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ORIGINAL ARTICLE

Eleven-year temporal trends of clinical characteristics and long-term outcomes in patients undergoing percutaneous coronary intervention for acute coronary syndrome in the Shinken database

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Abstract
Despite the increasing incidence of acute coronary syndrome (ACS) in Japan, its prognosis has improved. However, there is a paucity of longitudinal registry data providing trends of in-hospital care and prognosis of ACS in Japan. ACS patients undergoing percutaneous coronary intervention (PCI) included in the Shinken Database 2004–2014 were divided into two groups according to admission year (2004–2009, $n=390$; 2010–2014, $n=328$). Patient characteristics, lesion/procedure characteristics, medications at discharge, all-cause mortality, cardiovascular death, acute myocardial infarction (AMI), target lesion revascularization (TLR), re-PCI to new lesion, and coronary artery bypass graft (CABG) within 2 years after discharge were compared between the groups. Prevalence of hypertension, dyslipidemia, and dual antiplatelet/statin prescription increased significantly between periods. Usage of second-generation drug-eluting stents (DES) increased markedly between the two periods (2.6, 66.8%), while those of bare metal stents (64.4, 26.5%) and first-generation DES (25.6, 1.5%) decreased (all, $p<0.01$). Two-year event-free survival rate increased for all-cause mortality (94.6–98.3%, $p=0.01$), TLR (79.4–96.1%, $p<0.01$), and re-PCI to new lesion (87.3–95.1%, $p<0.01$). There were no significant differences in cardiovascular death, AMI, or CABG between the two periods. The event-free rates for TLR and re-PCI to new lesion in ACS patients have increased over the last decade in Japan. These observations should be confirmed in larger, longitudinal, multicenter registries.

Keywords Acute coronary syndrome · Percutaneous coronary intervention · Time trend

Introduction

Acute coronary syndrome (ACS) is a leading cause of morbidity and mortality worldwide. Although continuous decreases in mortality and morbidity by coronary artery disease have been reported in Western countries with improvement of risk control and medical care, [1, 2] the incidence of coronary artery disease has been increasing over the past several decades in Japan presumably due to westernization of lifestyles [3, 4].

However, the prognosis of ACS seems to be improving [5–7] presumably due to the development of new devices and strategies for percutaneous coronary intervention (PCI) and improvement of medical care. [8–11]. However, there is a paucity of longitudinal registry data providing trends of in-hospital care and prognosis after ACS in Japan.

In the present study, we examined time trends of clinical characteristics, treatment, and outcomes of ACS patients over time in a longitudinal single-center cohort from a cardiovascular hospital.

Methods

Study population

The Shinken database [12, 13], which was established in June 2004, contains data on all new patients attending the Cardiovascular Institute Hospital, Tokyo, Japan (abbreviated in Japanese as Shinken), excluding foreign travelers and patients with active cancer. A total of 24,785 new

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patients were registered in the database up to March 2015. In this database, we identified 2132 patients who underwent initial PCI in our hospital, where 718 were performed with a diagnosis of ACS.

The diagnosis of ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), was made by cardiologists in our hospital based on the definitions of the Joint Committee of the American College of Cardiology (ACC)/American Heart Association (AHA) [14, 15].

Data collection at the initial visit

After obtaining an electrocardiogram (ECG) and chest X-ray, the cardiovascular status of each patient was evaluated by echocardiography when necessary. In addition to gender, age, height, and weight, we collected data on cardiovascular diseases, including valvular heart disease (moderate or severe stenosis or regurgitation using echocardiography), coronary artery disease, hypertrophic and dilated cardiomyopathy, and history of disabling cerebral infarction or transient ischemic attack. The presence of cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg on admission), diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $\geq 6.5\%$ [National Glycohemoglobin Standardization Program (NGSP)], dyslipidemia (use of statins or drugs for lowering triglyceride, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL or triglyceride ≥ 150 mg/dL), chronic kidney disease [estimated glomerular filtration rate (GFR) < 60 mL/min/m^2], chronic obstructive pulmonary disease, and use of anticoagulant or antiplatelet medications. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The GFR was estimated using the new Japanese coefficient for the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) study equation [$\mathrm{GFR} = 194 \times \mathrm{SCr}^{-1.094} \times \mathrm{age}^{-0.287} \times 0.739$ (if female)].

