Long-Term Clinical Outcome After Surgical or Percutaneous Coronary Revascularization in Hemodialysis Patients

Yoshitaka Kumada, MD, PhD; Hideki Ishii, MD, PhD; Toru Aoyama, MD, PhD; Daisuke Kamoi, MD; Yoshihiro Kawamura, MD; Takashi Sakakibara, MD; Haruhiko Nagoki, MD, PhD; Hiroshi Takahashi, BSc; Toyoaki Murohara, MD, PhD

Background: Although revascularization via coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) has been widely performed, there are limited data on which procedure is best in hemodialysis (HD) patients.

Methods and Results: This 10-year follow-up study consisted of 997 HD patients electively undergoing coronary revascularization (CABG, n=210; PCI, n=787). With an adjustment for propensity scores with all baseline covariates, the incidence of major adverse cardiac events (MACE) was evaluated as a composite endpoint including all-cause death, non-fatal myocardial infarction (MI), and any revascularization. During the follow-up period, 465 MACE (death, n=325; non-fatal MI, n=45; revascularization, n=274) occurred. The 10-year freedom from MACE was higher in the CABG group compared to the PCI group (51.0% vs. 34.8%, adjusted hazard ratio (HR), 0.64; 95% confidence interval (CI): 0.49–0.82, P=0.0003). On landmark analysis, adjusted HR of death was higher during the first 6 months after CABG compared to PCI (1.72; 95% CI: 1.04–2.79, P=0.036), but lower from 6 months onward (0.68; 95% CI: 0.48–0.97, P=0.033). When compared to patients treated with drug-eluting stent alone (n=345) in the PCI group, the CABG group still had an advantage for any revascularization (adjusted HR, 0.38; 95% CI: 0.22–0.62, P<0.0001), but not for MACE (adjusted HR, 0.86; 95% CI: 0.64–1.15, P=0.33).

Conclusions: CABG was totally clinically advantageous compared to PCI in HD patients. (Circ J 2014; 78: 986–992)

Key Words: Coronary revascularization; Follow-up; Hemodialysis; Prognosis

C hronic kidney disease (CKD) is associated with the highest risk for cardiovascular disease (CVD), and CKD patients have a 10–30-fold higher risk for mortality due to CVD than the general population. In particular, in CKD patients who need hemodialysis (HD), coronary artery disease (CAD) reportedly presents in more than half of the patients even at the beginning of HD therapy, and is the leading cause of death, accounting for 43% of all-cause mortality.

Coronary revascularization, regardless of surgical or percutaneous procedures, improves the mortality and morbidity compared to medical therapy alone in HD patients with CAD. The prognosis of HD patients, however, is still markedly poorer after both surgical and percutaneous coronary intervention (PCI) compared to the general population. In this context, whether coronary artery bypass grafting (CABG) or PCI contributes to a better prognosis is a clinically important issue, but optimal revascularization remains controversial. Some studies have stated that the survival rate is significantly higher in patients treated with CABG compared to those treated with PCI, whereas other studies have found no significant difference in survival between the 2 strategies. Even in this contemporary era after the introduction of drug-eluting stents (DESs), controversy remains. We investigated long-term clinical outcome after CABG and PCI, including DES implantation, in a relatively large cohort of Japanese HD patients.
were enrolled in this study. Patients with acute myocardial infarction (AMI), those hospitalized due to other active diseases, and those with history of malignancy were excluded. Of the enrolled patients, 210 patients underwent CABG and 787 patients underwent PCI based on the decision made primarily by the patients or their physicians (Figure 1). In the CABG group,

