meaningful effect on change in TcO_2 (effect size: 1.04), at a one-sided significance level of $p = 0.05$. This trial was expected to have at least 90 % power to detect 10 mmHg changes in TcO_2 under an assumption that the SD of change in TcO_2 was 9.7 mmHg, which was derived from earlier clinical studies [19]. Changes in TcO_2, ABI, TBI, the distance walked in 6 min, and ulcer healing from baseline to week 4 or week 24 were examined with one-sided paired t tests. Changes in the category of the Rutherford classification, rest pain, and status of cyanosis were examined with one-sided Wilcoxon signed rank-sum tests. A p value <0.05 was taken to be significant without adjustment for multiplicity. Pre-specified subgroup analysis was planned for patients who had ASO, TAO, CKD, and for those without CKD individually. All analyses were performed according to the intention-to-treat principle and included all patients treated. All statistical analyses were performed by academic biostatisticians using SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

A total of 10 patients were entered into this study (66.9 ± 12.2 years old, seven males) (Table 1). Among them, seven patients were diagnosed with ASO and the others with Buerger's disease. Six patients had chronic kidney disease [estimate glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2].

Primary endpoints

There was no death or procedure-related adverse events attributable to topical use of sustained-release bFGF. The treatment did not induce focal inflammation or edema at the injection site. The post-procedural blood level of bFGF was undetectable or within the normal value in all patients.

There were two serious adverse events requiring hospitalization that occurred in the same patient (case 10) at 18 and 24 weeks after the treatment. These events were cellulitis (18 weeks after treatment) and intracranial hemorrhage (24 weeks after treatment). Neither of these severe adverse events was thought to be related to the treatment.

Concerning the adverse events, there were transient elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein, creatine phosphokinase, and creatinine according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03, published by the U.S. National Cancer Institute, 14 June 2010). These values, however, returned to the normal range without further treatment (Table 2).

TcO_2 (28.4 ± 8.4 mmHg, pretreatment), which is the main analysis of validity, showed a significant improvement at both 4 weeks (42.8 ± 10.3 mmHg, $p < 0.01$) and 24 weeks (46.2 ± 13.0 mmHg, $p < 0.01$) after treatment (Table 3).

Secondary endpoints (Table 3)

The distance walked in 6 min increased significantly at both 4 weeks ($p < 0.01$) and 24 weeks ($p = 0.02$) compared

Table 1 Patient characteristics

Case	Age/sex	Diagnosis	DM	CKD	The location of occlusive lesion	TcO_2 (mmHg)	ABI	TBI	6 min (meter)	Pain[b]	Cyanosis[c]	Foot ulcer
1	78/M	ASO	No	Yes	Right SFA	37.5	0.53	(–)[a]	275	+1	+3	No
2	73/M	ASO	No	Yes	Left SFA	18.5	0.63	0.32	180	+4	+2	Yes (1100 mm^2)
3	79/F	ASO	No	Yes	Left SFA	21.5	(–)[a]	(–)[a]	103	+1	+3	No
4	64/F	ASO	Yes	Yes	Right Pop. A	18.5	0.49	(–)[a]	190	+2	+3	Yes (234 mm^2)
5	75/M	ASO	Yes	Yes	Right Pop. A	40.5	0.9	(–)[a]	305	+1	+3	No
6	51/M	Buerger	No	No	Right Pop. A	25.5	0.64	(–)[a]	368	+1	+1	Yes (15 mm^2)
7	42/M	Buerger	No	No	Left Pop. A	25.0	0.8	(–)[a]	365	+1	+1	No
8	60/M	Buerger	No	No	Left SFA	32.5	0.64	0.3	415	+1	+1	No
9	68/M	ASO	Yes	Yes	Left SFA	39.0	0.42	(–)[a]	163	+3	+3	No
10	77/F	ASO	No	No	Left Pop. A	25.0	(–)[a]	0.32	190	+2	0	Yes (6500 mm^2)

ASO arteriosclerosis obliterans, *Buerger* thromboangiitis obliterans (Buerger's disease), *DM* diabetes mellitus, *CKD* chronic kidney disease, *SFA* superficial femoral artery, *Pop. A* popliteal artery, *TcO_2* transcutaneous oxygen pressure, *ABI* ankle-brachial pressure index, *TBI* toe-brachial pressure index, *6 min* the distance walked in 6 min, *Pain* rest pain scale (see above), *Cyanosis* cyanotic scale (see above)

[a] Unmeasurable

[b] Rest pain scale: 0, no pain; +1, very slight pain which did not require non-steroidal anti-inflammatory drugs (NSAIDs); +2, slight pain which disappeared with NSAIDs; +3, moderate pain with NSAIDs; +4, severe pain unresolved with NSAIDs

[c] Cyanotic scale: 0, no cyanosis; +1, localized on toes; +2, extensively on toes; +3, extended to dorsum of foot; +4, extended to ankle joint

Table 2 Adverse events within 6 months according to CTCAE version 4.03

Case	Adverse events	The time of peak after treatment	Prognosis of event	Review result
3	↑ C-reactive protein (maximum: 2.4 mg/dl)	6 months	Recovered without treatment	No relation
6	↑ AST/ALT (maximum AST: 54 IU/l, ALT: 84 IU/l)	2 days	Recovered without treatment	Unknown
6	↑ Creatine phosphokinase (maximum: 342 IU/l)	3 months	Recovered without treatment	No relation
9	↑ AST/ALT (maximum AST: 107 IU/l, ALT: 75 IU/l)	7 days	Recovered without treatment	Unknown
9	↑ Creatinine (pretreatment: 1.7 mg/dl, maximum: 2.3 mg/dl)	2 months	Recovered without treatment	No relation
10	↑ AST/ALT (maximum AST: 98 IU/l, ALT: 96 IU/l)	3 days	Recovered without treatment	Unknown

The normal range: C-reactive protein <0.2 mg/dl, AST: 10–34 IU/l, ALT: 7–55 IU/l, creatine phosphokinase: 22–198 IU/l, creatinine: 0.6–1.3 mg/dl

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Table 3 Changes in parameters (mean ± SD)

	Pretreatment	4 weeks	24 weeks
TcO_2 (mmHg)	28.4 ± 8.4	42.8 ± 10.3*	46.2 ± 13.0*
ABI	0.60 ± 0.15	0.59 ± 0.15	0.63 ± 0.18
TBI	0.31 ± 0.01	0.35 ± 0.11	0.28 ± 0.06
6 min (m)	255 ± 105	336 ± 93*	318 ± 127*
Rutherford classification	4.4 ± 0.5	3.4 ± 1.2*	3.1 ± 1.5*
Rest pain scale	1.7 ± 1.0	1.2 ± 1.3*	1.2 ± 1.3*
Cyanotic scale	2.0 ± 1.1	1.1 ± 0.7*	0.9 ± 0.9*
Foot ulcer (mm^2)	785 ± 2037	752 ± 2036	495 ± 1243

4 and 24 weeks after treatment

Abbreviations (see Table 1)

* $p < 0.05$ vs. pretreatment

with pretreatment results. Regarding the Rutherford classification, the parameter was improved significantly at both 4 weeks ($p = 0.02$) and 24 weeks ($p = 0.02$) after treatment. Six patients were changed for the better at 4 and 24 weeks, and no patients worsened. In terms of the rest pain scale, significant improvement was observed at both 4 weeks ($p = 0.03$) and 24 weeks ($p = 0.03$) after treatment, with five patients showing improvement.

Concerning the cyanotic scale, the parameter improved significantly at 4 weeks ($p = 0.03$) and 24 weeks ($p < 0.01$) after treatment. The area of the foot ulcer was found to have been reduced at both 4 weeks ($p = 0.13$) and 24 weeks ($p = 0.14$) when compared with the pretreatment area, but it did not result in any significant improvement. Among the improved patients, an intractable ulcer disappeared in 1 of the 4 patients, and ischemic rest pain disappeared in 4 of the 10 patients at 24 weeks after treatment.

The ankle-brachial pressure index did not increase at either 4 weeks ($p = 1.00$) or 24 weeks ($p = 0.22$) after treatment. Similarly, the toe-brachial pressure index did not increase at either 4 weeks ($p = 0.13$) or 24 weeks ($p = 1.00$).

Subgroup analyses (Tables 4 and 5)

We conducted subanalyses of ASO or TAO, and the presence or absence of chronic kidney disease (CKD). There were seven patients with ASO and six with CKD. Regarding ASO patients, TcO_2 significantly increased at both 4 weeks ($p < 0.01$) and 24 weeks ($p < 0.01$) after treatment. In terms of TAO patients, TcO_2 also significantly increased at 4 weeks ($p = 0.03$). Although a significant difference was not found at 24 weeks in TAO patients ($p = 0.053$) because of the small number of cases, TcO_2 did show an improvement tendency. Among patients with CKD, TcO_2 significantly improved at both 4 weeks ($p < 0.01$) and 24 weeks ($p < 0.01$) after treatment. In patients without CKD, TcO_2 also significantly improved at both 4 weeks ($p < 0.01$) and 24 weeks ($p = 0.01$).

