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Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Report from the Japanese Nationwide Registry

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Title: Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Report from the Japanese Nationwide Registry

Running Title: Mortality risk model after PCI in Japan

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Abstract (291 words)

Objectives— Percutaneous coronary intervention (PCI) is applied in broad spectrum of coronary artery disease and accurate risk stratification is required to support clinical decision-making, and must be performed in the acute setting. We sought to develop and validate the risk model predicting in-hospital mortality in broad spectrum of patients after in Japan.

Design— Retrospective cohort study.

Setting— The Japanese PCI (J-PCI) registry includes a nationally representative retrospective sample of patients underwent PCI and covers approximately 88% of all PCIs in Japan.

Participants— A total of 669,181 patients who underwent PCI between January 2014 and December 2016 in 1018 institutes.

Main outcome measures— In-hospital death.

Results— Study population (N=669,181; mean [SD] age, 70.1 [11.0] years; female, 24.0%) was divided into a 50% sample for model derivation (N=334,591), with the remaining 50% used for model validation (N=334,590). Form derivation cohort, both "full" and "pre-procedure" risk models were developed using logistic regression. Using validation cohort, developed risk models were internally validated. In-hospital mortality rate was 0.7%. Pre-procedure model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoking, renal dysfunction, dialysis, peripheral vascular disease, previous heart failure, cardiogenic shock. Angiographic information, such as number of diseased vessel and location of target lesion was also included in the full model. Both models performed well in the entire validation cohort (C-indexes: 0.929 for full model and 0.926 for pre-procedure model, respectively) and among pre-specified subgroups, with good calibration, although both models underestimated the risk of mortality in high-risk patients with elective procedure.

Conclusions—These simple models from a nationwide Japanese PCI registry, easily applicable in clinical practice, and readily available directly at the patients' presentation, is a valid tool for pre-procedural risk stratification in patients undergoing

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PCI in contemporary Japanese practice.

Key Words: Risk model; Percutaneous coronary intervention; In-hospital mortality

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Article Summary

Strengths and limitations of this study

- We developed and internally validated the risk model predicting in-hospital mortality using a nationally representative sample of >650,000 patients underwent PCI in Japan, which enables to provide risk-adjusted mortality in benchmark report.
- For the clinical use, "pre-procedure" risk model that does not require procedure-related variables and a simplified integer risk score based on the pre-procedure model were also developed and internally validated, aiding in stratifying patients at risk of death pre-procedurally.
- Several variables selected in other risk models were not included in the J-PCI registry and may further refine risk prediction.
- The models underestimated the risk of mortality and could not provide an accurate estimation in elective procedure, mainly due to the small number of in-hospital deaths.

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Background

In Japan, percutaneous coronary interventions (PCIs) are widely available for both elective and acute settings, and >200,000 procedures are performed annually in >900 hospitals. On the advent of technology and technique in interventional cardiology, the current in-hospital mortality rate is about 1%.(1,2) However, PCI is applied onto wide spectrum of coronary artery disease, and its indication varies substantially across hospitals, especially between low and high volume centers, suggesting an opportunity for improvement.(1,2) Adjusted risk mortality is a core component of performance measures and used even for public reporting;(3) therefore, adjustment for the variation in patient risk across hospitals is critically important to enable an accurate assessment of each hospital's performance and opportunity to improve.

A number of risk prediction models for short-term mortality after PCI were developed within the last decade.(4-9) However, almost all of them share certain limitations: 1) they were not validated; 2) they were derived from small studies; and 3) the parameters used cannot be easily assessed directly in the catheterization lab. Furthermore, given favorable patient and laboratory profile (e.g. lesser risk of bleeding) for percutaneous procedures amongst the East Asian patients, PCI is applied onto significantly complex and 'sicker' group of patients in Japan. Hence, there remains a challenge to use these existing models for the risk adjustment due to the differences in biological responses for medication or procedure among ethnicities and practice pattern among counties.(10-12)

The risk prediction model from its own dataset is mandatory, especially when considering the adjustment for mortality in benchmark, eventually leading to improve quality of care in PCIs. The aims of this study were, using the nationwide Japanese PCI registry (J-PCI), 1) to develop two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings, one based on all available variables including both pre-procedure– and procedure-related variables, and the other based on pre-procedural variables only, 2) to internally validate the developed risk models, and 3) to develop and validate a clinician-friendly simplified integer risk score to enable pre-PCI risk stratification in clinical care.

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Methods

Data source

We analyzed patients who underwent PCI between January 2014 and December 2016 (n = 680,947) and were registered in the J-PCI. The J-PCI was established in 2007 and is a prospective Japanese nationwide multicenter registry of the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) designed to collect clinical variables and in-hospital outcome data on PCI patients.(1,13-15) Variables regarding patient background, clinical presentation, angiographic and procedure-related information, and in-hospital outcomes were collected for each patient. The CVIT registry subcommittee designed the software for the web-based data collection system, and each data manager in the participating hospitals submits data through this system annually. Because registration in the J-PCI database is mandatory for the application for board certification and renewal, although participation in the J-PCI is voluntary, data completeness is high. According to the annual reports of the Japanese Registry Of All cardiac and vascular Disease (JROAD), 773,359 PCIs (209,920 PCIs for acute indications and 563,439 PCIs for non-acute indications) were performed during the current study period (http://www.j-circ.or.jp/jittai_chosa/, accessed on February 14, 2018). Since we included a total of 680,947 PCIs, approximately 88% of all procedures in Japan were estimated to be registered in our registry. The accuracy of submitted data is maintained by data auditing (20 institutions annually), which is operated by members of the CVIT registry subcommittee.

