Original Article

Long-term outcomes of multiple and single arterial off-pump coronary artery bypass grafting

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Background: To compare the clinical outcomes between multiple arterial (MA) and single arterial (SA) off-pump coronary artery bypass grafting (OPCAB) when applied to left main coronary disease or three-vessel disease.

Methods: A total of 537 patients with left main coronary disease or three-vessel disease underwent MA OPCAB (n=114) or SA OPCAB (n=423) in our center from January 2006 to December 2008. The propensity score matching (PSM) was used to obtain the risk-adjusted outcome. Both the perioperative and long-term results were analyzed.

Results: The median follow-up time was 117 months (interquartile range, 110 to 128 months). There was no statistical difference in postoperative mortality and the volume of drainage. The intensive care unit (ICU) length of stay (LOS) of the MA group was shorter than that of the SA group {1 [1–2] *vs.* 2 [1–3], P=0.001). In the long term, the mortality (5.7% *vs.* 17.5%, P=0.006), cardiac mortality (1.0% *vs.* 8.8%, P=0.008), fatal myocardial infarction (MI) rate (0.0% *vs.* 6.1%, P=0.015) and incidence of readmission for heart failure (19.8% *vs.* 37.7%, P=0.003) were lower in the MA group than in the SA group. The distributions of NYHA class (P<0.001) and CCS class (P<0.001) were better in the MA group than in the SA group. There was no significant difference in other outcomes. These results were consistent with the K-M curves of freedom from the adverse events.

Conclusions: MA OPCAB was as safe as SA OPCAB, providing better perioperative recovery and better long-term clinical outcomes in the treatment of left main coronary disease or three-vessel disease.

Keywords: Multiple arterial (MA); off-pump coronary artery bypass grafting (OPCAB); propensity score matching (PSM); left main coronary disease or three-vessel disease

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Introduction

Coronary artery bypass grafting (CABG) is commonly used to treat left main coronary disease or three-vessel disease with significant efficacy (1). It is the current gold standard to anastomose the left internal mammary artery (LIMA) to the lesioned left anterior descending artery (LAD), while the other lesions are often treated with saphenous vein grafts (SVG) (2). The 10-year patency of LIMA grafts was over 90%, whereas that of venous grafts was only about 50% (3,4). Due to the satisfactory long-term efficacy of single internal mammary artery graft (SIMA) (5), surgeons try to complete CABG with multiple arterial (MA) grafts, especially with bilateral internal mammary artery (BIMA) grafts (6). Several meta-analyses have shown that the 10-year all-cause mortality in the BIMA group was approximately 20% lower than that in the SIMA group (7-11). An observational study showed the improved survival with radial artery (RA) versus vein conduits in CABG with LIMA-LAD grafting (12). The result of the Radial Artery Database International Alliance (RADIAL) project showed decreased main adverse cardiovascular and cerebrovascular events (MACCE) rate with RA versus SVG (13).

Additionally, the current US and European guidelines encourage the use of arterial grafts (AGs) in patients with long life expectancies (14,15). However, the current evidence on the clinical effects of using multiple versus single AG for CABG is still controversial. The ten-year result of Arterial Revascularization Trial (ART), an international multi-center randomized controlled trial (RCT) enrolling more than 3,000 patients to compare BIMA with SIMA, was released in ESC2018. It showed no survival benefit of BIMA. A recent pooled analysis of individual patient data from the six RCTs comparing the RA to the SVG found no significant reduction of follow-up death 5 years after surgery (13).

Meanwhile, it is worth noting that the use of AGs remains limited all around the world. Currently, in the USA, less than 6% of all CABG patients receive more than 1 AG (16), while the rate of BIMA use is slightly above 12% in Australia (17). A possible explanation for the slow diffusion of the use of AGs is the lack of substantial evidence concerning its clinical benefits. Off-pump coronary artery bypass grafting (OPCAB) is a safe and effective operation for treating multivessel disease with multiple AGs (18).

Most articles about MA CABG had strict limitations for the type of AGs, and mostly compared LIMA + RA with LIMA + SVG or BIMA with SIMA. However, the mid-term patency rate of the RA and right internal mammary artery (RIMA) was similar in a previous study (19). Thus, it may be that the number of AG matters, but not the type of AG. In this study, the patients were divided according to the number of AGs. The purpose of this study was to find whether, in patients undergoing primary isolated non-emergent OPCAB, the use of 2 or more AGs compared with a single AG is associated with a reduction in the long-term adverse events.

