# Therapeutic Efficacy of a Staged Hybrid Technique vs. Coronary Artery Bypass Surgery Grafting in The Treatment of Multi-Vessel Coronary Artery Disease

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## ABSTRACT

**Objective:** Hybrid coronary revascularization (HCR) integrates the advantages of coronary artery bypass surgery grafting (CABG) and percutaneous coronary intervention (PCI) and provides another effective treatment for multivessel coronary artery disease (CAD). This study aimed to investigate the short- and intermediate-term efficacies of a staged hybrid technique vs. CABG in treating older patients with multi-vessel CAD.

**Methods**: Patients, who received elective revascularization for multi-vessel CAD between May 2016 and May 2018, were recruited. They were divided into the CABG group (N = 38) and HCR group (N = 38). The major adverse cardiovascular and cerebrovascular events (MACCE), including myocardial infarction and stroke, were recorded. The results of death and second revascularization also were recorded.

**Results**: In this study, 90.1% of patients received follow up for a median time of 24 months. At 60 days after surgery, the cumulative mortality in the CABG group was significantly higher than in the HCR group, but the incidence of second revascularization in the CABG group was markedly lower than in the HCR group. The incidence of MACCE was comparable between the two groups.

**Conclusion:** In older patients with multi-vessel CAD, the mortality after CABG is higher than after HCR, but the incidence of second revascularization after CABG is lower than after HCR.

### INTRODUCTION

Multi-vessel coronary artery disease (CAD) often is characterized by obscure or intermediate lesions that may be both contiguous and complex, suggesting multiple regions in need

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of revascularization, and is common in stable and unstable patients; the prevalence of the disease is 30% ~ 60% [Corpus 2004; Cho 2018]. Hybrid coronary revascularization (HCR) first was introduced by Angelini in 1996 [Angelini 1996]. HCR is defined as a combination of coronary artery bypass surgery grafting (CABG) and PCI to treat CAD [Kiaii 2019]. Currently, the time interval between two treatments in HCR is only several minutes, several hours, or several days. The HCR integrates bridging between the left internal mammary artery and the anterior descending artery with PCI of other vessels and can provide effective treatment for different types of CAD. Traditional CABG gradually has been replaced in the last decade, and previous studies have found that dangerous events, such as depression [Stanicki 2020], stroke [Newman 2001; Tarakji 2011], and delirium [Martin 2012] occur after CABG, which not only decreases the quality of life but also worsens the prognosis of patients. Moreover, some patients have concomitant diseases in clinical practice, such as diabetes mellitus, chronic obstructive pulmonary disease, ascending aortic disease, peripheral vascular disease, and malignancies. These patients have a higher intra-operative risk during CABG, and the source of a vessel cannot be assured in some patients, which significantly limits the wide application of traditional CABG. HCR integrates the advantages of CABG and PCI and provides another effective treatment for multivessel CAD.

In our center, HCR was employed for the treatment of CAD in a lot of patients in the past three years. Patients first were treated with minimally invasive direct coronary artery bypass surgery (MIDCAB) in the Department of Heart Surgery and then received PCI in the Department of Cardiology. In the treatment of CAD, the patients' screening, surgical approaches, perioperative treatments, and anticoagulation therapy were standardized, and the therapeutic efficacy was favorable in available patients. In this study, we aimed to investigate the short-term and intermediate-term efficacy of the staged hybrid technique and CABG in the treatment of old patients with multi-vessel CAD.

#### METHODS

**Study subjects**: Patients with multi-vessel CAD between May 2016 and May 2018 were recruited from our

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center. The inclusion criteria were as follows: (1) patients diagnosed with multi-vessel CAD; (2) age≥65; (3) patients accepted either HCR or CABG. Criteria for subjects receiving HCR: multi-vessel disease involving the proximal segment of left anterior descending coronary (LAD) one or more non-LAD coronary lesions suitable for PCI. Criteria for subjects receiving CABG: left-main (LM) coronary lesion and three-vessel disease that are not suitable for PCI. Exclusion criteria: (1) the patients were not treated with HCR or CABG; (2) age<65; (3) patients had a prior history of heart surgery. A total of 76 patients, 38 in the HCR group and 38 in the CABG group, were enrolled and their postoperative data were assessed. This study was reviewed by our hospital's medical ethics committee and each subject signed informed consent.