The study protocol of the J-PCI registry was approved by the Institutional Review Board Committee at the Network for Promotion of Clinical Studies (a specified nonprofit organization affiliated with Osaka University Graduate School of Medicine, Osaka, Japan) and complied with the principles contained within the Declaration of Helsinki. Written informed consent was waived due to the retrospective study design.

Data Definitions

The primary outcome measure of the J-PCI analysis was in-hospital mortality, which

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was defined as all-cause mortality during hospitalization. Cardiogenic shock was defined as a sustained episode of systolic blood pressure <80 mmHg, and/or a cardiac index of <1.8 L/min/m^2 determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support including an intra-aortic balloon pump to maintain blood pressure and a cardiac index above the specified levels within 24 hour prior to the PCI procedures. Renal dysfunction in this registry was defined as the presence of proteinuria, or serum creatinine ≥1.3 mg/dL, or estimated glomerular filtration rate ≤60 mL/min/1.73m^2 according to guidelines from the Japanese Society of Nephrology.(16) The other definitions of J-PCI variables are available online (http://www.cvit.jp/registry/jpci_definition.pdf, accessed on February 14, 2018).

Statistical Analysis

The study cohort was randomly divided in a 1:1 ratio into derivation (n = 334,591) and validation (n = 334,590) cohorts, respectively. The demographics and clinical patient characteristics were summarized by enrollment year, and the data are presented as mean ± SD or as proportion (%), depending on the variables. Trend tests were performed using the Cochrane-Armitage test for trend.

All variables in **Table 1** except for procedure details were listed as initial candidate variables. Age was treated as continuous variable and the others were as dichotomous variables. For diagnosis, unstable angina, ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI) were included in the list of candidate variables from clinical judgment. After accounting for multicollinearity among candidate variables, final candidates for inclusion in the multivariable model were selected as follows: age, sex, clinical presentation (unstable angina, STEMI, NSTEMI), previous PCI, previous coronary artery bypass grafting, previous myocardial infarction (MI), diabetes, hypertension, dyslipidemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis, renal dysfunction on dialysis), chronic lung disease, peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure, number of diseased vessel (two vessel disease, three vessel disease, left main trunk lesion), and involvement of left anterior descending artery or left main trunk as a target lesion. Age was treated as a continuous variable, and other variables were treated dichotomously. Multivariable

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logistic regression with a backward selection method was then performed to identify independent predictors of in-hospital death. Package "step" in R was used for backward selection, in which elimination process was based on Akaike's Information Criterion.

From the derivation cohort, we developed two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings, one based on all available variables including both pre-procedure– and procedure-related variables ("full" model), and the other based on pre-procedural variables only (pre-procedure model). In addition, an integer score was assigned to each variable selected in the pre-procedure model in proportion to the estimated regression coefficient (0.23) defined from an incremental risk ratio per 10 years of age. The regression coefficient for each level of every risk factor was subsequently divided by this reference value (0.23) to compute its weights for the risk score.(17,18)

Using the validation cohort, the performance of the developed models was examined by using C-statistics to assess discrimination and by demonstrating calibration plots to evaluate calibration. After assessing discrimination and calibration across the entire validation cohort, we examined model performance for clinically distinct patient populations. These included acute coronary syndrome (ACS) vs. non-ACS, female vs. male, and advanced age (>70) vs. younger age (≤70).

All variables had less than 3% missingness. To account for missing data, single imputation was used for each variable; "STEMI" for type of MI, "transradial" for access site, and "No" for others. Data were analyzed using R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). All P-values are 2-sided with $P<0.05$ being considered statistically significant.

Patient and Public Involvement

Lack of the risk model predicting in-hospital mortality in patients undergoing PCI at hospitals participating in the J-PCI registry was the motivation to conduct this study. The development of the risk model enables to provide risk-adjusted mortality in benchmark report to each institute, leading to the improvement in quality of care and

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patient outcome in the field of PCI.

Results

Population Characteristics

After excluding patients with missing information regarding age and/or sex (n = 3410), patients outside the age range of 20 to 100 years (n = 281), missing information regarding outcomes (n = 647), and missing information regarding diagnosis (n = 43), a total of 669,181 patients from 1018 institutes were included in the analysis (**Figure 1**). The baseline demographics, lesion characteristics, and procedure details are summarized in **Table 1**, and in-hospital outcomes are shown in **Table 2**, stratified by enrollment year. About 40% of PCIs were performed for ACS and 3% of patients were complicated with cardiogenic shock within 24 hours prior to PCI. During the indexed hospitalization, a total of 4788 (0.7%) experienced death after PCI. The bivariate relationships between patient characteristics and in-hospital mortality are shown in the supplement (**eTable 1** for the derivation cohort and **eTable 2** for the validation cohort).