Methods

Study design

The local Research Ethics Board of Ruijin Hospital approved this retrospective cohort study (No. 2018-40). The local Research Ethics Board waived the written patient consent. Data were collected from the local database of Ruijin Hospital. The patients between January 2006 and December 2008 were selected for analysis. The inclusion criteria were as follows: (I) the patient underwent OPCAB; (II) the patient had left main coronary disease or three-vessel disease; (III) LIMA-to-LAD anastomosis was performed. The exclusion criteria were as follows: (I) the operation was emergent; (II) the incision was not median sternotomy; (III) the patient had a conversion to on-pump CABG with other procedures, such as valve repair; (IV) the OPCAB was a redo surgery.

The patients were divided into the MA group and the single arterial (SA) group according to the number of AGs. The patients who had at least 2 AGs, one of which was LIMA-LAD were included into the MA group. For example, the patients with LIMA + RA, LIMA + RIMA, LIMA + RA + SVG or LIMA + RIMA + RA + SVG were all in the MA group. The SA group only included the patients with LIMA + SVG. *Figure 1* shows the detailed flow of this study.

Surgical procedure

The cardiac stabilizer was used to locally secure and fully expose the anastomotic site. A shunt of appropriate size was used to protect the distal myocardial blood supply. An aerosol spray device was used to keep the anastomotic site clear of blood. The proximal anastomosis to the aorta used a 5-0 prolene suturing with an aortic side-biting clamp. The epicardial tissue on the anterior wall of aorta should be removed, and the hole puncher was used for punching a hole on the aorta. After the anastomosis completed, the air was discharged by water flush or blood flow before knotting. The distal anastomosis to the target vessels used 7-0 prolene.

A total of 537 LIMA grafts were involved in this study and anastomosed to LAD in situ. Twelve cases were treated with RIMA, 3 of which were free. The proximal ends were anastomosed to LIMA with end-to-side anastomosis and the distal to OM1 (n=3). The other RIMA grafts were anastomosed to Dia1 (n=8) and RCA (n=1) in situ. A total of 108 cases were treated with RA grafts. The proximal end of the RA graft was anastomosed to LIMA (n=21) and the aorta (n=84) and SVG (n=3) with end-to-side anastomosis. The RA graft was then sequentially anastomosed to the targeted vessels. Only 3 patients used the gastroepiploic arteries (GEA). The GEA grafts were all anastomosed

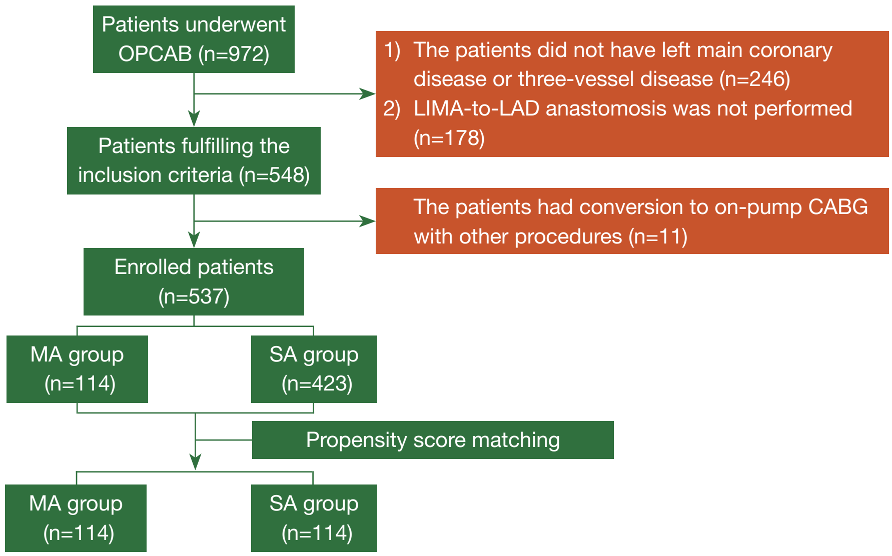

Figure 1 The flow chart of this study. OPCAB, off-pump coronary artery bypass grafting; LIMA, left internal mammary artery; LAD, left anterior descending artery; CABG, coronary artery bypass grafting; MA, multiple arterial; SA, single arterial.

