Risk Factors for Poor Prognosis of Coronary Artery Bypass Grafting in the Patients with Diabetes

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Background: Diabetes is one of the most frequent comorbidities in patients undergoing coronary artery bypass grafting (CABG). Today, half of the patients who need CABG suffer from diabetes. Those patients tend to present poor prognosis as compared with nondiabetic patients. However, the most influential factor in surgical outcomes of CABG patients with diabetes remains unclear. The purpose of this study was to identify risk factors that contribute to poor post-CABG prognosis in patients with diabetes. **Methods:** A total of 1,139 patients underwent CABG from January 2000 through July 2015. Of those patients, 599 patients had diabetes (DM group), and the other 540 patients did not (non-DM group). We retrospectively investigated early and late clinical outcomes between the 2 groups. In the DM group, multivariable analysis was performed to identify the risk factors for survival. **Results:** The diabetic patients had more incidents of comorbidities than the nondiabetic patients. However, hospital mortality after CABGs between the two groups was similar even though the incidence of deep sternal infection, renal failure, and respiratory failure were higher in the DM group than in the non-DM group. All-cause mortality during follow-up was significantly higher in the DM group. The predictors of poor prognosis for diabetic patients after CABGs were old age, peripheral vascular diseases, severity of carotid atherosclerosis, and hemodialysis, not the number of arterial grafts used. **Conclusions:** Poor prognosis factors after CABGs in diabetic patients were concomitant chronic renal failure and advanced atherosclerosis. The number of arterial grafts used in the CABGs had no influence on the long-term mortality of patients with diabetes.

KEY WORDS: carotid artery atherosclerosis, coronary artery bypass grafting, diabetes mellitus, peripheral artery disease, risk assessment

I. Introduction

Diabetes has become a worldwide health problem that affected 415 million people in 2015¹⁾. A further 318 million people are estimated to have impaired glucose tolerance. This trend is apparent in Japan where the number of diabetic patients in now 10.8 million²⁾. The presence of diabetes is known to be associated with poor prognosis of coronary artery diseases³⁾. Recent trials have proven the superiority of coronary artery bypass grafting (CABG) for coronary revascularization in patients with diabetes^{4–7)}. However, in general, patients with diabetes tend to present poor prognosis when compared with patients without di-

abetes^{8, 9)}. To improve the long-term survival of these patients, use of multiple arterial grafting has been advocated^{10, 11)} even though multiple arterial bypass grafting consumes more procedural time and may increase operative risks. Which factors most influence the surgical outcomes of CABG patients with diabetes has not been fully elucidated. The purpose of this study was to identify risk factors for poor prognosis after CABGs in patients with diabetes.

II. Methods

study design

We conducted a retrospective analysis from consecutive patients using our database at Kurashiki Central Hospital. A total of 1,139 patients received elective isolated CABGs between January 2000 and July 2015. Of those patients, 599 had diabetes (DM group) and 540 did not (non-DM group). In the DM group, 98 patients were treated with diet, 293 patients with oral medication, and 208 patients with insulin. The study excluded patients who underwent emergency procedures because preoper-

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This paper was presented at the 29th Annual Meeting of the Japanese Coronary Association in 2015.

Received June 1, 2016; Accepted September 5, 2016

J-STAGE Advance Published Date November 4, 2016

doi: 10.7793/jcoron. 22.16-00014

ative assessments, including carotid ultrasound, were insufficient. The primary endpoints of this study were perioperative outcomes, including in-hospital death and perioperative complications. Secondary end points were all-cause mortality and freedom from cardiac events (e.g., cardiac death, myocardial infarction, readmission for heart failure, or catheter re-intervention). Furthermore, we investigated risk factors for all-cause mortality in patients with diabetes.

Definitions

Diabetes was defined as glycated hemoglobin A_{1c} (HbA_{1c}) with an NGSP (National Glycohemoglobin Standardization Program) value $\geq 6.5\%$ in the blood data since April 2012 or $\geq 6.1\%$ by JDS (Japan Diabetes Society) until March 2012. Patients being treated with antidiabetic agents or insulin were also defined as having diabetes regardless of their HbA_{1c} levels. Peripheral arterial disease (PAD) was defined as any experience of claudication at rest or exertion, treatment for surgical or endovascular interventions, and documentations of significant stenosis of peripheral arteries with abnormal ankle-arm index. Postoperative complications were defined as follows: stroke (a central neurologic deficit persisting for more than 24 hours or new infarcted lesion detected by head CT scan); deep sternal infection (any chest infection involving the sternum or mediastinal tissues excepting for superficial tissue infection); renal failure (creatinine $> 2\text{mg/dl}$ or 100% increase of the preoperative value, with or without hemodialysis); and respiratory failure (mechanical ventilator support lasting more than 24 hours).

