ottawa Scale (NOS) score of 6 or higher was regarded as of high quality.

The study of patients who meet at least one of the following criteria is considered as a high-risk patient study (9): (I) unstable angina; (II) severe left main stenosis (more than 70 percent); (III) early post-acute MI or ongoing chest pain; (IV) post percutaneous coronary intervention (PCI) complication; (V) sever left ventricular dysfunction (left ventricular ejection fraction is less than 35 percent); (VI) severe renal failure; (VII) EuroSCORE score greater than 9.

Two independent reviewers (Chen Wang and Yefan Jiang) evaluated the research on the titles and abstracts of the searched articles based on our above selection and exclusion criteria which were summarized according to the PICOS (patient, intervention, comparator, outcome, and study design) approach, and then retrieved the full text of all possible eligible studies to determine the final selection. Any disagreements in the process will be resolved through discussion with the superior (Si Chen).

# Data collection

The above two independent reviewers used standardized spreadsheets to extract data individually according to the first author, publication year, study location, study time span, study design, patient population, number of patients in groups, inclusion/exclusion criteria and outcome indicators.

# Research variables

Our primary outcome was the early mortality rate in hospital and the long-term survival rate after surgery. Secondary outcomes was: (I) postoperative morbidity: MI, LOS, arrhythmia, renal dysfunction, hemodialysis (necessary for renal failure), reoperation due to bleeding, cerebrovascular disease, including stroke and transient ischemic attack, pulmonary complications, including lung infections and respiratory insufficiency; (II) perioperative outcomes: intra-aortic balloon pump (IABP) use; (III) graft outcomes: number of distal anastomoses and incidence of incomplete revascularization.

#### Quality score and risk of bias analysis

Two authors (Chen Wang and Yefan Jiang) used the Jadad composite scale (10) to assess the quality of RCTs and the modified Newcastle-Ottawa Quality Assessment Scale (11) to rate the quality of observational studies, then gave an evaluation score for each study. High-quality studies were defined as those with a Jadad score of 2 or higher (maximum, 5), or a modified Newcastle-Ottawa score of 5 or higher (maximum, 9). The risk of bias of the included literature was assessed according to Cochrane guidelines (12).

### Statistical analysis

The meta-analysis uses a weighted fixed effects model to analyze the data. For our primary outcomes, the odds ratio (OR) and the logarithm of hazard ratio (HR) with 95% confidence interval (CI) were used as summary statistics to calculate survival differences. For secondary outcomes, categorical variables were evaluated using OR. The point estimate of the OR was considered statistically significant if P was less than 0.05 and the 95% CI did not include the value 1. Continuous variables are evaluated using weighted mean difference (WMD). The point estimate of WMD was considered to be statistically significant if P was less than 0.05 and the 95% CI did not include 0.

## Heterogeneity

If statistically significant heterogeneity is found in the included studies, random effects models can also be used for pooled analysis, and subgroup analysis and sensitivity analysis can be performed to discover the source of heterogeneity. Cochran's Q test was used to test the heterogeneity of the included studies. The significance level was set to P value <0.10, and was quantified by using the  $I^2$  statistic, where value of 50% or greater indicated substantial heterogeneity. Sensitivity analyses were performed by omitting each study in sequence. Publication bias was assessed by visual inspection of funnel plots.

This meta-analysis conducted not only a systematic analysis of all entered documents that meet the standards to

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 Table 1 Synopsis of including studies

Reference	Place of study	Enrolment	Study design	Study population	Outcomes
Afrasiabirad (14), 2015	Tabriz, Iran	1999.6–2011.12	SC-R-O	High-risk	1, 2
Borowski (15), 2002	Cologne, Germany	1996.4–1998.4	SC-R-O	General	1, 2, 6
Erkut (16), 2013	Erzurum, Turkey	2009.8–2012.6	SC-R-O	High-risk	1, 2, 3, 4, 5, 6
Jalal (17), 2007	Riyadh, Kingdom of Saudi Arabia	2003.2-2004.4	SC-P-RCT	General	5
Lin CC (18), 2010	Taiwan, China	2006.8-2008.2	SC-R-O	General	1, 2, 3, 5
Lin CY (19), 2010	Taiwan, China	2007.1-2008.12	SC-P-O	General	1, 2, 3, 4
Prifti (20), 2001	Pirenze, Italy	1993.1–2000.12	SC-R-O	High-risk	1, 2, 3, 4, 6, 7
Munos (9), 2011	Pessac, France	2008.1-2010.1	SC-R-O	High-risk	1, 2, 3, 4, 5, 6
Kim (21), 2018	Republic of Korea	2006–2012	SC-R-PM	General	1, 2, 3, 4, 6, 7
Edgerton (22), 2003	Dallas, Texas, USA	2000.1-2002.12	SC-R-O	General	1, 2, 3, 4, 7
Miyahara (23), 2008	Aichi, Japan	1999.1–2005.3	SC-R-O	High-risk	1, 2
Kim (24), 2001	Seoul, Korea	1998.1–1999.7	SC-P-O	General	1, 2, 4, 6
Yu (25), 2014	Shenyang, China	2005.1-2013.9	SC-R-O	High-risk	1, 2, 3, 4
Zhu (26), 2019	Australian & New Zealand	2001–2015	SC-R-PM	High-risk	1, 2, 4, 5, 7
Uva (27), 2004	Lisboa, Portugai	2001.1-2001.7	SC-R-O	General	1, 4
Sabban (28), 2007	Riyadh, Kingdom of Saudi Arabia	2005.1-2006.1	SC-R-O	General	1
Narayan (29), 2011	Bristol, UK	2003.1-2004.10	SC-P-RCT	General	1, 7
Chen (30), 2017	Taiwan, China	2010.1-2012.12	SC-R-O	General	1, 2, 3
Mizutani (31), 2007	Aichi, Japan	1999.1–2005.3	SC-R-PM	General	1, 2, 5
Pegg (32), 2008	Oxford, UK	2005–2007	SC-P-RCT	General	1
Quan (33), 2013	Zhengzhou, China	2009.1-2012.1	SC-R-O	General	1
Tsai (34), 2012	Taiwan, China	2002.1-2010.1	SC-R-O	High-risk	1, 2, 5, 6, 7
Izumi (35), 2006	Hokkaido, Japan	1998.1–2004.6	SC-R-O	High-risk	1

O, observational; P, prospective; PM, propensity matched; R, randomized; RCT, randomized controlled trial; SC, single center; R-O, retrospective observational; P-O, prospective-observational; 1, early mortality; 2, renal failure; 3, dialysis (renal failure); 4, myocardial infarction; 5, incidence of incomplete revascularization; 6, low cardiac output syndrome; 7, long-term survival.

make an overall comparison between ON-BH CABG and C-CABG, but also a systematic analysis of the literature on high-risk patients to evaluate the clinical effects of ON-BH CABG. The meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Project for Systematic Reviews and Meta-analysis) guidelines, following Cochrane recommendations and using Review Manager 5.3 software.