Between 2014 and 2016, demographics and risk factors of patients undergoing PCI did not change in terms of clinically meaningful difference. Regarding diagnosis at the time of PCI, the proportion of silent ischemic heart disease was slightly increased over time from 15.9% in 2014 to 17.4% in 2016, whereas PCIs for STEMI were decreasing from 18.6% to 17.3% (P values for trend <0.001). Procedures significantly changed during the study period. The rate of transradial approach increased significantly from 60.6% to 66.9%, in parallel with the decreasing trend of transfemoral approach (P values for trend <0.001). Similarly, the use of drug eluting balloon and drug eluting stent showed an increasing trend, whereas the use of bare metal stent decreased significantly (all P values for trend <0.001). In patients with STEMI, the use of thrombus aspiration remained stable during the study period, although its trend demonstrated the statistically significant increase (P value for trend =0.011).

Development of Full and Pre-procedure Models

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Table 3 shows the results of the multivariable logistic regression analyses. Pre-procedure variables selected in the final models were age, sex (female), STEMI, NSTEMI, unstable angina, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis, renal dysfunction on dialysis), peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure. All angiographic information, such as three-vessel disease, left main trunk lesion, and involvement of left anterior descending artery or left main trunk as a target lesion, were retained in the full model.

Discrimination and Calibration Performance of Full and Pre-procedure Models

In the entire validation cohort, discrimination performance of the full model was excellent, with C-index of 0.929 (95% confidence interval [CI], 0.924 – 0.935). The exclusion of the angiographic information from the full model resulted in only a slight decrement in the overall model discriminatory performance, and the C-index of the pre-procedure model was 0.926 (95% CI, 0.920 – 0.931). Both full and pre-procedure models performed well even in the pre-specified sub-groups, and C-index were ranging from 0.829 to 0.933 for the full model and from 0.820 to 0.926 for the pre-procedure model, respectively (**eTable 3 in the supplement**). There was excellent calibration performance of both models in the entire validation cohort (**eFigure 1 in the supplement)**. The calibration performance was also acceptable in the pre-specified subgroups, although both models were likely to underestimate the risk of mortality in high-risk patients with elective procedure (**eFigure 2 and eFigure 3 in the supplement**).

Development and Validation of Integer Simple Risk Score

The integer point for each variable derived from beta coefficients in the multivariable models are listed in **Figure 2**. The highest number of points was 12 for cardiogenic shock, whereas the lowest was −3 for dyslipidemia. The possible total points ranged from −6 to 43. The agreements between the observed and estimated risks of mortality with the developed risk-scoring methods were assessed across 5 groups in the entire

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validation cohort (**Figure 2**). Overall, the agreements were acceptable, although the integer score underestimated mortality risk in the higher risk patients, where the observed and predicted mortalities were 1.2% and 0.9% in the second highest risk group, 6.9% and 6.6% in the highest-risk group, respectively.

Discussion

Using the nationally representative cohort of Japanese patients undergoing PCI with >660,000 procedures from 1018 institutes, we developed and internally validated risk models predicting in-hospital mortality in patients after PCI. The final full model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoker, renal dysfunction, peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure, and angiographic information. The model performed very well in an independent validation cohort, as well as in various subgroups stratified by age, sex, and clinical presentation. The model performance was retained even after excluding angiographic information, and a simplified integer risk score based on the pre-procedure model also performed well. These developed risk prediction models enable to provide risk-adjusted mortality in benchmark report, compare an institution's performance with that of national experience, and stratify patient at risk pre-procedurally.

For the purpose of risk adjustment for benchmarking and comparing institutional performances, rigorous adjustment is warranted. It is well known that there are significant differences in patient demographics, biological response to medication or procedure, and practice pattern in PCI between Japan and the Western countries.(10,19) For example, patients are likely to be more advanced age and have lower body mass weight, and more frequently experienced bleeding complications. Furthermore, the proportion of PCIs for elective indications in Japan is greater than those in other countries. Regarding practice patterns, thrombus aspiration is still widely performed for treating patients with STEMI despite the recent downgrade of the relevant recommendations in the US and European guidelines.(20,21) In spite of these significant differences, some risk models or clinical scores that are derived from the Western countries have been externally validated and proved to be useful in Japanese

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patients.(10,22,23) Kohsaka et al. applied the in-hospital mortality risk model derived from the National Cardiovascular Data Registry CathPCI Registry, which is the nationwide PCI registry in the US, to the regional PCI registry from 15 Japanese institutes near Tokyo area, and demonstrated that the US model was clinically applicable in Japanese population with excellent discrimination and acceptable calibration performances.(10) However, given its limited calibration performance in high-risk patients, the risk model derived from its own dataset is preferable to provide an accurate adjusted mortality.

A number of risk models were developed from various registries to predict risk of mortality in patients undergoing PCI. Individual components varied among risk models, but the several components, such as age, clinical presentation or urgency, renal dysfunction, cardiogenic shock were consistently included in the model.(4-9) Our developed risk models also allied with the previous ones and included these core variables. Although angiographic information was also serving as a component of our full model, its incremental predictive value may be limited, given the sufficient performance of the pre-procedure model. This finding is consistent with the work of others and Peterson et al. showed that in-hospital mortality was driven primarily by pre-existing patient comorbidities and makers of clinical instability.(4) It has important clinical implications in that it allows patients and physicians to obtain a reasonable estimate of mortality pre-procedurally.