Preoperative assessments

All patients underwent cardiac catheterization before surgical consultations. As a routine preprocedural assessment, chest CT scan (without contrast enhancements) and carotid ultrasound were performed to evaluate calcification on the aorta and atherosclerosis in carotid arteries. Carotid artery scans were acquired with a 7.5MHz linear probe by lab technicians. Longitudinal and transverse views of both common, internal, and external carotid arteries were obtained to measure carotid intima-media thickness (IMT) and to evaluate the presence of carotid plaque. IMT was measured in 1cm-long segment of the common carotid arteries located 0.5cm below the carotid bulb. The degree of the carotid arterial atherosclerosis was categorized as 0 (normal), 1 (mild), 2 (moderate), and 3 (severe atherosclerosis). Normal was defined as $\text{IMT} < 1.0\text{mm}$ without any plaque, mild atherosclerosis as $\text{IMT} > 1.0\text{mm}$ without any plaque, moderate atherosclerosis as $\text{IMT} > 1.0\text{mm}$ with plaque causing less than 50% stenosis, severe atherosclerosis as $\text{IMT} > 1.0\text{mm}$ with plaque causing more than 50% stenosis or arterial occlusions.

Surgical techniques and postoperative managements

The CABG was performed mostly off-pump at our institution (about 80% of isolated procedures were performed off-pump).

Our revascularization strategies were as follows: (1) If a patient was less than 80 years old, we considered multiple arterial grafting including left internal thoracic artery (LITA), right ITA (RITA), radial artery (RA) and right gastroepiploic artery (GEA) according to the coronary anatomy and the patient's backgrounds, (2) The LITA was usually anastomosed to the left descending artery. The second arterial graft, including RITA and RA, was mostly anastomosed to the circumflex coronary artery, (3) The third arterial graft was mainly anastomosed to the right coronary territory. The internal thoracic arteries were harvested with an ultrasonic scalpel (Harmonic Scalpel, Ethicon Endo-Surgery, OH) using the skeletonized fashion. The radial artery was harvested as a pedicle graft from the left arm. The GEA was harvested with surrounding tissues. Saphenous veins were harvested in conventional fashion, mainly from the lower legs. During the operations, all bypassed grafts were examined using transit-time flow measurement (TTFM). If the TTFM presented abnormal flow pattern, we revised the grafts intraoperatively. For postoperative blood glucose control, a continuous insulin infusion (not to exceed 200mg/dl of blood glucose level) was used during an intensive care stay. After patients left intensive care, blood glucose was controlled intermittently by a subcutaneous insulin injections or oral diabetic medications not to exceed 200mg/dl. After patients were discharged from hospital, a follow-up was performed at least annually at our institution's outpatient clinic.

Statistical analysis

All analyses were performed with the SPSS statistical package version 20 (IBM, Armonk, NY). Clinical characteristics between the 2 groups were compared using the *t* test for normally distributed variables and the chi-square test for categorical variables. The estimated survival rates and freedom from cardiac events were calculated using the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazard regression model was used to identify predictors of overall death in patients with diabetes. All results were considered statistically significant at a level of *p* less than 0.05. The study was approved by the Institutional Ethics Committee, and informed consent was waived due to the study's retrospective nature.

III. Results

Early outcomes

The preoperative patients' profiles in the both groups are summarized in Table 1. There were no differences in terms of age, sex, body mass index, presence of hyperlipidemia, chronic obstructive pulmonary disease, mitral regurgitation more than mild, SYNTAX score, and STS score. However, presence of hypertension, HbA_{1c}, renal insufficiency (i.e., eGFR and hemodialysis), PAD, low EF ($< 40\%$), previous stroke, and degree of carotid arterial atherosclerosis were significantly higher in the DM group