### Results

Our research identified 24 studies (9,13-35) according

to our inclusion and exclusion criteria initially. However, one observational study (13) was excluded because its Newcastle-Ottawa score was below 4. Finally, 23 studies (9,14-35) were included in our research incorporating a total of 6,862 patients (1,847 ON-BH CABG; 5,015 C-CABG). The main characteristics of the included studies are listed in *Table 1* and the demographic data characteristics are listed in *Table 2*. Three studies (17,29,32) were randomized controlled trials, 2 (19,24) were prospectively non-randomized controlled studies, and 18 (9,14-16,18,20-23,25-28,30,31,33-35) were retrospective observational

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	Patier	Patients (No.)	Mean age (ye	ge (years)	Male/1	Male/female	Distal anas	Distal anastomoses (No.)	Urgent/	Urgent/elective	Re-interven	Re-intervention rate (%)	Euro	EuroSCORE
Reference	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG	ON-BH CABG	C-CABG
Afrasiabirad (14), 2015	157	157	56	57	117/40	119/38	3.1	2.9	NR	R	NR	NR	R	R
Borowski (15), 2002	12	22	55	64	NR	NR	4.2	3.9	NR	NR	NR	NR	NR	NR
Erkut (16), 2013	65	66	68	65	33/32	34/32	3.0	3.1	NR	NR	NR	NR	NR	NR
Jalal (17), 2007	15	15	63	55	8/7	15/0	3.2	2.8	NR	NR	NR	NR	NR	NR
Lin CC (18), 2010	132	66	64	64	99/33	63/36	3.0	3.4	4/128	06/6	3.8	10.1	5.0	6.0
Lin CY (19), 2010	13	12	63	64	8/5	8/4	3.0	2.9	NR	NR	NR	NR	NR	NR
Prifti (20), 2001	78	78	66	66	50/28	48/30	3.3	3.3	NR	NR	0.0	10.3	NR	NR
Munos (9), 2011	51	106	73	75	35/16	73/33	2.5	2.4	23/28	48/58	NR	NR	13.3	12.8
Kim (21), 2018	173	173	63	63	49/124	43/130	3.0	3.0	NR	NR	2.3	1.7	NR	NR
Edgerton (22), 2003	364	2,332	63	63	272/92	1,775/557	3.3	3.5	242/122	1,426/906	NR	NR	NR	NR
Miyahara (23), 2008	38	23	66	65	28/10	18/5	2.0	2.9	NR	NR	NR	NR	9.9	9.0
Kim (24), 2001	19	65	59	63	12/7	46/19	3.6	3.7	6/13	22/43	NR	NR	NR	NR
Yu (25), 2014	55	49	66	66	35/20	30/19	3.2	3.3	4/51	4/45	NR	NR	NR	NR
Zhu (26), 2019	77	154	68	67	56/21	119/35	2.5	3.4	0/27	154/0	0.0	1.3	9.6	9.6
Uva (27), 2004	47	66	66	66	36/11	46/20	NR	NR	NR	NR	NR	NR	3.1	3.1
Sabban (28), 2007	33	73	64	59	NR	NR	3.7	2.9	7/26	14/59	NR	NR	NR	NR
Narayan (29), 2011	40	41	65	67	33/7	32/9	2.9	3.0	16/24	20/21	NR	NR	2.0	2.0
Chen (30), 2017	159	95	64	63	130/29	76/19	3.1	3.3	47/112	14/81	3.1	3.2	7.3	5.4
Mizutani (31), 2007	114	114	66	67	88/26	94/20	2.1	2.7	64/50	64/50	NR	NR	NR	NR
Pegg (32), 2008	25	25	68	64	22/3	25/0	4.0	4.0	11/14	7/18	NR	NR	12.0	8.0
Quan (33), 2013	66	48	63	57	54/12	34/14	3.4	3.2	NR	NR	NR	NR	NR	NR
Tsai (34), 2012	48	82	63	64	31/17	50/32	3.2	3.2	13/35	20/62	2.1	3.7	11.4	9.9
lzumi (35), 2006	15	16	66	66	12/3	11/5	2.5	2.3	NR	NR	NR	NR	NR	NR

#### A Early mortality

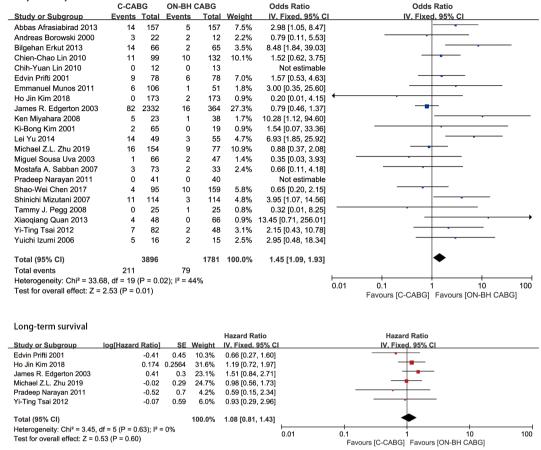


Figure 2 Forest plots of outcomes on ON-BH CABG and C-CABG groups. (A) Early mortality, (B) long-term survival. CI, confidence interval; IV, inverse variance; SE, standard error; ON-BH CABG, on-pump beating heart coronary artery bypass graft; C-CABG, conventional on-pump coronary artery bypass graft.

studies, of which three studies (21,26,31) were propensity score matching for risk adjustment. A total of nine studies (9,14,16,20,23,25,26,34,35) focused on high-risk patients.

The present part is structured in the following sections: (I) primary outcome (early mortality and long-term survival); (II) secondary outcome (major postoperative complication); (III) high-risk patients.

### Primary outcome

В

The forest plot results of primary outcomes were shown in *Figure 2*. Early death was defined as death occurring within 30 days after surgery or as an in-hospital death at any time. A total of 22 studies (9,14-16,18-35) reported data related to early (<30 days) mortality. The early (<30 days) mortality

was higher in conventional CABG when compared with OP-BH CABG in the fixed-effects model (OR, 1.45; 95% CI, 1.09 to 1.93; P=0.01), without significant heterogeneity (I<sup>2</sup>=44%). Exclusion of each study in sequence did not influence the overall results (*Figure 2A*). It was worth noting that the retrospective study by Edgerton *et al.* (22) was the only study that accounts for more than 20% of the population and similar result can be obtained after removing this study. Six studies (20-22,26,29,34) providing details related to the long-term survival were included in the long-term survival analysis. No difference was found in long-term survival between BH-ONCAB and C-ONCAB in the fixed-effects model (HR, 1.08; 95% CI, 0.81 to 1.43), with no heterogeneity (I<sup>2</sup>=0%) (*Figure 2B*).

#### Secondary outcome

The forest plot results of secondary outcomes were shown in *Figure 3*. Ten studies (9,16,19-22,24-27) provided data on postoperative MI. C-CABG was with a significantly higher risk compared with OP-BH CABG and is statistically different (OR, 2.60; 95% CI, 1.41 to 4.78; P=0.002). No significant heterogeneity was observed in included studies (P=0.60, I<sup>2</sup>=0%) (*Figure 3C*).

There were 7 studies (9,15,16,20,21,24,34) reporting the occurrence of postoperative LOS, and the risk in C-CABG was significantly higher than that in ON-BH CABG in the fixed-effects model (OR, 2.56; 95% CI, 1.55 to 4.23; P<0.001). No significant heterogeneity was observed in included studies (P=0.35, I<sup>2</sup>=10%) (*Figure 3D*).

There were 16 studies (9,14-16,18-26,30,31,34) reporting the occurrence of renal failure. However, one study (22) was excluded because it significantly increased the heterogeneity due to more patients with renal failure before surgery in the ON-BH CABG group than in the C-CABG group with statistical difference. When it was removed, the I<sup>2</sup> value of the index of heterogeneity dropped from 70% to 27% (Figure 4). The risk of postoperative renal failure in C-CABG is significantly higher than that of OP-BH CABG with a statistical difference (OR, 1.84; 95% CI, 1.38 to 2.44; P<0.01) (Figure 3A). However, in the study of data provided by 7 studies (9,16,18,19,22,25,30) on postoperative patients requiring hemodialysis due to renal failure, it was found that there was no significant difference in hemodialysis caused by the two surgical methods (OR, 1.25; 95% CI, 0.74 to 2.12; P=0.41) (Figure 3B).