Surgical procedures: In the HCR group, all patients received MIDCAB and then PCI. Aspirin was administered until one day before surgery. The surgery process was detailed as follows. First, patients received general anesthesia and were implanted with a double-lumen endotracheal tube. The patient was supine with a left chest pad 30cm high. Automatic defibrillation electrodes were affixed to the right anterior and left posterior chest wall and connected to an external automatic defibrillation apparatus. A left anterolateral thoracic 4th or 5th intercostal incision was made, approximately 5 to 6 cm in length. After entering the chest cavity, a new type of suspension internal mammary artery retracting system was placed. After retracting the chest wall, all openings were made at the internal thoracic fascia on the lateral side of the left internal mammary artery, and then the left internal mammary artery was dissociated downward. The two obvious branches of the left internal mammary artery adjacent to the phrenic nerve to the pericardium routinely were severed and separated upward to the upper margin of the first costal and downward to the fifth costal. In one case, this was not used due to internal mammary artery injury/poor blood flow. The heart was stabilized with a suction cup cardiac stabilizer, and the anastomosis of the left internal mammary artery to the left anterior descending artery was completed while the heart was beating. In 38 patients, angiography was performed in the left internal mammary artery/radial artery - great saphenous vein bridge. Unfractionated heparin was administered for six h after surgery. After extubation, 100 mg aspirin and 75 mg clopidogrel were administered once daily for antiplatelet therapy. PCI was performed within five days after antiplatelet therapy. Before angiography, 150 mg clopidogrel was administered. After surgery, antiplatelet therapy with both aspirin and clopidogrel continued for one year. In the control group, routine CABG was performed, and 100 mg aspirin was administered once daily before and after surgery. In the PCI part of HCR, stents should be placed for non-LAD lesions.

**Measurements**: The Society of Thoracic Surgeons (STS) score was used in the baseline. At 30 days and 60 days after surgery, the major adverse cardiovascular and cerebrovascular events (MACCE), including myocardial infarction and stroke, were recorded. Also, the results of death and second revascularization were recorded. Besides, the SYNTAX score

is calculated by entering the patient's coronary angiogram results into the online scoring system. Two coronary interventionalists independently calculate the score based on the coronary angiogram, and the average of the two judges is the final score. The patients were followed up 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years after the operation. Follow up included cardiac death, revascularization, major cardiovascular and cerebrovascular events, myocardial infarction, recurrence of angina pectoris, and patency of coronary artery. Considering the large number of followup visits in this study (6 times), the use of coronary angiography in follow up would bring a burden to patients, so we used coronary CTA to evaluate whether the coronary artery was unobstructed.

**Statistical analysis:** Statistical analysis was performed with SPSS version 19.0. Continuous data are expressed as mean  $\pm$  standard deviation () and compared with an independent sample t-test. Non-continuous data are presented as a percentage and compared with the test. A P-value of < 0.05 was considered statistically significant.

## RESULTS

Characteristics of subjects: In this study, 71.1% of patients were males in the CABG group and 68.4% in the HCR group, and the average ages were  $72\pm8.5$  and  $70\pm5.5$ , respectively. In addition, the differences in age, gender, smoking, BMI, and STS score between the two study groups were not statistically significant and were comparable. Regarding follow up, 90.1% of patients received it, and the median follow-up period was 24 months. In the CABG group, the internal mammary artery was used in 85.9% of patients, 1.2±0.11 stents were placed, and 48.5% of patients receiving CABG received  $\geq 2$  stents. In the HCR group, PCI was performed, followed by placement of a drug-eluting stent at  $6.2 \pm 2.2$  days after MIDCAB, and  $1.5 \pm 0.37$  stents were placed in these patients, and 50.2% of patients received implantation of  $\ge 2$ stents and 48.5% of patients receiving CABG received ≥2 stents. More details about patients' characteristics at baseline are shown in Table 1. (Table 1)

The results of clinical presentations: The clinical presentations of CAD and findings from coronary angiography are shown in Table 2. (Table 2) Compared with the HCR group, the incidences of unstable angina, 3-vessel lesions, proximal anterior descending branch lesions, and chronic complete obstruction were comparable with no statistical difference (P > 0.05 for all). The representative image of coronary angiography is shown in Figure 1. (Figure 1)

**The results of incidence of MACCE and death**: The results of MACCE and death are presented in Table 3. (Table 3) At 30 days after surgery, the incidence of MACCE and mortality in the CABG group were significantly higher than in the HCR group (MACCE: 7.9% vs. 2.6%; mortality: 5.3% vs. 2.6%; P < 0.05).