Table 1 Patients' profiles

Variables	Non-DM (n=540)	DM (n=599)	p-value
Age (year)	68.0±10.5	67.8±8.5	0.582
Male (%)	85%	83%	0.469
BMI	23.7	23.6	0.633
Hypertension	74%	80%	0.020
Hyperlipidemia	65%	67%	0.538
HbA _{1c}	5.4±0.6	6.9±1.3	<0.001
COPD	2.4%	1.7%	0.377
eGFR	61±24	54±28	<0.001
HD	4%	12%	<0.001
PAD	9%	21%	<0.001
Low EF(<40%)	14%	18%	0.009
Previous stroke	11%	18%	0.001
The degree of carotid atherosclerosis			0.015
0 (normal)	47%	37%	
1 (mild)	37%	44%	
2 (moderate)	13%	15%	
3 (severe)	2%	4%	
MR more than mild	14%	15%	0.838
SYNTAX score	27±10	28±11	0.139
STS score	3.1±5.2	3.7±5.8	0.092

BMI: body mass index, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, EF: ejection fraction, HD: hemodialysis MR: mitral regurgitation, PAD: peripheral arterial disease, STS score determined by the Society of Thoracic Surgeon's risk calculator.

than in the non-DM group. Table 2 presents postoperative outcomes for both groups. Although in-hospital mortality was similar for both groups (non-DM: 2.2% ; DM: 2.5% ; $p=0.747$), the incidence of perioperative complications such as renal and respiratory failure was higher in DM patients than nondiabetic patients. Moreover, deep sternal infection tended to be observed more often in diabetic patients (non-DM: 0.9% ; DM: 2.0% ; $p=0.137$). In terms of cerebrovascular events, the incidence of postoperative stroke was similar in both groups (non-DM: 2.0% ; DM: 1.8% ; $p=0.556$). Although the number of bypass grafts per patient was significantly larger in the DM group (non-DM: 3.2 ± 0.9 ; DM: 3.4 ± 0.9 ; $p=0.027$), the number of arterial grafts used was similar in both groups (non-DM: 2.0 ± 0.6 ; DM: 2.0 ± 0.7 ; $p=0.557$).

Long-term outcomes

Follow-up was completed in 95% of all patients in this study, and the mean follow-up duration was 5.7 ± 4.0 years (range: 0.2–14.7 years). The Kaplan-Meier cumulative survival rate was significantly higher ($p=0.003$) in the non-DM patients (Fig. 1a). However, there was no difference in terms of freedom from cardiac events ($p=0.132$) in the two groups (Fig. 1b). Table 3 pres-

Table 2 Clinical outcomes

	Non-DM (n=540)	DM (n=599)	p-value
OPCAB (%)	79%	80%	0.575
No. of grafts	3.2 ± 0.9	3.4 ± 0.9	0.027
No. of arterial grafts	2.0 ± 0.6	2.0 ± 0.7	0.557
Post-ope renal failure	25 (4.6%)	53 (8.8%)	0.005
Post-ope respiratory failure	32 (5.9%)	53 (8.8%)	0.053
Stroke	11 (2.0%)	11 (1.8%)	0.556
Deep sternal infection	5 (0.9%)	12 (2.0%)	0.137
In-hospital death	12 (2.2%)	15 (2.5%)	0.747

OPCAB: off-pump coronary artery bypass grafting.

ents the Cox proportional hazards model that identified the independent predictor of all-cause death in diabetic patients. The predictors of poor late survival of diabetic patients after CABGs were old age ($p=0.032$), PAD ($p=0.038$), severity of carotid atherosclerosis ($p=0.045$), and hemodialysis ($p=0.016$). The number of arterial grafts used was not a predictor of late survival in diabetic patients ($p=0.216$). Other factors that could affect the prognosis in diabetic patients with coronary artery diseases, such as SYNTAX score and insulin dependence, were not predictors of late survival when diabetic patients underwent CABGs.

IV. Discussion

Although patients with diabetes have a greater chance of coronary diseases and poor prognosis than nondiabetic patients, CABG has consistently shown improved survival over percutaneous coronary interventions (PCI)^{5, 12}. The recent randomized FREEDOM trial clearly demonstrated that CABGs are superior to PCI in reducing major adverse cardiovascular events and all-cause mortality in diabetic patients with multivessel diseases⁴. Today, CABG is the first choice for revascularization strategy in diabetic patients. However, clinical outcomes after CABGs in patients with diabetes are still inferior to those of nondiabetic patients¹³. In this study, we found the factors which contribute most significantly to the poor outcomes after CABGs in diabetic patients.