Five studies (9,16,18,26,34) focused on the incidence of incomplete revascularization and no difference was found in the incidence of incomplete revascularization between ON-BH CABG and C-CABG (OR, 0.65; 95% CI, 0.40 to 1.05; P=0.08), without significant heterogeneity (P=0.79, I<sup>2</sup>=0%) in the fixed effects model (*Figure 3E*).

#### High-risk patients

Data for high-risk patients were available for 9 studies (9,14,16,20,23,25,26,34,35). We further explored the clinical outcomes of those two surgical methods in high-risk patients. The forest plot results of outcomes of high-risk patients were shown in *Figures 5* and 6. The early mortality rate of high-risk patients in C-CABG was significantly higher than that of ON-BH CABG in the fixed-effect model (OR, 2.37; 95% CI, 1.53 to 3.68; P<0.01) and there was

no significant heterogeneity (P=0.14;  $I^2=34\%$ ) (Figure 5A). However, no significant difference existed in the long-term survival rate between those two surgical methods (HR, 1.08; 95% CI, 0.70 to 1.69; P=0.72) (Figure 5B). Compared with C-CABG, patients of ON-BP CABG had significantly lower incidence of postoperative MI (OR, 3.68; 95% CI, 1.72 to 7.87; P<0.01) (Figure 5C), LOS (OR, 3.18; 95% CI, 1.86 to 5.44; P<0.01) (Figure 5D), renal failure (OR, 2.50; 95% CI, 1.67 to 3.75; P<0.01) and hemodialysis (OR, 4.00; 95% CI, 1.93 to 8.28; P<0.01), IABP usage (OR, 2.03; 95% CI, 1.44 to 2.84; P<0.01), pulmonary complication (OR, 2.11; 95% CI, 1.13 to 3.94; P=0.02) (Figure 6A, B, D, F). Except for IABP use, none of the other results showed obvious heterogeneity. There was no significant difference in arrhythmia (OR, 1.10; 95% CI, 0.68 to 1.78; P=0.69), cerebrovascular disease (OR, 2.17; 95% CI, 0.94 to 5.01; P=0.07), the incidence of incomplete revascularization (OR, 0.77; 95% CI, 0.41 to 1.43; P=0.41) and reoperation due to bleeding (OR, 1.64; 95% CI, 0.79 to 3.40; P=0.19) in high-risk patients between C-CABG and ON-BH CABG (Figure 6C, E, G, H).

#### Discussion

The results demonstrated that ON-BH CABG had a lower early morbidity, lower mortality, and similar longterm survival compared with C-CABG. The incidences of MI, low output syndrome (LOS), and renal failure of ON-BH CABG are lower significantly than that of C-CABG. In high-risk patients, ON-BH CABG had obvious advantages on reducing early mortality and the incidence of complications after coronary artery bypass grafting surgery but did not improve long-term survival. Those results indicate the promising clinical potential of ON-BH CABG.

Our meta-analysis shows that ON-BH CABG has lower incidence of postoperative MI and cardiac LOS. This result may be explained by the difference in technology of these two methods. Both ON-BH CABG and C-CABG use the support of CPB during the operation to enable mechanical stability. The difference is that ON-BH CABG avoids aortic cross-clamping and cardioplegic arrest (36). The avoidance of cross-clamping of the aorta in severe atherosclerosis could minimize the risk of embolization from atherosclerotic debris (37). The avoidance of cardioplegic arrest could preserve native coronary blood flow, prevent overall myocardial ischemia and ischemiareperfusion injury (23,38), thus preserve more myocardial function and reduce the occurrence of postoperative MI

#### Α Renal failure

	C-CAI	BG	ON-BH (	CABG		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% C	I IV. Fixed, 95% CI
Abbas Afrasiabirad 2013	10	157	4	157	5.9%	2.60 [0.80, 8.48]	
Andreas Borowski 2000	2	22	2	12	1.8%	0.50 [0.06, 4.09]	
Bilgehan Erkut 2013	11	66	2	65	3.4%	6.30 [1.34, 29.67]	· · · · · · · · · · · · · · · · · · ·
Chien-Chao Lin 2010	8	99	11	132	9.0%	0.97 [0.37, 2.50]	
Chih-Yuan Lin 2010	0	12	0	13		Not estimable	
Edvin Prifti 2001	45	78	28	78	19.6%	2.44 [1.28, 4.64]	
Emmanuel Munos 2011	8	106	1	51	1.8%	4.08 [0.50, 33.55]	
Ho Jin Kim 2018	2	173	8	173	3.3%	0.24 [0.05, 1.15]	
Ken Miyahara 2008	2	23	0	38	0.9%	8.95 [0.41, 195.18]	
Ki-Bong Kim 2001	4	65	1	19	1.6%	1.18 [0.12, 11.24]	
Lei Yu 2014	8	49	3	55	4.2%	3.38 [0.84, 13.56]	
Michael Z.L. Zhu 2019	19	154	9	77	11.4%	1.06 [0.46, 2.48]	<b>_</b>
Shao-Wei Chen 2017	44	95	48	159	29.5%	2.00 [1.18, 3.38]	
Shinichi Mizutani 2007	6	114	3	114	4.1%	2.06 [0.50, 8.43]	
Yi-Ting Tsai 2012	10	82	2	48	3.3%	3.19 [0.67, 15.24]	
Total (95% CI)		1295		1191	100.0%	1.84 [1.38, 2.44]	•
Total events	179		122				
Heterogeneity: Chi <sup>2</sup> = 17.8	6, df = 13	(P = 0.	16); l <sup>2</sup> = 27	%			
Test for overall effect: Z =	4.17 (P < 0	.0001)					0.01 0.1 1 10 100 Favours [C-CABG] Favours [ON-BH CABG]

#### В Renal failure requiring hemodialysis

	C-CA	BG	ON-BH (	CABG		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% C		IV, Fixed, 95% CI	
Bilgehan Erkut 2013	5	66	0	65	3.3%	11.72 [0.63, 216.33]			$\rightarrow$
Chien-Chao Lin 2010	8	99	11	132	30.9%	0.97 [0.37, 2.50]			
Chih-Yuan Lin 2010	0	12	0	13		Not estimable			
Emmanuel Munos 2011	8	106	1	51	6.3%	4.08 [0.50, 33.55]			
James R. Edgerton 2003	25	2332	4	364	24.8%	0.98 [0.34, 2.82]			
Lei Yu 2014	8	49	3	55	14.5%	3.38 [0.84, 13.56]			
Shao-Wei Chen 2017	4	95	11	159	20.3%	0.59 [0.18, 1.91]			
Total (95% CI)		2759		839	100.0%	1.25 [0.74, 2.12]		<b>•</b>	
Total events	58		30						
Heterogeneity: Chi <sup>2</sup> = 7.50,	df = 5 (P	= 0.19)	; I <sup>2</sup> = 33%				0.01	0.1 1 10	100
Test for overall effect: Z = 0	).83 (P = 0	0.41)					0.01	Favours [C-CABG] Favours [ON-BH CABG]	100