Few studies reported the risk model predicting mortality after PCI derived from Japanese population. Tanaka et al. developed the Kyoto Model using the CREDO-Kyoto Registry, which is one of the most established PCI registries in Japan.(24) However, the Kyoto Model intended to predict long-term mortality after revascularization and was not applicable to patients undergoing PCI for MI, because the dataset excluded the patients with acute MI within 1 week of the index procedure. Furthermore, the dataset included patients with revascularization between 2000 and 2002, and could not be directly applied to current practice. Our study is the first to report the risk model predicting in-hospital mortality in Japan using the nationwide PCI registry in the contemporary PCI practice. Thus, it will enable the Japanese cardiovascular society to provide an instrument for the pre-PCI risk stratification and

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to distribute the risk-adjusted mortality in benchmark reports, leading to improve quality of care and clinical outcome in PCI.

Several variables, such as prior PCI, hypertension, dyslipidemia, and current smoker, were identified as independent factors associated with reduction in mortality. Although some controversies remain and they may be attributed to confounding, their associations with improved mortality are consistent with the previous reports.(4,5,25-27) Smoker's paradox is a well-known phenomenon and has been reported in patients undergoing PCI.(26,27) Recent data have demonstrated a specific pharmacodynamic enhancement of platelet inhibition by clopidogrel among smokers,(28) which may hold important implications for patients treated with PCI, given that clopidogrel is still widely used for patients treated with PCI in Japan.(19) The protective effect of dyslipidemia may be related to the pre-PCI statin use. Meta-analysis demonstrated that statin administration before PCI significantly reduced the risk of post-procedural MI, resulting in the reduction in mortality.(29,30)

Limitations

This study has several limitations. First, J-PCI is a voluntary registry; the contributing hospitals may have larger procedure volume than the average institutes in Japan. However, J-PCI included >85% of all PCIs performed in Japan and assured high participation rate by linking to the application for board certification and renewal. Second, improving the quality of the database is a continuing issue in J-PCI. For data accuracy, not only is data auditing important but also the education of persons inputting data at each site to enable adherence to correct data definitions. Third, the candidate variables for the risk models were limited to those available in J-PCI. Actually, several variables selected in other risk models were not included in our dataset and may further refine risk prediction. Fourth, the models underestimated the risk of mortality in high-risk patients with elective procedure, although their discrimination and calibration performances were acceptable. Since the developed risk models cover patients with broad range of mortality risk, it is challenging to provide an accurate estimation for all patients, especially in low-risk patients mainly due to the small number of in-hospital deaths. Further works may be required to generate separate

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models according to the clinical presentation for the better risk prediction. Finally, the models have been validated using only J-PCI data; it has not been validated on an external dataset.

Conclusion

Using the nationwide Japanese PCI registry, we have developed and internally validated the risk models for predicting in-hospital mortality after PCI. The models performed very well in broad spectrum of patients undergoing PCI as well as in clinically important subgroups. These models should enable to improve patient mortality after PCI by facilitating pre-PCI risk stratification, improving hospital quality assessment, and providing an accurate adjusted risk in benchmark reports.

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Author Contributions

T Inohara and S Kohsaka had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: **T Inohara and S Kohsaka**

Acquisition, analysis, or interpretation of data: **T Inohara, S Kohsaka, K Yamaji, H Ishii, T Amano, S Uemura, K Kadota, H Kumamaru, H Miyata, and M Nakamura**

Drafting of the manuscript: **T Inohara and S Kohsaka**

Critical revision of the manuscript for important intellectual content: **S Kohsaka, K Yamaji, H Ishii, T Amano, S Uemura, K Kadota, H Kumamaru, H Miyata, and M Nakamura**

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Study supervision: **S Kohsaka, H Kumamaru, H Miyata, and M Nakamura**

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Data Sharing Statement

In addition to data in this manuscript, all data in the J-PCI registry are available to investigators from >1000 sites participating in the J-PCI registry. The dataset are stored in servers of the National Clinical Database (NCD). Local investigators can submit proposal for data use for research purposes.

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Figure Legends

Figure 1. Study cohort creation
Abbreviations: PCI, percutaneous coronary intervention

Figure 2. Integer score and its calibration performance
The agreements between the observed and expected risks of mortality with the developed integer score were assessed across 5 groups of the total points in the validation cohort.
Abbreviations: Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort

eFigure 2. Calibration plots of full model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

eFigure 3. Calibration plots of pre-procedure model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