At 60 days after surgery, the cumulative mortality in the HCR group was significantly lower than in the CABG group (3.6% vs. 7.9%, P < 0.05), but the incidence of second

revascularization in the HCR group was markedly higher than in the CABG group (5.3% vs. 3.6%, P < 0.05). There was no marked difference in the incidence of MACCE. At 30 days, the survival rate in the CABG group was significantly lower than in the HCR group (94.7% vs. 97.4%, P < 0.05), but there was no marked difference in the survival rate at 60 days after surgery (92.1% vs. 94.7%, P > 0.05).

# DISCUSSION

Revascularization is a widely accepted treatment for multi-vessel CAD, and the efficacy of PCI and CABG for revascularization has been confirmed in some clinical trials. CABG may achieve favorable long-term effectiveness; however, it could increase some operative complications, such

Table 1. Patient characteristics at baseline in the CABG and HCR groups

Variables	CABG group ( $N = 38$ )	HCR group ( $N = 38$ )	P-value	
Age (y)	72 ± 8.5	70 ± 5.5	0.894	
Male	28 (71.1)	26 (68.4)	0.357	
Family history of CAD	1 (2.6)	1 (2.6)	0.930	
History of smoking	24 (63.2)	25 (65.8)	0.674	
BMI (kg/m²)	24.2 ± 5.5	25.1 ± 7.2	0.571	
DM	8 (21.1)	10 (26.3)	0.480	
History of cerebrovascular disease	3 (7.9)	3 (7.9)	0.925	
Heart valve disease	0 (0.0)	1 (2.6)	0.089	
History of kidney disease	2 (5.3)	3 (7.9)	0.148	
COPD	1 (2.6)	1 (2.6)	0.113	
Creatinine (µmol/L)	85.7 ± 7.3	82.8 ± 2.3	0.281	
Hemoglobin (g/L)	115.4 ± 9.2	120.7 ± 4.9	0.358	
High-density lipoprotein cholesterol (mmol/L)	1.08 ± 7.1	1.3173 ± 4.9	0.647	
Low-density lipoprotein cholesterol (mmol/L)	$\textbf{2.4}\pm\textbf{6.5}$	2.5±5.1	0.674	
LVEF <40%	2 (5.3)	2 (5.3)	0.810	
LVEF	55.78 ± 6.2	54.41 ± 7.5	0.675	
STS Score	7.2 ± 3.2	8.1 ± 2.8	0.521	
Preoperative LVEF (%)	$42.25 \pm 6.2$	43.11 ± 6.8	0.289	
Postoperative LVEF (%)	45.69 ± 7.1	45.99 ± 7.5	0.412	

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction

Variables	CABG group (N = 38)	HCR group ( <i>N</i> = 38)	P-value	
Unstable angina	30 (78.9)	29 (76.3)	0.121	
Stable angina	7 (18.4)	7 (18.4)	0.974	
Two-vessel disease	9 (23.7)	11 (28.9)	0.135	
Three-vessel disease	27 (71.1)	24 (18.4)	0.089	
Proximal left anterior descending artery lesion	24 (63.2)	34 (89.4)	0.052	
Left main coronary artery lesion	5 (13.2)	4 (10.5)	0.847	
Chronic total occlusion	20 (52.6)	13 (34.2)	0.133	
In-stent restenosis	1 (2.6)	3 (7.9)	0.014	
SYNTAX score	36 ± 1.2	35 ± 2.0	0.638	

Table 2. Clinical presentations of CAD and coronary angiography (%)