#### С Myocardial infarction

C-CAI	20		CARC		Odde Patio		Odde Patio	
				Weight			IV. Fixed, 95% CI	
11	66	1	65	8.6%	12.80 [1.60, 102.31]			<b>_</b> →
0	12	0	13		Not estimable			
8	78	1	78	8.4%	8.80 [1.07, 72.14]			-
8	106	1	51	8.3%	4.08 [0.50, 33.55]			
2	173	1	173	6.4%	2.01 [0.18, 22.39]	-	· · ·	
24	2332	3	364	25.5%	1.25 [0.37, 4.18]			
2	65	0	19	3.9%	1.54 [0.07, 33.36]			
10	49	6	55	30.8%	2.09 [0.70, 6.27]			
6	154	1	77	8.1%	3.08 [0.36, 26.06]			
0	66	0	47		Not estimable			
	3101		942	100.0%	2.60 [1.41, 4.78]		-	
71		14						
df = 7 (P	= 0.60)	; l² = 0%						
.08 (P = 0	).002)						I IC-CABG1 Eavoure ION	10 100
	Events 111 0 8 8 2 24 2 2 4 2 10 6 0 71 df = 7 (P	11         66           0         12           8         78           2         173           24         2322           2         65           10         49           6         154           0         66           3101         71	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{tabular}{ c c c c c } \hline { transformation transformatio transformation tr$	$\begin{tabular}{ c c c c c c } \hline { {\bf Events } & {\bf Total \ Weight } \\ \hline {\bf Events } & {\bf Total \ Weight } \\ \hline {\bf 11} & 66 & 65 & 8.6\% \\ 0 & 12 & 0 & 13 \\ 8 & 78 & 1 & 78 & 8.4\% \\ 8 & 78 & 1 & 78 & 8.4\% \\ 8 & 106 & 1 & 51 & 8.3\% \\ 2 & 173 & 1 & 173 & 6.4\% \\ 24 & 2323 & 3 & 364 & 25.5\% \\ 2 & 65 & 0 & 19 & 3.9\% \\ 10 & 49 & 6 & 55 & 30.8\% \\ 6 & 154 & 1 & 77 & 8.1\% \\ 0 & 66 & 0 & 47 \\ \hline {\bf 3101} & {\bf 942} & {\bf 100.0\% } \\ \hline {\bf 71} & {\bf 14} \\ df = 7 (P = 0.60); P = 0\% \\ \hline \end{tabular}$	Events         Total         Events         Total         Weight         IV. Fixed. 95% CI           11         66         1         65         8.6%         12.80 (1.60, 102.31)           0         12         0         13         Not estimable           8         78         1         78         8.4%         8.80 [10.7, 72.14]           8         106         1         65         1.8.3%         A.06 [0.50, 33.55]           2         173         1         173         6.4%         2.01 [0.18, 22.39]           2         2332         3         64         25.5%         1.25 [0.37, 4.18]           2         265         0         19         3.9%         1.54 [0.07, 33.36]           10         49         6         55         30.8%         2.09 [0.70, 6.27]           16         154         1         77         8.1%         3.08 [0.36, 26.06]           0         66         0         47         Not estimable           3101         942         100.0%         2.60 [1.41, 4.78]           71         14         4         7	Events         Total         Weight         IV. Fixed. 95% CI           111         66         1         65         8.6%         12.80 [1.60, 102.31]           0         12         0         13         Not estimable           8         78         1         78         8.4%         8.80 [1.07, 72.14]           8         106         1         51         8.3%         4.08 [1.05, 0.355]           2         173         1         173         6.4%         2.01 [0.18, 22.39]           24         2332         3         364         25.5%         1.25 [0.37, 4.18]           2         65         0         19         3.9%         1.54 [0.07, 0.6.27]           6         154         1         77         8.1%         3.08 [0.36, 26.06]           0         66         0         47         Not estimable           3101         942         100.0%         2.60 [1.41, 4.78]           71         14         4         4           67         10.1         9.0         0.01	Events         Total         Weight         IV. Fixed, 95% CI         IV. Fixed, 95% CI           11         66         1         65         8.6%         12.80 [1.60, 102.31]         IV. Fixed, 95% CI           0         12         0         13         Not estimable         IV. Fixed, 95% CI         IV. Fixed, 95% CI           8         76         1         78         8.4%         8.80 [1.07, 72.14]         IV. Fixed, 95% CI           8         706         1         78         8.4%         8.80 [1.07, 72.14]         IV. Fixed, 95% CI           2         173         1         713         8.4%         2.01 [0.18, 22.39]         IV. Fixed, 95% CI           2         265         0         19         3.9%         1.54 [0.07, 33.36]         IV. Fixed, 95% CI           10         49         6         55         3.08 [0.36, 26.60]         IV. Fixed, 95% CI         IV. Fixed, 95% CI           3101         942         100.0%         2.60 [1.41, 4.78]         IV. Fixed, 95% CI         IV. Fixed, 95% CI           71         14         IV. Fixed, 95% CI         IV. Fixed, 95% CI         IV. Fixed, 95% CI         IV. Fixed, 95% CI

Favours [C-CABG] Favours [ON-BH CABG]

