



# Temporal Trends in Clinical Outcomes Following Percutaneous Coronary Intervention in Patients with Renal Insufficiency

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**Aim:** Renal insufficiency is associated with worse clinical outcomes in patients with coronary artery disease. Since the introduction of percutaneous coronary intervention (PCI), the revascularization therapy has evolved with advances of devices, improvements in operator techniques, and the establishment of medical therapy. We examined temporal trends of the clinical outcomes following PCI in patients with renal insufficiency.

**Methods:** Patients with renal insufficiency after PCI at Juntendo University across three eras (plain balloon angioplasty, bare metal stent (BMS), and drug-eluting stent (DES)) were examined in this study. The primary endpoint was a composite of all-cause mortality, nonfatal acute coronary syndrome, nonfatal stroke, and repeat revascularization within 3-years after the index revascularization.

**Results:** A total of 1,420 patients were examined. Baseline characteristics have become unfavorable over time, whereas administration rate of medications for secondary prevention has increased. The event-free survival rates for the endpoint were different among the groups. Adjusted relative risk reduction for the endpoint was 35% and 51% in the BMS and DES eras (using the plain angioplasty era as reference). The adjusted relative risk reduction of the DES era was 26% compared with that of the BMS era.

**Conclusions:** The incidence of cardiovascular events after PCI has reduced during the 26-year period mainly because of the reduction in repeat revascularization in patients with renal insufficiency, despite the higher risk profiles in the recent era.

**Key words:** Renal insufficiency, Percutaneous coronary intervention, Temporal trends

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## Introduction

Renal insufficiency is an independent risk factor for coronary artery disease (CAD)<sup>1-6</sup>. Furthermore, previous studies reported that CAD patients with renal insufficiency had worse clinical outcomes compared with those without renal insufficiency<sup>7-9</sup>. Since the introduction of plain old balloon angioplasty (POBA) for CAD in 1977, percutaneous coronary intervention (PCI) has evolved because of the technological advances of devices, improvements in operator

techniques, and the establishment of medical therapy for secondary prevention<sup>10-12</sup>. In particular, the advent of drug-eluting stents (DESs) has significantly reduced the occurrence of target lesion revascularization from 20% to 30% in the bare metal stent (BMS) era to below 10%<sup>13, 14</sup>. Recently, we reported that clinical outcomes following PCI improved across POBA, BMS, and DES era<sup>15</sup>. Therefore, it is of interest to know the temporal trends of clinical outcomes after PCI in patients with renal insufficiency who were at high risk of morbidity and mortality.

## Aim

The aim of this study was to know the temporal trends of clinical outcomes following PCI in CAD patients with renal insufficiency.

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## Methods

### Study Population

We analyzed the data from database of the Juntendo PCI Registry in which information of patients who underwent PCI at Juntendo University Hospital (Tokyo, Japan) from January 1984 to February 2010 was available. This database has been maintained since the introduction of PCI in our institution. The study population was divided into three groups according to the time period of the index PCI (POBA era: January 1984–December 1997, BMS era: January 1998–July 2004, and DES era: August 2004–February 2010).

### Clinical Outcomes

The endpoints included major adverse cardiovascular events that occurred within 3 years after the index PCI procedure. MACE was defined as one or more of the following: (1) all-cause mortality, (2) non-fatal acute coronary syndrome (ACS), (3) nonfatal stroke, and (4) repeat revascularization. Information regarding the clinical outcomes was collected during clinical visits, via telephone interviews or from the referring physician. The Institutional Review Board of Juntendo University Hospital approved the protocol of this study, which was performed in accordance with the principles established in the Declaration of Helsinki and our institutional ethics policy, and written informed consent was obtained from all study participants.