Discussion

In the present study, we have shown the efficacy of the sustained release of bFGF using biodegradable gelatin hydrogel, as evaluated by TcO_2, the distance walked in 6 min, the rest pain scale, and the cyanotic scale. Regarding foot ulcers, the area of the ulcer also tended to shrink. These results indicate an increase in blood flow in the ischemic limb. In terms of safety, there was no death or major procedure-related adverse event. In the subclass analyses, the primary endpoint also improved significantly in patients with ASO, TAO, CKD, and in those without CKD. In addition, the mean ± SD value of TcO_2 before treatment was 28.4 ± 8.4 mmHg in this study, while the mean value of TcO_2 before treatment was 53.5 ± 5.2 mmHg in our previous study [19]. Although this study included more severe cases than did the previous one, we revealed that the therapeutic efficacy was equivalent to that of our previous study. We therefore believe this method offers a promising form of therapy, especially in terms of its safety and efficacy.

Table 4 Subanalysis of changes in patients with ASO or TAO (mean ± SD)

	ASO (7 patients)			Buerger (3 patients)		
	Pretreatment	4 weeks	24 weeks	Pretreatment	4 weeks	24 weeks
TcO_2 (mmHg)	28.6 ± 10.0	44.4 ± 12.1*	45.8 ± 14.3*	27.7 ± 4.2	39.0 ± 3.0*	47.2 ± 11.8
ABI	0.57 ± 0.16	0.57 ± 0.16	0.57 ± 0.18	0.69 ± 0.09	0.63 ± 0.12	0.75 ± 0.13
TBI	0.31 ± 0.01	0.38 ± 0.12	0.28 ± 0.05	0.30 ± 0.00	0.28 ± 0.00	0.28 ± 0.08
6 min (m)	201 ± 69	291 ± 67*	265 ± 114	383 ± 28	441 ± 42*	441 ± 34
Foot ulcer (mm^2)	1119 ± 2407	1074 ± 2411	706 ± 1463	5 ± 8.7	0 ± 0	0 ± 0

Abbreviations (see Table 1)

ASO arteriosclerosis obliterans, *Buerger* thromboangiitis obliterans (Buerger's disease)

* $p < 0.05$ vs. pretreatment

Table 5 Subanalysis of changes in patients with CKD or without CKD (mean ± SD)

	Patients with CKD (6 patients)			Patients without CKD (4 patients)		
	Pretreatment	4 weeks	24 weeks	Pretreatment	4 weeks	24 weeks
TcO_2 (mmHg)	29.3 ± 10.8	46.0 ± 12.3*	44.3 ± 15.0*	27.0 ± 3.7	37.9 ± 3.3*	49.1 ± 10.4*
ABI	0.59 ± 0.17	0.59 ± 0.16	0.60 ± 0.19	0.62 ± 0.16	0.58 ± 0.14	0.67 ± 0.19
TBI	0.30 ± 0.01	0.36 ± 0.13	0.27 ± 0.05	0.31 ± 0.01	0.33 ± 0.10	0.30 ± 0.07
6 min (m)	203 ± 75	302 ± 66*	300 ± 70*	334 ± 99	387 ± 113*	343 ± 197
Foot ulcer (mm^2)	222 ± 440	170 ± 328	162 ± 276	1629 ± 3248	1625 ± 3250	994 ± 1988

Abbreviations (see Table 1)

CKD chronic kidney disease

* $p < 0.05$ vs pretreatment

There are between 500 and 1000 new cases of CLI every year in a European or North American population of one million, and the incidence of major amputations from large population or nationwide data ranges from 120 to 500/million/year [1]. Although treatment of CLI is improving [1, 25] and surgical or endovascular revascularization helps to alleviate CLI [2, 3], they have not become well-established treatment protocols for CLI patients. Among CLI patients, about 20 % are not indicated for percutaneous transluminal angioplasty or surgical revascularization [26]. Therefore, efforts at improving regenerative medicine have been increasing. Recently, numerous clinical trials for CLI have been conducted based on advances in regenerative medicine, as have been done on myocardial regeneration therapy [27, 28], and although they may have shown good results and appropriate levels of safety, there are still concerns [5, 29–32]: the half-life period of angiogenic factors is short, gene therapy could not control the expression period and level of expression, and there are immune or inflammatory responses of genetic materials [33, 34].

For cell transplantation, the collection of cells requires general anesthesia or the systemic administration of G-CSF [5]. We were able to overcome these problems using bFGF and gelatin hydrogel microspheres as the DDS. Although the biological half-life of bFGF in its free form is very short [35], the half-life period of bFGF can be prolonged through its combination with gelatin hydrogel. In fact, since it has been shown that bFGF-incorporated gelatin hydrogel microspheres persist for a few weeks [8, 9], this therapy does not require high dosages or repeated administration. We have previously used bFGF with gelatin hydrogel microspheres and shown its efficacy in several animal [10–18] and clinical studies [19]. The basic fibroblast growth factor we used is recombinant human bFGF, which has already been clinically utilized for the treatment of bedsores and ulcers in Japan, and our gelatin hydrogel microspheres were made in accordance with GMP standards. Therefore, the advantages of this method are safety and efficacy.

In the present study, there was no death or procedure-related adverse event attributable to topical use of sustained-release bFGF, but some adverse drug reactions, such as the elevation of Cr, AST, and ALT, were observed. It is said that bFGF (FGF-2) is mitogenic for many renal cell types including glomerular endothelial and glomerular epithelial cells but this is also the case for mesangial and proximal tubule cells of the kidney [36]. In this study, only one patient's Cr increased from 1.7 mg/dl at pretreatment to 2.3 mg/dl at 12 weeks after treatment. At 24 weeks, however, this patient's Cr declined to 1.5 mg/dl without

further treatment. The effects of bFGF with gelatin hydrogel microsphere were thought to disappear after approximately 1 month [37, 38], so the possibility of a causal relationship with other treatments seemed to be very low.

In contrast to the improvement of other endpoints, ABI and TBI did not show significant improvement. Some studies of angiogenesis for CLI patients, which showed an efficacy of ulcer healing, an increase of collaterals, or an improvement of claudication walking distance, did not show any significant improvement in ABI [30, 32]. Shigematsu et al. [30] reported that the change in ABI was not associated with the ulcer healing, suggesting that HGF plasmid may act at the micro vascular level. Lee et al. [32] also reported that no change in ABI was noteworthy because this value primarily depends on the pressure of large arteries, and adipose tissue-derived mesenchymal stem cells form numerous small collateral arteries. Since TBI also depends on large arteries, the same could be said of our ABI and TBI results.

Therapeutic angiogenesis tended to be more effective in patients with TAO (Buerger's disease) than in patients with ASO [39, 40]. Concerning the long-term clinical outcome of angiogenic therapy using bone marrow mononuclear cells implantation, Matoba et al. [41] reported that the 3-year overall mortality rate was 0 % in the TAO group and 20 % in the ASO group, and that the 3-year amputation rate was 9 % in the TAO group and 40 % in the ASO group. Actually, PAD commonly results from ASO in the lower extremities [1], which was consistent with the findings of our study. Chronic kidney disease also exacerbates the condition of patients with CLI. The occurrence of CLI in patients with kidney insufficiency portends a strikingly high rate of subsequent major amputation and mortality, compared to those patients without kidney insufficiency [42]. In this study, TcO_2 significantly increased in not only TAO patients but also in ASO patients both at 4 and 24 weeks after treatment. Similarly, TcO_2 improved significantly in patients with CKD as well as in patients with normal kidney function. Since subset analyses based on a comparison of underlying disease were less convincing due to the underpowered size of the cohort, we did not perform a comparative analysis among subgroups. Therefore, a larger cohort of patients would be needed for a subsequent examination of this nature.

This study presents some challenges to subsequent studies. First, dialysis patients with CLI were excluded because most dialysis-dependent patients are in poor physical condition, which can be a strong confounding factor. Second, the number of the patients was not sufficient to conclude statistical significance. While the data of the subanalyses were not the validation results of the efficacy in our phase I–IIa study, and we understood the problem of sample size, we reported that the results of these subanalyses will provide important information for a future study. Third, because this study was a phase I (-IIa) open-label study, we did not include a control group, nor did we assess the dosage effect. There is an ethical concern related to having a control group whose patients had an increased possibility of lower leg amputation as a result of the disease. Additionally many reports on therapeutic angiogenesis [43–47] for CLI also did not have a control group because of these same concerns, so we felt it was the better ethical choice. Fourth, since the follow-up period was a mere 24 weeks, the long-term efficacy still needs to be evaluated. Therefore, we intend to address the above issues when investigating the benefits of this method in greater detail in further studies.

Conclusion

These data provide encouraging evidence of therapeutic angiogenesis via the sustained release of bFGF through the use of gelatin hydrogel. Additionally, more appropriately powered clinical investigations are warranted.

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Conflict of interest None declared.