#### D low output syndrome

	C-CAI	BG	ON-BH C	ABG		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV. Fixed, 95% Cl	IV. Fixed, 95% CI
Andreas Borowski 2000	3	22	3	12	7.9%	0.47 [0.08, 2.83]	
Bilgehan Erkut 2013	16	66	4	65	18.7%	4.88 [1.53, 15.53]	
Edvin Prifti 2001	30	78	15	78	47.8%	2.63 [1.27, 5.42]	_ <b>_</b>
Emmanuel Munos 2011	10	106	1	51	5.8%	5.21 [0.65, 41.85]	
Ho Jin Kim 2018	0	173	1	173	2.4%	0.33 [0.01, 8.19]	
Ki-Bong Kim 2001	3	65	0	19	2.8%	2.18 [0.11, 44.15]	
Yi-Ting Tsai 2012	13	82	3	48	14.6%	2.83 [0.76, 10.48]	+
Total (95% CI)		592		446	100.0%	2.56 [1.55, 4.23]	◆
Total events	75		27				
Total events							
Heterogeneity: Chi <sup>2</sup> = 6.67	7, df = 6 (F	P = 0.3	5); l² = 10%	5			0.04 0.4 40 400
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z =	3.68 (P =	0.0002	2)	5			0.01 0.1 1 10 100 Favours [C-CABG] Favours [ON-BH CABG]
Heterogeneity: Chi <sup>2</sup> = 6.67	3.68 (P =	0.0002 Ilariza	2) tion			Odds Ratio	Favours [C-CABG] Favours [ON-BH CABG]
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete	3.68 (P = e revascu C-CAB	0.0002 Ilariza 3G	2) tion ON-BH C	ABG	Weight	Odds Ratio	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u>	3.68 (P = e revascu C-CAR Events	0.0002 Ilariza BG Total	2) tion ON-BH C Events	ABG Total	Weight 24.5%	IV. Fixed, 95% CI	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013	3.68 (P = e revascu C-CAE Events 9	0.0002 Ilariza BG <u>Total</u> 66	2) tion ON-BH C <u>Events</u> 10	ABG Total 65	24.5%	IV. Fixed. 95% CI 0.87 [0.33, 2.30]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010	3.68 (P = e revascu C-CAE Events 9 7	0.0002 Ilariza BG <u>Total</u> 66 99	2) tion ON-BH C Events 10 13	<b>ABG</b> <u>Total</u> 65 132	24.5% 25.3%	IV. Fixed. 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>a</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010 Emmanuel Munos 2011	3.68 (P = e revascu C-CAE <u>Events</u> 9 7 4	0.0002 Ilariza 3G <u>Total</u> 66 99 106	2) tion ON-BH C Events 10 13 2	ABG Total 65 132 51	24.5% 25.3% 7.7%	IV. Fixed. 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82] 0.96 [0.17, 5.43]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010	3.68 (P = e revascu C-CAE Events 9 7	0.0002 Ilariza BG <u>Total</u> 66 99	2) tion ON-BH C Events 10 13	<b>ABG</b> <u>Total</u> 65 132	24.5% 25.3%	IV. Fixed. 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010 Emmanuel Munos 2011 Michael Z.L. Zhu 2019 Yi-Ting Tsai 2012	3.68 (P = e revascu C-CAE Events 9 7 4 15	0.0002 Ilariza 3G <u>Total</u> 66 99 106 154	2) tion ON-BH C Events 10 13 2 15	<b>ABG</b> 65 132 51 77 48	24.5% 25.3% 7.7% 38.6%	IV. Fixed, 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82] 0.96 [0.17, 5.43] 0.45 [0.21, 0.97] 1.18 [0.10, 13.31]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Ch <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010 Ermanuel Munos 2011 Michael Z.L. Zhu 2019 Yi-Ting Tsai 2012 Total (95% CI)	3.68 (P = e revascu C-CAE Events 9 7 4 15	0.0002 Ilariza 3G <u>Total</u> 66 99 106 154 82	2) tion ON-BH C Events 10 13 2 15	<b>ABG</b> 65 132 51 77 48	24.5% 25.3% 7.7% 38.6% 3.9%	IV. Fixed. 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82] 0.96 [0.17, 5.43] 0.45 [0.21, 0.97]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio
Heterogeneity: Chi <sup>a</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bigehan Erkut 2013 Chien-Chao Lin 2010 Ermanuel Munos 2011 Michael Z.L. Zhu 2019 Yi-Ting Tsai 2012 Total (95% CI) Total events	3.68 (P = e revascu C-CAE <u>Events</u> 9 7 4 15 2 37	0.0002 Ilariza 3G Total 66 99 106 154 82 507	2) tion ON-BH C Events 10 13 2 15 1 1 41	<b>ABG</b> 65 132 51 77 48	24.5% 25.3% 7.7% 38.6% 3.9%	IV, Fixed, 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82] 0.96 [0.17, 5.43] 0.45 [0.21, 0.97] 1.18 [0.10, 13.31] 0.65 [0.40, 1.05]	Favours [C-CABG] Favours [ON-BH CABG]
Heterogeneity: Ch <sup>2</sup> = 6.67 Test for overall effect: Z = Incidence of incomplete <u>Study or Subgroup</u> Bilgehan Erkut 2013 Chien-Chao Lin 2010 Ermanuel Munos 2011 Michael Z.L. Zhu 2019 Yi-Ting Tsai 2012 Total (95% CI)	3.68 (P = e revascu C-CAE <u>Events</u> 9 7 4 15 2 37 9, df = 4 (P	0.0002 Ilariza 3G Total 66 99 106 154 82 507	2) tion ON-BH C Events 10 13 2 15 1 1 41	<b>ABG</b> 65 132 51 77 48	24.5% 25.3% 7.7% 38.6% 3.9%	IV, Fixed, 95% CI 0.87 [0.33, 2.30] 0.70 [0.27, 1.82] 0.96 [0.17, 5.43] 0.45 [0.21, 0.97] 1.18 [0.10, 13.31] 0.65 [0.40, 1.05]	Favours [C-CABG] Favours [ON-BH CABG] Odds Ratio

Figure 3 Forest plots outcomes on ON-BH CABG and C-CABG groups. (A) Renal failure, (B) renal failure requiring hemodialysis, (C) myocardial infarction, (D) low output syndrome, (E) incomplete revascularization. CI, confidence interval; IV, inverse variance; ON-BH CABG, on-pump beating heart coronary artery bypass graft; C-CABG, conventional on-pump coronary artery bypass graft.

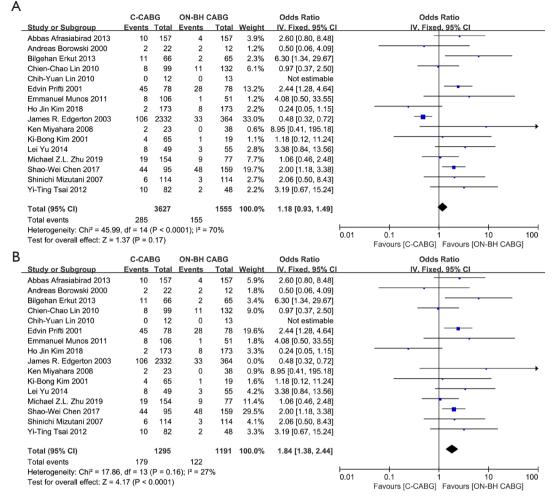


Figure 4 Sensitivity analysis of postoperative renal failure. (A) Forest plot with the study of Edgerton *et al.*, (B) Forest plot without the study of Edgerton *et al.* 

and LOS. It has been reported that while the functional myocardium was lost in the infarcted area, the remaining non-infarcted myocardium would undergo adaptive response rapidly to compensate for the infarcted area after acute MI (19). For example, adenosine triphosphate, phosphocreatine and glycogen were depleted, while lactate and oxygen consumption were increased (39). Consequently, if the non-infarcted myocardium is further damaged by ischemia and reperfusion due to cardioplegic arrest and aortic cross-clamping, its metabolic state may be even more impaired, thus leading to profound damage to myocardial function (39-41). The effect of myocardial protection of ON-BH CABG had also been confirmed in the studies of Izumi (35), Borowski (15) and Miyahara (23). Despite all these supporting evidence, the opposite research results also

exist. Pegg *et al.* (32) reported that the incidence of new irreversible myocardial injury was significantly higher in ON-BH CABG and the technique was related with poorer early and late cardiac remodeling. Ueki *et al.* (42) found that the opposite result might be explained by the relatively low mean arterial pressure (50–60 mmHg) during ON-BH CABG in the series of Pegg because another similar study (29) reported no significant difference in myocardial injury with higher mean arterial pressures (70–80 mmHg). Thus, they suggested that maintaining a relatively high mean arterial pressure during ON-BH CABG is essential to improve myocardial perfusion.

