Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Patients With Versus Without Chronic Kidney Disease

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Chronic kidney disease (CKD) might be an important determinant in choosing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). However, there is a scarcity of studies evaluating the effect of CKD on long-term outcomes after PCI relative to CABG in the population including severe CKD. Among 30257 consecutive patients patients who underwent first coronary revascularization with PCI or isolated CABG in the CREDO-Kyoto PCI/CABG registry Cohort-2 (n = 15330) and Cohort-3 (n = 14,927), we identified the current study population of 12,878 patients with multivessel or left main disease, and compared long-term clinical outcomes between PCI and CABG stratified by the subgroups based on the stages of CKD (no CKD: eGFR >=60 ml/min/1.73m^2, moderate CKD: 60> eGFR >=30 ml/min/1.73m^2, and severe CKD: eGFR <30 ml/min/1.73m^2 or dialysis). There were 6,999 patients without CKD (PCI: n = 5,268, and CABG: n = 1,731), 4,427 patients with moderate CKD (PCI: n = 3,226, and CABG: n = 1,201), and 1,452 patients with severe CKD (PCI: n = 989, and CABG: n = 463). During median 5.6 years of follow-up, the excess mortality risk of PCI relative to CABG was significant regardless of the stages of CKD without interaction (no CKD: HR, 1.36; 95%CI, 1.12 to 1.65; p = 0.002, moderate CKD: HR, 1.40; 95%CI, 1.17 to 1.67; p <0.001, and severe CKD: HR, 1.33; 95%CI, 1.09 to 1.62; p = 0.004, Interaction p = 0.83). There were no significant interactions between CKD and the effect of PCI relative to CABG for all the outcome measures evaluated. In conclusion, PCI compared with CABG was associated with significantly higher risk for all-cause death regardless of the stages of CKD without any significant interaction. **(Am J Cardiol 2021;145:37−46)**

Chronic kidney disease (CKD) is an increasingly prevalent condition in the rapidly aging societies and is strongly associated with increased cardiovascular morbidity and mortality.[1] CKD might be an important determinant in choosing coronary revascularization modalities. However, the optimal revascularization strategy for coronary artery disease (CAD) in patients with CKD is still controversial, because previous randomized controlled trials (RCTs)

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This study was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan (Tokyo, Japan).

See page 44 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.12.079

comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) have included only a very small proportion of patients with CKD, especially severe CKD.[2–7] Some observational studies have suggested that CABG had significant long-term survival benefit as compared with PCI in CAD patients with CKD,[8–10] although there are a few reports that PCI had comparable long-term survival outcomes in comparison with CABG in patients with multivessel disease and CKD.[11–13] Moreover, there is a scarcity of studies evaluating the effect of CKD on long-term clinical outcomes after PCI relative to CABG in the population including severe CKD. Therefore, we sought to evaluate long-term clinical outcomes after PCI relative to CABG in patients with multivessel CAD or left main coronary artery disease (LMCAD) stratified by the stages of CKD in a pooled population of 2 large-scale, all-comer registries of patients patients who underwent first coronary revascularization in Japan (CREDO-Kyoto PCI/CABG registry Cohort-2 and Cohort-3).

Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry Cohort-2 and Cohort-3 are physician-initiated, noncompany-sponsored, multicenter registries enrolling consecutive patients who underwent first coronary revascularization with PCI or isolated CABG without combined non-coronary surgery in the first-generation drug-eluting stents (DES) era (January 2005-December 2007) for Cohort-2 and in the new-generation DES era (January 2011-Decemver 2013) for Cohort-3 (Supplemental Appendix A). Of a total of 30,257 patients enrolled in the registries (Cohort-2: n = 15,330, and Cohort-3: n = 14,927), we excluded those patients who refused study participation (Cohort-2: n = 99, and Cohort-3: n = 60), acute myocardial infarction (Cohort-2: n = 4,892, and Cohort-3: n = 5,510), 1-vessel disease (Cohort-2: n = 3,431, and Cohort-3: n = 3,341), and without information on baseline estimated glomerular filtration rate (eGFR) (Cohort-2: n = 34, and Cohort-3: n = 12), and the current study population consisted of 12,878 patients with multivessel CAD or LMCAD (Figure 1). In the present study, we compared long-term clinical outcomes between PCI and CABG stratified by the stages of CKD at the index procedure (no CKD: eGFR >=60 ml/min/1.73m^2, moderate CKD: 60> eGFR >=30 ml/min/1.73m^2, and severe CKD: eGFR <30 ml/min/1.73m^2 or dialysis).

The relevant ethics committees in all the participating centers approved the study protocol. Because of the retrospective enrollment, written informed consents from the patients were waived; however, we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

Baseline eGFR was calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.[14] The primary outcome measure of this study was all-cause death. The secondary outcome measures included cardiovascular death, non-cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, major bleeding, and any coronary revascularization. Definitions