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Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With End-Stage Renal Disease Requiring Dialysis (5-Year Outcomes of the CREDO-Kyoto PCI/CABG Registry Cohort-2)

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Ischemic heart disease is a major risk factor for morbidity and mortality in patients with end-stage renal disease. However, long-term benefits of percutaneous coronary intervention (PCI) relative to coronary artery bypass grafting (CABG) in those patients is still unclear in the drug-eluting stent era. We identified 388 patients with multivessel and/or left main disease with end-stage renal disease requiring dialysis among 15,939 patients undergoing first coronary revascularization enrolled in the Coronary REvascularization Demonstrating Outcome Study in Kyoto PCI/CABG Registry Cohort-2 (PCI: 258 patients and CABG: 130 patients). The CABG group included more patients with 3-vessel (38% vs 57%, p <0.001) and left main disease (10% vs 34%, p <0.001). Preprocedural Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score in the CABG group was significantly higher than that in the PCI group (23.5 ± 8.7 vs 29.4 ± 11.0, p <0.001). Unadjusted 30-day mortality was 2.7% for PCI and 5.4% for CABG. Cumulative 5-year all-cause mortality was 52.3% for PCI and 49.9% for CABG. Propensity score–adjusted all-cause mortality was not different between PCI and CABG (hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.85 to 2.09, p = 0.219). However, the excess risk of PCI relative to CABG for cardiac death was significant (HR 2.10, 95% CI 1.11 to 3.96, p = 0.02). The risk of sudden death was also higher after PCI (HR 4.83, 95% CI 1.01 to 23.08, p = 0.049). The risk of myocardial infarction after PCI tended to be higher than after CABG (HR 3.30, 95% CI 0.72 to 15.09, p = 0.12). The risk of any coronary revascularization after PCI was markedly higher after CABG (HR 3.78, 95% CI 1.91 to 7.50, p <0.001). Among the 201 patients who died during the follow-up, 94 patients (47%) died from noncardiac morbidities such as stroke, respiratory failure, and renal failure. In patients with multivessel and/or left main disease undergoing dialysis, 5-year outcomes revealed that CABG relative to PCI reduced the risk of cardiac death, sudden death, myocardial infarction, and any revascularization. However, the risk of all-cause death was not different between PCI and CABG. **(Am J Cardiol 2014;114:555–561)**

Several studies have shown that chronic kidney disease is associated with increased mortality after coronary revascularization, particularly in patients with end-stage renal disease (ESRD) requiring chronic dialysis.[1–3] Several randomized trials have reported the outcomes after revascularization in complex coronary lesions. However, patients with ESRD undergoing chronic dialysis have been excluded from any randomized evaluation for the comparative efficacy of coronary revascularization strategies.[4] Regarding observational studies comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in the drug-eluting stents (DES) era, only a few single-center studies with less complex coronary lesions with small sample size have been available so far.[5,6] In the present study, we sought to investigate 5-year outcomes comparing PCI with CABG in ESRD patients on chronic dialysis with multivessel coronary and/or left main coronary disease using a large observational database in Japan.

Methods

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG

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See page 560 for disclosure information.

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Table 1
Baseline characteristics of patients with hemodialysis with multivessel and/or left main disease

Variable	PCI (n = 258)	CABG (n = 130)	p Value
Age	66.2 ± 10.6	66.5 ± 8.7	0.75
>75 years	61 (24%)	23 (18%)	0.18
Men	187 (73%)	104 (80%)	0.11
Body mass index (kg/m^2)	22.3 ± 3.9	21.8 ± 2.9	0.20
>25	207 (80%)	111 (85%)	0.21
Hypertension	229 (89%)	107 (82%)	0.08
Diabetes mellitus	167 (65%)	77 (59%)	0.29
On insulin therapy	80 (31%)	37 (29%)	0.61
Current smoker	46 (18%)	20 (15%)	0.55
Ejection fraction (%)	53.3 ± 14.0	52.1 ± 14.0	0.43
Mitral regurgitation grade 3/4	28 (11%)	9 (6.9%)	0.21
Previous myocardial infarction	45 (17%)	24 (19%)	0.80
Heart failure	87 (34%)	43 (33%)	0.90
Atrial fibrillation	33 (13%)	29 (22%)	0.02
Previous stroke	40 (16%)	23 (18%)	0.58
Peripheral artery disease	68 (26%)	39 (30%)	0.45
Anemia (hemoglobin <11.0 g/dl)	155 (60%)	73 (56%)	0.46
Platelet count <100 × 10^9/L)	16 (6%)	8 (6%)	0.99
Chronic obstructive pulmonary disease	2 (1%)	2 (2%)	0.48
Liver cirrhosis	13 (5%)	6 (5%)	0.86
Malignancy	18 (7%)	11 (9%)	0.60
Procedural characteristics			
Number of target coronary lesions or anastomoses	1.7 ± 0.8	3.0 ± 1.1	<0.001
Number of coronary artery narrowed	1.6 ± 0.7	2.4 ± 0.6	<0.001
Extent of coronary artery disease			
3	97 (38%)	74 (57%)	<0.001
2	136 (52%)	12 (9%)	<0.001
Left main	25 (10%)	44 (34%)	<0.001
Target of proximal left anterior descending artery	133 (52%)	109 (84%)	<0.001
Target of chronic total occlusion	49 (19%)	44 (34%)	<0.001
PCI profile			
Drug-eluting stent use	190 (73%)	(-)	n/a
Bare-metal stent use only	46 (18%)	(-)	n/a
Balloon angioplasty only	22 (9%)	(-)	n/a
Off-pump CABG	(-)	78 (60%)	n/a
Emergency procedure	7 (3%)	8 (6%)	0.10
SYNTAX score*	23.5 ± 8.7	29.4 ± 11.0	<0.001
Medications at discharge			
Ticlopidine/clopidogrel	237 (93%)	14 (11%)	<0.001
Aspirin	251 (97%)	123 (95%)	0.18
Statins	63 (24%)	12 (9%)	<0.001
Beta-blockers	57 (22%)	28 (22%)	0.90
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	119 (46%)	45 (35%)	0.03
Nitrates	98 (38%)	41 (32%)	0.21
Calcium channel blocker	139 (54%)	62 (48%)	0.25
Warfarin	16 (6%)	51 (39%)	<0.001

Mean ± standard deviation, or number of patients and percentage.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.
* SYNTAX scores were available in 119 patients for PCI (98%) and 106 patients for CABG (90%), respectively.

Table 2
30-Day outcomes after revascularization in patients requiring dialysis

Variable	PCI n = 258	CABG n = 130
Death (total)	7 (3%)	7 (5%)
Heart failure	2	1
Respiratory failure	0	3
Peripheral artery disease	2	0
Gastrointestinal	0	2
Stroke	1	0
Renal failure	1	0
Infection	1	0
Nonfatal stroke	4 (2%)	2 (2%)
Nonfatal myocardial infarction	4 (2%)	1 (1%)

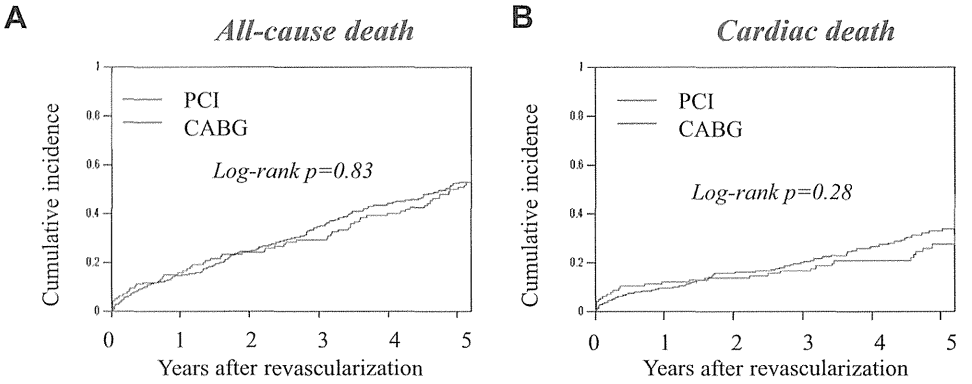
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Registry Cohort-2 is a physician-initiated, noncompany-sponsored, multicenter registry that enrolled consecutive patients undergoing first coronary revascularization in 26 centers in Japan from January 2005 through December 2007. The relevant ethics committees in all 26 participating centers (see Supplementary Data A) approved the research protocol. Because of retrospective enrollment, written informed consent from the patients was waived. However, patients who refused participation in the study when contacted for follow-up were excluded.

The study design and patient enrollment in the registry have been described in detail previously.[7] Of 15,939 patients enrolled in the registry, the study population for the present subanalysis of the CREDO-Kyoto PCI/CABG Registry Cohort-2 consisted of 388 patients with ESRD with multivessel and/or left main coronary artery disease on long-term dialysis (258 patients with PCI and 130 patients with isolated CABG) excluding those patients who refused study participation (n = 99), who had concomitant noncoronary surgery (n = 609), who had acute myocardial infarction (MI; n = 4,892), who had single-vessel disease (n = 3,431), and those without chronic dialysis (n = 6,520).