At present, there is no meta-analysis that compares the incidence of renal failure and hemodialysis between ON-BH CABG and C-CABG at the same time. Our analysis

#### A Farly mortality

<i>,</i> ,	Early mortality								
		C-CABG	ON-BH C			Odds Ratio		Odds Ratio	
	Study or Subgroup	Events Tota			Weight			IV, Fixed, 95% Cl	
	Abbas Afrasiabirad 2013	14 157	-	157	17.6%	2.98 [1.05, 8.47]			
	Bilgehan Erkut 2013	14 66	_	65		8.48 [1.84, 39.03]			
	Edvin Prifti 2001	9 78	-	78	16.3%	1.57 [0.53, 4.63]			
	Emmanuel Munos 2011	6 106		51		3.00 [0.35, 25.60]			
	Ken Miyahara 2008	5 23		28		7.50 [0.81, 69.63]			
	Lei Yu 2014	14 49	-	55		6.93 [1.85, 25.92]			
	Michael Z.L. Zhu 2019	16 154		77	25.6%	0.88 [0.37, 2.08]			
	Yi-Ting Tsai 2012	7 82		48		2.15 [0.43, 10.78]			
	Yuichi Izumi 2006	5 16	2	15	5.8%	2.95 [0.48, 18.34]			
	Total (95% CI)	731		574	100.0%	2.37 [1.53, 3.68]		•	
	Total events	90	31	014	100.070	2.07 [1.00, 0.00]		-	
	Heterogeneity: Chi <sup>2</sup> = 12.1					ł			
	Test for overall effect: Z =						0.01	0.1 1 10	100
		0.000 (1 0.0000 )	/					Favours [C-CABG] Favours [ON-BH CABG]	
В									
D	Long-term survival				Haz	ard Ratio		Hazard Ratio	
	Study or Subgroup	log[Hazard F	Ratio] SE	Weig	ht IV, I	Fixed, 95% CI		IV, Fixed, 95% CI	
	Edvin Prifti 2001		0.41 0.45	25.1	% 1.5	1 [0.62, 3.64]			
	Michael Z.L. Zhu 2019		-0.02 0.29	60.4	% 0.9	8 [0.56, 1.73]			
	Yi-Ting Tsai 2012		-0.07 0.59	14.6	% 0.9	3 [0.29, 2.96]			
	0								
	Total (95% CI)			100.0	0% 1.08	3 [0.70, 1.69]		◆	
	Heterogeneity: Chi <sup>2</sup> = 0.7	72, df = 2 (P = 0	0.70); l <sup>2</sup> = 0%	6		0.01		0.1 1 10	100
	Test for overall effect: Z	= 0.36 (P = 0.72	2)			0.01		Favours [C-CABG] Favours [ON-BH CABG]	100
~									
C	Myocardial infarction								
		C-CABG	ON-BH CA			Odds Ratio		Odds Ratio	
	Study or Subgroup	Events Total			Weight	IV, Fixed, 95% C		IV, Fixed, 95% Cl	
	Bilgehan Erkut 2013	11 66	1	65		12.80 [1.60, 102.31]			
	Edvin Prifti 2001	8 78	1	78	13.0%	8.80 [1.07, 72.14]			
	Emmanuel Munos 2011	8 106	1	51	13.0%	4.08 [0.50, 33.55]			
	Lei Yu 2014	10 49	6	55	48.0%	2.09 [0.70, 6.27]			
	Michael Z.L. Zhu 2019	6 154	1	77	12.6%	3.08 [0.36, 26.06]		-	
	Total (95% CI)	453		326	100.0%	3.68 [1.72, 7.87]			
	Total events	43	10	010		0.00 [ 2, 1.0.]		-	
	Heterogeneity: Chi <sup>2</sup> = 3.09						H		
	Test for overall effect: Z =						0.01	0.1 1 10	100
		0.000(1 0.0000	-)					Favours [C-CABG] Favours [ON-BH CABG]	
_									
D	Low output syndrom	e							
		C-CABG	ON-BH C			Odds Ratio		Odds Ratio	
	Study or Subgroup	Events Tota		Total			1	IV. Fixed, 95% Cl	
	Bilgehan Erkut 2013	16 66		65					
	Edvin Prifti 2001	30 78	3 15	78	55.0%	2.63 [1.27, 5.42]			
	Emmanuel Munos 2011	10 106	31	51	6.6%	5.21 [0.65, 41.85]			
	Yi-Ting Tsai 2012	13 82	2 3	48	16.8%	2.83 [0.76, 10.48]		+ •	
	T-4-1 (05% OI)			0.45	400.00	0 40 14 00 5 4 5			
	Total (95% CI)	332		242	100.0%	3.18 [1.86, 5.44]			
	Total events	69	23				<u> </u>		
	Heterogeneity: Chi <sup>2</sup> = 1.04						0.01	0.1 1 10	100
	Test for overall effect: Z =	4.22 (P < 0.000	)1)				5.01	Favours [C-CABG] Favours [ON-BH CABG]	
								- [ ] [	

**Figure 5** Forest plots of outcomes on ON-BH CABG and C-CABG groups in high-risk patients. (A) Early mortality, (B) long-term survival, (C) myocardial infarction, (D) low output syndrome. CI, confidence interval; IV, inverse variance; SE, standard error; ON-BH CABG, on-pump beating heart coronary artery bypass graft; C-CABG, conventional on-pump coronary artery bypass graft.

demonstrated the incidence of renal failure after ON-BH CABG was significantly lower than that of C-CABG, which was more pronounced in high-risk patients. This result suggested that ON-BH technology somehow protected the renal function of patients. The protective effect might be related to the avoidance of systemic hypothermia and visceral blood flow hypoperfusion, and the reduction of CPB time during ON-BH CABG surgery (43-45). Recovery from myocardial stunning and rewarming on CPB have been proven to be risk factors for acute kidney injury (AKI) (44). In addition, the lower incidence of MI and LOS after ON-BH CABG protects the kidney from damage due to insufficient perfusion caused by unstable hemodynamics. Previously, some scholars proposed that OP-BH technology reduced the damage on important organs during the operation by avoiding the release of inflammatory factors related to ischemia-reperfusion injury caused by cardiac arrest. Rothenburger *et al.* (46) proved that both cardiac