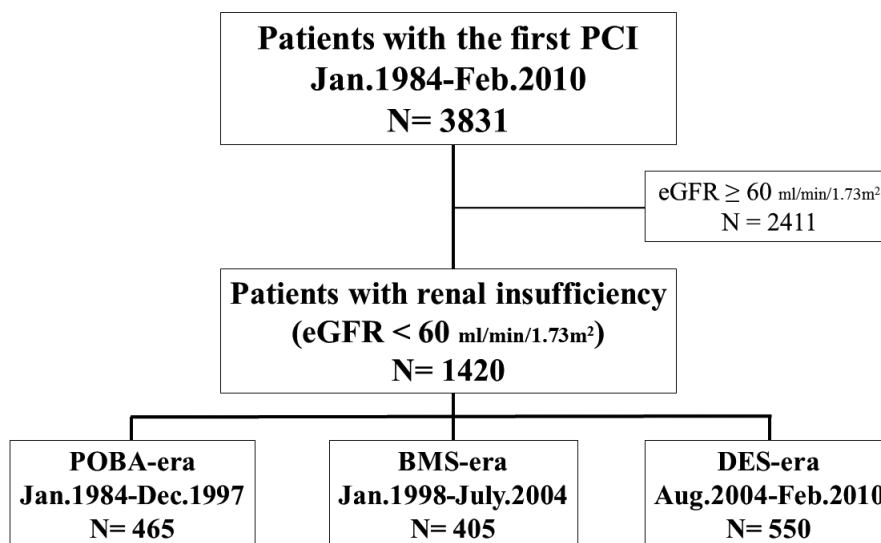
### Definitions

Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) of  $< 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$ , calculated using the modification of diet in renal disease (MDRD) equation modified with a Japanese coefficient using baseline serum creatinine<sup>16</sup>. Diabetes mellitus was defined as glycated hemoglobin A1c (HbA1c) of National Glycohemoglobin Standardization Program (NGSP) value  $\geq 6.5\%$ , by a previous diagnosis from medical records or being treated with any oral antidiabetic agents or insulin. We converted HbA1c [Japan Diabetes Society (JDS)] values to HbA1c (NGSP) units using the following equation:  $\text{NGSP}(\%) = 1.02 \times \text{JDS}(\%) + 0.25\%$ <sup>17</sup>. Hypertension was defined as systolic blood pressure  $\geq 140 \text{ mmHg}$  and diastolic blood pressure  $\geq 90 \text{ mmHg}$  or treatment with antihypertensive medications. Dyslipidemia was defined by a previous diagnosis from medical records, lipid profiles, i.e., triglyceride  $\geq 150 \text{ mg/dl}$ , low-density lipoprotein cholesterol  $\geq 140 \text{ mg/dl}$  or high-density lipoprotein cholesterol  $< 40 \text{ mg/dl}$  or being treated with antidiabetic medications. All these blood sampling data were measured in the morning of

the day when the index PCI was performed, whereas in emergent cases, the measurement was performed at the timing of the emergent admission. We defined current smokers as individuals who smoked at the time of admission or who had quit within 1 year before the study period. ACS was defined as unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI) or STEMI. UAP was defined as angina at rest or in an accelerating pattern with negative cardiac biomarkers, with or without ECG changes indicative of myocardial ischemia (e.g., ST segment depression or transient elevation or new T-wave inversion). Myocardial infarction (MI) was diagnosed in the presence of two of the following three criteria: (1) typical chest pain for at least 20 min, (2) increased serum creatine kinase level to twice the upper normal range, and (3) a new Q wave on electrocardiography. Procedural success of PCI was defined as a decrease in residual luminal diameter stenosis to  $< 50\%$  or an achievement of thrombolysis in MI grade 3 in the final angiogram of the procedure.

### Statistical Analyses

Continuous variables were expressed as the mean and standard deviation. Categorical data were expressed as counts and percentages. Continuous variables were compared using one-way analysis of variance followed by post-hoc analysis using Dunnett's test for multiple comparisons. The POBA era served as a control group in the post-hoc analysis. The continuous variables with statistical significance in the analysis are marked with \*. Categorical variables were analyzed by the chi-square test or Fisher's exact probability test. Analysis of the intergroup comparison with the POBA era group for categorical variables was calculated with Bonferroni's correction. The categorical variables with statistical significance in the analysis are marked with †. In the analysis, a  $P$ -value  $< 0.025$  was considered to be significant. Cochran–Armitage test for trend was performed to assess for presence of an association between the incidence of 3-year MACE and the PCI eras. Unadjusted cumulative event rates for 3-year MACE were estimated using Kaplan–Meier methods and compared using the log-rank test across the three groups. To identify whether the PCI eras (with the POBA era as the reference) were associated with the clinical outcomes following PCI, univariate Cox regression analysis was performed. Furthermore, multivariate Cox regression analysis, including age, gender, body mass index (BMI), hypertension, diabetes, dyslipidemia, current smoking, hemodialysis, and a presentation of ACS at the index PCI as confounding factors was performed. The hazard ratio (HR) and 95% confidence intervals were also calculated. A