Patient outcomes

The patient outcomes determined in our study were all-cause mortality, cardiovascular death, acute myocardial infarction (AMI), target lesion revascularization (TLR), re-PCI to new lesion, and coronary artery bypass graft (CABG) within 2 years after discharge.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). In all analyses, $p < 0.05$ was taken to indicate statistical significance. Means and standard deviation (SD) were calculated for continuous variables. Numbers and percentages were calculated for categorical variables.

The patients were divided into two groups according to the date of admission for ACS [June 2004 to March 2010, and April 2010 to March 2015 (expressed by fiscal years in Japan as 2004–2009 and 2010–2014, respectively)]. First, we compared patient characteristics, laboratory data and physiological exam data on admission, lesion and procedure characteristics, medications at discharge, and the choice of stent. The differences in continuous and categorical variables were tested using the unpaired *t* test and Chi square test, respectively. The incidences of all-cause mortality, cardiovascular death, AMI, TLR, re-PCI to new lesion, and CABG within 2 years after discharge were estimated by the Kaplan–Meier method, and the differences between the two time periods were tested by the log rank test. Cox hazard analysis was performed to estimate the hazard ratio of the time period (2010–2014 vs. 2004–2009) for the outcomes. In the multivariate model, the effect of time period was adjusted for the covariates significantly associated with the outcomes in the univariate models using the stepwise method.

Ethical issues

The ethics committee of the Cardiovascular Institute granted ethical approval for this study and all patients provided written informed consent.

Results

Patient characteristics

Among the 2132 patients who underwent PCI between 2004 and 2014, 718 (33.7%) had ACS, while the remaining 1414 (66.3%) did not. The characteristics of the ACS patients according to the two time periods are presented in Table 1. The male prevalence rates were 86.4 and 86.9% in 2004–2009 and 2010–2014, respectively; the difference between the two periods was not significant ($p = 0.85$). Although the mean (SD) value of age tended to decrease slightly over time [64.8 (12.1) and 63.1 (12.0) years in 2004–2009 and 2010–2014, respectively; $p = 0.06$], there were increases in number of patients with hypertension, dyslipidemia, and history of PCI. Serum albumin, hemoglobin,

Table 1 Patient characteristics

	2004–2009 ($n=390$)	2010–2014 ($n=328$)	p value
Demographics			
Age (years old)	64.8 ± 12.1	63.1 ± 12.0	0.06
Age > 75 years old (%)	64 (19.5)	91 (23.3)	0.21
Male sex (%)	337 (86.4)	285 (86.9)	0.85
BMI (kg/cm^2)	24.6 ± 3.4	24.5 ± 3.8	0.80
Comorbidities and risk factors			
Smokers (%)	137 (41.8)	167 (42.8)	0.78
Hypertension (%)	234 (60.0)	220 (67.1)	0.05
Diabetes (%)	131 (33.6)	98 (29.9)	0.29
Dyslipidemia (%)	227 (58.2)	218 (66.5)	0.02
CKD (%)	92 (23.6)	86 (26.2)	0.42
Hyperuricemia (%)	64 (16.4)	62 (18.9)	0.38
Medical history of CVD			
OMI (%)	25 (6.4)	17 (5.2)	0.49
Prior PCI (%)	18 (4.6)	29 (8.8)	0.02
Prior CABG (%)	4 (4.0)	8 (2.4)	0.14
Diagnosis			
UA (%)	139 (35.6)	129 (39.3)	0.31
NSTEMI (%)	60 (15.4)	42 (12.8)	0.32
STEMI (%)	191 (49.0)	156 (47.6)	0.71
Laboratory data			
Albumin (g/dL)	3.9 ± 0.6	4.2 ± 0.5	<0.01
eGFR (mL/min/1.73 m^2)	72.3 ± 25.0	69.3 ± 20.2	0.09
HbA1c (%)	6.2 ± 1.4	6.1 ± 1.2	0.44
LDL-Chol (mg/dL)	122.9 ± 37.5	124.0 ± 40.0	0.73
HDL-Chol (mg/dL)	49.3 ± 13.3	53.7 ± 14.4	<0.01
TG (mg/dL)	148.0 ± 128.0	149.2 ± 132.4	0.90
Hemoglobin (mg/dL)	13.2 ± 2.0	14.5 ± 1.6	<0.01
Max CK (IU/l)	1528.6 ± 2186.8	1325.6 ± 1832.5	0.18
LVEF (%)	59.5 ± 13.2	59.7 ± 12.1	0.83
Vital sign			
Systolic blood pressure (mmHg)	136.2 ± 27.2	136.5 ± 24.2	0.90
Diastolic blood pressure (mmHg)	79.1 ± 16.1	80.2 ± 16.6	0.43
Heart rate (bpm)	77.5 ± 17.8	75.5 ± 15.3	0.11
Killip classification			
I (%)	116 (82.9)	65 (87.8)	0.43
II (%)	12 (8.6)	6 (8.1)	1.00
III (%)	4 (2.9)	1 (1.4)	0.66
IV (%)	8 (5.7)	2 (2.7)	0.50
Medication at discharge			
Dual antiplatelet therapy (%)	366 (93.8)	321 (97.9)	0.01
Anticoagulation (%)	42 (10.8)	21 (6.4)	0.05
Statin (%)	232 (59.5)	255 (77.7)	<0.01
β-Blocker (%)	141 (36.2)	119 (36.3)	1
RAS inhibitor (%)	216 (55.4)	180 (54.9)	0.89
Ca blocker (%)	170 (43.6)	132 (40.2)	0.40
Vasodilator agent (%)	144 (36.9)	85 (25.9)	<0.01
Diuretics (%)	63 (16.2)	28 (8.5)	<0.01
Aldosterone antagonist (%)	21 (5.4)	7 (2.1)	0.03
Hypouricemic agent (%)	46 (11.8)	35 (10.7)	0.72
Hypoglycemic agent (%)	99 (25.4)	72 (22.0)	0.29