**Methods**

From April 1999 to December 2010, a total of 997 consecutive maintenance HD patients electively undergoing first coronary revascularization at Nagoya Kyoritsu Hospital (Nagoya, Japan) and Matsunami General Hospital (Kasamatsu, Japan) were enrolled in this study. Patients with acute myocardial infarction (AMI), those hospitalized due to other active diseases, and those with history of malignancy were excluded. Of the enrolled patients, 210 patients underwent CABG and 787 patients underwent PCI based on the decision made primarily by the patients or their physicians (Figure 1). In the CABG group,
endpoint using Cox proportional hazards analysis. To adjust for differences in baseline characteristics between the 2 procedures, a propensity score analysis was performed using multivariate logistic regression modeling, including all baseline covariates such as sex, age, duration of HD, diabetes, hypertension, dyslipidemia, smoking status, body mass index (BMI), previous MI, previous stroke, previous peripheral artery disease (PAD), left ventricular ejection fraction (LVEF) <40%, multi-vessel disease, left main trunk disease and left anterior descending disease. The score was then incorporated into Cox proportional hazards model as a covariate. Differences were considered statistically significant at P<0.05.

Results

Prevalence of diabetes (66.2% vs. 57.7%, P=0.026), previous history of PAD (34.8% vs. 25.4%, P=0.0069), LVEF <40% (23.3% vs. 9.8%, P<0.0001), multi-vessel disease (83.9% vs. 56.8%, P<0.0001), left main trunk lesion (16.2% vs. 4.3%, P<0.0001) and left anterior descending disease (82.9% vs. 72.6%, P=0.0029) were significantly higher in patients undergoing CABG than those undergoing PCI. Inversely, BMI (20.9±3.1 vs. 21.5±3.4, P=0.017) and previous history of stroke (11.4% vs. 18.3%, P=0.018) were significantly lower in the CABG

![Figure 2. Kaplan-Meier event-free survival for major adverse cardiac events (MACE) after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).](image-url)
CABG vs. PCI in HD

CABG vs. PCI in HD

Table 3. Freedom From Clinical Events for CABG vs. PCI and Disease Status

<table>
<thead>
<tr>
<th>Event</th>
<th>Single-vessel disease</th>
<th>Multi-vessel disease</th>
<th>MACE</th>
<th>Single-vessel disease</th>
<th>Multi-vessel disease</th>
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<tbody>
<tr>
<td>Crude</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>Propensity score-adjusted</td>
<td>HR (95% CI)</td>
<td>P-value</td>
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<tr>
<td>MACE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Single-vessel disease</td>
<td>0.86 (0.52–1.38)</td>
<td>0.52</td>
<td>0.94 (0.57–1.54)</td>
<td>0.81</td>
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<tr>
<td>Multi-vessel disease</td>
<td>0.58 (0.43–0.77)</td>
<td>0.0002</td>
<td>0.56 (0.42–0.75)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Any revascularization</td>
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<td></td>
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<tr>
<td>Single-vessel disease</td>
<td>0.32 (0.13–0.79)</td>
<td>0.014</td>
<td>0.35 (0.14–0.88)</td>
<td>0.025</td>
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<td>Multi-vessel disease</td>
<td>0.24 (0.14–0.40)</td>
<td>&lt;0.0001</td>
<td>0.23 (0.13–0.40)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
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<td></td>
<td></td>
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<tr>
<td>Single-vessel disease</td>
<td>0.77 (0.10–6.12)</td>
<td>0.81</td>
<td>0.48 (0.05–4.73)</td>
<td>0.53</td>
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<tr>
<td>Multi-vessel disease</td>
<td>0.60 (0.25–1.44)</td>
<td>0.25</td>
<td>0.52 (0.21–1.28)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>1.31 (0.78–2.19)</td>
<td>0.31</td>
<td>1.13 (0.67–1.92)</td>
<td>0.65</td>
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</tr>
<tr>
<td>Multi-vessel disease</td>
<td>0.81 (0.59–1.12)</td>
<td>0.20</td>
<td>0.74 (0.53–1.04)</td>
<td>0.081</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1, 2.

Figure 3. Kaplan-Meier event-free survival for all-cause mortality (A) after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI); and (B) before and 6 months after operation.