**Fig. 1.** A flow chart of the study population

A total of 1,420 patients with renal insufficiency who underwent the first percutaneous coronary intervention in our institution were analyzed in this study.

$P$ -value  $< 0.05$  was considered to be statistically significant. All data were analyzed using JMP version 10.0 for Windows (SAS Institute, Cary, NC).

## Results

A flow chart of the study population is provided in **Fig. 1**. A total of 1,420 patients were analyzed (POBA era,  $n=465$ ; BMS era,  $n=405$ ; and DES era,  $n=550$ ). The baseline characteristics are shown in **Table 1**. The mean age was highest in the DES era and the prevalence of hypertension and diabetes. The percentage of severe renal insufficiency (eGFR  $< 30$ ) was higher, and the prevalence of hemodialysis was also higher in the DES era. The percentage of current smoking was higher in the POBA era than in the other eras. Lipid profiles were more favorable in the DES and BMS eras than in the POBA era. HbA1c was higher in the POBA era, whereas hemoglobin level and left ventricular ejection fraction were lower in the DES and BMS eras. The success rate of PCI was also higher in these eras than in the POBA era. In addition, the DES and BMS eras included more patients who presented with ACS at the time of the initial PCI. The use of evidence-based medical therapy (i.e., aspirin, statins, ACEI/ARBs, and  $\beta$ -blockers) for secondary prevention of cardiovascular events significantly increased over time (**Table 1**). Lesion characteristics showed that diseased vessels differed between the groups, and a higher prevalence of MVD was noted in the DES and BMS eras than in the POBA era (**Table**

**1**). Information regarding 3-year clinical outcomes was collected from all patients in this study. The incidence of each individual clinical outcome is provided in **Table 2**. The unadjusted cumulative event-free survival rate for 3-year MACE was significantly different across the three eras (**Fig. 2**). The incidence of 3-year MACE was reduced over the three eras ( $P$  for trend = 0.0009) (**Fig. 3**). The univariate Cox regression analysis for 3-year MACE showed that the relative risk reduction was 23% [HR: 0.77, 95% confidential interval (CI): 0.61–0.96,  $P=0.02$ ] in the BMS era and 35% (HR: 0.65, 95% CI: 0.52–0.80,  $P<0.0001$ ) in the DES era (using the POBA era as reference). **Table 3** shows that adjusted relative risk reduction for 3-year MACE was 35% (HR: 0.65, 95% CI: 0.51–0.84,  $P=0.0009$ ) in the BMS era and 51% (HR: 0.49, 95% CI: 0.38–0.63,  $P<0.0001$ ) in the DES era. Compared with the BMS era, the adjusted relative risk reduction of the DES era was 26% (HR: 0.74, 95% CI: 0.58–0.95,  $P=0.02$ ). High age, male gender, low BMI, diabetes mellitus, ACS, and hemodialysis were also associated with increased 3-year MACE (**Table 3**). Regarding all-cause mortality that is considered to be an important endpoint for patients with renal insufficiency, multivariable Cox regression analysis revealed that the DES era had a tendency toward lower incidence of 3-year all-cause mortality compared with the POBA era (**Fig. 4**).