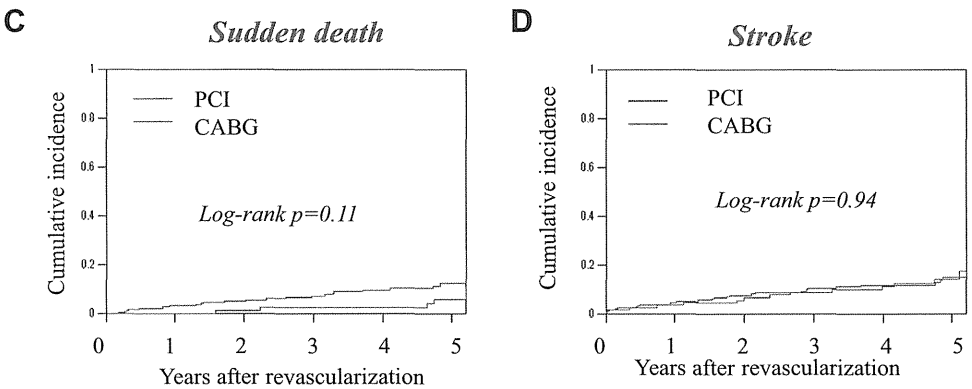
Demographic, angiographic, and procedural data were collected from hospital charts according to the prespecified definitions by experienced research coordinators in an independent research organization (Research Institute for Production Development, Kyoto, Japan; see Supplementary Data B). Definitions for clinical characteristics are described in Supplementary Data C.

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score was calculated in those with 3-vessel and/or left main coronary artery disease, in whom diagnostic coronary angiograms for both left and right coronary arteries were available for analysis. The SYNTAX scores were available in 119 patients (98%) for PCI and 106 patients (90%) for CABG, respectively. The SYNTAX score was calculated using the SYNTAX score calculator (available at *http://www.syntaxscore.com*) by a dedicated SYNTAX score committee (see Supplementary Data D) in a blinded fashion to the clinical data. Intra- and inter-observer variabilities of the



Interval (years)	0	1	3	5
PCI group				
No. of patients with events		37	87	126
No. of patients at risk	258	217	161	76
Cumulative incidence (%)		14.5	34.6	52.3
CABG group				
No. of patients with events		20	36	60
No. patients at risk	130	103	85	53
Cumulative incidence (%)		15.8	29.0	49.9

Interval (years)	0	1	3	5
PCI group				
No. of patients with events		24	47	69
No. of patients at risk	258	217	161	76
Cumulative incidence (%)		9.6	19.9	32.7
CABG group				
No. of patients with events		15	20	29
No. of patients at risk	130	103	85	53
Cumulative incidence (%)		11.8	16.6	27.2



Interval (years)	0	1	3	5
PCI group				
No. of patients with events		7	15	22
No. of patients at risk	258	217	161	76
Cumulative incidence (%)		3.0	7.0	12.1
CABG group				
No. of patients with events		0	2	4
No. of patients at risk	130	103	85	53
Cumulative incidence (%)		0	2.1	5.5

Interval (years)	0	1	3	5
PCI group				
No. of patients with events		11	22	27
No. of patients at risk	258	210	152	69
Cumulative incidence (%)		4.6	10.3	14.8
CABG group				
No. of patients with events		4	9	13
No. of patients at risk	130	101	80	52
Cumulative incidence (%)		3.4	8.7	14.1

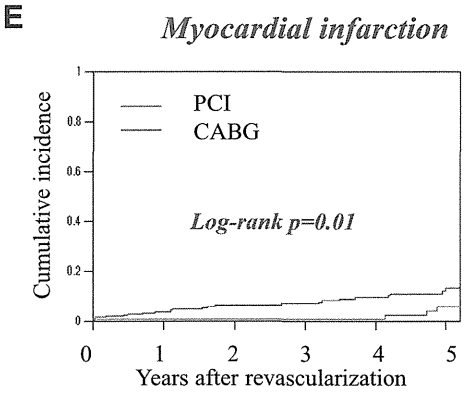
Figure 1. Kaplan-Meier curves comparing PCI or CABG in patients on dialysis during 5 years. *(A)* All-cause death. *(B)* Cardiac death. *(C)* Sudden death. *(D)* Stroke. *(E)* Myocardial infarction. *(F)* Any coronary revascularization.

SYNTAX score calculation in our group were previously reported.[8]

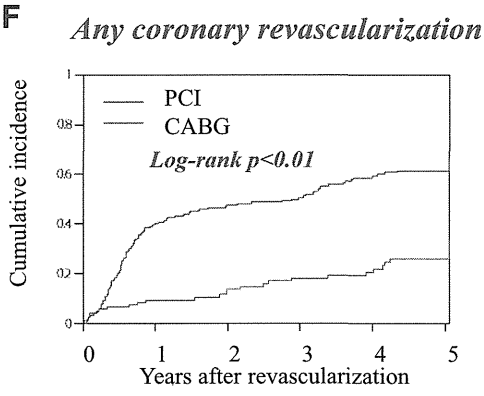
Collection of follow-up information was conducted mainly through review of inpatient and outpatient hospital charts by clinical research coordinators in the independent research organization. Additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions on vital status and additional hospitalizations. Death, MI, stent thrombosis, and stroke were adjudicated by the clinical events committee (see Supplementary Data E).

The primary outcome measure for the present analysis was death from any cause. Other prespecified end points included cardiac death, sudden death, stroke, MI, and any coronary revascularization. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Any death during the index hospitalization for coronary revascularization was regarded as cardiac death. Sudden death was defined as unexpected death in previously stable patients. MI was defined according to the definition in the Arterial Revascularization Therapy Study.[9] Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. Scheduled staged coronary revascularization procedures performed within 3 months of the initial procedure were not regarded as follow-up events but were included in the index procedure.

All continuous variables are expressed as the mean ± SD. Differences in baseline characteristics between the 2 groups were examined by unpaired *t* test and Fisher's exact



Interval (years)	0	1	3	5
PCI group				
No. of patients with events		9	15	23
No. of patients at risk	258	210	155	70
Cumulative incidence (%)		3.7	6.7	13.3
CABG group				
No. of patients with events		1	1	4
No. of patients at risk	130	103	85	52
Cumulative incidence (%)		0.8	0.8	5.7



Interval (years)	0	1	3	5
PCI group				
No. of patients with events		92	112	128
No. of patients at risk	258	128	77	30
Cumulative incidence (%)		40.1	50.6	61.6
CABG group				
No. of patients with events		11	19	25
No. of patients at risk	130	98	73	45
Cumulative incidence (%)		9.4	18.1	26.0

Figure 1. (*continued*).

Table 3
Propensity-score-adjusted hazard ratios stratified to dialysis comparing PCI with CABG in patients undergoing dialysis with multivessel and/or left main disease

Variable	Number of Patients (Event/Total)		PCI vs. CABG			
	PCI (n = 258)	CABG (n = 130)	Hazard Ratio	95% CI		p
Death	134 (52%)	67 (52%)	1.33	0.85	2.09	0.22
Cardiac death	76 (30%)	31 (24%)	2.10	1.11	3.96	0.02
Sudden death	24 (9%)	6 (4.6%)	4.83	1.01	23.08	0.049
Stroke	30 (12%)	16 (12%)	1.05	0.42	2.63	0.92
Myocardial infarction	25 (10%)	4 (3%)	3.30	0.72	15.09	0.12
Any coronary revascularization	130 (50.4%)	26 (20.0%)	3.78	1.91	7.50	<0.001

Outcomes after PCI or CABG are compared with propensity-score analysis. Confounding factors in the propensity-score analysis included age, sex, body mass index, hypertension, dyslipidemia, diabetes mellitus, current smoker, heart failure, mitral regurgitation grade 3/4, prior myocardial infarction, prior stroke, peripheral vascular disease, atrial fibrillation, chronic kidney disease, dialysis, anemia, platelet count, chronic obstructive lung disease, liver cirrhosis, malignancy, emergency procedure, number of diseased vessel, left main disease, target of chronic total occlusion, target of proximal left anterior descending coronary artery, and institute.

CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

test. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed using log-rank test. Propensity scores, which were the probabilities that a patient would undergo PCI, were estimated with multivariate logistic regression analyses including age, gender, body mass index, hypertension, dyslipidemia, diabetes mellitus, current smoker, heart failure mitral regurgitation grade 3 or 4, previous MI, previous stroke, peripheral arterial disease, atrial fibrillation, chronic kidney disease, hemodialysis, anemia, platelet count, chronic obstructive lung disease, liver cirrhosis, malignancy, emergency procedure, number of diseased vessels, left main disease, target of chronic total occlusion, target of proximal left anterior descending coronary artery, and institute. These variables were consistent with previous reports from the current registry. Continuous variables except age were dichotomized using clinically meaningful reference values or median values. We incorporated the 26 participating centers in the propensity score estimation as the stratification variable. The hazard ratios (HRs) of PCI compared with CABG were estimated by the stratified Cox proportional hazard models; the models included PCI or CABG as the covariate and were stratified by the quartiles of propensity score and institute to adjust for confounding. Effects of PCI compared with CABG for individual end points were expressed as HRs with 95% confidence intervals. All reported p values were 2-sided, and p values <0.05 were regarded as statistically significant.

All analyses were conducted by a statistician with the use of SAS software, version 9.3 (SAS Institute Inc Cary, North Carolina), and S-Plus, version 7.0 (Insightful Corp). The investigators had full access to the data and take responsibility for its integrity. All investigators have read and agreed to the manuscript as written.