In recent studies^{14, 15}, multiple arterial grafts have been documented to improve long-term clinical outcomes of CABGs. Suzuki et al. reported promising results of total arterial off-pump CABG for diabetic patients¹¹. In their propensity analysis of 775 total arterial off-pump CABGs, the 10-year freedom from all-cause mortality was found to be similar between diabetic and non-diabetic patients if total arterial bypass grafting was performed. They previously mentioned the importance of the GEA as the third arterial graft in addition to use of both ITAs¹⁶. The 7-year freedom from all-cause death in patients bypassed with

Fig. 1 a: Freedom from all-cause death. b: Freedom from cardiac events (Cardiac events including cardiac death, myocardial infarction, readmission for heart failure, catheter re-intervention, or other cardiac events).

Table 3 Cox proportional hazards regression for all-cause death in diabetic patients

Variables	HR	95%CI	p-value
Age (year)	1.052	1.004-1.102	0.032
Hypertension	1.062	0.461-2.446	0.887
Hyperlipidemia	0.560	0.298-1.051	0.071
COPD	2.602	0.293-23.13	0.391
eGFR	0.982	0.962-1.003	0.088
HD	6.342	1.405-28.63	0.016
PAD	2.106	1.040-4.261	0.038
Low EF(<40%)	1.413	0.355-5.642	0.338
Previous stroke	0.725	0.333-1.581	0.419
The degree of carotid atherosclerosis	1.480	1.009-2.169	0.045
MR more than mild	0.661	0.205-2.131	0.488
SYNTAX score	1.002	0.974-1.032	0.868
No. of grafts	1.129	0.789-1.616	0.507
No. of arterial grafts	0.711	0.414-1.221	0.216
HbA _{1c}	1.002	0.763-1.319	0.982
Insulin-dependent	1.236	0.651-2.349	0.517

CI: confidence interval, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, HD: hemodialysis, EF: ejection fraction, MR: mitral regurgitation, PAD: peripheral arterial disease

the GEA to the right coronary artery (RCA) was significantly better than those with saphenous vein graft (SVG) to RCA (GEA group, 96% ; SVG group, 82% ; $p=0.03$). By contrast, Esaki et al. did not find any superiority of the GEA as the third arterial graft¹⁷⁾. The 7-year freedom from cardiac events were similar in both configurations (GEA group, 77% ; SVG group, 79% ; $p=0.46$). Although both studies included nondiabetic patients, clear benefits of a third arterial graft in diabetic patients were not established. In the present study, the number of arterial grafting did not affect all-cause mortality after CABGs in patients with diabetes. CABGs in our cardiac center used the average number of 2 arterial grafts, including ITAs, RA, and GEA. The present study did not consider the graft configuration of arterial grafts. However, our previous study concluded that the use of both ITAs increased the incidence of deep sternal infection rather than that of the single ITA usage, even though all ITA grafts were harvested using the skeletonized fashion¹⁸⁾.

Many papers^{19, 20)} have shown that the use of both ITAs in patients with diabetes significantly increased the risk of deep sternal infections. Hoffman et al.²¹⁾ reported on a retrospective study comparing the use of left ITA ($n=659$) or both ITAs ($n=502$) in patients with diabetes. The sternal wound infection was more frequently observed in the both ITA group (3.5%) than the single ITA group (0.5%). This problem will be more concerning in cases of insulin-dependent diabetic patients. Gatti et al.²²⁾ docu-

mented that the incidence of deep sternal infection was as high as 11.7% in 188 insulin-dependent diabetic patients with bilateral ITA grafting. Once a sternal wound infection occurs, postoperative care becomes complicated and may affect quality of life after surgery. When evaluating the use of multiple arterial grafts in diabetic patients, the balance between increased perioperative morbidity and long-term better graft patency should be considered. In this study, other factors of existing comorbidities were shown to be more important prognostic factors for long-term survival in diabetic patients than the use of multiple arterial grafting.