Table 1 (continued)

	2004–2009 ($n=390$)	2010–2014 ($n=328$)	p value
Insulin (%)	15 (3.8)	16 (4.9)	0.58

BMI body mass index, *CKD* chronic kidney disease, *OMI* old myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *UA* unstable angina, *NSTEMI* non-ST elevated myocardial infarction, *STEMI* ST elevated myocardial infarction, *eGFR* estimated glomerular filtration rate, *LDL-Chol* low-density lipoprotein cholesterol, *HDL-Chol* high-density lipoprotein cholesterol, *TG* triglyceride, *CK* creatinine kinase, *LVEF* left ventricular ejection fraction, *RAS* renin angiotensin

Categorical and consecutive data are presented as numbers (%) and means ± standard deviation, respectively

and high-density lipoprotein cholesterol (HDL-Chol) values were significantly increased ($p<0.01$) in 2010–2014 compared to 2004–2009. There were no significant differences in left ventricular ejection fraction between the two time periods. The rate of dual antiplatelet/statin prescription increased significantly ($p=0.01$ and $p<0.01$, respectively), while those of vasodilator agent and diuretics decreased (both, $p<0.01$).

Procedure characteristics

The procedure characteristics are shown in Table 2. There were no significant differences in the distribution of culprit lesions in ACS. The number of cases with 1-vessel disease decreased from 61.7 to 52.5%, while that of cases with a 3-vessel disease increased from 8.9 to 18.1% ($p=0.04$). With regard to the puncture site, use of the transfemoral approach decreased significantly from 96.4 to 84.1% ($p<0.01$), while use of the transradial approach increased significantly from 3.6 to 16.2% ($p<0.01$). The amount of contrast agent decreased from 243.0 to 173.1 mL ($p<0.01$). With regard to the choice of stent, the usage of second-generation drug-eluting stents (DES) increased from 2.6 to 66.8% ($p<0.01$), while those of bare metal stents (BMS) and first-generation DES decreased from 64.4 and 25.6 to 26.5 and 1.5%, respectively (both, $p<0.01$) (Table 2 and Fig. 1).

Patient outcomes

Kaplan–Meier curves of patient outcomes are shown in Fig. 2. The event-free survival rates at 2 years increased from 2004–2009 to 2010–2014 for all-cause mortality (94.6 vs. 98.3%, $p=0.01$), TLR (79.4 vs. 96.1%, $p<0.01$), and re-PCI to new lesion (87.3 vs. 95.1%, $p<0.01$). Meanwhile, the event-free survival rates for cardiovascular death, AMI, and CABG were similar between 2004–2009 and 2010–2014 ($p=0.22$, $p=0.27$, and $p=0.26$, respectively).