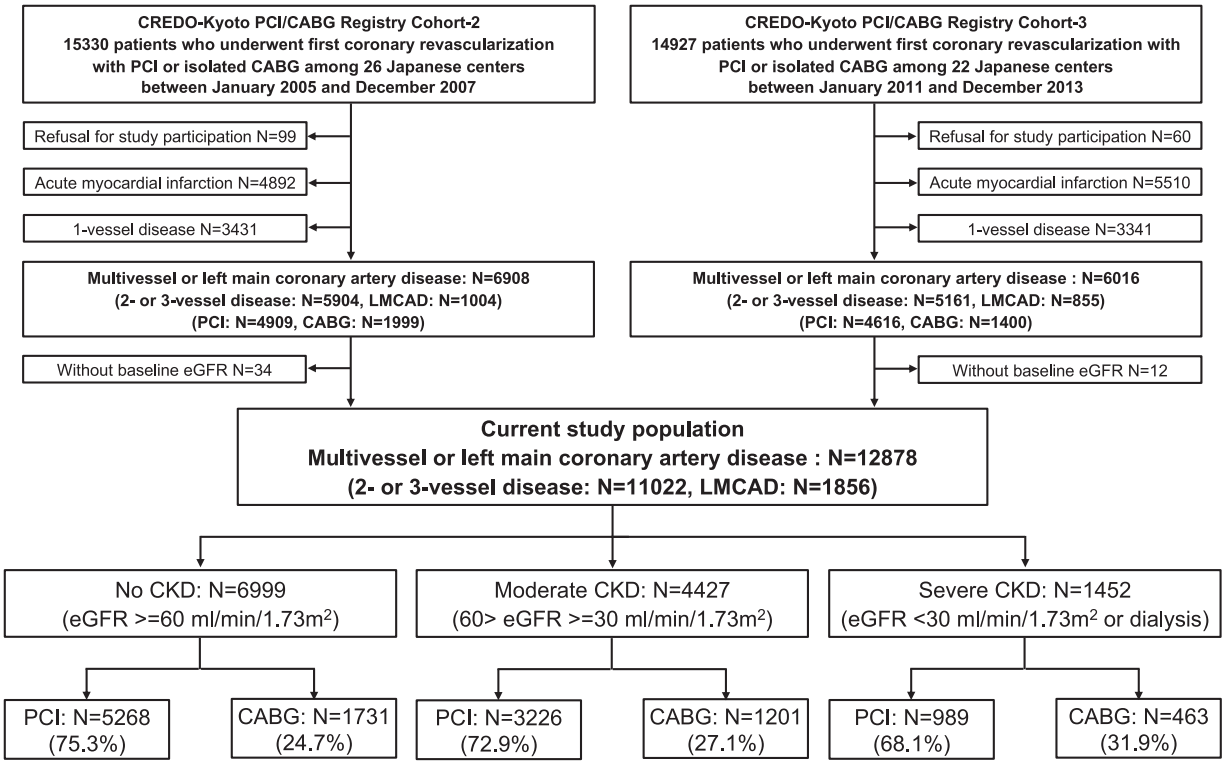


Figure 1. Study flowchart. CABG=coronary artery bypass grafting; CKD=chronic kidney disease; CREDO-Kyoto=Coronary Revascularization Demonstrating Outcome study in Kyoto; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention; LMCAD = left main coronary artery disease.

of the outcome measures were described in the Supplemental Methods.

Clinical, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by the experienced clinical research coordinators belonging to an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix). Follow-up data were collected from the hospital charts and/or obtained by contacting with patients, their relatives or referring physicians. The clinical event committee adjudicated those events such as death, myocardial infarction, stroke, and major bleeding (Supplemental Appendix).

Categorical variables were presented as number and percentage, and compared with the chi-square test. Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR). Continuous variables were compared with the Student's *t* test or Wilcoxon rank sum test based on their distributions. Cumulative incidence of the outcome measures was estimated by the Kaplan-Meier method, and the differences were assessed with the log-rank test. The effects of PCI relative to CABG for the outcome measures were estimated by the Cox proportional hazard models throughout the entire follow-up period, and were expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs). The adjusted HRs were estimated by the multivariable Cox proportional hazard models adjusting for the 24 clinically relevant factors listed in Table 1. Continuous variables were dichotomized by clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with our previous reports.[15] The study variable was also incorporated as an adjusting variable because the proportional hazard assumptions for study variable as well as other risk adjusting variables were acceptable with the plots of log (time) versus log (-log [survival]) stratified by the variables. We evaluated the outcomes after PCI relative to CABG stratified by the stages of CKD. We estimated the interaction p-values between the stages of CKD and the effect of PCI relative to CABG on the clinical outcome measures in the multivariable Cox proportional hazard models. Statistical analyses were performed with JMP 14.0 software (SAS Institute, Inc., Cary, North California). All statistical analyses were 2 tailed, and p values of <0.05 were considered statistically significant.

Results

In the present study population of 12878 patients, there were 6999 patients without CKD (eGFR >=60 ml/min/1.73m^2) (PCI: n = 5,268, and CABG: n = 1,731), 4,427 patients with moderate CKD (60> eGFR >=30 ml/min/1.73m^2) (PCI: n = 3,226, and CABG: n = 1,201), and 1,452 patients with severe CKD (eGFR <30 ml/min/1.73m^2 or dialysis) (PCI: n = 3,226, and CABG: n = 1,201). PCI was less often selected as the renal function deteriorated (no CKD: 75.3%, moderate CKD: 72.9%, and severe CKD: 68.1%, p <0.001).

Patients with CKD were older, and more often women, and more often had low body weight, hypertension, diabetes, heart failure, systolic dysfunction, mitral regurgitation, prior myocardial infarction, prior stroke, peripheral vascular disease, anemia, thrombocytopenia, liver cirrhosis, and 3-vessel disease than those without CKD (Supplemental Table 1).

In patients both with and without CKD, patients in the PCI group were older, but less often had diabetes, heart failure, and prior myocardial infarction than those in the CABG group (Table 1). Regarding angiographic and procedural characteristics, the CABG group compared with the PCI group had greater number of target lesions or anastomoses and chronic total occlusion targets regardless of CKD stages (Table 1). Statins, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, and calcium channel blockers were more often prescribed in the PCI group than in the CABG group, while nicorandil, oral anticoagulants, and proton pump inhibitors were more often prescribed in the CABG group than in the PCI group regardless of CKD stages (Table 1).