Table 1 Distribution of conduits according to the target vessel

Target vessel	Before PSM		After PSM	
	MA group, N=114	SA group, N=423	MA group, N=114	SA group, N=114
LAD	114	423	114	114
Dia1	65	273	65	72
Dia2	3	32	3	12
Ramus	13	41	13	7
LCX	3	4	3	1
OM1	99	310	99	85
OM2	33	127	33	32
RCA	12	35	12	7
AM	1	2	1	1
PDA	79	332	79	84
RPL	13	96	13	25

MA, multiple arterial; SA, single arterial; PSM, propensity score matching; LAD, left anterior descending artery; Dia1, the first diagonal branch; Dia 2, the second diagonal branch; LCX, left circumflex coronary artery; OM1, the first obtuse marginal branch; OM2, the second obtuse marginal branch; RCA, right coronary artery; AM, acute marginal branch; PDA, posterior descending artery; RPL, right posterolateral branch.

to PDA in situ. SVG was anastomosed with sequential anastomosis or using the "Y/T" anastomosis techniques. The distribution of the conduits according to the target vessels is shown in *Table 1*.

All patients received 100 mg of aspirin and 75 mg clopidogrel daily in the first year following the surgery. Then, 100 mg of daily aspirin was continued for life.

Data collection

The preoperative characteristics and the postoperative data, including rates of death, IABP support, the volume of drainage, and length of stay (LOS) in the intensive care unit (ICU), were obtained from the local database of Ruijin Hospital.

Follow-up

Follow-up was completed via a telephone interview annually from our unit. For the patients in this study, an additional telephone interview was performed. The incidence of death, cardiac death, myocardial infarction (MI), fatal MI, stroke, readmission for heart failure and target vessel revascularization (TVR) were recorded. The MACCE was defined as a composite outcome of death, MI and stroke. The primary outcome was cardiac death.

Propensity score matching (PSM)

A total of 114 patients in the MA group and 423 patients in the SA group fulfilled the inclusion and exclusion criteria. To adjust for significant unbalanced individual characteristics between multiple and SA OPCAB patients, we used propensity scores (PSs) to reduce this imbalance (17). A multivariate logistic regression model was employed to estimate PSs using all of the preoperative characteristics. We chose caliper matching without a replacement for this study. A subset of the SA group was matched to the MA group with calipers a width of 0.2 the standard deviation of the logit of the PS. Covariate balance was measured using the standardized mean difference (SMD). An SMD between −10% and 10% indicated a well-matching balance.

Statistical analysis

Continuous variables were summarized as mean ± SD (standard deviation) or median (the 25th percentile, the 75th percentile) and categorical variables were categorized as frequencies and percentages. After PSM, for early outcomes, continuous variables were compared using paired *t*-tests or Wilcoxon signed-rank test, and categorical variables were compared using McNemar's test. In the other situations, continuous variables were compared using a two-tailed Student's t-test. Categorical variables were compared using the χ^2 test or Fisher exact test. The time to the first occurrence of any one of the long-term outcomes was described by Kaplan-Meier curves (K-M curves), and the comparisons of K-M curves were performed with a stratified log-rank analysis. A Cox proportional hazards model was used to calculate the unadjusted hazard ratio (HR), and the HR was adjusted via the PS for both data sets relating to all-cause and cardiovascular death for the MA group compared with the SA group. All analysis was performed with SPSS version 22.0 (Chicago, IL, USA) and R version 3.4.3. A P value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics of patients

A total of 114 patients in the MA group and 423 patients in the SA group fulfilled the inclusion and exclusion criteria, and there were 114 patients in each group after PSM. All SMDs were less than 0.10, representing negligible differences across all of the preoperative characteristics. *Table 2* displays the preoperative patient characteristics before and after PSM.

Furthermore, there were no differences between the numbers of grafts for the two groups before (3.82±0.91 *vs.* 3.96±0.94, P=0.156) and after (3.82±0.91 *vs.* 3.86±0.92, P=0.601) PSM.

Postoperative outcomes

Table 3 shows the postoperative results of the two groups. The mortality, the incidence of IABP support, and the volume of drainage were comparable between the two groups before and after PSM (P>0.05). The LOS in ICU was significantly shorter in the MA group, compared with the SA group either before or after PSM (P=0.001).