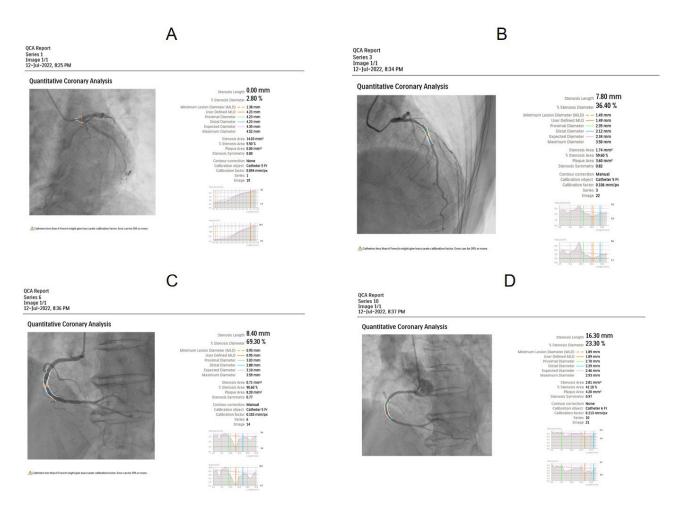


Figure 1. Representative images of quantitative coronary angiography. A 76-year-old female patient was admitted to the hospital and underwent coronary angiography, due to recurrent chest tightness and chest pain for more than one month and aggravated on the second day. (A) There was a severe lesion of 80% stenosis at ostial segment of the left main coronary artery. (B) There was a 30% stenosis at proximal segment and a 70% stenosis at middle segment of the left anterior descending artery. (C) There was an 80% stenosis at middle segment of the right coronary artery. (D) Post-intervention image: The middle part of right coronary artery was dilated with a 3.0\*15mm drug-coated balloon.

Table 3.	The results	of death	and MACCE	between	the two	groups (	(%)
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Variable	30 days				60 days			2 years		
	CABG	HCR	P-value	CABG	HCR	P-value	CABG	HCR	P-value	
Cardiac-related death	2 (5.3)	1 (2.6)	0.014	3 (2.6)	1 (2.6)	0.003	5 (13.1)	4 (10.5)	0.214	
Second revascularization	0 (0.0)	0 (0.0)	0.857	1 (2.6)	2 (5.3)	0.010	5 (13.1)	7 (18.4)	0.021	
Myocardial infarction	0 (0.0)	0 (0.0)	0.935	1 (2.6)	1 (2.6)	0.321	2 (5.3)	3 (7.9)	0.104	
Stroke	1 (2.6)	0 (0.0)	0.002	1 (0.0)	0 (0.0)	0.002	1 (2.6)	0 (0.0)	0.043	
Atrial fibrillation	9 (23.7)	8 (21.1)	0.435	11 (28.9)	11 (28.9)	0.796	13 (34.2)	12 (31.6)	0.318	
Overall MACCE	3 (7.9)	1 (2.6)	0.001	5 (13.1)	4 (10.5)	0.067	7 (18.4)	8 (21.1)	0.473	

as a cerebrovascular event, infection, and blood transfusion [Yamamoto 2021]. In the United States, up to 14% of patients develop postoperative complications within 30 days of discharge each year, and the morbidity and mortality of postoperative complications are significant [Montrief 2018]. PCI is a minimally invasive technique, the recovery after PCI is more rapid, and patients with large myocardial infarction may benefit more from PCR, but the long-term incidence of in-stent restenosis is relatively high [Chieffo 2010]. The incidence of long-term adverse events reduces significantly with the wide application of drugeluting stents. Currently, the recommended level of PCI is increased for low to intermediate-risk patients (SYNTAX score  $\leq$ 32) and is comparable to that of CABG. However, for high-risk patients (SYNTAX score >32), CABG still is the treatment of choice [Han 2015]. For CAD patients, the left anterior descending branch is the main vessel for the maintenance of the quality of life, and the long-term patency rate is closely related to the quality of life and survival time. The advantage of CABG is the revascularization of the left internal mammary artery (LIMA), which has been found to benefit patients more postoperatively, in terms of all-cause mortality, cardiac mortality, and repeat revascularization at long-term follow up [Xie 2021]. In the revascularization of vessels other than the left anterior descending branch, the great saphenous vein (SVG), radial artery, and inferior epigastric artery can be used, but the collection of the radial artery and inferior epigastric artery is relatively difficult and has some complications. Thus, in clinical practice, SVG is preferred for revascularization. As compared with the artery, the long-term patency rate of SVG is compromised [Kim 2008; Zhao 2021]. Although there is no comparative study between them, available findings indirectly reveal that the incidence of restenosis at 12 months after implantation of drug-eluting stents (DES) is lower than that after SVG [Wu 2010]. The replacement of DES with SVG for the revascularization of vessels other than the left anterior descending branch may benefit patients more.