Median follow-up for survivors was 5.6 (IQR: 4.8 to 6.4) years in the entire cohort (Cohort-2: 5.4 [IQR: 4.6 to 6.1] years, and Cohort-3: 6.0 [IQR: 5.1 to 6.8] years): 5.7 (IQR: 4.8 to 6.5) years in patients without CKD, 5.6 (IQR: 4.8 to 6.4) years in patients with moderate CKD, and 5.4 (IQR: 4.6 to 6.3) years in patients with severe CKD. Complete 1-, 3-, and 5-year clinical follow-up information were obtained in 97.9%, 96.0%, and 75.4% of patients in patients without CKD, 97.5%, 95.1%, and 76.2% in patients with moderate CKD, and 96.8%, 93.6%, and 80.4% in patients with severe CKD. Complete 1- and 3-year clinical follow-up rates were lower in the CABG group than in the PCI group (95.4% vs 98.5%, and 93.4% vs 96.2%), while complete 5-year clinical follow-up rate was similar in the CABG and PCI groups (76.5% vs 76.2%). Follow-up information for Cohort-2 and Cohort-3 was described in the Supplemental Materials.

The cumulative 5-year incidence of all-cause death was significantly higher in the PCI group than in the CABG group in patients without CKD and with severe CKD, and trended to be higher in the PCI group than in the CABG group in patients with moderate CKD (11.1% vs 9.7%, log-rank p = 0.03, 48.1% versus 41.2%, log-rank p = 0.01, and 19.5% versus 17.1%, log-rank p = 0.15, respectively) (Figure 2). After adjusting confounders, the excess mortality risk of PCI relative to CABG was significant regardless of the stages of CKD without any significant interaction (no CKD: HR, 1.36; 95% CI, 1.12 to 1.65; p = 0.002, moderate CKD: HR, 1.40; 95% CI, 1.17 to 1.67; p <0.001, and severe CKD: HR, 1.33; 95% CI, 1.09 to 1.62; p = 0.004, Interaction p = 0.83) (Figure 3). The excess risk of PCI relative to CABG for cardiovascular and non-cardiovascular death also trended to be higher in the PCI group than in the CABG regardless of the stages of CKD without interaction (Interaction p = 0.65, and p = 0.57) (Figure 3).

Regardless of the stages of CKD, the excess risk of PCI relative to CABG was significant for myocardial infarction, hospitalization for heart failure, and any coronary revascularization, while the lower risk of PCI relative to CABG was significant for major bleeding (Figure 3). The excess risk of PCI relative to CABG was significant for stroke in patients with moderate CKD, but not in patients without CKD and with severe CKD (Figure 3). There were no significant interactions between CKD and the effect of PCI relative to CABG for all these outcome measures (Figure 3).