Long-term outcomes

The median follow-up time was 117 months (interquartile range, 110 to 128 months). The follow-up rates of the MA and SA groups were 93.0% and 91.7% respectively, both before PSM (93.0%), and after PSM (100%). Before PSM, the incidences of cardiac death, MACCE, MI, fatal MI, stroke, readmission for heart failure, and TVR were comparable between the two groups (P>0.05), but the mortality of the MA group was significantly lower than that of the SA group (P=0.026) (*Table 4*). After PSM, there was no difference in the incidences of MACCE, MI, stroke, and TVR between the two groups (P>0.05). However, the frequency of death (P=0.006), cardiac death (P=0.008), fatal MI (P=0.015) and readmission for heart failure (P=0.003) were all significantly lower in the MA group when it was compared with the SA group (*Table 4*). The distributions of NYHA class (P<0.001) and CCS class (P<0.001) were better in the MA group than in the SA group either before or after PSM (*Figure 2A,B*).

Long-term freedom from adverse events was estimated for each group using Kaplan-Meier analysis after PSM. The ten-year freedom from death, cardiac death, fatal MI and readmission for heart failure were 93.9% *vs.* 85.5% (P=0.009), 99.1% *vs.* 92.1% (P=0.007), 100% *vs.* 93.9% (P=0.008) and 82.3% *vs.* 65.2% (P=0.039) in the MA group and in the SA group, respectively (*Figure 3A,B,C,D*). The ten-year freedom from MACCE, MI, stroke, and TVR were not significantly different between the two groups

Table 2 Preoperative characteristics of patients undergoing MA and SA OPCAB before and after PSM

Preoperative characteristics	Before PSM			After PSM		
	MA group, N=114	SA group, N=423	SMD	MA group, N=114	SA group, N=114	SMD
Male	105	360	0.22	105	104	0.03
Age (yrs)	57.2±8.3	64.0±8.1	0.83	57.2±8.3	57.9±8.5	0.08
BMI	25.3±2.4	24.8±2.3	0.21	25.3±2.4	25.2±2.4	0.04
Hypertension	65	263	0.11	65	64	0.02
DM	23	120	0.19	23	24	0.02
Hyperlipoidemia	10	50	0.10	10	11	0.03
MI	19	48	0.15	19	20	0.02
Recent MI	2	18	0.15	2	3	0.06
Smokers	30	56	0.33	30	28	0.04
Stroke	4	36	0.21	4	5	0.05
COPD	1	10	0.12	1	1	0.00
EF (%)	63 [58–68]	63 [57–68]	0.06	63 [58–68]	63 [57–68]	0.10
CKD	1	4	0.01	1	2	0.08
NYHA class						
I	21	100	0.13	21	20	0.02
II	82	263	0.21	82	80	0.04
III	10	48	0.09	10	13	0.09
IV	1	12	0.15	1	1	0.00
CCS class						
No angina	6	19	0.04	6	6	0.00
I	23	92	0.04	23	22	0.02
II	74	254	0.10	74	72	0.04
III	9	45	0.09	9	11	0.06
IV	2	13	0.09	2	3	0.06
Euroscore II (%)	1.5±1.0	2.0±1.2	0.45	1.5±1.0	1.6±1.3	0.09

MA, multiple arterial; SA, single arterial; OPCAB, off-pump coronary artery bypass; PSM, propensity score matching; SMD, standardized mean difference; BMI, body mass index; DM, diabetes mellitus; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; CKD, chronic kidney disease. NYHA class, New York Heart Association class; CCS class, Canadian Cardiovascular Society class.

Table 3 Postoperative outcomes of patients undergoing MA and SA OPCAB before and after PSM

Postoperative outcomes	Before PSM			After PSM		
	MA group, N=114	SA group, N=423	P value	MA group, N=114	SA group, N=114	P value
Death	0	4	0.668	0	1	1.000
IABP	0	0	–	0	0	–
Drainage	495 [340–640]	440 [310–650]	0.314	495 [340–640]	429 [302–604]	0.062
LOS in ICU	1 [1–2]	2 [1–3]	0.001*	1 [1–2]	2 [1–3]	0.001*

*, means there was a significant difference between the two groups (P<0.05). MA, multiple arterial; SA, single arterial; OPCAB, off-pump coronary artery bypass; PSM, propensity score matching; IABP, intra-aortic balloon pump; LOS, length of stay; ICU, intensive care unit.