The results of multivariate Cox hazard analyses are shown in Fig. 3. Although the hazard ratios (HRs) of time period (2010–2014 compared with 2004–2009) showed significant negative relationships with TLR, re-PCI to new lesions, and all-cause mortality in the univariate models, the respective results were different in the multivariate models, i.e., an independent negative relationship with TLR, a marginally independent relationship with re-PCI to new lesion, and no independent relationship with all-cause mortality. There was no significant association with cardiovascular death, AMI, or CABG (Fig. 3).

In addition, we developed bivariate Cox hazard models for re-PCI to new lesions and TLR to identify the confounding roles of statin and 2nd-generation DES with time period in the preventive effect on their occurrence. Both time period and use of statin showed significant associations with re-PCI to new lesions not only in the univariate models [time period (2010–2014), HR = 0.40, 95% confidence interval (CI) 0.22–0.72, $p<0.01$; statin, HR = 0.53, 95% CI 0.32–0.88, $p=0.01$), but also in the multivariate models (time period, HR = 0.45, 95% CI 0.24–0.84, $p=0.01$; statin, HR = 0.57, 95% CI 0.33–0.98, $p=0.04$) after adjusting for age, male gender, BMI, hypertension, DM, CKD, LDL-Chol, and HDL-Chol (Table 3). Although both time period and use of 2nd-generation DES significantly affected TLR in the univariate models (time period, HR = 0.17, 95% CI 0.09–0.32, $p<0.01$; 2nd-generation DES, HR = 0.28, 95% CI 0.14–0.53, $p<0.01$), only the former showed a significant association in the multivariate models (time period, HR = 0.17, 95% CI 0.08–0.33, $p<0.01$) after adjusting for the same cofactors (Table 4).

Discussion

Major findings

The results of the present study indicated significant increases in the usage of statins and 2nd-generation DES, significant decreases in re-PCI to new lesions and TLR, and no significant changes in all-cause mortality or cardiovascular death, AMI, or CABG between 2004–2009 and 2010–2014.

Table 2 Lesion and procedure characteristics

	2004–2009 ($n=390$)	2010–2014 ($n=328$)	p value
Lesion characteristics			
Culprit lesion			
RCA (%)	125 (32.1)	113 (34.6)	0.48
LMT (%)	12 (3.1)	8 (2.4)	0.61
LAD (%)	213 (54.6)	168 (51.2)	0.40
LCX (%)	84 (21.5)	62 (18.9)	0.38
HL (%)	8 (2.1)	2 (0.6)	0.10
Graft (%)	0 (0)	2 (0.6)	0.12
Number of target vessels			0.08
1 (%)	346 (88.7)	295 (89.9)	
2 (%)	40 (10.3)	24 (7.3)	
3 (%)	1 (0.3)	0 (0)	
Amount of contrast (mL)	243.0 ± 87.3	173.1 ± 68.3	<0.01
Procedure characteristics			
Puncture site			
TFI (%)	376 (96.4)	276 (84.1)	<0.01
TRI (%)	14 (3.6)	53 (16.2)	<0.01
TBI (%)	1 (0.3)	2 (0.6)	0.47
Complications			
Perforation (%)	3 (0.8)	2 (0.6)	0.80
Slow or no flow (%)	23 (5.9)	12 (3.7)	0.17
Puncture site problems (%)	4 (1.0)	4 (1.2)	0.81
Cerebral infarction (%)	5 (1.3)	0 (0)	0.04
Myocardial infarction (%)	4 (1.0)	4 (1.2)	0.81
Death in hospital (%)	9 (2.3)	2 (0.6)	0.06
Stent			
Non stenting (%)	41 (10.5)	21 (6.4)	0.05
BMS (%)	251 (64.4)	87 (26.5)	<0.01
1st generation DES (%)	100 (25.6)	5 (1.5)	<0.01
2nd generation DES (%)	10 (2.6)	219 (66.8)	<0.01

RCA right coronary artery, *LMT* left main trunk, *LAD* left ascending artery, *LCX* left circumflex, *HL* high lateral branch, *TFI* transfemoral intervention, *TRI* transradial intervention, *TBI* transbrachial intervention, *BMS* bare metal stent, *DES* drug-eluting stent

Categorical and consecutive data are presented as numbers (%) and means ± standard deviation, respectively