Table 4
Causes of death after revascularization during 5 years

Cardiac Death (n = 107)	PCI (n = 76)	CABG (n = 31)
Ischemic heart disease (total)	49 (37%)	25 (37%)
Acute myocardial infarction	8 (6%)	3 (5%)
Heart failure	15 (11%)	2 (3%)
Others	26 (19%)	20 (30%)
Sudden cardiac death	24 (18%)	6 (9%)
Valvular	3 (2%)	0 (0%)
Non-Cardiac Death (n = 94)	**PCI (n = 58)**	**CABG (n = 36)**
Cerebrovascular	11 (8%)	8 (12%)
Respiratory failure	12 (9%)	2 (3%)
Renal failure	10 (8%)	3 (5%)
Infection	5 (4%)	4 (6%)
Gastrointestinal	4 (3%)	5 (8%)
Malignancy	4 (3%)	4 (6%)
Peripheral artery disease	3 (2%)	3 (5%)
Liver failure	1 (1%)	3 (5%)
Trauma	3 (2%)	1 (2%)
Aortic aneurysm/dissection	1 (1%)	1 (2%)
Others	3 (2%)	2 (3%)
Unknown	1 (1%)	0 (0%)

Among the 201 patients who died during the follow-up, 94 patients (47%) died of noncardiac morbidities.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Results

Baseline clinical characteristics were not different between the PCI and CABG groups except the rate of atrial fibrillation (Table 1). Regarding the complexity of coronary artery anatomy, the CABG group included more patients with 3-vessel disease, left main disease, target of proximal left anterior descending artery, and target of chronic total occlusion. SYNTAX score was significantly higher in the CABG group. Median follow-up duration for the surviving patients was 1,821 days.

Unadjusted 30-day mortality was 2.7% for PCI and 5.4% for CABG (Table 2). Cumulative 5-year incidence of all-cause death was not significantly different between the PCI and CABG groups (Figure 1). Similarly, cumulative 5-year incidences of cardiac death, sudden death, and stroke were not different between the 2 groups (Figure 1). Cumulative incidences of MI and any coronary revascularization after PCI were significantly higher than those after CABG (Figure 1).

After adjusting for the propensity score and institute, the risk of PCI relative to CABG for all-cause death remained statistically insignificant (Table 3). However, adjusted risks for cardiac death and sudden death after PCI were significantly higher than after CABG. The risk for any coronary revascularization after PCI was markedly higher than after CABG. The risk for stroke was not significantly different between the 2 groups.

During the 5-year follow-up, 201 patients (52% of all patients) died (Table 4). Among them, 107 patients (53%) died from cardiac causes: 76 patients in the PCI group and 31 patients in the CABG group, respectively. The proportions of death from heart failure and sudden death in total death tended to be higher after PCI than after CABG (11% vs 3% and 18% vs 9%, respectively; Table 4). The specific causes for noncardiac death in 94 patients (47%) included cerebrovascular disease, respiratory failure, and renal failure (Table 4).

Discussion

There were increasing number of patients requiring dialysis in Japan and >300,000 patients on dialysis in 2012. Approximately 30% of patients requiring dialysis died from cardiogenic causes such as heart failure and MI. Several studies have reported high mortality and morbidity after cardiac surgery for dialysis patients.[10,11] Because coronary lesions in dialysis patients are often characterized by extensive atherosclerotic lesions with heavy calcification, it remains controversial which strategy is more beneficial for coronary revascularization in dialysis patients: aggressive treatment with CABG or less invasive treatment with PCI.

In the bare-metal stent era, several studies comparing PCI with CABG have reported poor outcomes after both revascularization procedures in dialysis patients. Herzog et al[12] reported poor 2-year survival after PCI and CABG, although survival after CABG was significantly higher than PCI (56.4% vs 48.2%, p <0.0001). The advantage was more prominent in diabetic patients. Hemmelgarn et al[13] noted that 8-year adjusted survival after coronary revascularization was 44.8% for CABG and 41.2% for PCI, respectively. Adjusted mortality was not different between CABG and PCI in dialysis patients, although CABG was associated with a significant lower risk of death in both patients without chronic kidney disease or patients with nondialysis kidney disease.[13]

In the DES era, few reports have been available in more complex lesions such as 3-vessel disease or left main disease. The advantage of CABG over PCI has been controversial. Sunagawa et al[14] compared the midterm outcomes between PCI with DES and CABG in 104 patients undergoing dialysis. They reported that CABG relative to PCI significantly reduced the incidence of cardiac death, major adverse cardiac events, and target lesion revascularization.[14] The DES carried a higher risk for sudden death, which might be associated with stent thrombosis. Recently, Shroff et al[4] compared the outcomes of bare-metal stent, DES, and CABG using large data from the United States Renal Data System to define a cohort of 23,033 patients. Although their data included less complex coronary lesions, they showed that in-hospital mortality was higher after CABG but long-term survival was superior with use of internal thoracic artery (ITA). In-hospital mortality was lower for patients receiving DES, but the probability of repeat revascularization was higher and comparable to that of patients receiving a bare-metal stent. They concluded that revascularization decisions for dialysis patients should be individualized.

In the present study, 5-year mortality was about 50% both in the PCI and CABG groups, which was considerably lower than previous reports.[4,11,12] The reason was unclear. That may be partly due to the improved Japanese health-care system for the dialysis patients across the country provided by a universal public insurance system. Japanese national registry revealed that 5-year mortality of whole dialysis

patients has been about 60% in recent 5 years, which is also better than those reported in the United States or Europe.[11] As shown in the present study, approximately 1/2 of dialysis patients died from noncardiac co-morbidities; therefore, not only cardiac management but also systemic care may contribute to improve long-term outcomes in dialysis patients.

As shown in the present study, overall mortality after PCI or CABG was high. Several studies evaluated whether the technical developments such as off-pump CABG or use of bilateral ITA might improve the outcomes after CABG in dialysis patients. Regarding off-pump CABG, Shroff et al[15] reported that no difference was noted in the in-hospital mortality rate with off-pump versus on-pump CABG (9.7% vs 11.0%, $p = 0.06$). Cardiac mortality during the 3-year follow-up was similar between on- and off-pump CABG groups (23.6% vs 23.8%, HR 0.95, 95% confidence interval 0.86 to 1.04, $p = 0.26$). They also demonstrated that use of ITA was independently associated with improved survival after coronary artery bypass surgery (HR 0.92, 95% confidence interval 0.87 to 0.98, $p = 0.0057$).[15] However, Nakatsu et al[6] reported that CABG with bilateral ITA grafts showed no advantages on long-term outcomes even in patients with diabetes mellitus. Because there has been very little available evidence regarding the benefit of off-pump CABG or ITA use in dialysis patients, further studies are necessary to demonstrate their advantages.

In the present study, patients undergoing PCI with DES received double antiplatelet therapy (thienopyridine derivative plus aspirin) at least for 1 year after PCI. Patients with bare-metal stet alone or balloon angioplasty alone received double antiplatelet therapy for 1 month. We have shown that prolonged thienopyridine therapy beyond 4 and 13 months appeared not to be associated with reduction in ischemic events but to be associated with a trend toward increased bleeding.[16] We also have shown that the risk of ischemic and bleeding complications in surgical procedures after PCI was low, and in patients selected to receive DES or bare-metal stents, there were no differences in the incidence of death, MI, stent thrombosis, or bleeding complications.[17] Medications after PCI are important parameters that could have affected the outcomes; however, we could not evaluate the effects of the medications after PCI because of small sample size and insufficient statistical power.

There are several important limitations to this study. First and most importantly, the observational study design precluded drawing definitive conclusions regarding the superiority of PCI or CABG because of selection bias and unmeasured confounders. The distribution of atrial fibrillation and extent of coronary artery disease differed significantly between the 2 groups, and there is a potential of residual confounding bias due to unmeasured factors, although we adjusted for relevant measured confounders in the propensity score analysis. Second, the number of patients enrolled was still small and there may be an insufficient statistical power, particularly in the analysis of 30-day outcomes.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2014.05.034.

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ORIGINAL ARTICLE
Cardiovascular Surgery

Preoperative Chronic Kidney Disease as a Strong Predictor of Postoperative Infection and Mortality After Coronary Artery Bypass Grafting

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Background: The aim of this study was to determine the influence of preoperative kidney dysfunction (ie, chronic kidney disease (CKD)) on postoperative cardiovascular events, infection, acute kidney injury and hospital mortality in patients undergoing coronary artery bypass grafting (CABG).

Methods and Results: A multi-institutional retrospective study was performed at 14 hospitals of adult patients undergoing isolated CABG from 2007 to 2008 (n=1,522). We classified CKD level according to preoperative estimated glomerular filtration rate (eGFR): normal, eGFR >90 ml·min^{-1}·1.73 m^{-2}; mild, eGFR 60–90 ml·min^{-1}·1.73 m^{-2}; moderate, eGFR 30–59 ml·min^{-1}·1.73 m^{-2}; and severe, eGFR <30 ml·min^{-1}·1.73 m^{-2}, and assessed postoperative outcome. Preoperative CKD distribution was as follows: normal, n=121 (8%); mild, n=713 (47%); moderate, n=515 (34%); and severe, n=169 (11%). Risk of infection was strongly correlated with CKD level (normal, 3.3%; mild, 7.0%; moderate, 8.3%; severe, 17.0%; P<0.01). The risk of in-hospital death was also strongly correlated with CKD level (normal, 1.7%; mild, 1.0%; moderate, 1.6%; severe, 5.9%; P<0.01). On multivariate logistic regression analysis, CKD level was identified as a significant risk factor for postoperative infection, acute kidney injury, and in-hospital death.