Table 4 Long-term outcomes of patients undergoing MA and SA OPCAB before and after PSM

Long-term outcomes	Before PSM			After PSM		
	MA group, N=106	SA group, N=388	P value	MA group, N=106	SA group, N=114	P value
Death	6	57	0.026*	6	20	0.006*
Cardiac death	1	21	0.087	1	10	0.008*
MACCE	25	112	0.210	25	36	0.186
MI	8	25	0.466	8	10	0.741
Fatal MI	0	13	0.087	0	7	0.015*
Stroke	12	58	0.254	12	17	0.431
Readmission for heart failure	21	122	0.117	21	43	0.003*
TVR	12	35	0.474	12	13	0.985

*, means there was a significant difference between the two groups (P<0.05). MA, multiple arterial; SA,single arterial; OPCAB, off-pump coronary artery bypass; PSM, propensity score matching; MACCE, main adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; TVR, target vessel revascularization.

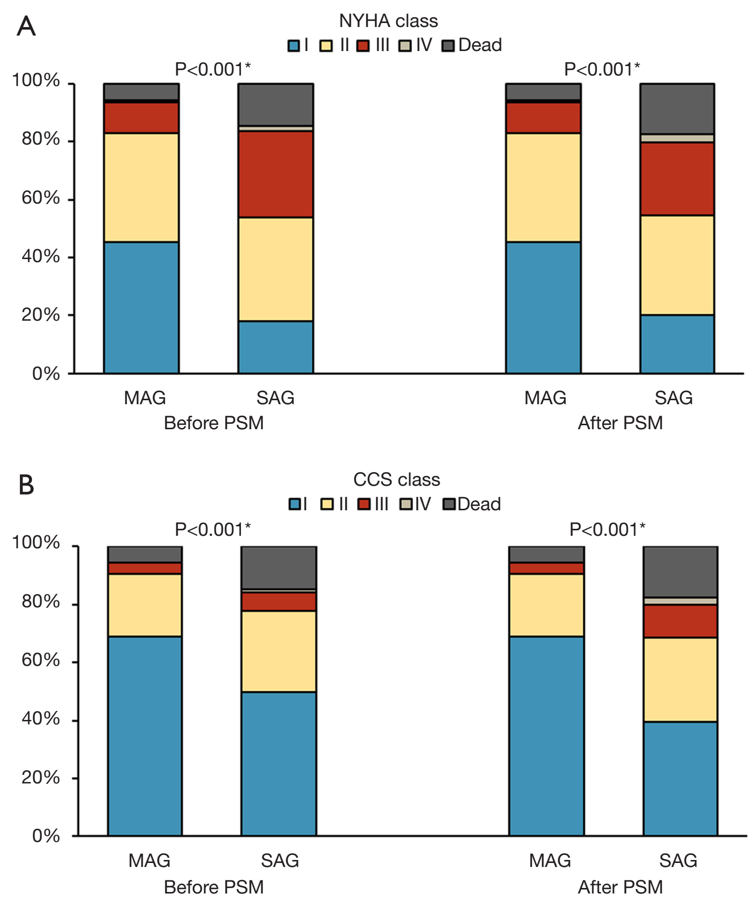

Figure 2 The NYHA and CCS class of two groups before and after PSM. Symptom status according to NYHA class (A) and CCS class (B) are shown at long-term between patients in the MA and SA group. *, means there was a significant difference between the two groups (P<0.05). NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; MA, multiple arterial; SA, single arterial; PSM, propensity score matching.