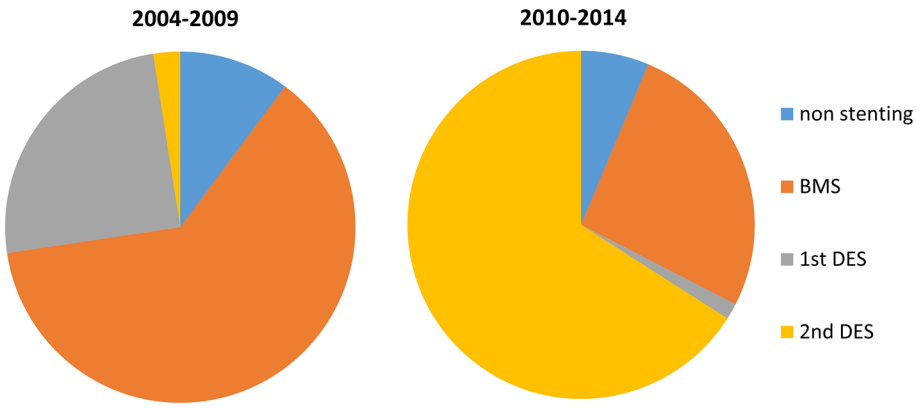

Fig. 1 Change in choice of stent. The percentages of each stent are shown in Table 2