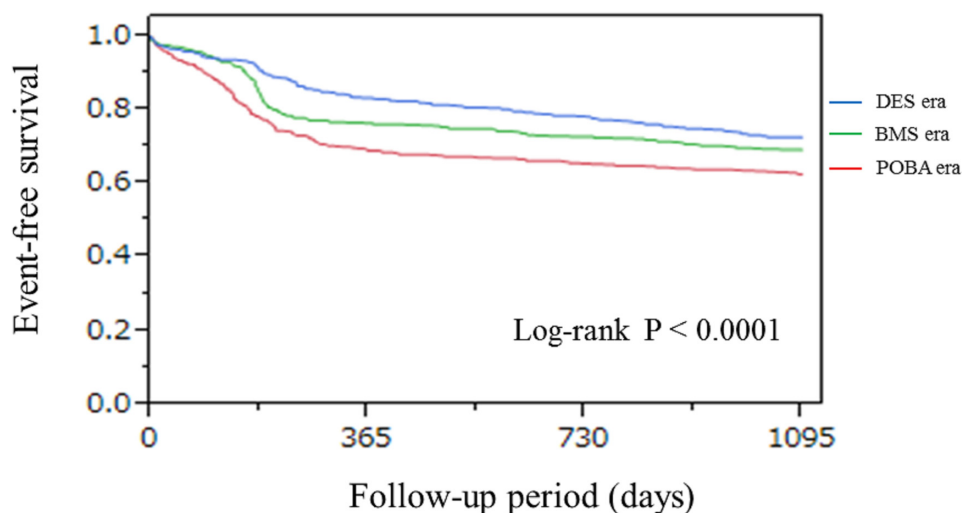
**Table 1.** Patients' characteristics

	POBA era (N=465)	BMS era (N=405)	DES era (N=550)	p value
Age, year	61.6 ± 9.6	67.3 ± 9.0*	69.8 ± 9.9*	< 0.0001
Male, n (%)	395 (85.0)	324 (80.0)	440 (80.0)	0.07
BMI, kg/m <sup>2</sup>	23.5 ± 3.7	24.0 ± 3.8	23.8 ± 3.3	0.2
Hypertension, n (%)	310 (66.7)	291 (71.9)	429 (78.0) <sup>†</sup>	0.000
Diabetes mellitus, n (%)	167 (35.9)	164 (40.5)	245 (44.6)	0.02
Dyslipidemia, n (%)	348 (74.1)	252 (62.5)	390 (70.9)	0.001
Current smoking, n (%)	273 (59.1)	74 (18.4) <sup>†</sup>	112 (20.4) <sup>†</sup>	< 0.0001
Family history, n (%)	122 (26.3)	115 (28.9)	138 (25.1)	0.5
LDL-C, mg/dL	133.8 ± 42.9	116.4 ± 32.1*	109.8 ± 33.3*	< 0.0001
HDL-C, mg/dL	42.6 ± 12.1	44.2 ± 13.7	43.2 ± 13.1	0.2
TC, mg/dL	205.3 ± 47.8	187.5 ± 6.6*	180.6 ± 9.0*	< 0.0001
TG, mg/dL	144.4 ± 73.4	134.7 ± 82.2	135.3 ± 75.9	0.09
HbA1c (NGSP), %	7.0 ± 3.2	6.2 ± 1.2*	6.2 ± 1.1*	0.009
Hb, g/dL	13.3 ± 1.7	12.8 ± 2.0*	12.6 ± 2.1*	0.000
LVEF, %	65.3 ± 13.1	63.4 ± 14.0	58.6 ± 14.2*	< 0.0001
eGFR, mL/min/1.73 m <sup>2</sup>	46.7 ± 12.5	45.2 ± 14.8	42.5 ± 17.7*	< 0.0001
Severity of renal insufficiency				< 0.0001
eGFR < 15	23 (5.0)	31 (7.7)	83 (15.1)	
15 ≤ eGFR < 30	16 (3.44)	22 (5.4)	19 (3.4)	
30 ≤ eGFR < 45	101 (21.7)	85 (21.0)	105 (19.1)	
45 ≤ eGFR < 60	325 (69.9)	267 (65.9)	343 (62.4)	
Hemodialysis, n (%)	18 (3.9)	31 (7.7) <sup>†</sup>	81 (14.7) <sup>†</sup>	< 0.0001