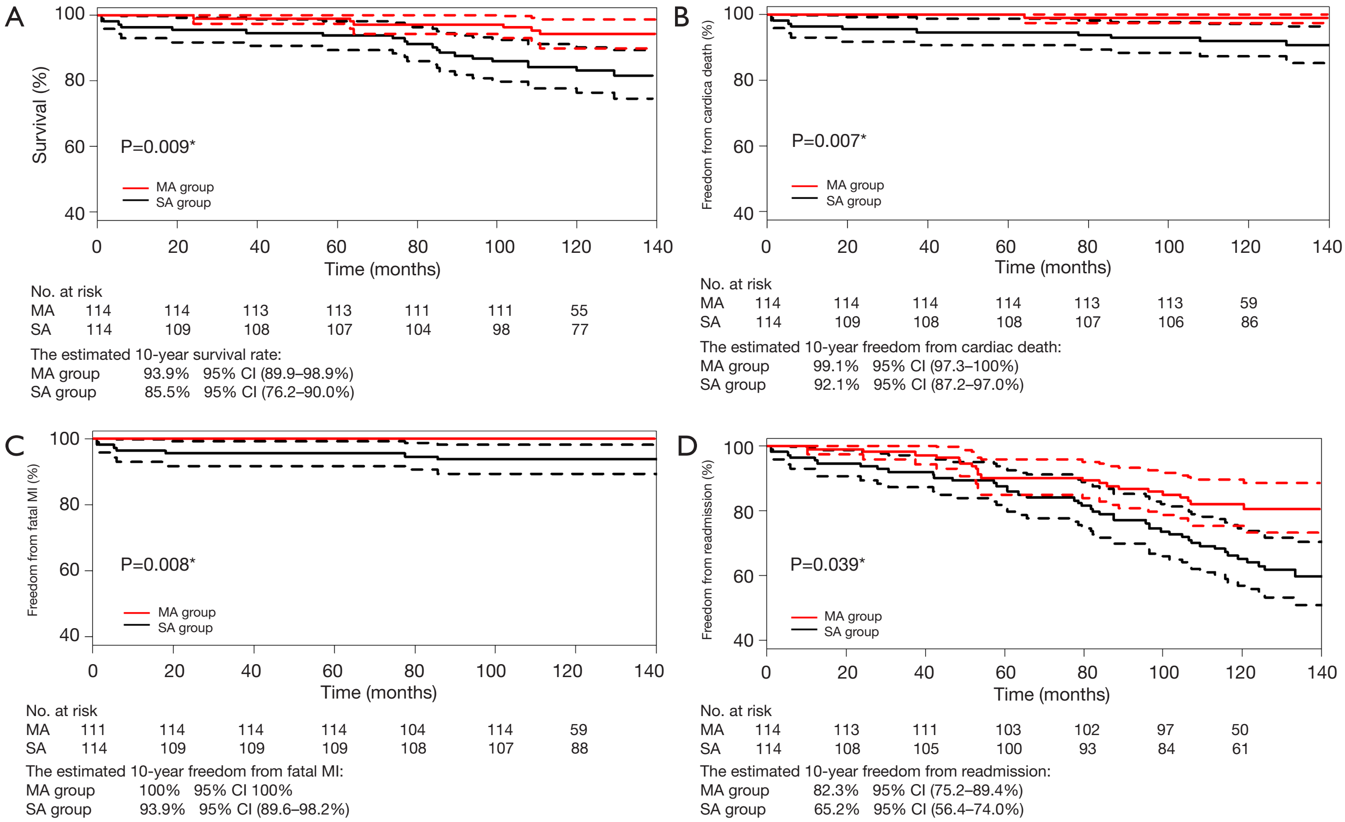

Figure 3 The K-M curves of overall survival, freedom from cardiac death, fatal MI and readmission for heart failure. The survival rates (A) and freedom from cardiac death (B), fatal MI (C), and readmission for heart failure (D) were calculated with Kaplan–Meier methods and compared with log-rank test. The survival rates (P=0.009) and freedom from cardiac death (P=0.007), fatal MI (P=0.008), and readmission for heart failure (P=0.039) of the MA group were all significantly higher than those of the MA group. *, means there was a significant difference between the two groups (P<0.05). K-M, Kaplan-Meier; MI, myocardial infarction; MA, multiple arterial; SA, single arterial.

(P>0.05) (*Figure 4A,B,C,D*).

The univariate Cox proportional hazard model demonstrated that MAOPCAB was significantly associated with decreased risks for all causes of death (HR =0.358, 95% CI: 0.280 to 0.458) and cardiac death (HR =0.167, 95% CI: 0.071 to 0.392). After being adjusted for PS, MAOPCAB were found to be significant determinants for all-cause death (HR =0.546, 95% CI: 0.357 to 0.835) and cardiac death (HR =0.291, 95% CI: 0.104 to 0.818).

Discussion

In recent years, OPCAB and the application of multiple artery grafts have gained more and more attention. The 5-year results of the CORONARY study showed that OPCAB had no significant effect on the incidence of MACCE when it was compared with an on-pump CABG, which meant OPCAB was as safe as the conventional procedure (20). Meanwhile, OPCAB can avoid the microthrombus hypoperfusion and systemic inflammation caused by CPB, which reduces patient injury and is conducive to postoperative recovery. The use of multiple artery grafts offers long-term survival benefits for patients who are under the age of 60 (21), male (22), with DM (23) or with a BMI under 30 (24), compared the use of single artery graft. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for CABG recommended the use of multiple artery grafts to treat patients under 60 years of age with severe coronary artery stenosis (≥90% in the right coronary artery, ≥70% in the left coronary artery) (14). This study attempted to investigate the long-term clinical benefit of MA OPCAB in treating left main coronary disease or three-vessel disease, compared with SA OPCAB.