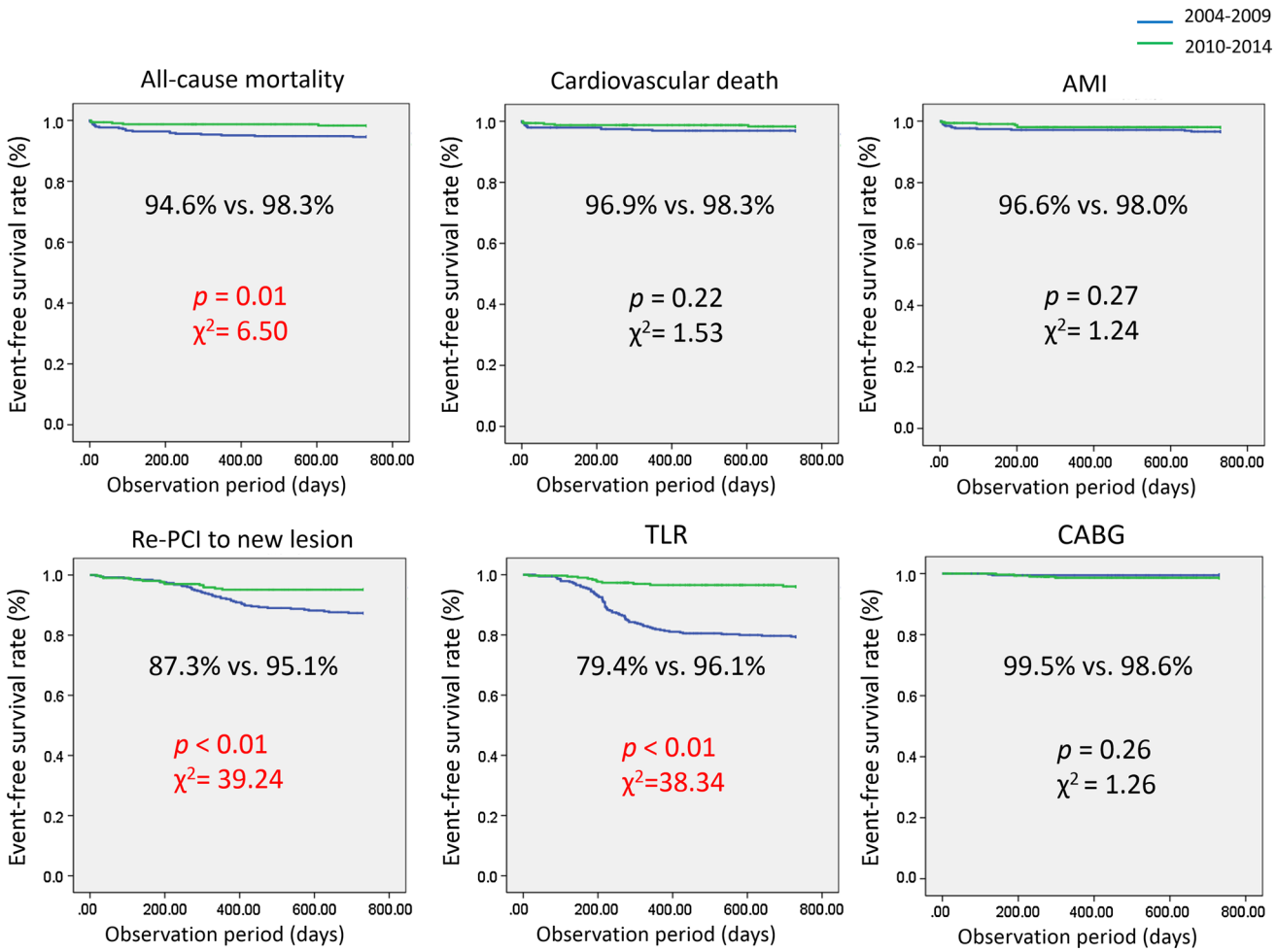

Fig. 2 Kaplan–Meier curves for patient outcomes

Temporal trends in patient outcomes

In the present study, we found remarkable decreases in the incidence rates of re-PCI to new lesions and TLR between 2004–2009 and 2010–2014.

Use of statins and time period (2010–2014 compared to 2004–2009) were significantly associated with the decrease in re-PCI to new lesions. It has been established that statins have atheroprotective and antiinflammatory effects, independent of their lipid-lowering effects, via improvement of endothelial function, reduction of smooth muscle cell proliferation and migration, and reduction in the number of smooth muscle cells along with reduction of the collagen content in plaques [16–19]. Therefore, it is natural that statin use was associated with a decrease in progression of new lesions. However, it is difficult to explain why time period (2010–2014 compared with 2004–2009) was independently associated with a decrease in re-PCI to new lesions even after adjustment for various cofactors, including the use of statins, regardless of the significant increases in hypertension and dyslipidemia. The time period may represent the current strict control of risk factors recommended by the guidelines [20–23]. Although there were no significant changes in SBP/DBP and/or LDL-Chol/HDL-Chol between two time periods at baseline, the control of risk factors may differ during the time course; unfortunately, however, our database lacks data regarding this issue.

Both time period (2010–2014 compared with 2004–2009) and 2nd-generation DES were significantly associated with decrease in TLR in univariate analysis. We assumed that the large increase in usage of 2nd-generation DES in 2010–2014 affected the difference between the two time periods. Unexpectedly, however, the effect of 2nd-generation DES on TLR was attenuated in the multivariate model, and time period was the only predictor of decrease in TLR. We speculated that the time period may represent change in stent selection from BMS in 2004–2009 to 2nd-generation DES in 2010–2014, because these stents accounted for approximately two-thirds of PCI in the respective time periods. However, there was a partial inverse relationship between