Table 1
Baseline characteristics and management during the index hospitalization

	No CKD (n = 6,999)			Moderate CKD (n = 4,427)			Severe CKD (n = 1,452)		
	PCI (n = 5,268)	CABG (n = 1,731)	p value	PCI (n = 3,226)	CABG (n = 1,201)	p value	PCI (n = 989)	CABG (n = 463)	p value
(A) Clinical characteristics									
Age (years)	67.7±10.2	66.9±9.5	0.009	73.5±8.8	71.2±8.4	<0.001	70.5±10.7	69.2±9.0	0.02
Age >=75*	1,430 (27.1%)	390 (22.5%)	<0.001	1,538 (47.7%)	471 (39.2%)	<0.001	399 (40.3%)	136 (29.4%)	<0.001
Men*	3,923 (74.5%)	1,324 (76.5%)	0.09	2,214 (68.6%)	919 (76.5%)	<0.001	659 (66.6%)	336 (72.6%)	0.02
Body mass index (kg/m^2)	24.0±3.6	23.6±3.3	<0.001	23.9±3.5	23.7±3.3	0.054	22.8±3.8	22.9±3.4	0.71
<25.0*	3,428 (65.1%)	1,190 (68.7%)	0.005	2,115 (65.6%)	820 (68.3%)	0.09	758 (76.6%)	357 (77.1%)	0.85
Unstable angina pectoris	347 (6.6%)	107 (6.2%)	0.55	184 (5.7%)	64 (5.3%)	0.63	57 (5.8%)	40 (8.6%)	0.04
Hypertension*	4,376 (83.1%)	1407 (81.3%)	0.09	2,888 (89.5%)	1,040 (86.6%)	0.006	904 (91.4%)	409 (88.3%)	0.06
Diabetes mellitus*	2,228 (42.3%)	817 (47.2%)	<0.001	1,437 (44.5%)	616 (51.3%)	<0.001	622 (62.9%)	298 (64.4%)	0.59
on insulin	466 (8.8%)	252 (14.6%)	<0.001	371 (11.5%)	217 (18.1%)	<0.001	285 (28.8%)	138 (29.8%)	0.7
Current smoker*	1424 (27.0%)	399 (23.1%)	0.001	598 (18.5%)	233 (19.4%)	0.51	187 (18.9%)	85 (18.4%)	0.8
Heart failure*	625 (11.9%)	256 (14.8%)	0.002	757 (23.5%)	331 (27.6%)	0.005	393 (39.7%)	186 (40.2%)	0.87
LVEF (%)	61.3±12.3	61.1±12.9	0.51	59.2±13.9	57.6±14.6	0.002	54.3±14.4	54.3±14.4	0.97
LVEF <=40%	313 (6.9%)	128 (7.8%)	0.19	325 (11.7%)	171 (15.0%)	0.004	151 (18.5%)	88 (20.0%)	0.49
Mitral regurgitation grade >=3/4	198 (4.0%)	54 (3.2%)	0.13	225 (7.5%)	66 (5.6%)	0.03	117 (12.8%)	36 (7.9%)	0.007
Prior myocardial infarction*	862 (16.4%)	345 (19.9%)	0.001	668 (20.7%)	306 (25.5%)	0.001	216 (21.8%)	115 (24.8%)	0.2
Prior stroke (symptomatic)*	600 (11.4%)	220 (12.7%)	0.14	565 (17.5%)	210 (17.5%)	0.98	224 (22.6%)	93 (20.1%)	0.27
Peripheral vascular disease*	505 (9.6%)	179 (10.3%)	0.36	458 (14.2%)	172 (14.3%)	0.92	217 (21.9%)	80 (17.3%)	0.04
Hemodialysis	-	-	-	-	-	-	568 (57.4%)	240 (51.8%)	0.046
Anemia (Hemoglobin <11.0 g/dL)*	331 (6.3%)	157 (9.1%)	<0.001	511 (15.8%)	208 (17.3%)	0.24	549 (55.5%)	256 (55.3%)	0.94
Thrombocytopenia (Platelet <100 × 10^9/L)*	57 (1.1%)	30 (1.7%)	0.03	48 (1.5%)	22 (1.8%)	0.41	54 (5.5%)	28 (6.0%)	0.65
Chronic obstructive pulmonary disease*	197 (3.7%)	67 (3.9%)	0.8	130 (4.0%)	51 (4.2%)	0.75	34 (3.4%)	12 (2.6%)	0.39
Liver cirrhosis*	155 (2.9%)	55 (3.2%)	0.62	76 (2.4%)	30 (2.5%)	0.78	41 (4.1%)	16 (3.5%)	0.53
Malignancy*	600 (11.4%)	175 (10.1%)	0.14	424 (13.1%)	133 (11.1%)	0.06	119 (12.0%)	63 (13.6%)	0.4
(B) Procedural characteristics									
Number of target coronary narrowings or anastomoses	1.8±0.9	3.3±1.0	<0.001	1.8±0.9	3.2±1.0	<0.001	1.7±0.8	3.2±1.0	<0.001
Proximal LAD target*	3324 (63.1%)	1495 (86.4%)	<0.001	1922 (59.6%)	1058 (88.1%)	<0.001	571 (57.7%)	412 (89.0%)	<0.001
Chronic total occlusion target*	1,035 (19.6%)	703 (40.6%)	<0.001	603 (18.7%)	518 (43.1%)	<0.001	158 (16.0%)	175 (37.8%)	<0.001
Emergency procedure	342 (6.5%)	86 (5.0%)	0.02	160 (5.0%)	46 (3.8%)	0.11	42 (4.2%)	23 (5.0%)	0.54
Number of coronary arteries narrowed			<0.001			<0.001			<0.001
2	2,988 (56.7%)	196 (11.3%)		1712 (53.1%)	120 (10.0%)		482 (48.7%)	38 (8.2%)	
3	1,875 (35.6%)	945 (54.6%)		1,260 (39.1%)	695 (57.9%)		420 (42.5%)	291 (62.9%)	
LMCA	405 (7.7%)	590 (34.1%)		254 (7.9%)	386 (32.1%)		87 (8.8%)	134 (28.9%)	
Total number of coronary stents	2 (1-3)	-	-	2 (1-3)	-	-	2 (1-3)	-	-
Total stent length (mm)	45 (24-72)	-	-	41 (23-69)	-	-	41 (23-66)	-	-
Stent use	5,082 (96.5%)	-	-	3,099 (96.1%)	-	-	935 (94.5%)	-	-
DES use	4,219 (80.1%)	-	-	2,576 (79.9%)	-	-	790 (79.9%)	-	-
New-generation DES use	2,259 (42.9%)	-	-	1,384 (42.9%)	-	-	431 (43.6%)	-	-
IVUS use	3,356 (63.7%)	-	-	2,100 (65.1%)	-	-	620 (62.7%)	-	-
Staged PCI	1,764 (33.5%)	-	-	1,000 (31.0%)	-	-	261 (26.4%)	-	-
Internal thoracic artery graft use	-	1,695 (97.9%)	-	-	1,175 (97.8%)	-	-	450 (97.2%)	-

(*continued on next page*)