CABG vs. PCI in HD

CABG vs. PCI in HD

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group than in the PCI group (Table 1). A total of 151 patients (71.9%) were treated with the off-pump technique, and internal thoracic arteries were used in 78.1% of those in the CABG group. In the PCI group, 345 patients (43.8%) were treated with DES. Periprocedural intra-aortic balloon pumping was used in 2 PCI patients and in 1 CABG patient.

Thirty-day mortality occurred in 7 patients (3.3%) in the CABG group (pneumonia, n=2; mediastinitis, n=2; ischemic colitis, n=1; low output syndrome, n=1; and fatal arrhythmia, n=1) and in 9 (1.1%) in the PCI group (pneumonia, n=1; MI, n=2; congestive heart failure, n=1; fatal arrhythmia, n=1; stroke, n=1; gastrointestinal hemorrhage, n=1; chronic obstructive pulmonary disease, n=1; and cardiac rupture, n=1), respectively (P=0.040). Of CABG patients, the prevalence of 30-day mortality tended to be lower in the off-pump group compared to the on-pump group (2.0% vs. 6.8%, P=0.082).

During the follow-up period (mean, 51±39 months), 465 MACE occurred (death, n=325; non-fatal MI, n=45; and repeat revascularization, n=274). Kaplan-Meier analysis showed that the 10-year freedom from MACE was higher in the CABG group compared to the PCI group (51.0% vs. 34.8%, propensity score-adjusted HR, 0.64; 95% CI: 0.49–0.82, P=0.0003; Figure 2; Table 2). CABG, however, was not observed to be as advantageous for MACE in patients with single-vessel disease (adjusted HR, 0.94; 95% CI: 0.57–1.54, P=0.81) as it was in those with multi-vessel disease (adjusted HR, 0.56; 95% CI: 0.42–0.75, P<0.0001; Table 3). For the CABG patients, the freedom from MACE was similar between the off- and on-
eluting stents (EES) were implanted. Because the follow-up period did not reach 10 years in the DES group, the mean follow-up period was shorter than that in the CABG group (44 ± 25 months vs. 52 ± 41 months, P=0.039). During the 7-year follow-up period, event-free survival rates in the CABG and DES groups were similar for MACE (57.1% vs. 53.4%; adjusted HR, 0.86; 95% CI: 0.64–1.15, P=0.33), and for mortality (65.0% vs. 60.2%; adjusted HR, 1.07; 95% CI: 0.76–1.51, P=0.68), although CABG still was better for any revascularization (86.0% vs. 71.6%; adjusted HR, 0.38; 95% CI: 0.22–0.62, P<0.0001; Table 4; Figure 4). Freedom from non-fatal MI was also similar between the 2 groups (96.2% vs. 95.5%, P=0.74).

**Discussion**

The main findings in the present study are summarized as follows: first, the survival rate in the CABG and PCI groups was similar during the overall 10-year follow-up period. On landmark analysis, however, PCI had the advantage within the 6 post-procedure months and CABG had the advantage only thereafter. Second, CABG was totally superior for the reduction of MACE compared to PCI, but this superiority was limited to pump groups (49.3% vs. 53.3%, P=0.27).

Figure 3 shows the 10-year survival rate. On landmark analysis, adjusted HR of death was higher during the 6 months following CABG compared to PCI (1.72; 95% CI: 1.04–2.79, P=0.036), but lower from 6 months onwards (0.69; 95% CI: 0.48–0.97, P=0.033; Table 2). Also, CABG tended to have an advantage for survival compared with PCI in patients with multivessel disease (adjusted HR, 0.74; 95% CI: 0.53–1.04, P=0.081), but not in those with single-vessel disease (adjusted HR, 1.13; 95% CI: 0.67–1.92, P=0.65; Table 3). Regarding the causes of death during follow-up in the CABG and PCI groups, the frequencies of most of the causal diseases were similar in the 2 groups, but infectious disease tended to be more prevalent in the CABG group than in the PCI group (11.9% vs. 7.9%, P=0.067).