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Table 1. Baseline characteristics by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	*P*
Demographics				
Age, yrs, mean (SD)	69.97 (10.99)	70.08 (11.04)	70.26 (11.07)	<0.001
Female	50747 (24.1)	52048 (23.9)	57677 (24.0)	0.218
Diagnosis				<0.001
Elective setting				
Stable angina	80244 (38.1)	83258 (38.2)	91894 (38.2)	
Silent ischemic heart disease	33550 (15.9)	36431 (16.7)	41764 (17.4)	
Old myocardial infarction	12528 (6.0)	13034 (6.0)	14152 (5.9)	
Acute setting				
Unstable angina	33985 (16.1)	33582 (15.4)	37599 (15.6)	
Myocardial infarction	50237 (23.9)	51684 (23.7)	55239 (23.0)	
STEMI	39140 (18.6)	40050 (18.4)	41740 (17.3)	
NSTEMI	9217 (4.4)	9844 (4.5)	11453 (4.8)	
Risk Factors				
Previous PCI	96877 (46.2)	99896 (46.6)	110163 (46.5)	0.022
Previous CABG	8871 (4.2)	8525 (4.0)	8949 (3.8)	<0.001
Previous MI	48620 (23.4)	49547 (23.3)	54073 (22.9)	0.001
Diabetes Mellitus	90152 (42.8)	94250 (43.2)	105066 (43.7)	<0.001
Hypertension	155985 (74.1)	162075 (74.4)	178889 (74.3)	0.083

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Hypercholesterolemia	130740 (62.1)	137264 (63.0)	153059 (63.6)	<0.001
Current smoker	64368 (30.6)	67385 (30.9)	74027 (30.8)	0.054
Renal Insufficiency	35366 (16.8)	37857 (17.4)	43460 (18.1)	<0.001
On dialysis	13099 (6.2)	13649 (6.3)	15601 (6.5)	<0.001
Chronic lung disease	3347 (1.6)	4039 (1.9)	5336 (2.2)	<0.001
Peripheral Vascular Disease	13273 (6.3)	15169 (7.0)	18064 (7.5)	<0.001
Previous heart failure	26105 (12.8)	27667 (13.1)	31478 (13.4)	<0.001
Cardiopulmonary arrest on arrival	3285 (1.6)	3311 (1.6)	4137 (1.7)	<0.001
Cardiogenic shock within 24 hrs	6023 (2.9)	6307 (3.0)	7429 (3.1)	<0.001
Acute heart failure within 24 hrs	8217 (4.0)	8082 (3.8)	9347 (4.0)	0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	126593 (60.1)	133649 (61.3)	150477 (62.5)	<0.001
Two vessel disease	55997 (26.6)	56117 (25.7)	60936 (25.3)	<0.001
Three vessel disease	27205 (12.9)	27371 (12.6)	28424 (11.8)	<0.001
Left main trunk	8322 (4.0)	9129 (4.2)	9688 (4.0)	<0.001
Lesion Location:				
RCA	73309 (34.8)	74356 (34.1)	81482 (33.9)	<0.001
LAD/Left Main	106996 (50.8)	111132 (51.0)	123788 (51.4)	<0.001
LCX	54314 (25.8)	55638 (25.5)	60444 (25.1)	<0.001
Bypass graft	2163 (1.0)	1189 (0.5)	1202 (0.5)	<0.001
Procedure details				
Approach				<0.001

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Transradial	127686 (60.6)	138397 (63.5)	161104 (66.9)	
Transfemoral	71473 (33.9)	67668 (31.0)	67166 (27.9)	
Others (e.g. brachial)	11376 (5.4)	11924 (5.5)	12378 (5.1)	
Device				
Thrombus aspiration[a]	21551/39140 (55.1)	21640/40050 (54.0)	22605/41740 (54.2)	<0.001
Distal protection	7392 (3.5)	8077 (3.7)	7519 (3.1)	<0.001
Rotablader	7294 (3.5)	7686 (3.5)	8910 (3.7)	<0.001
Drug eluting balloon	12922 (6.1)	15769 (7.2)	22916 (9.5)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	166194 (78.9)	184327 (84.6)	206323 (85.7)	<0.001
Bare metal stent	14854 (7.1)	7807 (3.6)	4966 (2.1)	<0.001
TIMI flow post-procedure				
Flow 3	205978 (97.8)	213709 (98.0)	235969 (98.1)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; TIMI, Thrombolysis in Myocardial Infarction.

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Table 2. Crude outcomes by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	*P*
In-hospital death	1523 (0.7)	1479 (0.7)	1786 (0.7)	0.033
Bleeding complication	546 (0.3)	701 (0.3)	779 (0.3)	<0.001
Access site bleeding	334 (0.2)	429 (0.2)	460 (0.2)	0.007
Non-access site bleeding	223 (0.1)	287 (0.1)	341 (0.1)	0.003
Periprocedural MI	875 (0.4)	921 (0.4)	1140 (0.5)	0.005
Tamponade	317 (0.2)	287 (0.1)	350 (0.1)	0.234
Post-procedure shock	1920 (0.9)	1927 (0.9)	2145 (0.9)	0.603
Acute stent thrombosis	407 (0.2)	331 (0.2)	297 (0.1)	<0.001
Emergent operation	206 (0.1)	213 (0.1)	204 (0.1)	0.246

Abbreviations: MI, myocardial infarction.