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A Renal failure

	Renal failure								
	Study or Subgroup	C-CA Events		ON-BH		al Weigh	Odds Ratio t IV. Fixed, 95%	CI	Odds Ratio IV. Fixed, 95% Cl
	Abbas Afrasiabirad 2013	10			15				
	Bilgehan Erkut 2013	11			6				
	Edvin Prifti 2001	45			7				<b></b>
	Emmanuel Munos 2011				5				
	Ken Miyahara 2008	2			3				,
	Lei Yu 2014	Ē			5				+
	Michael Z.L. Zhu 2019	19			7				<b>_</b>
	Yuichi Izumi 2006	10			1			-	
				-		0.17	10.00 [1.1.0, 00.00	-1	
	Total (95% CI)		649	Ð	53	6 100.0%	6 2.50 [1.67, 3.75	5]	•
	Total events	113	3	49					
	Heterogeneity: Chi <sup>2</sup> = 8.9				6			0.01	0.1 1 10 100
	Test for overall effect: Z =	4.44 (P <	0.000	01)					Favours [C-CABG] Favours [ON-BH CABG]
3									
	Renai failure requiring	C-CAB		ON-BH CA	BG		Odds Ratio		Odds Ratio
	Study or Subgroup	Events 1			Total V		IV, Fixed, 95% CI		IV, Fixed, 95% Cl
	Bilgehan Erkut 2013	5	66	0	65		1.72 [0.63, 216.33]		
	Edvin Prifti 2001	19	78	7	78	61.1%	3.27 [1.29, 8.30]		
	Emmanuel Munos 2011	8	106	1		12.0%	4.08 [0.50, 33.55]		
	Lei Yu 2014	8	49	2	55	20.7%	5.17 [1.04, 25.67]		
	Total (95% CI)		299	40	249 1	00.0%	4.00 [1.93, 8.28]		
	Total events	40	- 0 0	10			L		
	Heterogeneity: Chi <sup>2</sup> = 0.80,			I <sup>2</sup> = 0%			, (	0.01	0.1 1 10 100
	Test for overall effect: Z = 3	∠ (P = 0	.0002)						Favours [C-CABG] Favours [ON-BH CABG]
-									
-	Arrhythmia								
	Arrhythmia	C-CA	BG	ON-BH	CABG		Odds Ratio		Odds Ratio
	Study or Subgroup	Events			Total	Weight	IV, Fixed, 95% Cl		IV, Fixed, 95% Cl
	Emmanuel Munos 2011	35	106	17	51	45.4%	0.99 [0.49, 2.00]		<b>+</b>
	Lei Yu 2014	12	49	11	55		1.30 [0.51, 3.28]		
	Yi-Ting Tsai 2012	17	82	9	48	28.1%	1.13 [0.46, 2.79]		
	-								
	Total (95% CI)		237		154	100.0%	1.10 [0.68, 1.78]		-
	Total events	64		37					
	Heterogeneity: Chi <sup>2</sup> = 0.22 Test for overall effect: Z =			u); I <sup>z</sup> = 0%				0.01	0.1 1 10 100
		0.40 (1 -	0.00)						Favours [C-CABG] Favours [ON-BH CABG]
)	IABP use								
	INDI USC	C-CAE	BG	ON-BH C	ABG		Odds Ratio		Odds Ratio
	Study or Subgroup	Events		Events	Total	Weight	IV, Fixed, 95% C	1	IV. Fixed, 95% CI
	Abbas Afrasiabirad 2013	20	157	9	157	17.0%	2.40 [1.06, 5.45]		
	Bilgehan Erkut 2013	22	66	4	65	8.9%	7.63 [2.45, 23.69]		
	Edvin Prifti 2001	22	78	14	78	19.8%	1.80 [0.84, 3.84]		+
	Emmanuel Munos 2011	10	106	0	51		11.21 [0.64, 195.13]		
	Ken Miyahara 2008	3	23	0	38		13.15 [0.65, 267.04]		
	Lei Yu 2014	19	49	8	55	12.8%	3.72 [1.45, 9.57]		
	Michael Z.L. Zhu 2019	55	154	27	77	34.9%	1.03 [0.58, 1.82]		_ <b>+</b> _
	Yi-Ting Tsai 2012	5	82	2	48	4.0%	1.49 [0.28, 8.01]		
	Total (95% CI)		715		569	100.0%	2.03 [1.44, 2.84]		
	Total events	156		64				L	
	Heterogeneity: Chi <sup>2</sup> = 15.4 Test for overall effect: Z = -				•			0.01	
		( (							Favours [C-CABG] Favours [ON-BH CABG]
-									
	Cerebrovascular disea								
	Study of Sub-	C-CAI		ON-BH (		14/-1-1	Odds Ratio		Odds Ratio
	Study or Subgroup	Events				Weight			IV, Fixed, 95% Cl
	Bilgehan Erkut 2013	4	66	2	65	23.3%	2.03 [0.36, 11.50]		
	Edvin Prifti 2001	3	78	3	78	26.2%	1.00 [0.20, 5.11]		
	Emmanuel Munos 2011	4	106	0	51	8.1%	4.52 [0.24, 85.61]		-
	Ken Miyahara 2008 Lei Yu 2014	0 2	23 49	0 1	38 55	11 00/	Not estimable 2.30 [0.20, 26.16]		
	Michael Z.L. Zhu 2019	2	49 154	1	55 77	15.9%	4.16 [0.51, 33.91]		
	Yi-Ting Tsai 2012	5	82	1	48		3.05 [0.35, 26.93]		
		5							
	Total (95% CI)		558		412	100.0%	2.17 [0.94, 5.01]		
	Total events	26		8				<u> </u>	
	Heterogeneity: Chi <sup>2</sup> = 1.58			J); I <sup>2</sup> = 0%				0.01	0.1 1 10 100
		1.02 (P =	0.07)						Favours [C-CABG] Favours [ON-BH CABG]
	Test for overall effect: Z =								
=	Test for overall effect: Z =	ion							
=			ß	ON-BH (	ABG		Odds Ratio		Odds Ratio
=	Test for overall effect: Z =	ion C-CAB Events		ON-BH ( Events		Weight	Odds Ratio IV. Fixed, 95% C	:1	Odds Ratio IV. Fixed. 95% Cl
=	Test for overall effect: Z = Pulmonary complicat	C-CAB							
=	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u>	C-CAB Events	Total	Events	Total		IV. Fixed, 95% C		
=	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u> Bilgehan Erkut 2013	C-CAB Events 6	Total 66	Events 4	Total 65	22.7% 18.2%	IV, Fixed, 95% C 1.52 [0.41, 5.68] 1.71 [0.39, 7.43]		
=	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u> Bilgehan Erkut 2013 Edvin Prifti 2001 Lei Yu 2014	C-CAB Events 6 5	<u>Total</u> 66 78	Events 4 3	<u>Total</u> 65 78	22.7% 18.2%	IV. Fixed. 95% C 1.52 [0.41, 5.68]		
=	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u> Bilgehan Erkut 2013 Edvin Prifti 2001	C-CAB Events 6 5 17	Total 66 78 49	Events 4 3 7	Total 65 78 55	22.7% 18.2% 40.1%	IV. Fixed. 95% C 1.52 [0.41, 5.68] 1.71 [0.39, 7.43] 3.64 [1.36, 9.78]		
=	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u> Bilgehan Erkut 2013 Edvin Prifti 2001 Lei Yu 2014	C-CAB Events 6 5 17	Total 66 78 49	Events 4 3 7	Total 65 78 55 48	22.7% 18.2% 40.1%	IV. Fixed. 95% C 1.52 [0.41, 5.68] 1.71 [0.39, 7.43] 3.64 [1.36, 9.78]		
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:	Test for overall effect: Z = Pulmonary complicat <u>Study or Subgroup</u> Bilgehan Erkut 2013 Edvin Priti 2001 Lei Yu 2014 Yi-Ting Tsai 2012 Total (95% CI)	C-CAB Events 6 5 17 6 34	Total 66 78 49 82 275	Events 4 3 7 3	Total 65 78 55 48 246	22.7% 18.2% 40.1% 19.0%	IV. Fixed. 95% C 1.52 [0.41, 5.68] 1.71 [0.39, 7.43] 3.64 [1.36, 9.78] 1.18 [0.28, 4.97]		

G incidence of incomplete revascularization ON-BH CABG C-CABG Odds Ratio Odds Ratio Study or Subara vents Total Weight IV. Fixed, 95% C V. Fixed. 95% CI Bilgehan Erkut 2013 66 65 15.7% 4.97 [1.03, 23.99] 9 2 7 106 51 13.0% nmanuel Munos 2011 0.96 [0.17, 5.43] Michael Z.L. Zhu 2019 15 154 15 77 64.7% 0.45 [0.21, 0.97] Yi-Ting Tsai 2012 2 82 48 6.6% 1.18 [0.10, 13.31] Total (95% CI) 241 100.0% 0.77 [0.41, 1.43] 408 . Total events 30 20 Heterogeneity; Chi<sup>2</sup> = 7,48, df = 3 (P = 0.06); l<sup>2</sup> = 60% 0.01 10 100 Test for overall effect: Z = 0.83 (P = 0.41) Favours [C-CABG] Favours [ON-BH CABG] н Reoperation due to bleeding C-CARG ON-BH CABG Odds Ratio Odds Ratio IV. Fixed, 95% C Study or Subgroup Total Weight IV. Fixed. 95% C Events Total Events Bilgehan Erkut 2013 Edvin Prifti 2001 30.9% 6.5% 65 1.52 [0.41, 5.68] 6 66 78 .93 [1.07, 333.93] 78 8 4 Emmanuel Munos 2011 106 51 10.8% 1.96 (0.21, 18.00) 10.8% 25.1% Lei Yu 2014 4 49 55 77 4.80 [0.52, 44.49] Michael Z.L. Zhu 2019 154 5 0.83 [0.19, 3.56] Yi-Ting Tsai 2012 3 82 2 48 16.0% 0.87 [0.14, 5.42] Total (95% CI) 535 374 100.0% 1.64 [0.79. 3.40] Total events 30 Heterogeneity: Chi<sup>2</sup> = 5.02, df = 5 (P = 0.41); l<sup>2</sup> = 0% 0.01 100 10 Test for overall effect: Z = 1.32 (P = 0.19) Favours [C-CABG] Favours [ON-BH CABG]