Acute coronary syndrome, n (%)	56 (12.0)	93 (23.0) <sup>†</sup>	148 (26.9) <sup>†</sup>	< 0.0001
Success rate, n (%)	401 (86.2)	385 (95.1) <sup>†</sup>	526 (95.6) <sup>†</sup>	< 0.0001
Type of procedure, n (%)				< 0.0001
POBA	448 (96.3)	79 (19.8)	34 (6.4)	
BMS	17 (3.7)	320 (80.2)	188 (35.1)	
DES	0 (0)	0 (0)	313 (58.5)	
Medication, n (%)				
Aspirin	324 (70.7)	354 (90.3) <sup>†</sup>	511 (93.3) <sup>†</sup>	< 0.0001
Other anti-platelet agent	355 (78.0)	278 (70.9)	474 (86.7)	< 0.0001
Statin	78 (35.5)	151 (38.3)	305 (55.6) <sup>†</sup>	< 0.0001
ACEI/ARB	52 (11.4)	173 (44.1) <sup>†</sup>	303 (55.3) <sup>†</sup>	< 0.0001
β-blocker	124 (27.1)	171 (43.6) <sup>†</sup>	286 (52.2) <sup>†</sup>	< 0.0001
Calcium channel blocker	233 (50.9)	168 (43.0) <sup>†</sup>	236 (43.1) <sup>†</sup>	0.02
Diseased vessel				< 0.0001
LAD	223 (48.0)	165 (40.7)	237 (43.1)	
LCX	64 (13.8)	77 (19.0)	112 (20.4)	
RCA	120 (25.8)	141 (34.8)	171 (31.1)	
LMT	7 (1.5)	5 (1.2)	19 (3.5)	
Others	51 (11.0)	17 (4.2)	11 (2.0)	
Number of diseased vessel	1.6 ± 0.8	1.7 ± 0.8	1.9 ± 0.8*	< 0.0001
MVD	214 (46.6)	198 (48.9) <sup>†</sup>	357 (65.4) <sup>†</sup>	< 0.0001
QCA				
Reference diameter, mm	3.0 ± 0.7	3.0 ± 0.5	2.8 ± 0.5*	< 0.0001
MLD (pre), mm	0.59 ± 0.41	0.51 ± 0.46	0.42 ± 0.37*	0.000
MLD (post), mm	2.15 ± 0.74	2.57 ± 0.77*	2.66 ± 0.58*	< 0.0001
Stent diameter, mm		3.17 ± 0.4	2.97 ± 0.41	< 0.0001
Stent length, mm		16.7 ± 4.2	19.7 ± 6.2	< 0.0001