Hybrid surgery has a favorable long-term patency rate of internal mammary artery bridge and comparable complete revascularization to traditional CABG [Kim 2008; Halkos 2014]. However, hybrid surgery is not available for most hospitals in China, and only staged hybrid surgery is available in these settings. That is, MIDCAB and PCI are independently performed at distinct time points and different sites. However, complete revascularization is not achieved during the treatment, and patients have a higher risk for cardiovascular events [Zhou 2010]. For staged hybrid surgery, the order of MIDCAB and PCI still is controversial in clinical practice. PCI is performed first, which may recover the blood supply to a part of the myocardium, before MIDCAB; if PCI fails, traditional CABG can be performed. If MIDCAB is performed first, antiplatelet therapy is not necessary before surgery, which may not increase the perioperative risk for bleeding, and PCI can be performed with good protection of the left anterior descending branch; angiography also may be done to visualize the LIMA [Gosev 2014].

In the present study, patients in the HCR group had a high risk if PCI was performed for multi-vessel disease in the Department of Cardiology, and they had concomitant risk factors, such as advanced age, left ventricular dysfunction, diabetes mellitus, and chronic obstructive pulmonary disease. HCR finally was selected after consultation with the clinician in the Department of Cardiology and Department of Heart Surgery. This may be the reason for the higher incidence of the second revascularization in subjects in the HCR group.

After intermediate follow up, the incidences of death of any cause, cerebrovascular events, myocardial infarction, second revascularization, MACCE, and angina pectoris recurrence were comparable between the two groups (P = NS). In addition, there were no marked differences in the postoperative actual survival rate, 2-year survival rate, 2-year revascularization-free rate, and 2-year MACCE-free rate between the two groups (P = NS). Kon et al. (2008) reported similar findings: The overall patency rate at one year shown by CTA was 97% in the HCR group and 85% in the OPCAB group, showing no significant difference.

According to our experience, most patients who are suitable for hybrid surgery have diffuse anterior descending branch lesion or occlusion, and thus they are not suitable for PCI; therefore, it seems to be reasonable for PCI to be performed first, followed by MIDCAB. A few patients, who had lesions in vessels other than the left anterior descending branch, were suitable for PCR and could receive PCI first. In staged hybrid surgery, PCI and MIDCAB are performed at different time points, and thus the perioperative management is crucial; the appropriate management and anti-platelet therapy are needed to prevent the thrombosis in stents and the ischemic events of untreated coronary artery; in addition, excess anti-platelet therapy may increase the risk for bleeding and should be avoided. Based on above findings, HCR is a safe, effective, and feasible treatment for multi-vessel CAD in patients with high-risk factors, such as advanced age, left ventricular dysfunction, diabetes mellitus, chronic obstructive pulmonary disease, and the intermediate-term efficacy is favorable. As compared with CABG, the incidence of inhospital adverse events is lower, and thus HCR safely can be applied in these patients with high-risk factors.

However, there were some limitations in this study. The sample size was small, and the follow up was relatively short. In HCR, revascularization of LIMA-LAD involves middle sternotomy and MIDCAB. Traditional CABG involves the beating heart CABG under extracorporeal or non-extracorporeal circulation. Whether the difference in these techniques may influence the clinical outcome still is unclear.

### CONCLUSION

In conclusion, the mortality after CABG is higher than that after HCR in old patients with multi-vessel CAD, but the incidence of second revascularization after CABG is lower than that after HCR. HCR is a safe, effective, and feasible treatment for multi-vessel coronary artery disease.

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