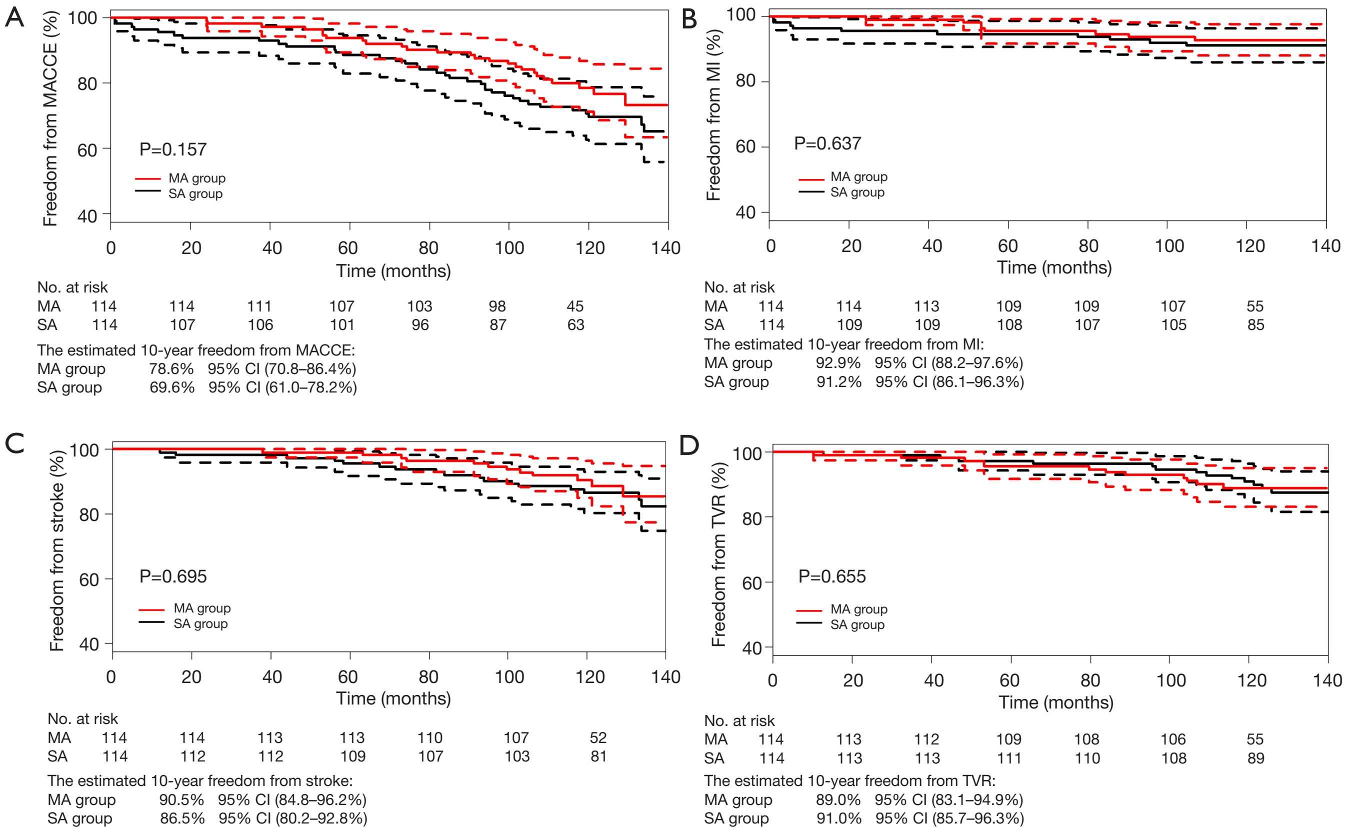

Figure 4 The K-M curves of freedom from MACCE, MI, stroke, and TVR. Freedom from MACCE (A), MI (B), stroke (C), and TVR (D) were calculated with Kaplan–Meier methods and compared with the log-rank test. There was no significant difference in freedom from MACCE, MI, stroke, and TVR between the two groups (P>0.05). K-M, Kaplan-Meier; MACCE, main adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; MA, multiple arterial; SA, single arterial.