BMI; body mass index, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TC; total cholesterol, TG; triglyceride, HbA1c; glycosylated hemoglobin, Hb; hemoglobin, LVEF; left ventricular ejection fraction, eGFR; estimated glomerular filtration rate, POBA; plain old balloon angioplasty, BMS; bare metal stents, DES; drug-eluting stents, ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, LAD; left anterior descending artery, LCX; left circumflex, RCA; right coronary artery, LMT; left main trunk, MVD; multivessel coronary artery disease, QCA; quantitative coronary angiography, MLD; minimum lumen diameter

**Table 2.** The incidence rate of each individual clinical outcome

	POBA era (N=465)	BMS era (N=405)	DES era (N=550)
All-cause mortality, (%)	38 (8.1)	46 (11.4)	80 (14.5)
Non-fatal acute coronary syndrome, (%)	14 (3.0)	28 (6.9)	26 (4.7)
Non-fatal stroke, (%)	5 (1.1)	27 (6.7)	21 (3.8)
Repeat revascularization, (%)	140 (30.1)	64 (15.8)	61 (11.1)

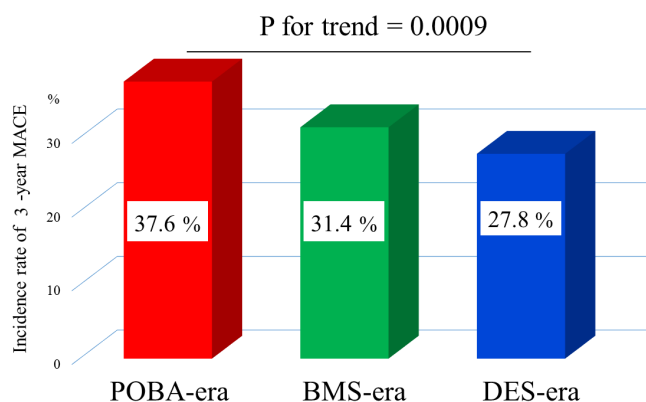


Number at risk

DES era	550	456	428	397
BMS era	405	308	293	279
POBA era	465	321	304	291

**Fig. 2.** Kaplan–Meier curves for 3-year MACE

Kaplan–Meier curves for 3-year major adverse cardiovascular events show a significant difference across the three eras. The event rate was the lowest in the drug-eluting stent era.

**Fig. 3.** The overall incidence of 3-year major adverse cardiovascular events across three eras

Unadjusted incidence of 3-year major adverse cardiovascular events was significantly decreased across plain old balloon angioplasty, bare metal stent, and drug-eluting stent eras.

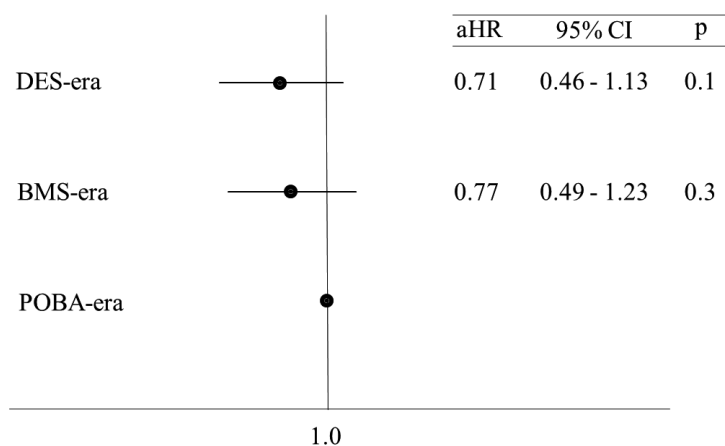
## Discussion

The main findings of this study that examined the clinical outcomes following PCI in patients with renal insufficiency are as follows: (1) the baseline characteristics have become unfavorable over the recent two decades in terms of higher age and higher prevalence of comorbid diseases (hypertension, diabetes, and hemodialysis); (2) the success rate of PCI and the use of evidence-based medical therapy for secondary prevention have increased over time; and (3) the incidence of 3-year MACE has significantly decreased over time, whereas the incidence of 3-year all-cause mortality tended to be lower in the DES era. These findings suggest that the improvement of PCI devices and the increased use of evidence-based medical therapy for secondary prevention of CAD have led to the improved long-term clinical outcomes following PCI

**Table 3.** Multivariable Cox regression analyses for 3-year major adverse cardiovascular events

	Hazard ratio	95% CI	<i>p</i>
Age, 1 year increase	1.02	1.01-1.03	0.000
Male gender, yes	1.35	1.04-1.76	0.02
BMI, 1 kg/m <sup>2</sup> increase	0.97	0.95-0.99	0.049
Diabetes mellitus, yes	1.26	1.04-1.53	0.017
Dyslipidemia, yes	0.99	0.81-1.22	0.9
Hypertension, yes	1.08	0.87-1.34	0.5
Current smoking, yes	1.08	0.86-1.34	0.5
ACS, yes	1.45	1.15-1.81	0.002
Hemodialysis, yes	2.03	1.51-2.69	<0.0001
BMS era (POBA era as reference)	0.65	0.51-0.84	0.001
DES era (POBA era as reference)	0.49	0.38-0.63	<0.0001

BMI; body mass index, ACS; acute coronary syndrome, BMS; bare metal stent, POBA; plain old balloon angioplasty, DES; drug-eluting stent

**Fig. 4.** Cox regression analysis for 3-year all-cause mortality

The forest plot demonstrates adjusted hazard ratio and 95% confidence interval for 3-year all-cause mortality of drug-eluting stent and bare metal stent eras against plain old balloon angioplasty era after controlling following variables (age, male gender, body mass index, diabetes mellitus, hypertension, dyslipidemia, current smoking, hemodialysis, and acute coronary syndrome).

mainly because of the reduction in repeat revascularization, even in high-risk patients with renal insufficiency. To the best of our knowledge, this is the first study examining clinical outcomes following PCI across the POBA, BMS, and DES eras in patients with renal insufficiency.