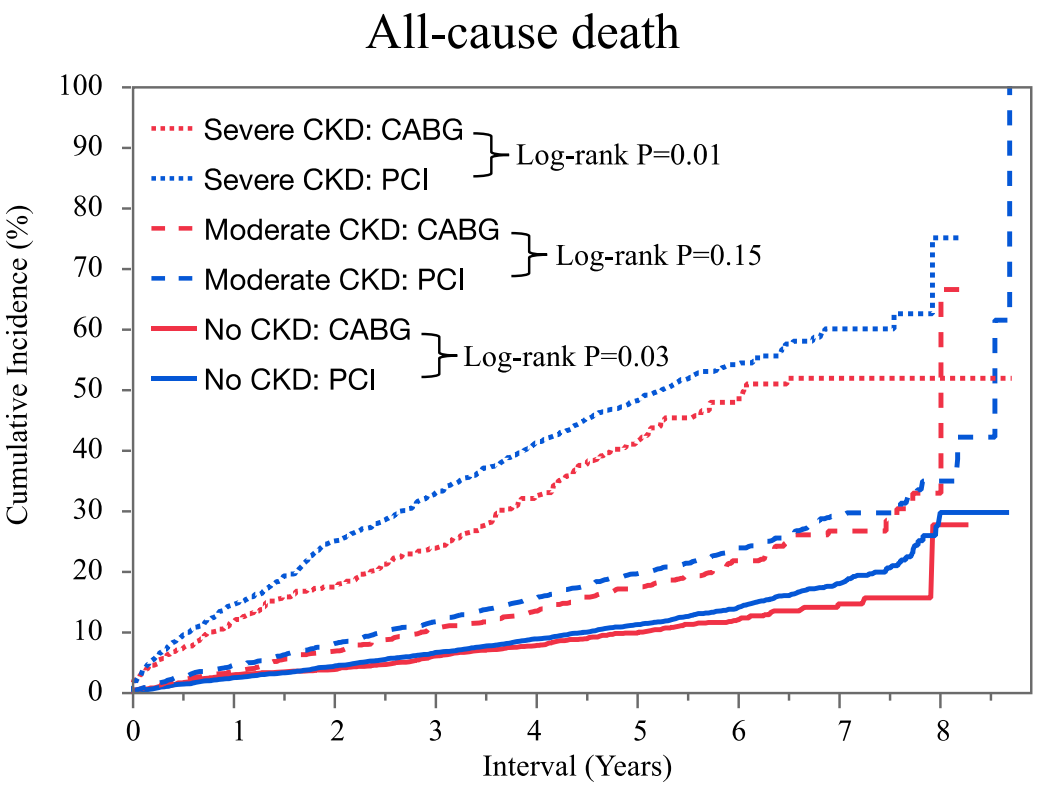
Table 1 (***Continued***)

	No CKD (n = 6,999)			Moderate CKD (n = 4,427)			Severe CKD (n = 1,452)		
	PCI (n = 5,268)	CABG (n = 1,731)	p value	PCI (n = 3,226)	CABG (n = 1,201)	p value	PCI (n = 989)	CABG (n = 463)	p value
Off pump surgery	-	1,081 (62.4%)	-	-	744 (61.9%)	-	-	293 (63.3%)	-
(C) Baseline medications									
Thienopyridine	5,216 (99.0%)	254 (14.7%)	<0.001	3,192 (98.9%)	172 (14.3%)	<0.001	976 (98.7%)	71 (15.3%)	<0.001
Ticlopidine	2,477 (47.0%)	106 (6.1%)		1,524 (47.2%)	75 (6.2%)		466 (47.1%)	32 (6.9%)	
Clopidogrel	2,716 (51.6%)	148 (8.5%)		1,663 (51.5%)	96 (8.0%)		509 (51.5%)	39 (8.4%)	
Unknown	23 (0.4%)	0 (0%)		5 (0.2%)	1 (0.1%)		1 (0.1%)	0 (0%)	
Aspirin	5,219 (99.1%)	1,715 (99.1%)	0.98	3,186 (98.8%)	1,174 (97.8%)	0.01	973 (98.4%)	451 (97.4%)	0.21
Cilostazol	361 (6.9%)	80 (4.6%)	0.001	233 (7.2%)	69 (5.7%)	0.08	81 (8.2%)	40 (8.6%)	0.77
Statins*	3,566 (67.7%)	833 (48.1%)	<0.001	1,997 (61.9%)	519 (43.2%)	<0.001	417 (42.2%)	151 (32.6%)	0.001
High-intensity statins†	101 (1.9%)	11 (0.6%)	<0.001	40 (1.2%)	7 (0.6%)	0.06	10 (1.0%)	3 (0.6%)	0.49
Beta-blockers*	1,451 (27.5%)	666 (38.5%)	<0.001	1,095 (33.9%)	426 (35.5%)	0.34	359 (36.3%)	174 (37.6%)	0.64
ACE-I/ARB*	2,786 (52.9%)	474 (27.4%)	<0.001	2,035 (63.1%)	384 (32.0%)	<0.001	535 (54.1%)	169 (36.5%)	<0.001
Nitrates	1,686 (32.0%)	430 (24.8%)	<0.001	1,059 (32.8%)	323 (26.9%)	<0.001	317 (32.1%)	114 (24.6%)	0.004
Calcium channel blockers*	2,581 (49.0%)	748 (43.2%)	<0.001	1,728 (53.6%)	556 (46.3%)	<0.001	589 (59.6%)	241 (52.1%)	0.007
Nicorandil	1,073 (20.4%)	642 (37.1%)	<0.001	689 (21.4%)	475 (39.6%)	<0.001	213 (21.5%)	188 (40.6%)	<0.001
Oral anticoagulants*	343 (6.5%)	759 (43.8%)	<0.001	329 (10.2%)	515 (42.9%)	<0.001	96 (9.7%)	189 (40.8%)	<0.001
Warfarin	311 (5.9%)	749 (43.3%)	<0.001	303 (9.4%)	514 (42.8%)	<0.001	96 (9.7%)	189 (40.8%)	<0.001
DOAC	32 (0.6%)	10 (0.6%)	0.89	27 (0.8%)	1 (0.1%)	0.005	0 (0%)	0 (0%)	NA
Proton pump inhibitors or histamine type-2 receptor blockers*	2,921 (55.4%)	1,442 (83.3%)	<0.001	1,849 (57.3%)	976 (81.3%)	<0.001	669 (67.6%)	377 (81.4%)	<0.001
Proton pump inhibitors	2,017 (38.3%)	1,036 (59.8%)	<0.001	1,278 (39.6%)	686 (57.1%)	<0.001	524 (53.0%)	294 (63.5%)	<0.001
Histamine type-2 receptor blockers	924 (17.5%)	410 (23.7%)	<0.001	583 (18.1%)	294 (24.5%)	<0.001	148 (15.0%)	86 (18.6%)	0.08
(D) Study*									
Cohort-2	2,744 (52.1%)	987 (57.0%)	<0.001	1,648 (51.1%)	735 (61.2%)	<0.001	486 (49.1%)	274 (59.2%)	<0.001
Cohort-3	2,524 (47.9%)	744 (43.0%)		1,578 (48.9%)	466 (38.8%)		503 (50.9%)	189 (40.8%)	