Conclusions: Advanced preoperative CKD is a strong predictor of postoperative infection, acute kidney injury and in-hospital death after CABG. (*Circ J* 2014; **78:** 2225–2231)

Key Words: Chronic kidney disease; Complication; Coronary artery bypass grafting; Infection; Mortality

It is well recognized that chronic kidney disease (CKD) of any degree entails a worsened prognosis for patients with coronary artery disease (CAD).[1–7] In addition, CKD itself can accelerate atherosclerotic pathophysiology in patients with CAD, and the level of CKD is an independent predictor for CAD.[2,3] It has also been reported that the presence of diabetes mellitus (DM), which is a leading cause of end-stage renal disease (ESRD), accelerates the disease process of CAD and decreases late survival in CKD patients.[1,8] Advanced CKD is certainly a preliminary step towards ESRD, subsequently requiring renal replacement therapy such as hemodialysis (HD) or kidney transplant.[9] In patients with ESRD, cardiovascular disease is definitely the leading cause of death, limiting long-term survival.[10]

Editorial p2151

There is a growing body of literature that supports the con-

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Table 1. Baseline Subject Characteristics vs. Preoperative CKD Level

Variables	Normal eGFR >90 (n=121)	Mild CKD eGFR 60–90 (n=713)	Moderate CKD eGFR 30–59 (n=515)	Severe CKD eGFR <30 (n=169)	P value
Age (years)	62.8±12.2	67.2±9.0	71.3±7.7	69.2±8.8	<0.01
Age ≥75	18 (14.9)	153 (21.5)	189 (36.7)	45 (26.6)	<0.01
Male gender	95 (78.5)	570 (79.9)	386 (75.0)	124 (73.4)	0.03
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	112.6 (99.8)†	72.8 (72.6)†	49.1 (50.7)†	14.7 (12.4)†	<0.01
BMI ($kg \cdot m^{-2}$)	23.0±3.3	23.7±3.1	23.7±3.1	23.1±3.6	0.72
Hypertension	76 (62.8)	520 (72.9)	389 (75.5)	142 (84.0)	<0.01
Dyslipidemia	58 (47.9)	432 (60.6)	311 (60.4)	71 (42.0)	0.10
DM	51 (42.1)	351 (49.2)	297 (57.7)	112 (66.3)	<0.01
On insulin	13 (10.7)	91 (12.8)	83 (16.1)	50 (29.6)	
Preoperative HbA1c (%)	6.0±1.0	6.1±1.1	6.2±1.1	6.1±1.1	0.60
Preoperative steroid use	1 (0.8)	9 (1.3)	12 (2.3)	6 (3.6)	0.02
CHF	18 (14.9)	103 (14.4)	85 (16.5)	44 (26.0)	<0.01
COPD	16 (13.2)	52 (7.3)	43 (8.3)	21 (12.4)	0.54
PAD	23 (19.0)	117 (16.4)	123 (23.9)	57 (33.7)	<0.01
LVEF <50%	26 (21.5)	133 (18.7)	136 (26.4)	49 (29.0)	<0.01
Operative status					
Elective	92 (76.0)	602 (84.4)	455 (88.3)	132 (78.1)	0.41
Urgent	19 (15.7)	71 (10.0)	40 (7.8)	24 (14.2)	
Emergency	10 (8.3)	40 (5.6)	20 (3.9)	13 (7.7)	
Bilateral ITA use	63 (52.1)	373 (52.3)	218 (42.3)	57 (33.7)	<0.01
Intraoperative steroid use	52 (43.0)	236 (33.1)	147 (28.5)	53 (31.4)	0.02
On-pump or off-pump					
On-pump	32 (26.4)	173 (24.3)	120 (23.3)	54 (32.0)	0.36
On-pump beating	4 (3.3)	28 (3.9)	18 (3.5)	6 (3.6)	
Off-pump	85 (70.2)	512 (71.8)	377 (73.2)	109 (64.5)	

Data given as mean±SD, †median (eGFR) or n (%). BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ITA, internal thoracic artery; PAD, peripheral artery disease.

tention that CKD is associated with poor prognosis for patients undergoing CABG,[8,11,12] but it is not well understood exactly how CKD influences the outcome of CABG patients. We previously reported that the presence of DM itself was not a statistically significant risk factor for morbidity and mortality in patients undergoing CABG, whereas preoperative advanced CKD was a much stronger independent risk factor for postoperative infection and in-hospital mortality.[13] Here, we conducted sub-analyses as a host-hoc study to identify the significance of preoperative kidney dysfunction level, classified as estimated glomerular filtration rate (eGFR), on morbidity and mortality. Also, we assessed the impact of chronic HD on postoperative complications among severe CKD patients.

Methods

From January 2007 until December 2008, a total of 1,522 adult patients underwent isolated CABG in 14 cardiac surgery centers in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. All the patient characteristics and operative data were extracted from the prospective national database (Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in North America. Other study-specific data such as preoperative hemoglobin A1c and postoperative complications, including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These 2 sets of data were merged, then blinded and sent to a data center (EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables and their definitions have been described elsewhere.[13] Preoperative CKD level was classified according to eGFR, calculated using the Modification of Diet in Renal Disease formula for Japanese patients:[14]

$$eGFR\ (ml \cdot min^{-1} \cdot 1.73\,m^{-2}) = 194 \times serum\ creatinine^{-1.094} \times age^{-0.287} \times 0.739\ (\text{if female}).$$

Of note, the presence and level of proteinuria were not measured, and the cause of kidney dysfunction was also not considered in this study. CKD level was then classified only according to eGFR: normal (eGFR $>90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$), mild CKD (eGFR 60–$90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$), moderate CKD (eGFR 30–$59\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$), and severe CKD (eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$). DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Also, patients without a previous diagnosis of DM who had preoperative hemoglobin A1c ≥6.5% (National Glycohemoglobin Standardization Program) were included.

Internal thoracic arteries (ITA) were harvested in a skeletonized fashion using the harmonic scalpel (Ethicon, West Somerville, NJ, USA) at most of the participating centers. In terms of intraoperative steroid use, a large amount of steroid

Table 2. Adverse Events and Outcomes vs. Preoperative CKD Level

Events and outcomes	Normal eGFR >90 (n=121)	Mild CKD eGFR 60–90 (n=713)	Moderate CKD eGFR 30–59 (n=515)	Severe CKD eGFR <30 (n=169)
Perioperative MI	1 (0.83)	15 (2.1)	7 (1.4)	2 (1.2)
Related death	1 (0.83)	2 (0.28)	0	0
Cerebrovascular events	2 (1.7)	6 (0.84)	10 (1.94)	1 (0.59)
Related death	0	0	1 (0.19)	0
Other cardiovascular events	2 (1.7)	8 (1.1)	14 (2.7)	3 (1.8)
Related death	0	1 (0.14)	3 (0.48)	0
Deep sternal wound infection	1 (0.83)	6 (0.84)	9 (1.75)	9 (5.3)
All infection	4 (3.3)	50 (7.0)	43 (8.3)	28 (16.6)
Related death	1 (0.83)	2 (0.28)	2 (0.39)	8 (4.7)
Acute kidney injury	0	3 (0.42)	9 (1.7)	7 (4.1)
Related death	0	1 (0.14)	0	0
Postoperative ventilator time (h)	19.0†	26.4†	33.8†	56.7†
In-hospital death	2 (1.7)	7 (0.98)	8 (1.6)	10 (5.9)

Data given as n (%) or †mean. MI, myocardial infarction. Other abbreviations as in Table 1.

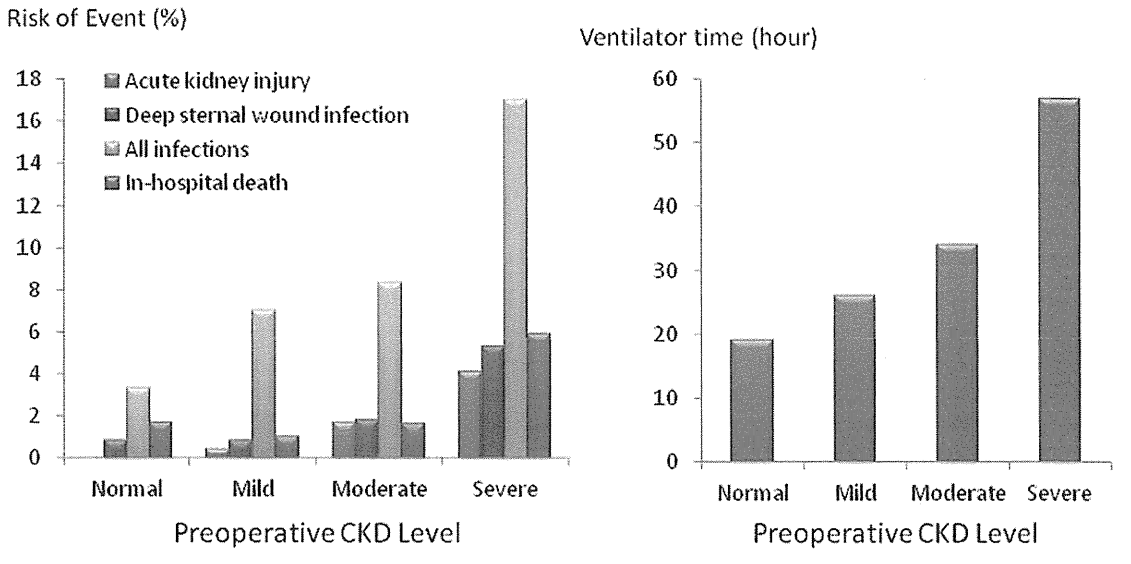

Figure. (**Left**) Risk of events and (**Right**) mean postoperative ventilator time vs. chronic kidney disease (CKD) level.