Renal insufficiency is considered to be an independent risk factor for CAD<sup>1-6</sup>; furthermore, CAD patients with renal insufficiency have worse clinical outcomes compared with patients without renal insufficiency<sup>7-9</sup>. Coronary revascularization has been demonstrated to be effective in improving prognosis in CAD patients with renal insufficiency<sup>18, 19</sup>. In addition, PCI has been evolving with new devices,

improved operator skills, and the establishment of medical therapy for secondary prevention.

To date, there are few studies examining the temporal trends in clinical outcomes after PCI in patients with renal insufficiency. Krishnaswami et al. conducted a retrospective study evaluating the temporal trends in mortality following coronary revascularization in patients with end-stage renal disease requiring hemodialysis during the following three time periods: 1996–1999, 2000–2003, and 2004–2008<sup>20</sup>. They reported that the relative risk reduction for 3-year mortality after coronary revascularization was 34% in the 2004–2008 period compared with the 1996–1999 period. The result was partially consistent with our

results that showed a significant reduction in 3-year MACE and a tendency toward reduction in 3-year all-cause mortality over 26 years. However, in that study, not only PCI but also coronary artery bypass grafting was included as a coronary revascularization strategy, which differed from our study. Thus, no study has reported the temporal trends in clinical outcomes after PCI in patients with renal insufficiency using a longitudinal cohort. In this regard, our study is considered to be novel. In our study, the adjusted risk for 3-year all-cause mortality tended to be lower in the DES era than in the POBA era. The adjusted relative risk for 3-year MACE was the lowest in the DES era compared with the POBA and the BMS eras, and also the relative risk was lower in the BMS era than in the POBA era, despite the higher risk profiles of the patients in the later time periods. Reduction in the incidence of cardiovascular events over the 26-year period of this study could be explained by the following: advances in PCI devices such as the advent of DES, the high rate of PCI success, the increased use of evidence-based therapies for secondary prevention (i.e., aspirin, statins,  $\beta$ -blockers, and ACEI/ARBs), and smoking cessation. Indeed, the Global Registry of Acute Coronary Events has previously shown that adherence to guideline-recommended medical therapy for secondary prevention yielded favorable clinical outcomes after acute coronary events<sup>21</sup>). The present study could help us ascertain the importance of advances in PCI technology, medical therapy for secondary prevention, and smoking cessation in reducing cardiovascular events, even in high-risk patients with renal insufficiency following PCI.

### Limitations

Our study has several limitations. First, this study was conducted at a single institution, and the study population was small, limiting the generalizability of our results. However, our data are important because PCI has been utilized in our institution from the beginning of the use of PCI in Japan. Second, there was a lack of data regarding medication use, causes of renal insufficiency, and detailed information about the volume of contrast medium used in the index PCI and the effect on periprocedural deterioration of renal function. Third, because of the long-term follow-up period across three generations of PCI, unmeasured factors that were not assessed in this study might have effects on the incidence of clinical outcomes.

### Future Perspectives

The present study and the previous reports indicate the importance of adhering to evidence-based medical and nonpharmacological therapy for secondary prevention and the necessity of further establishing renewed measures to reduce fatal cardiovascular events. Considering that increased physical activity and nutrition therapy have been demonstrated to have positive effects on lowering cardiovascular events<sup>22, 23</sup>), future studies are necessary to consider nonpharmacological interventions for such issues for the prevention of cardiovascular events.

### Conclusion

Long-term clinical outcomes following PCI in patients with renal insufficiency in our institution improved over the past 26 years mainly because of the reduction in repeat revascularization, despite the higher risk profiles of the patients in the recent era.

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### Disclosures

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The other authors report no conflicts.

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