Continuous variables were expressed as mean ± standard deviation, or median (interquartile range). Categorical variables were expressed as number (percentage). Values were missing for LVEF in 1518 patients, and for mitral regurgitation in 689 patients.

* Risk adjusting variables selected for the Cox proportional hazard models.

† High-intensity statin therapy was defined as the statin doses greater than or equal to atorvastatin 20 mg, pitavastatin 4 mg, or rosuvastatin 10 mg. ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; DES = drug-eluting stent; DOAC = direct oral anticoagulants; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.



Interval	0 day	30 days	1 year	3 years	5 years
Severe CKD: CABG group					
N of patients at risk	463	444	384	320	201
Cumulative incidence		2.6%	11.7%	23.7%	41.2%
Severe CKD: PCI group					
N of patients at risk	989	957	831	624	348
Cumulative incidence		2.6%	14.5%	32.6%	48.1%
Moderate CKD: CABG group					
N of patients at risk	1201	1172	1114	1007	733
Cumulative incidence		0.5%	3.4%	10.6%	17.1%
Moderate CKD: PCI group					
N of patients at risk	3226	3195	3027	2720	1860
Cumulative incidence		0.5%	4.4%	11.6%	19.5%
No CKD: CABG group					
N of patients at risk	1731	1693	1605	1524	1143
Cumulative incidence		0.5%	2.8%	5.9%	9.7%
No CKD: PCI group					
N of patients at risk	5268	5247	5084	4768	3426
Cumulative incidence		0.2%	2.3%	6.5%	11.1%

Figure 2. Kaplan-meier event curves for all-cause death in patients with no CKD, moderate CKD, and Severe CKD. CABG=coronary artery bypass grafting; CKD = chronic kidney disease; PCI = percutaneous coronary intervention.

Discussion

The main findings of this study comparing PCI with CABG in patients with multivessel CAD or LMCAD were as follows; (1) PCI compared with CABG was associated with significantly higher risk for all-cause death regardless of the stages of CKD; (2) There were no significant interactions between CKD and the effect of PCI relative to CABG for all the outcome measures evaluated.

Endpoints	PCI N of patients with event / N of patients at risk (Cumulative 5-year incidence)	CABG N of patients with event / N of patients at risk (Cumulative 5-year incidence)	Crude HR [95% CI]	P value	Adjusted HR [95% CI]	P value	P value for interaction
All-cause death							
No CKD	718/5268 (11.1%)	191/1731 (9.7%)	1.19 [1.02-1.40]	0.03	1.36 [1.12-1.65]	0.002	
Moderate CKD	717/3226 (19.5%)	238/1201 (17.1%)	1.12 [0.96-1.29]	0.14	1.40 [1.17-1.67]	<0.001	0.83
Severe CKD	496/989 (48.1%)	198/463 (41.2%)	1.24 [1.05-1.47]	0.01	1.33 [1.09-1.62]	0.004	
Cardiovascular death							
No CKD	287/5268 (4.4%)	91/1731 (5.1%)	1.00 [0.79-1.27]	0.998	1.28 [0.96-1.71]	0.09	
Moderate CKD	348/3226 (10.1%)	125/1201 (9.0%)	1.04 [0.85-1.27]	0.74	1.41 [1.09-1.81]	0.008	0.65
Severe CKD	332/989 (34.7%)	130/463 (28.9%)	1.26 [1.03-1.55]	0.02	1.40 [1.10-1.78]	0.007	
Non-cardiovascular death							
No CKD	431/5268 (7.0%)	100/1731 (4.9%)	1.36 [1.10-1.71]	0.004	1.41 [1.09-1.83]	0.01	
Moderate CKD	369/3226 (10.5%)	113/1201 (8.9%)	1.20 [0.98-1.49]	0.08	1.37 [1.07-1.77]	0.01	0.57
Severe CKD	164/989 (20.5%)	68/463 (17.2%)	1.20 [0.91-1.61]	0.19	1.22 [0.87-1.72]	0.25	
Myocardial infarction							
No CKD	278/5268 (4.8%)	44/1731 (2.6%)	2.04 [1.50-2.84]	<0.001	2.20 [1.53-3.18]	<0.001	
Moderate CKD	179/3226 (5.3%)	34/1201 (2.9%)	1.96 [1.38-2.87]	<0.001	2.11 [1.38-3.23]	0.001	0.3
Severe CKD	112/989 (13.4%)	18/463 (5.4%)	3.16 [1.97-5.38]	<0.001	3.00 [1.73-5.19]	<0.001	
Stroke							
No CKD	302/5268 (5.4%)	120/1731 (6.6%)	0.80 [0.65-0.99]	0.04	0.89 [0.68-1.15]	0.37	
Moderate CKD	273/3226 (8.3%)	96/1201 (7.3%)	1.06 [0.84-1.34]	0.64	1.39 [1.05-1.85]	0.02	0.34
Severe CKD	113/989 (13.2%)	54/463 (13.1%)	1.03 [0.75-1.44]	0.84	0.98 [0.66-1.45]	0.92	
Hospitalization for heart failure							
No CKD	317/5268 (5.5%)	92/1731 (4.9%)	1.09 [0.87-1.38]	0.45	1.37 [1.04-1.81]	0.03	
Moderate CKD	423/3226 (13.3%)	138/1201 (11.5%)	1.14 [0.94-1.39]	0.17	1.44 [1.14-1.82]	0.003	0.24
Severe CKD	234/989 (28.7%)	78/463 (20.2%)	1.52 [1.18-1.98]	0.001	1.58 [1.17-2.14]	0.003	
Major bleeding (GUSTO moderate or severe)							
No CKD	534/5268 (9.6%)	826/1731 (47.5%)	0.16 [0.15-0.18]	<0.001	0.16 [0.14-0.19]	<0.001	
Moderate CKD	498/3226 (15.7%)	731/1201 (60.5%)	0.18 [0.16-0.20]	<0.001	0.16 [0.14-0.19]	<0.001	0.2
Severe CKD	303/989 (36.7%)	405/463 (87.2%)	0.17 [0.14-0.20]	<0.001	0.15 [0.12-0.18]	<0.001	
Any coronary revascularization							
No CKD	2011/5268 (37.9%)	227/1731 (13.1%)	3.28 [2.86-3.77]	<0.001	3.62 [3.09-4.24]	<0.001	
Moderate CKD	1084/3226 (34.9%)	152/1201 (12.7%)	3.00 [2.54-3.57]	<0.001	3.30 [2.72-4.00]	<0.001	0.73
Severe CKD	411/989 (49.7%)	70/463 (18.0%)	3.55 [2.77-4.61]	<0.001	3.59 [2.69-4.79]	<0.001	