(methylprednisolone, 500–1,000 mg) was primed in the cardiopulmonary bypass circuit in some centers for on-pump CABG patients. Also, some surgeons and anesthesiologists preferred to give a moderate amount of i.v. steroid (methylprednisolone 125–500 mg) immediately after starting off-pump CABG in order to prevent systemic inflammatory response.

Postoperative variables were acute myocardial infarction, cerebrovascular events, acute kidney injury and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after percutaneous coronary intervention). Acute kidney injury was defined as increased creatinine >2-fold preoperative baseline level and ≥2.0 mg/dl, or newly requiring HD. Postoperative infection was defined as a composite of deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, bloodstream infection, urinary tract infection, and pneumonia. In-hospital death included all-cause death within 30 days of operation or during initial hospitalization.

Statistical Analysis

Baseline patient characteristics according to preoperative CKD level are given as mean±SD for continuous variables and proportions for categorical variables. They were compared with trend tests using univariate general linear models and with the chi-squared test, respectively.

Logistic regression analysis was conducted to estimate the effect of CKD (moderate CKD, and severe CKD as compared to normal or mild CKD as the reference group) on the risks of acute kidney injury, all infection, and all-cause death with the following potential adjustment factors: DM, age, gender, hypertension, dyslipidemia, body mass index, congestive heart failure, chronic obstructive pulmonary disease (COPD), periph-

Table 3. Multivariate Predictors of Acute Kidney Injury

	OR	95% CI	P-value
Moderate CKD (vs. normal or mild CKD)	5.10	1.06–24.60	0.04
Severe CKD (vs. normal or mild CKD)	14.82	3.02–72.84	<0.01
Age (10-year increments)	2.30	1.16–4.57	0.02
Urgent (vs. elective)	4.02	1.31–12.32	0.01
Emergency (vs. elective)	3.85	0.80–18.60	0.09

CI, confidence interval; OR, odds ratio. Other abbreviation as in Table 1.

Table 4. Multivariate Predictors of Infection

	OR	95% CI	P-value
Moderate CKD (vs. normal or mild CKD)	1.04	0.65–1.67	0.87
Severe CKD (vs. normal or mild CKD)	2.48	1.44–4.27	<0.01
DM (vs. normal)	1.23	0.82–1.85	0.32
Age (10-year increments)	1.02	0.81–1.28	0.90
Male gender (vs. female)	0.60	0.38–0.93	0.02
Hypertension (vs. normal)	1.01	0.63–1.61	0.97
Dyslipidemia (vs. normal)	0.67	0.44–1.01	0.05
BMI (1-unit increments)	1.06	1.00–1.12	0.06
CHF (vs. normal)	0.88	0.48–1.63	0.69
COPD (vs. normal)	1.95	1.05–3.61	0.03
PAD (vs. normal)	0.93	0.56–1.54	0.78
LVEF <50% (vs. ≥50%)	1.35	0.86–2.12	0.20
BITA use (vs. no use)	1.57	1.02–2.42	0.04
Off-pump (vs. on-pump)	0.53	0.33–0.84	0.01
Urgent (vs. elective)	1.14	0.57–2.29	0.70
Emergency (vs. elective)	1.29	0.47–3.50	0.62
Intraoperative steroid use (vs. no use)	0.62	0.39–0.97	0.04

BITA, bilateral internal thoracic artery. Other abbreviations as in Tables 1,3.

Table 5. Multivariate Predictors of In-Hospital Death

	OR	95% CI	P-value
Moderate CKD (vs. normal or mild CKD)	1.26	0.47–3.35	0.65
Severe CKD (vs. normal or mild CKD)	3.29	1.26–8.63	0.02
Diabetes mellitus (vs. normal)	2.13	0.90–5.03	0.09
Dyslipidemia (vs. normal)	0.31	0.13–0.74	<0.01
CHF (vs. normal)	3.37	1.50–7.60	<0.01
COPD (vs. normal)	3.91	1.50–10.56	<0.01
Off-pump (vs. on-pump)	0.30	0.13–0.68	<0.01

Abbreviations as in Tables 1,3.

eral artery disease, left ventricular ejection fraction (<50%), bilateral ITA (BITA) use, off-pump technique, operative status (elective vs. urgent or emergency), and intraoperative steroid use. The number of acute kidney injury and of all-cause deaths in this study was low and we therefore screened the adjustment factors in logistic regression analysis of these outcomes through a backward variable selection procedure with a critical value of $P<0.1$. Odds ratios (OR) and their associated 95% confidence intervals were calculated. All reported P-values are 2-sided and the significance level was set at 5%. All statistical analysis was done by an academic statistician (S. Tanaka) using SAS version 9.3 (SAS Institute, Cary, NC, USA).

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1,522 enrolled patients were classified into 4 groups according to preoperative kidney function level: normal, n=121 (8%); mild CKD, n=713 (47%); moderate CKD, n=515 (34%); and severe CKD, n=169 (11%). Of note, 4 patients were excluded from the original cohort due to lack of creatinine data. Patient baseline characteristics are listed in Table 1. The mean age in the normal group was significantly younger than that in the other groups. Patients older than 75 years were most numerous in the moderate CKD group (36.7%). The prevalence of systemic hypertension, DM, peripheral arterial disease, and

Table 6. Severe CKD Baseline Characteristics vs. Need for HD

Variables	Severe CKD (n=169)		P-value
	HD (–) (n=85)	HD (+) (n=84)	
Age (years)	71.9±7.9	66.4±8.8	<0.01
Age ≥75	31 (36.5)	14 (16.7)	<0.01
Male gender	57 (67.1)	67 (79.8)	0.06
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	22.0±5.7	6.7±3.5	<0.01
BMI ($kg \cdot m^{-2}$)	23.6±3.2	22.5±3.8	0.04
Hypertension	71 (83.5)	71 (84.5)	0.86
Dyslipidemia	43 (50.6)	28 (33.3)	0.02
DM	57 (67.1)	55 (65.5)	0.83
On insulin	23 (27.1)	27 (32.1)	
Preoperative HbA1c (%)	6.3±1.1	5.7±1.1	<0.01
Preoperative steroid use	3 (3.5)	3 (3.6)	0.99
CHF	23 (27.1)	21 (25.0)	0.76
COPD	15 (17.6)	6 (7.1)	0.04
PAD	29 (34.1)	28 (33.3)	0.91
LVEF <50%	29 (34.1)	20 (23.8)	0.14
Operative status			
Elective	68 (80.0)	64 (76.2)	0.50
Urgent	12 (14.1)	12 (14.3)	
Emergency	5 (5.9)	8 (9.5)	
BITA use	31 (36.5)	26 (31.0)	0.45
Intraoperative steroid use	21 (24.7)	32 (38.1)	0.06
On-pump or off-pump			
On-pump	20 (23.5)	34 (40.5)	0.02
On-pump beating	3 (3.5)	3 (3.6)	
Off-pump	62 (72.9)	47 (56.0)	

Data given as mean±SD or n (%). HD, hemodialysis. Other abbreviations as in Tables 1,4.

Table 7. Adverse Events in Severe CKD vs. Need for HD

Events and outcomes	Severe CKD (n=169)	
	HD (–) (n=85)	HD (+) (n=84)
Perioperative MI	0	2 (2.4)
Related death	0	0
Cerebrovascular events	1 (1.2)	0
Related death	0	0
Other cardiovascular events	2 (2.4)	1 (1.2)
Related death	0	0
Deep sternal wound infection	3 (3.5)	6 (7.1)
All infection	14 (16.5)	14 (16.7)
Related death	4 (4.7)	4 (4.8)
Postoperative ventilator time (h)	59.4†	54.1†
In-hospital death	6 (7.1)	4 (4.8)

Data given as n (%) or †mean. Abbreviations as in Tables 1,2,6.

congestive heart failure were correlated with elevated CKD, but there were no significant differences observed for preoperative hemoglobin A1c, prevalence of dyslipidemia, COPD, or status of operation (elective vs. emergency) among the groups. Preoperative oral steroid use was most common in the severe CKD group. BITA were used in the majority of patients in the normal and mild CKD groups (both >50%), but BITA use was less common in the severe CKD group (33.7%, P<0.01). In addition, the off-pump technique was less frequently used in the severe CKD group (64.5%) compared to the other groups (all >70%) although this was not statistically significant.

Perioperative adverse events are listed in Table 2. Although there were no correlations in terms of perioperative myocardial infarction and cerebrovascular accident, the risks of acute kidney injury, all infections including anterior mediastinitis, and in-hospital death increased significantly as CKD progressed (Figure). In addition, postoperative mechanical ventilator support time became significantly longer as CKD progressed. Notably, the risk of infection was more than double even in the mild CKD group (7.0%) and more than 5-fold in the severe CKD group (17%), compared to that in the normal group (3.3%). The in-hospital mortality rate was extremely high in the severe CKD group (5.9%) compared to that in the other groups (<2%). Of note, there were too few events in each subgroup to conduct any meaningful statistical analysis of the data in Table 2.