The 10-year freedom from any revascularization was markedly higher in CABG patients than in PCI patients (83.4% vs. 56.0%; adjusted HR, 0.25; 95% CI: 0.15–0.39, P<0.0001; Figure 4). The incidence of non-fatal MI, however, was similar between the 2 groups (96.2% vs. 93.5%; adjusted HR, 0.52; 95% CI: 0.20–1.14, P=0.10).

Of patients treated with DES, 228 sirolimus-eluting stents (SES), 71 paclitaxel-eluting stents (PES) and 46 everolimus-eluting stents (EES) were implanted. Because the follow-up period did not reach 10 years in the DES group, the mean follow-up period was shorter than that in the CABG group (44±25 months vs. 52±41 months, P=0.039). During the 7-year follow-up period, event-free survival rates in the CABG and DES groups were similar for MACE (57.1% vs. 53.4%; adjusted HR, 0.86; 95% CI: 0.64–1.15, P=0.33), and for mortality (65.0% vs. 60.2%; adjusted HR, 1.07; 95% CI: 0.76–1.51, P=0.68), although CABG still was better for any revascularization (86.0% vs. 71.6%; adjusted HR, 0.38; 95% CI: 0.22–0.62, P<0.0001; Table 4; Figure 4). Freedom from non-fatal MI was also similar between the 2 groups (96.2% vs. 95.5%, P=0.74).
patients with multi-vessel disease. Third, DES had no disadvantage in preventing MACE despite having the highest rate of any revascularization compared to CABG. These results were also confirmed after adjusting for differences in baseline characteristics between the patients who underwent the 2 procedures, using propensity score.

It remains controversial whether CABG provides better survival benefits for HD patients or not, compared to PCI. Most studies in which CABG was found to have beneficial effects on clinical outcome were conducted on large community-based cohorts of several thousands. In contrast, most studies with negative results were conducted in a single center with a small sample size and/or a short follow-up period. These previous results suggest that perhaps a few thousand patients need to be enrolled to obtain a statistical power large enough to justify the superiority of either CABG or PCI for mortality. Nevis et al., in their meta-analysis, reported that long-term mortality no longer differed between the 2 procedures after excluding 2 mega-studies. In this regard, the present study may be somewhat limited despite its relatively large cohort of nearly 1,000. We found, however, that CABG has a survival advantage over PCI but only after the 6 post-procedure months, and tends to have survival advantage only in patients with multi-vessel disease. From these results, CABG may be chosen in HD patients with multi-vessel disease or complex lesions.

A high mortality rate immediately after CABG is well-known in CKD patients. The operation-related mortality rate rises according to the progression of renal dysfunction, in particular, the mortality risk is 3.8-fold higher in CKD patients on HD compared to non-CKD patients. Also in Japan, the 30-day mortality rate was markedly higher in HD patients (4.8%) than in non-HD patients (1.8%) according to the Japan Adult Cardiovascular Surgery Survey Database. In the present study, the 30-day mortality rate of 3.3% after CABG was somewhat lower compared to the Japanese average mentioned here, but was still significantly higher than that after PCI (1.1%). Consequently, we confirmed that the survival benefit was associated with PCI for the short term (within 6 months after the procedure), and with CABG for the long term (from 6 months onward) in the Japanese HD cohort as well as in the 2 reports from the USA. Namely, Herzog et al. reported that log (–log [survival]) curves of mortality for CABG and PCI cross at 6 months, and Chang et al. also reported that PCI was more favorable at 6 months (HR, 1.08; 95% CI: 1.01–1.16). During the overall follow-up period in the present study, CABG tended to have the survival benefit compared to PCI, but only in patients with multi-vessel disease (P=0.081) and not those with single-vessel disease (P=0.65). As mentioned here, with a larger cohort having adequate statistical power, the difference may certainly reach statistical significance, but only in multi-vessel disease patients. Recently, Chang et al. clearly showed that multi-vessel CABG was associated with a significantly lower risk of death compared to PCI in a propensity score-matched cohort using data from US renal data systems. The present results are supported by this finding.