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Table 3. Full and pre-procedure risk model

	Full Model				Pre-procedure Model			
	Coefficient	OR	95% CI	*P*	Coefficient	OR	95% CI	*P*
Intercept	-8.878621				-8.472575			
Demographics								
Age, per 1 year	0.023744	1.02	1.02 - 1.03	<0.001	0.023608	1.02	1.02 - 1.03	<0.001
Female	0.177372	1.19	1.08 - 1.32	<0.001	0.155252	1.17	1.06 - 1.29	0.002
Diagnosis								
STEMI	2.528622	12.5	10.7 - 14.7	<0.001	2.530134	12.6	10.7 - 14.7	<0.001
NSTEMI	2.170769	8.77	7.24 - 10.6	<0.001	2.260405	9.59	7.93 - 11.6	<0.001
Unstable angina	1.108935	3.03	2.50 - 3.68	<0.001	1.163039	3.2	2.64 - 3.88	<0.001
Risk Factors								
Previous PCI	-0.121767	0.89	0.79 - 0.99	0.029	-0.170187	0.84	0.76 - 0.94	0.002
Previous CABG	0.371319	1.45	1.17 - 1.79	<0.001	0.38463	1.47	1.19 - 1.81	<0.001
Hypertension	-0.181962	0.83	0.76 - 0.91	<0.001	-0.175804	0.84	0.77 - 0.92	<0.001
Hypercholesterolemia	-0.55876	0.57	0.52 - 0.63	<0.001	-0.540339	0.58	0.53 - 0.64	<0.001
Current smoker	-0.19942	0.82	0.74 - 0.91	<0.001	-0.210493	0.81	0.73 - 0.90	<0.001
Renal Insufficiency without Dialysis	0.522425	1.69	1.51 - 1.88	<0.001	0.552934	1.74	1.56 - 1.93	<0.001
Renal Insufficiency on Dialysis	0.827209	2.29	1.95 - 2.69	<0.001	0.821163	2.27	1.94 - 2.67	<0.001
Peripheral Vascular Disease	0.457832	1.58	1.35 - 1.85	<0.001	0.498317	1.65	1.41 - 1.92	<0.001
Previous heart failure	0.451346	1.57	1.40 - 1.77	<0.001	0.491731	1.64	1.45 - 1.84	<0.001

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Cardiogenic shock within 24 hrs	2.540633	12.7	11.6 - 13.9	<0.001	2.67607	14.5	13.3 - 15.9	<0.001
Number of Diseased Vessels								
Three vessel disease	0.368771	1.45	1.31 - 1.60	<0.001				
Left main trunk	0.680996	1.98	1.75 - 2.23	<0.001				
Lesion Location								
LAD/Left Main	0.527633	1.69	1.55 - 1.86	<0.001				

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LAD, left anterior descending.

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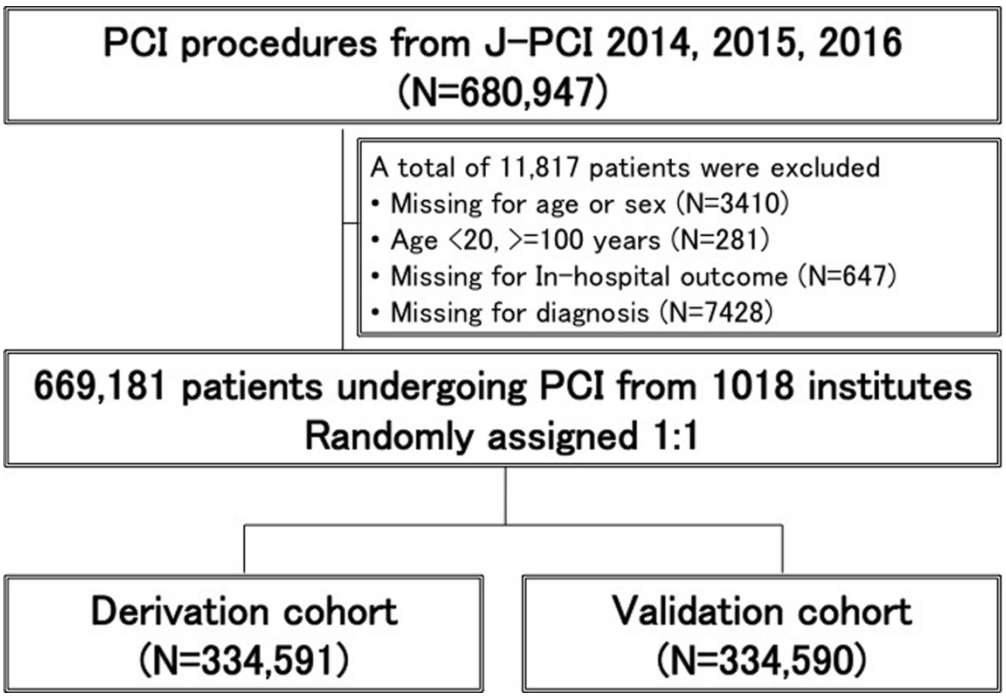

Figure 1. Study cohort creation

233x160mm (300 x 300 DPI)

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	Beta Coefficient	Score
Demograohics		
Age	0.023608	
20-29		0
30-39		1
40-49		2
50-59		3
60-69		4
70-79		5
80-89		6
90-99		7
Female	0.155252	1
Diagnosis		
STEMI	2.530134	11
NSTEMI	2.260405	10
Unstable angina	1.163039	5
Risk Factors		
Previous PCI	-0.170187	-1
Previous CABG	0.38463	2
Hypertension	-0.175804	-1
Hypercholesterolemia	-0.540339	-3
Current smoker	-0.210493	-1
Renal Insufficiency without Dialysis	0.552934	3
Renal Insufficiency on Dialysis	0.821163	4
Peripheral Vascular Disease	0.498317	3
Previous heart failure	0.491731	3
Cardiogenic shock within 24 hrs	2.67607	12