One of the most influential factors for long-term prognosis after CABG in diabetic patients was the presence of PAD. This result affirms previous reports that showed poor prognosis of existing PAD after CABG^{23, 24}. The SYNTAX trial found that PAD was an independent predictor of adverse long-term outcomes after CABG²⁵. In the RED-CABG trial²⁶, which was a multicenter, randomized double-blind, and placebo-controlled study of CABG, Weisel et al. reported that the predictors of outcomes after CABG were a history of heart failure, increasing age, presence of PAD, and not receiving aspirin before CABG. Patients with PAD showed as high as 160% increase in the risk of all-cause mortality after CABG. Patients with PAD could have polyvascular atherosclerosis with associated comorbidities as myocardial ischemia and cerebrovascular diseases²⁷. PAD was also reported as a prognosis factor in patients with renal dysfunction²⁸. In this study, PAD was one of the highest risk factors for all-cause death after CABG, the same as the presence of carotid artery atherosclerosis and chronic renal failure.

Several studies revealed that the presence of carotid artery diseases was highly related to existing coronary artery diseases^{29, 30}. Therefore, an ultrasound examination of carotid arteries is a useful modality to screen cardiac diseases. Hertzner et al. reported that 35% of patients with carotid stenosis presented severe coronary artery diseases³¹. In a Japanese population study, Kawarada et al.³² showed that the incidence of coronary diseases was 13.7% among Japanese patients undergoing CABGs for coronary artery diseases. Moreover, the severity of carotid diseases was associated with the severity of cardiovascular diseases. In our study we graded the severity of carotid atherosclerosis by ultrasound findings. In general, IMT < 1.0mm was defined as the normal range in atherosclerotic screening³³. Thicker IMT means that patients might have more advanced atherosclerosis. Moreover, the presence of carotid plaque is known to be more reliable evidence of advanced atherosclerosis than thicker IMT³⁴. Our data also has proven that the severity of carotid atherosclerosis is one of the strongest predictors for survival outcomes of diabetic patients undergoing CABGs. Advanced carotid atherosclerosis should indicate the severity of atherosclerosis in other vascular

beds, which increases the incidence of cardiac, vascular, and cerebral events. In other words, reducing the progression of widespread atherosclerosis will play an important role in improving the clinical outcome for diabetic patients undergoing CABGs.

In general, life expectancy of hemodialysis patients is known to be inferior to that of nonhemodialysis patients because they tend to have poor health conditions and multiple comorbidities³⁵. Among their health complications, cardiovascular disease is the most common cause of death in hemodialysis patients, accounting for almost half of all death³⁶. Furthermore, hemodialysis patients are also associated with higher mortality after CABGs³⁷. Wu et al.²⁴ presented predictive risk score after CABGs through their retrospective study in which hemodialysis was found to be the highest risk (hazard ratio: 5.53) for all-cause death. Moreover, several studies showed the multiple comorbidities with renal dysfunction presented the worst risk for late survival after CABG^{36, 37}. Takami et al.³⁶ presented that the predictors for late death in dialysis patients with CABGs were diabetes, PAD and low ejection fraction, not bilateral ITA use, which is congruent with the result of the present study.

This study had some limitations. First, the study was limited by its retrospective, nonrandomized methodology, which made it susceptible to various sources of bias. Second, the number of study patients was limited to indicate the precise incidence of perioperative complications and long-term lethal events. Third, the decision to pursue a grafting strategy, including the number of arterial grafts, could create a bias. We usually tried to use at least 2 arterial grafts, even with diabetic patients. The third arterial graft was used depending on the patient's age and background. By contrast, only a single arterial graft was used in some cases because of the quality of the arterial graft or coronary anatomy. Therefore, this surgical bias could affect the result of this study. There is no doubt that arterial graft is associated with better long-term patency than that of SVGs. However, in diabetic patients, other existing comorbidities could impact long-term survival rates more significantly than the number of arterial grafts used in CABGs.

In conclusion, there was no difference in early surgical mortality after CABG between diabetic and nondiabetic patients even though the incidence of perioperative complications such as infection and renal and respiratory failure was higher in diabetic patients. In long-term follow-up, all-cause mortality of diabetic patients was significantly higher than that of nondiabetic patients. Major risk factors of poor prognosis after CABGs in diabetic patients were preexisting chronic renal failure, PAD, and severe atherosclerosis of the carotid arteries. The number of arterial grafts used in CABGs did not influence long-term survival of patients with diabetes. Difficulties of coronary revascularization estimated by SYNTAX score also were not a risk factor in

long-term survival after CABGs. The presence of polyvascular diseases deeply affects poor prognosis for diabetic patients after CABGs.

Conflict of interest

All the authors have declared no competing interest.

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