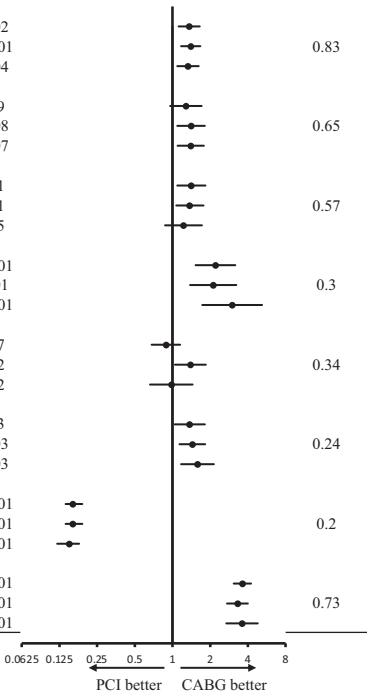


Figure 3. Forrest plots for the adjusted hazard ratios of PCI relative to CABG for clinical outcomes.
Number of patients with event was counted throughout the entire follow-up period, while the cumulative incidence was estimated at 5 years. The adjusted effects of PCI relative to CABG for the outcome measures were estimated by the multivariable Cox proportional hazard models throughout the entire follow-up period adjusting for the 24 clinically relevant factors listed in Table 1, and were expressed as HRs and their 95%CIs. CABG = coronary artery bypass grafting; CKD = chronic kidney disease; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR = hazard ratio; PCI = percutaneous coronary intervention.

The optimal revascularization strategy in patients with CKD is inconclusive, because previous RCTs comparing PCI with CABG have included only a very small proportion of patients with severe CKD.[2–7] Based on the favorable results of CABG relative to PCI in patients with CKD from some observational studies,[8–10] the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guideline have recommended that CABG is preferable over PCI in patients with CKD if the life expectancy is more than one year, while PCI is recommended in patients with a life expectancy of less than one year.[16–17] Consistent with the previous observational studies, CABG had long-term survival benefits compared with PCI in patients with moderate and severe CKD in the present study. Several pathophysiologic mechanisms could be postulated for the observed survival benefit of CABG over PCI in patients with CKD. First, CKD is characterized by an extensive atherosclerotic disease type and the benefits of CABG are most pronounced with complex CAD patients.[18] Second, increased atherosclerotic plaque vulnerability associated with CKD implies that the prophylactic effects of CABG for vulnerable lesions might be enhanced as the renal function deteriorates.[19] Indeed, the incidence of myocardial infarction in the PCI group was especially high in patients with severe CKD, and the lower risk of CABG relative to PCI for myocardial infarction was numerically greater in patients with severe CKD in the present study. A similar trend was also seen for hospitalization for heart failure, although the heart failure and systolic left ventricular dysfunction were more frequently seen in the CABG group than in the PCI group. The benefit of CABG relative to PCI for myocardial infarction and hospitalization for heart failure was consistent with the previous studies,[20–21] and more complete revascularization and more durable relief of myocardial ischemia achieved by CABG might be related to the survival benefit especially in patients with CKD. Third, it has been reported that the benefit of off-pump surgery was greater in patients with CKD than in those without,[22] and the higher prevalence of off-pump surgery in the present study might lead to the favorable results in CABG. On the other hand, some studies have suggested that CABG compared with PCI was associated with higher risks for periprocedural death and acute renal failure.[9,23] Acute renal failure requiring long-term dialysis is not a subtle issue, but is crucially important for patients, particularly for elderly patients. Appropriate shared decision-making for the selection of coronary revascularization modalities would be particularly important in patients with CKD considering the substantially higher procedural complications of CABG and shorter life expectancy after the procedures compared with those without CKD.