Multivariate logistic regression results are listed in Tables 3–5. Moderate CKD and severe CKD were found to be very strong predictors for risk of postoperative acute kidney injury (OR, 5.10, P=0.04 and OR, 14.82, P<0.01, respectively). Also, advanced age was a significant predictor for acute kidney injury (OR, 2.30; P=0.02). With regard to all infections (Table 4), the significant risk factors were severe CKD (OR, 2.48; P<0.01) and COPD (OR, 1.95; P=0.03). Also, the use of BITA was found to be a risk factor for infection (OR, 1.57; P=0.04). In contrast, male gender (OR, 0.60; P=0.02), off-pump technique (OR, 0.53; P=0.01), and intraoperative steroid use (OR, 0.62; P=0.04) were protective factors for infection. As shown in Table 5, the significant risk factors for in-hospital death were severe CKD (OR, 3.29; P=0.02), congestive heart failure (OR, 3.37; P<0.01), and COPD (OR, 3.91; P<0.01) on multivariate analysis. Of note, off-pump technique (OR, 0.30; P<0.01) was identified as a protective factor against in-hospital death.

In the severe CKD group, 84 patients were dependent on HD preoperatively. We divided these severe CKD patients into 2 subgroups: HD dependent (HD subgroup, n=84) and those who were not (non-HD subgroup, n=85). Baseline patient characteristics are listed in Table 6. Mean eGFR was $22.0 ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in the non-HD subgroup and $6.7 ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in the HD subgroup. HD patients were much younger, and male gender was more predominant. There was no difference in the prevalence of hypertension or DM between these subgroups, but preoperative hemoglobin A1c was significantly higher in the non-HD patients than in the HD patients (6.3% vs. 5.7%, P<0.01). Also, prevalence of COPD was much higher in the non-HD subgroup. Notably, the off-pump technique was less commonly used in the HD subgroup than in the non-HD subgroup (56.0% vs. 72.9%), although this was not statistically significant. Perioperative adverse events are listed in Table 7. Cardiovascular adverse events were rare, but all infections were common in both subgroups. In particular, deep sternal wound infection was more common in the HD subgroup (n=6, 7.1%) than in the non-HD subgroup (n=3, 3.5%). In contrast, in-hospital mortality was somewhat higher in the non-HD subgroup (n=6, 7.1%) than in the HD subgroup (n=4, 4.8%). Statistical analysis between 2 subgroups was not performed because there were too few events and the patient clinical features were so different.

Discussion

It is widely recognized that preoperative CKD is common among patients who require both surgical and interventional

coronary revascularization. A large-scale cohort study using the STS National database in the USA found that 51% of CABG patients had mild CKD, 24% had moderate CKD, 2% had severe CKD (excluding HD), and 1.5% of patients were HD dependent.[15] The prevalence of mild CKD in the current study (47%) was similar to that of the STS database, but the prevalence of moderate CKD and severe CKD including HD was higher in the present study, found in 34% and 11% of patients, respectively, than in the STS database (24% and 2.5%). In general, the prevalence of DM increases significantly as CKD advances. In the STS database, the prevalence of DM was 29.5% in the normal group, 25.8% in the mild CKD group, 35.3% in the moderate CKD group, and 62.6% in the severe CKD group. The prevalence of DM was lower in the STS database study at each CKD level compared to the present cohort (Table 1). In contrast, there were no significant differences in age or prevalence of peripheral artery disease between the 2 cohorts. This may reflect the fact that we Japanese cardiac surgeons are dealing with a more severely affected patient in current practice.

In terms of postoperative complications, the risk of cardiovascular events, including perioperative cerebrovascular accident and myocardial infarction, was not significantly correlated with preoperative CKD level. The risk of all infection, however, was strongly correlated with CKD level. Importantly, in even mild CKD patients, the risk of infection was more than double that in the normal group. Furthermore, the risk of infection was more than 5-fold higher in severe CKD patients than in normal patients. Accordingly, the risk of deep sternal wound infection was much higher in moderate and severe CKD patients. On multivariate analysis, severe CKD was found to be an independent predictor for infection (OR, 2.48; P<0.01). In addition to severe CKD, COPD and BITA use were identified as risk factors for infection on multivariate analysis (OR, 1.95, P=0.03 and OR, 1.57, P=0.04, respectively). In general, we have been very aggressive in using BITA. In the present study, the majority of normal and mild CKD patients received BITA grafting. As shown in Table 1, BITA use was significantly lower in the moderate and severe CKD groups. Although the use of BITA in high-risk patients with moderate or severe CKD had apparently been limited, BITA use still emerged as a risk factor for infection. The risk of in-hospital death was acceptable in the normal, mild, and moderate CKD groups (all <2%), but in-hospital mortality was extremely high (5.9%) in the severe CKD group. These results are consistent with those of other studies.[16–19] In the current study, the majority of deaths in severe CKD patients were related to infection (80%; Table 2). More strict intra- and postoperative blood glucose control might have reduced the risk of infection and in-hospital mortality, especially in the moderate and severe CKD groups,[20] although we were not able to identify an influence of postoperative blood glucose control level on postoperative infection in the previous analysis.[13]

It is now evident that CKD level has a significant impact on CABG outcome.[15,21] In particular, severe CKD is associated with much higher morbidity and mortality; but despite having analyzed the differences between the HD and non-HD patients in the severe CKD group, it is still unclear how preoperative HD status influences CABG outcome. As shown in Table 6, baseline characteristics were very different between the HD and non-HD subgroups.[22] This may indicate that the HD subgroup was more heterogeneous. In fact, ESRD requiring HD could be caused by either DM nephropathy or other kidney disease such as chronic glomerulonephritis. Obviously, those patients with chronic glomerulonephritis tend to be relatively young, non-diabetic, and have less likelihood of complications involving severe atherosclerotic disease of the carotid and/or peripheral arteries, and would be expected to have better long-term survival. In terms of postoperative complications, infection was very common in both groups. Importantly, deep sternal wound infection was higher in the HD subgroup (7.1%) than that in non-HD subgroup (3.5%), but in-hospital mortality was higher in the non-HD subgroup (7.1%) than that in HD subgroup (4.8%). It is possible that non-HD severe CKD patients are more likely to develop acute kidney injury after surgery, subsequently requiring HD. During the period of intensive care, including renal replacement therapy, non-HD severe CKD patients may be more likely to develop infections through a vascular access or a mechanical ventilator. Although the lack of detailed analysis precludes further discussion of results in this regard, it appears that non-HD severe CKD patients have at least as bad a short- and long-term prognosis as HD patients.[15,18,23] Cooper et al found that the use of ITA lessened operative mortality in both non-HD severe CKD patients and HD patients.[15] In addition, Nakayama et al showed that BITA use might improve long-term survival in HD patients undergoing CABG.[23] Further study however, failed to demonstrate an advantage of BITA grafting for long-term outcome.[24] Decisions regarding use of BITA should always weigh the long-term benefits vs. the risk of deep sternal wound infection, which directly affects short-term outcome, in each patient.

In Japan, the off-pump technique is very commonly used when performing CABG.[25] In a prospective randomized study, Modine et al found that the off-pump technique lessens subclinical acute kidney injury in DM patients undergoing CABG.[26] The incidence of postoperative acute kidney injury was very low in the normal and mild CKD groups in the present study, whereas 1.7% and 4.1% of patients developed this complication in the moderate and severe CKD groups, respectively. Our aggressive use of the off-pump technique may have resulted in this low incidence of acute kidney injury, given the fact that approximately 10% of severe CKD patients required HD after surgery in the STS database. In HD patients, however, it appears that surgeons tended to be less aggressive in using the off-pump technique, likely due to the presence of more severe CADs such as diffuse, calcified and complex lesions. On multivariate analysis, off-pump technique was found to be a protective factor for risk of infection and in-hospital death. Dewey et al showed that off-pump CABG improved the early mortality rate compared to on-pump CABG in HD patients, but long-term survival was better in the on-pump CABG group.[27] Also, Boulton et al showed that long-term survival was significantly lower in off-pump CABG in patients with mild to moderate CKD compared to that of on-pump CABG.[28] Surgeons should keep in mind that complete revascularization in patients undergoing CABG always yields a survival benefit.

Study Limitations

There are several limitations to this study. This was a retrospective, observational study, so the various unknown patient selection processes may have caused a bias. The definition of CKD was based only on preoperative eGFR, not evaluated with baseline diseases or presence of proteinuria. Although the total number of patients was sufficient to analyze the influence of CKD level as a predictor of in-hospital mortality and risk of infection, it was not sufficiently large to allow detailed subgroup analysis between HD and non-HD patients in order to identify the impact of HD. Also, this study was based on post-hoc analyses, and was not designed to evaluate long-term outcome, which may be more important to assess the true influ-

ence of preoperative CKD level.

Conclusions

Preoperative CKD was very common in patients undergoing CABG, and advanced CKD was a strong predictor of postoperative infection, acute kidney injury and in-hospital death.

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