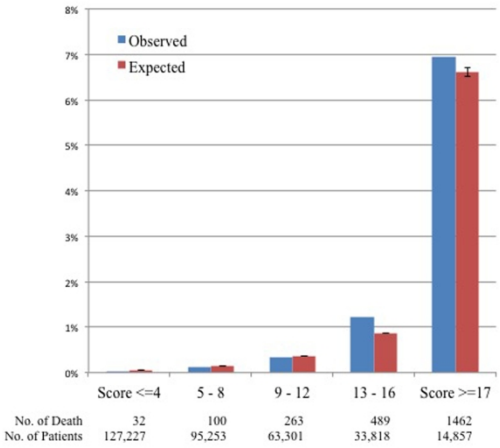

Figure 2. Integer score and its calibration performance

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Supplemental Material

eTable 1. Derivation cohort

	Overall N=334591	Death, No N=332130	Death, Yes N=2461	*P*
Demographics				
Age, yrs, mean (SD)	70.09 (11.03)	70.06 (11.02)	74.15 (12.13)	<0.001
Female	79981 (23.9)	79196 (23.8)	785 (31.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127639 (38.1)	127544 (38.4)	95 (3.9)	
Silent ischemic heart disease	55975 (16.7)	55894 (16.8)	81 (3.3)	
Old myocardial infarction	19862 (5.9)	19831 (6.0)	31 (1.3)	
Acute setting				
Unstable angina	52703 (15.8)	52490 (15.8)	213 (8.7)	
Myocardial infarction	78412 (23.4)	76371 (23.0)	2041 (82.9)	
STEMI	60408 (18.1)	58837 (17.7)	1571 (63.8)	
NSTEMI	15145 (4.5)	14850 (4.5)	295 (12.0)	
Risk Factors				
Previous PCI	153791 (46.5)	153216 (46.7)	575 (23.9)	<0.001
Previous CABG	13310 (4.0)	13192 (4.0)	118 (4.9)	0.041
Previous MI	75965 (23.1)	75499 (23.2)	466 (19.7)	<0.001
Diabetes Mellitus	144880 (43.3)	143857 (43.3)	1023 (41.6)	0.085
Hypertension	248534 (74.3)	246954 (74.4)	1580 (64.2)	<0.001
Hypercholesterolemia	210860 (63.0)	209898 (63.2)	962 (39.1)	<0.001
Current smoker	103072 (30.8)	102456 (30.8)	616 (25.0)	<0.001
Renal Insufficiency	58278 (17.4)	57455 (17.3)	823 (33.4)	<0.001
On dialysis	21174 (6.3)	20939 (6.3)	235 (9.5)	<0.001
Chronic lung disease	6383 (1.9)	6311 (1.9)	72 (2.9)	<0.001
Peripheral Vascular Disease	23270 (7.0)	23033 (6.9)	237 (9.6)	<0.001
Previous heart failure	42743 (13.2)	42249 (13.1)	494 (21.0)	<0.001
Cardiopulmonary arrest on arrival	5450 (1.7)	4476 (1.4)	974 (40.0)	<0.001
Cardiogenic shock within 24 hrs	9903 (3.0)	8512 (2.6)	1391 (57.3)	<0.001
Acute heart failure within 24 hrs	12952 (4.0)	11761 (3.6)	1191 (49.5)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	204905 (61.2)	203905 (61.4)	1000 (40.6)	<0.001
Two vessel disease	86917 (26.0)	86253 (26.0)	664 (27.0)	0.264
Three vessel disease	41600 (12.4)	40927 (12.3)	673 (27.3)	<0.001
Left main trunk	13483 (4.0)	13040 (3.9)	443 (18.0)	<0.001
Lesion Location:				

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RCA	114891 (34.3)	114069 (34.3)	822 (33.4)	0.337
LAD/Left Main	170823 (51.1)	169149 (50.9)	1674 (68.0)	<0.001
LCX	85244 (25.5)	84583 (25.5)	661 (26.9)	0.12
Bypass graft	2261 (0.7)	2234 (0.7)	27 (1.1)	0.015
Procedure details				
Approach				<0.001
Transradial	213314 (63.8)	212740 (64.1)	574 (23.3)	
Transfemoral	103410 (30.9)	101690 (30.6)	1720 (69.9)	
Others (e.g. brachial)	17864 (5.3)	17697 (5.3)	167 (6.8)	
Device				
Thrombus aspiration[a]	33067/60408 (54.7)	32264/58837 (54.8)	803/1571 (51.1)	<0.001
Distal protection	11468 (3.4)	11354 (3.4)	114 (4.6)	0.001
Rotablader	11937 (3.6)	11865 (3.6)	72 (2.9)	0.095
Drug eluting balloon	25907 (7.7)	25851 (7.8)	56 (2.3)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278173 (83.1)	276424 (83.2)	1749 (71.1)	<0.001
Bare metal stent	13927 (4.2)	13697 (4.1)	230 (9.3)	<0.001
TIMI flow post-procedure				
Flow 3	327771 (98.0)	325613 (98.0)	2158 (87.7)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 2. Validation cohort