It is still uncertain whether the magnitude of survival benefit of CABG over PCI is greater in patients with CKD than in patients without CKD. Some previous studies have

suggested that the survival benefit of CABG compared with PCI tended to be greater as the renal function got worse,[23–25] and there was a significant interaction between CKD and the mortality risk of PCI relative to CABG with excess risk in patients with CKD and neutral risk in patients without CKD.[24–25] However, in the present study, which was the largest study evaluating the effect of CKD on mortality after PCI versus CABG in population including severe CKD, there was excess mortality risk of PCI relative to CABG regardless of the stage of CKD without any significant interaction. The selection of coronary revascularization modalities might not be based on renal function, but should be based on other characteristics such as age, diabetes, and coronary anatomic complexity.[18] Further RCTs are warranted to compare contemporary PCI and CABG in patients with CKD.

There are several important limitations in this study. First, patients were not randomly allocated to each coronary revascularization strategy, and we could not deny the presence of the unmeasured confounders, selection bias, and some ascertainment bias, although we conducted extensive multivariable adjustment for the known confounders. We could not assess important confounders such as frailty, cognitive impairment, and valvular disease, which might have great influence on the choice between PCI and CABG, as well as on clinical outcomes. There were trends for excess risk of PCI relative to CABG for non-cardiovascular death, suggesting that there could still be the presence of selection bias and/or unmeasured confounders. Second, we performed a pooled analysis of the 2 different cohorts, because the small sample sizes of the individual cohorts might be insufficient for the subgroup analysis stratified by the stage of CKD. Indeed, patients enrolled in Cohort-2 underwent PCI with bare-metal stents and first-generation DES, while those enrolled in Cohort-3 were mainly treated with new-generation DES. Third, the practice patterns in the present study were much different from the current practice. The assessment of lesion-specific ischemia by fractional flow reserve was performed only in a small proportion of patients in the PCI group. Duration of dual antiplatelet therapy after PCI was relatively long in the current study, although recent studies have suggested clinical benefit with very short duration of dual antiplatelet therapy after PCI.[26–27] Moreover, the prescription rate of high-intensity statin therapy was extremely low, although the efficacy of high-intensity statin therapy was established in preventing cardiovascular events in patients with CAD.[28–29] Finally, patient demographics and practice pattern in patients patients who underwent coronary revascularization in Japan are markedly different from those outside Japan, such as older age, lower body weight, and so on. Moreover, prescription rate of oral anticoagulants was high in the CABG group, which might be higher bleeding risk in these patients. After operative atrial fibrillation might be one of the reasons. Besides, oral anticoagulants might have been used for prevention of graft occlusion, although it is not recommended to use oral anticoagulants to improve graft patency in patients without an indication for anticoagulants.[30] Therefore, we should be cautious about extrapolating the present study results outside of Japan.

In conclusion, PCI compared with CABG was associated with significantly higher risk for all-cause death regardless of the stages of CKD without any significant interaction.

Author Credit Statement

Ko Yamamoto: Methodology, Formal analysis, Investigation, Data curation, Writing-Original Draft; Masahiro Natsuaki: Methodology, Data curation, Writing-Review and Editing; Takeshi Morimoto: Methodology, Formal analysis, Writing-Review and Editing, Supervision; Hiroki Shiomi: Investigation, Data curation, Supervision, Project administration; Yasuaki Takeji: Investigation, Data curation; Kazushige Kadota: Investigation, Resources; Kazuaki Imada: Investigation, Data curation; Mamoru Toyofuku: Investigation, Resources; Naoki Kanemitsu: Investigation, Resources; Eiji Shinoda: Investigation, Resources; Satoru Suwa: Investigation, Resources; Atsushi Iwakura: Investigation, Resources; Toshihiro Tamura: Investigation, Resources; Yoshiharu Soga: Investigation, Resources; Tsukasa Inada: Investigation, Resources; Mitsuo Matsuda: Investigation, Resources; Tadaaki Koyama: Investigation, Resources; Takeshi Aoyama: Investigation, Resources; Eri Kato: Investigation, Data curation; Yukihito Sato: Investigation, Resources; Yutaka Furukawa: Investigation, Resources; Kenji Ando: Investigation, Resources; Fumio Yamazaki: Investigation, Resources; Tatsuhiko Komiya: Investigation, Resources; Kenji Minatoya: Investigation, Resources; Yoshihisa Nakagawa: Investigation, Resources; Takeshi Kimura: Conceptualization, Methodology, Writing-Review and Editing, Supervision, Project administration, Funding acquisition.

Disclosures

Dr. Morimoto reports honoraria from Bayer and Kowa, and expert witness from Boston Scientific and Sanofi. Dr. Shiomi reports honoraria from Abbott Vascular, and Boston Scientific. Dr. Furukawa reports honoraria from Bayer, Kowa, and Sanofi. Dr. Nakagawa reports research grant from Abbott Vascular and Boston Scientific, and honoraria from Abbott Vascular, Bayer, and Boston Scientific. Dr. Kimura reports honoraria from Abbott Vascular, Astellas, AstraZeneca, Bayer, Boston Scientific, Kowa, and Sanofi.

Acknowledgement

We appreciate the support and collaboration of the co-investigators participating in the CREDO-Kyoto PCI/CABG Registry Cohort-2 and -3. We are indebted to the clinical research coordinators for data collection.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.079.

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