**Figure 6** Forest plots of outcomes on ON-BH CABG and C-CABG groups in high-risk patients. (A) Renal failure, (B) renal failure requiring hemodialysis, (C) arrhythmia, (D) IABP use, (E) cerebrovascular disease, (F) pulmonary complication, (G) incomplete revascularization, (H) reoperation due to bleeding. CI, confidence interval; IV, inverse variance; ON-BH CABG, on-pump beating heart coronary artery bypass graft; C-CABG, conventional on-pump coronary artery bypass graft.

surgery and CPB can induce inflammation and antiinflammatory immune responses, and the imbalance between inflammation and anti-inflammatory mediators was essential for postoperative systemic inflammatory response syndrome. However, Narayan et al. (29) monitored the interleukins (IL-6, IL-8 and IL-10) in the ON-BH CABG and C-CABG group continuously after surgery and found that there was no statistical difference between the two groups. This may indicate that the protection of kidney in ON-BH CABG is not mainly achieved by reducing inflammation. The results of our analysis also showed that there was no significant difference in hemodialysis after these two surgical procedures in the overall comparison. By contrast, in the comparison of high-risk patients, the number of patients requiring hemodialysis after C-CABG was significantly higher than that of ON-BH CABG. This indicated that high-risk patients, especially those with abnormal renal function before surgery, could benefit more from ON-BH CABG surgery.

Whether ON-BH CABG could achieve complete cardiac revascularization and ensure the long-term survival is a question worthy of most attention. In recent years, offpump CABG has been questioned due to reports of high incidence of incomplete revascularization and less favorable long-term survival (47,48). Our meta-analysis showed that the ON-BH CABG and C-CABG groups had no significant differences in the incidence of incomplete revascularization and long-term survival, and no significant heterogeneity was found. ON-BH CABG benefits from the support of CPB, which could provide more stable hemodynamics and increase the tolerance of the heart to movement. This allows better exposure of target arteries and operation space for operators to achieve complete revascularization during operation. Edgerton et al. (22) report that ON-BH CABG can ensure complete revascularization of high risk patients with cardiogenic shock, requiring resuscitation, recent MI, a low ejection fraction, or unstable arrhythmias. Takagi et al. (49) showed that adequate and guaranteed complete revascularization is closely related to the long-term survival. To the opposite, a previous meta-analysis that included 14 literatures reported a significantly greater risk of incomplete revascularization in ON-BH CABG compared with C-CABG (42). However, that meta-analysis showed significant heterogeneity among studies included and there was no comprehensive analysis of the heterogeneity to determine its source. Therefore, our analysis results are supposed to be more reasonable and reliable.

Due to the high early mortality and morbidity in highrisk patients undergoing C-CABG surgery, a part of surgeons chose off-pump CABG as an alternative method for coronary revascularization in these cases. However, beside the concerns related to potentially inferior long-

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term survival and the high incidence of incomplete revascularization, hemodynamic instability might require emergent conversion to conventional on-pump CABG, especially in case of severe coronary disease, increasing the risk of operation enormously (22,48,50). A survey in Japan showed that 4.5% of emergency isolated CABG were converted from off-pumps to on-pump in 2004, and the hospital mortality for this part of patients even reached 23.8% (51). This meta-analysis has shown that ON-BH CABG has great advantages over reducing early mortality and the occurrence of postoperative MI, LOS, renal failure and pulmonary complications in high-risk patients compared with C-CABG. More importantly, ON-BH technology can similarly achieve coronary revascularization as C-CABG. Available evidence has indicated that complete revascularization is crucial for better long-term prognosis (52,53). Tsai et al. (34) reported ON-BH CABG even appeared survival advantage in the first post-operative vear compared with C-CABG. Consequently, ON-BH CABG is a safe and effective surgical method for coronary revascularization for high-risk patients.

Despite our research showed that ON-BH CABG had great advantages in reducing early mortality and morbidity compared with C-CABG, this surgical method also had its own limitations and indications. First of all, ON-BH CABG requires modified CPB techniques to keep coronary perfusion pressure, negative pressure stabilizer and intracoronary shunts to maintain blood perfusion in distal region, and other technologies related to operating on the beating heart (42,54). Consequently, any potential advantages afforded by ON-BH surgery may well have been lost due to the nuances of ON-BH technology and the insufficient proficiency of the surgical team (26). As mentioned above, due to the different mean arterial pressure during the operation, the results of the myocardial protection effect of ON-BH could be completely opposite. Michael and colleagues (26) found that the most favorable outcomes for ON-BH CABG came from single-centers where there may be well-developed existing technology and (or) a preference for ON-BH CABG. They reviewed the ANZSCTS (Australian & New Zealand Society of Cardiac & Thoracic Surgery) Database for patients undergoing emergency CABG, within 7 days of AMI, in Australia from 2001 to 2015 and found that only 1.3% (77 out of 5,851) of patients underwent ON-BH CABG across Australia. By contrast, in Japan, the proportion of emergency ON-BH CABG in 2014 were 24% (480 out of 1,986) (55). These figures show that ON-BH technology is utilized far more frequently and well-developed in Japan and several early studies originate from Japan had reported more positive results than those in Australia on ON-BH CABG (23,31,35). In addition, ON-BH CABG did not reduce the cost of surgery due to the use of CPB techniques, stabilizer and intracoronary shunt. Excessive surgery costs will increase the financial burden of poor patients.

costs will increase the financial burden of poor patients. Finally, different patient benefits differently from ON-BH CABG. Our results suggest that patients with severe aortic atherosclerosis, severe coronary stenosis, acute MI, left ventricular insufficiency and renal failure are more suitable for ON-BH CABG.

There are several limitations in this research. Firstly, most of the studies included in this meta-analysis were retrospective observational studies, which may have the potential for observer bias and affect the final summary analysis of the data. In addition, there was variability in selection criteria, preoperative risk profiles and sample size between including studies. Finally, the included studies have a long-time span, and the outcomes may have been affected by developing technology and the different profiles of patients in these periods. We hoped that there would be more randomized controlled trials and longer follow-ups to evaluate the clinical efficacy of OP-BH CABG to guide clinicians to choose the most appropriate surgical method according to the patient's condition.

### Conclusions

In conclusion, this meta-analysis is so far the most comprehensive and detailed research currently on the comparison between ON-BH CABG and C-CABG.

According to current evidence from our research, ON-BH CABG might reduce early morbidity and mortality, while maintaining a comparable long-term survival as C-CABG. Patients with severe aortic atherosclerosis, acute MI, severe coronary artery stenosis and (or) renal failure may benefit more from ON-BH CABG. Experienced and adept surgical team and mature ON-BH technology are indispensable to ensure the efficiency and success of the surgery.

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