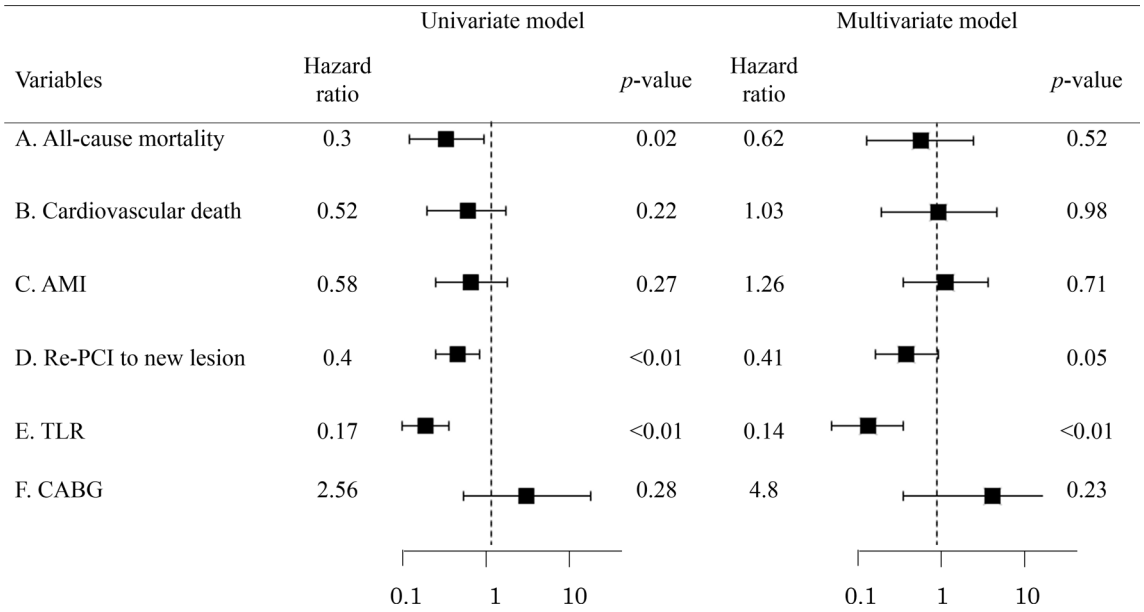

Fig. 3 Cox hazard analyses identified risk associated with time period (2010–2014 vs. with 2004–2009) for patient outcomes. The multivariate models were adjusted for 2nd-generation drug eluting stents, use of statins, age, male gender, body mass index, hypertension, diabetes mellitus, chronic kidney disease, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

Table 3 Bivariate models with time period and use of statin for Re-PCI to new lesions

Variables	Hazard ratio (95% CI)	*p* value
A. Univariate models		
2010–2014	0.40 (0.22–0.72)	<0.01
Use of statin	0.53 (0.32–0.88)	0.01
B. Multivariate model[a]		
2010–2014	0.45 (0.24–0.84)	0.01
Use of statin	0.57 (0.33–0.98)	0.04

[a]Adjusted for age, male gender, body mass index, hypertension, diabetes mellitus, chronic kidney disease, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

Table 4 Bivariate models with time period and 2nd-generation DES for TLR

Variables	Hazard ratio (95% CI)	*p* value
A. Univariate models		
2010–2014	0.17 (0.09–0.32)	<0.01
2nd-generation DES	0.28 (0.14–0.53)	<0.01
B. Multivariate model[a]		
2010–2014	0.14 (0.06–0.37)	<0.01
2nd-generation DES	1.24 (0.48–3.23)	0.65

DES drug-eluting stent

[a]Adjusted for age, male gender, body mass index, hypertension, diabetes mellitus, chronic kidney disease, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

the selection of stents and time period, where they were applied for some special cases with lesions showing irregular features, poorer patient background characteristics, lack of tolerance for dual antiplatelet therapy, etc. In this inverse relationship, DES was used in more complicated cases in 2004–2009, while BMS was unnecessarily applied for high-risk cases, and therefore the superiority of DES may have been partially weakened.

There were no significant differences in the incidence rates of cardiovascular death, AMI, or CABG between the two time periods. Considering the obvious improvements in both re-PCI to new lesions and TLR, we assumed that the small changes in incidence rates in these outcomes may have been due to the limited number of events in our hospital.

Limitations

Our study had several limitations. First, the study population was derived from a cohort of a single cardiovascular hospital. However, we can find that our data have a similarity, at least, to a large, multicenter cohort in Japan and in Chinese: (1) the distribution of ACS types in our population (STEMI 50%, NSTEMI 15%, and unstable angina 35%) was similar to that of the PACIFIC (Prevention of AtherothrombotiC Incidents Following Ischemic Coronary attack) Registry [6] in Japan, where STEMI, NSTEMI, and UAP accounted for 59, 10, and 30%, respectively (93.5% of patients underwent

PCI), and (2) in a Chinese multicenter registry [24], STEMI, NSTEMI, and UAP accounted for 45, 12, and 43%, respectively (the proportion of patients who underwent invasive procedure was 38%). Second, the follow-up period in the present study was within 2 years and the results cannot be extrapolated to those with longer term follow-up. Third, our data included patients with ACS in the initial PCI in our hospital, where the initial PCI accounted for one-third of whole PCI and ACS in the initial PCI accounted for half of whole ACS in our hospital. Accordingly, the population in the present study should have a smaller sample size and less severe conditions compared to those who repeatedly underwent PCI including ACS events.

Conclusions

This is a report from a longitudinal registration in a cardiovascular hospital in Japan, indicating that the event-free rates of TLR and re-PCI to new lesion have significantly decreased in patients with ACS undergoing PCI over the last decade. This evidence would serve to re-acknowledge the significance of PCI in ACS patients. However, real-world evidence should be confirmed in larger, longitudinal, multicenter registries.

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Compliance with ethical standards

Conflict of interest Dr. Suzuki and Dr. Takayuki Otsuka received research funding and remuneration from Nippon Boehringer Ingelheim. Dr. Yamashita received research funding from Nippon Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Nippon Boehringer Ingelheim, Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Eisai, and Ono Pharmaceutical.

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