The postoperative outcomes of MA CABG were satisfactory in previous literature. A pilot RCT showed that no patients who underwent MA or SA on-pump CABG died in hospital, and the incidences of postoperative MI and stroke were comparable between the two groups (25). In this study, there were no patients that died in the MA group in hospital, which was similar to the previous results of MA on-pump CABG, and there were no differences in the postoperative mortality, the incidence of IABP support and the volume of drainage between the two groups. However, the LOS in ICU was significantly shorter in the MA group than in the SA group (P=0.001). These results showed that MA OPCAB was as safe as either SA OPCAB or MA on-pump CABG and had better postoperative recovery compared with SA OPCAB.

For the comparison between SIMA and BIMA, the use of BIMA was associated with a significantly better long-term survival with a relative risk reduction of approximately 20% (26). A meta-analysis including 89,399 patients (27), reported that 8.6 years after surgery, the BIMA cohort had significantly better long-term survival, MI-free, and angina-free survival. Similar benefits have been achieved using an RA as a second AG in conjunction with a SIMA. At a mean follow up of 6.7 years, the use of the RA was associated with a 24% relative decrease in mortality, whereas operative mortality and morbidity were similar (28). Two independent meta-analyses have also found that the use of a third AG and total arterial revascularization are associated with a significant long-term survival benefit (29,30). The explanation for the benefit of multiple AGs is the better patency rate of the AGs compared to SVG. The use of the RA was associated with a 69% relative reduction in the risk of graft failure beyond 4 years of follow-up (31). For the RIMA, there were similar results (32). A network meta-analysis comparing the RA, RIMA, and SVG as the second conduit for CABG found that the SVG was associated with a significantly higher graft occlusion rate at a follow-up exceeding 4 years (19). Another explanation is that AGs can exert a protective effect on the coronary circulation, due to the downstream release of endothelial-derived antithrombotic and anti-inflammatory mediators (33).

However, the current evidence on MACABG is still controversial. The 5-year results (34) and 10-year results released in ESC2018 of ART, the largest RCT comparing BIMA and SIMA, showed no difference in survival and event-free survival between the two groups. After many years of observational evidence actively supporting the better clinical results of BIMA, the result of ART was a surprise for the cardiovascular community. A recent pooled analysis of individual patient data from the six RCTs with a mean follow-up of more than 2 years found a statistically significant reduction in the combined end-point of follow-up cardiac events, but not of follow-up death 5 years after surgery (13).

The mean follow-up time of this study was about 10 years, and the follow-up rate was above 90%, which means the results are high-qualified and may reflect the long-term effect of MA OPCAB. In this study, the incidences of MI were not different between two groups, but MA OPCAB was shown to significantly decrease the long-term impact of fatal MI, compared with SA OPCAB (P=0.015), perhaps resulting in the lower cardiac death rate (P=0.008) and mortality (P=0.006). The results of Kaplan-Meier analysis were consistent with the above results. MA OPCAB significantly improved the ten-year freedom of cardiac death (P=0.007) and death (P=0.009) by increasing the ten-year freedom from fatal MI (P=0.008), compared with SA OPCAB. The better distributions of NYHA class (P<0.001) and CCS class (P<0.001) in the MA group showed that MA OPCAB could lead to symptom improvement in promoting heart function and lowering angina, resulting in the lower readmission rate for heart failure (P=0.003), compared with SA OPCAB.

In conclusion, this study with a 10-year follow-up showed that MA OPCAB was a safe procedure in treating left main coronary disease or three-vessel disease with better postoperative recovery compared with SA OPCAB. MA OPCAB could significantly decrease the long-term incidence of fatal MI, compared with SA OPCAB, resulting in the lower cardiac death rate and mortality. Additionally, MA OPCAB could promote heart function and lower angina, leading to the lower readmission rate for heart failure in comparison with SA OPCAB. This study did not limit the type of AGs anastomosed to non-LAD lesions. Provided the LIMA-LAD anastomosis is completed, the use of 2 or more AGs, whatever the type, compared with a SAG is associated with a reduction in the long-term adverse events.

Limitations

Firstly, this is a nonrandomized comparison. The potential limitation of the study is that there still may be residual confounders, as well as differences between groups due to the nonblinding of both the patients and physicians. Secondly, the sample size was small, and we will design a study which includes more patients in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the local Research Ethics Board of Ruijin Hospital (No. 2018-40). The local Research Ethics Board waived the written patient consent.

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