When the incidence of MACE was considered as a composite endpoint in the present study, CABG was clearly superior to PCI due to the significantly lower rate of repeat revascularization. Aoki et al. reported that CABG was associated with reduced MACE more than PCI, although not with long-term mortality in 125 Japanese HD patients. The same results were also obtained by other studies in Japan. Thus, the advantage of CABG is still to be definitively confirmed, but its association with the reduction of MACE is clear. Importantly, the superiority of CABG for MACE was limited to patients with multi-vessel disease in the present study. We previously reported that multi-vessel disease was an independent risk factor for MACE after PCI or coronary stenting in HD patients. Although no guidelines regarding coronary revascularization are specific for HD patients with CAD, CABG is recommended for HD patients with multi-vessel (or left main trunk) disease and impaired left ventricular function. In this situation, the present findings may contribute to the decision of choice for revascularization procedures in chronic HD patients.

One of the breakthrough technologies among treatment options for CAD is DES. Although the restenosis rate at 8-month follow-up was still high after SES or PES implantation compared to bare metal stent in HD patients, use of first-generation DES, including SES and PES, has been associated with better prevention of repeat revascularization (31.3% vs. 45.6%, P=0.025) and MACE (42.5% vs. 58.0%, P=0.036) compared to bare metal stent for 6 years. Furthermore, the EES, a second-generation DES, has markedly reduced the incidence of restenosis compared to SES (8.7% vs. 21.2%, P=0.041), and is associated with a modest reduction of MACE (10.0% vs. 22.0%, P=0.10) at 8-month of follow-up. In this context, refined DES may have the potential to lower the MACE rate. Interestingly, the use of DES had no significant effect on the reduction of MACE in the present study (HR, 0.86; P=0.33), despite the still higher rate of repeat revascularization compared to CABG. This may be because the follow-up period was significantly shorter in the DES group than in the CABG group. As a somewhat casual explanation, it may be that the new generation DES, including EES, might be associated with a better clinical outcome. Unfortunately, we could not obtain a sufficient sample size or follow-up period for patients treated with EES because this treatment has been available only from June 2010 in Japan. In the future, a comparative study of CABG and EES should be conducted.

Finally, a randomized controlled trial is required to determine the optimal coronary revascularization strategies for chronic HD patients in Japan as well as in the USA. Organizing this prospective study, however, will be difficult because of the overall critical condition of this type of patient. In this context, the present study may be the first to report the comparatively long-term outcomes between CABG and PCI in a relatively large cohort of Japanese HD patients, and will surely provide useful information with regard to the optimal strategies for coronary revascularization.

There are several limitations to the present study. First, all the study subjects were Japanese, who reportedly have a better prognosis compared to HD patients in the USA and Europe; furthermore, subclinical atherosclerosis, coronary disease mortality and risk of coronary calcification are lower in Japanese HD patients. Second, this study was designed as a chart review but not a randomized trial. There may still be residual selection bias and confounding, despite adjustments for all baseline covariates using propensity score. Third, study subjects were included only from 2 centers. Fourth, precise medication at baseline or during follow-up was not evaluated in this study although this intervention is an important issue for outcome. Fifth, we did not evaluate bypass graft patency in patients undergoing CABG. Bypass graft occlusion might occur in some patients. Also, silent occlusion might occur in patients undergoing PCI.

Conclusions

CABG was totally advantageous for long-term clinical outcome compared to PCI in maintenance HD patients, especially those
with multi-vessel disease, but this advantage may be potentially reduced in the newly refined DES era.

References