	Overall N=334590	Death, No N=332263	Death, Yes N=2327	*P*
Demographics				
Age, yrs, mean (SD)	70.13 (11.04)	70.09 (11.03)	74.78 (11.95)	<0.001
Female	80491 (24.1)	79702 (24.0)	789 (33.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127757 (38.2)	127673 (38.4)	84 (3.6)	
Silent ischemic heart disease	55770 (16.7)	55680 (16.8)	90 (3.9)	
Old myocardial infarction	19852 (5.9)	19805 (6.0)	47 (2.0)	
Acute setting				
Unstable angina	52463 (15.7)	52243 (15.7)	220 (9.5)	
Myocardial infarction	78748 (23.5)	76862 (23.1)	1886 (81.0)	
STEMI	60522 (18.1)	59085 (17.8)	1437 (61.8)	
NSTEMI	15369 (4.6)	15083 (4.5)	286 (12.3)	
Risk Factors				
Previous PCI	153145 (46.3)	152590 (46.5)	555 (24.3)	<0.001
Previous CABG	13035 (3.9)	12931 (3.9)	104 (4.5)	0.175
Previous MI	76275 (23.2)	75832 (23.3)	443 (19.7)	<0.001
Diabetes Mellitus	144588 (43.2)	143595 (43.2)	993 (42.7)	0.612
Hypertension	248415 (74.2)	246933 (74.3)	1482 (63.7)	<0.001
Hypercholesterolemia	210203 (62.8)	209296 (63.0)	907 (39.0)	<0.001
Current smoker	102708 (30.7)	102209 (30.8)	499 (21.4)	<0.001
Renal Insufficiency	58405 (17.5)	57666 (17.4)	739 (31.8)	<0.001
On dialysis	21175 (6.3)	20959 (6.3)	216 (9.3)	<0.001
Chronic lung disease	6339 (1.9)	6259 (1.9)	80 (3.4)	<0.001
Peripheral Vascular Disease	23236 (6.9)	23027 (6.9)	209 (9.0)	<0.001
Previous heart failure	42507 (13.1)	42024 (13.0)	483 (21.8)	<0.001
Cardiopulmonary arrest on arrival	5283 (1.6)	4442 (1.4)	841 (36.5)	<0.001
Cardiogenic shock within 24 hrs	9856 (3.0)	8603 (2.6)	1253 (54.6)	<0.001
Acute heart failure within 24 hrs	12694 (3.9)	11605 (3.6)	1089 (48.0)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	205814 (61.5)	204889 (61.7)	925 (39.8)	<0.001
Two vessel disease	86133 (25.7)	85477 (25.7)	656 (28.2)	0.007
Three vessel disease	41400 (12.4)	40748 (12.3)	652 (28.0)	<0.001
Left main trunk	13656 (4.1)	13247 (4.0)	409 (17.6)	<0.001
Lesion Location:				
RCA	114256 (34.1)	113461 (34.1)	795 (34.2)	1
LAD/Left Main	171093 (51.1)	169519 (51.0)	1574 (67.6)	<0.001
LCX	85152 (25.4)	84496 (25.4)	656 (28.2)	0.003

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Bypass graft	2293 (0.7)	2276 (0.7)	17 (0.7)	0.889
Procedure details				
Approach				<0.001
Transradial	213873 (63.9)	213341 (64.2)	532 (22.9)	
Transfemoral	102897 (30.8)	101265 (30.5)	1632 (70.1)	
Others (e.g. brachial)	17814 (5.3)	17651 (5.3)	163 (7.0)	
Device				
Thrombus aspiration[a]	32729/60522 (54.1)	31993/59085 (54.1)	736/1437 (51.2)	<0.001
Distal protection	11520 (3.4)	11430 (3.4)	90 (3.9)	0.284
Rotablader	11953 (3.6)	11874 (3.6)	79 (3.4)	0.684
Drug eluting balloon	25700 (7.7)	25637 (7.7)	63 (2.7)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278671 (83.3)	277032 (83.4)	1639 (70.4)	<0.001
Bare metal stent	13700 (4.1)	13451 (4.0)	249 (10.7)	<0.001
TIMI flow post-procedure				
Flow 3	327885 (98.0)	325799 (98.1)	2086 (89.6)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 3. Discrimination performance of full and pre-procedure models

			Full Model		Pre-procedure Model	
	Sample, n	Death, n	C-index	95% CI	C-index	95% CI
Derivation cohort	334591	2461	0.929	0.924 - 0.935	0.926	0.920 - 0.931
Validation cohort	334590	2327	0.923	0.917 - 0.928	0.918	0.912 - 0.923
Subgroups (in validation cohort)						
ACS	131211	2106	0.886	0.879 - 0.893	0.876	0.868 - 0.883
Elective	203379	221	0.829	0.800 - 0.858	0.82	0.790 - 0.850
Female	80491	789	0.907	0.897 - 0.918	0.901	0.890 - 0.912
Male	254099	1538	0.927	0.920 - 0.934	0.922	0.915 - 0.929
Age >70	176629	1570	0.912	0.905 - 0.920	0.908	0.900 - 0.915
Age <=70	157204	757	0.933	0.924 - 0.942	0.926	0.916 - 0.935

Abbreviations: ACS, acute coronary syndrome.

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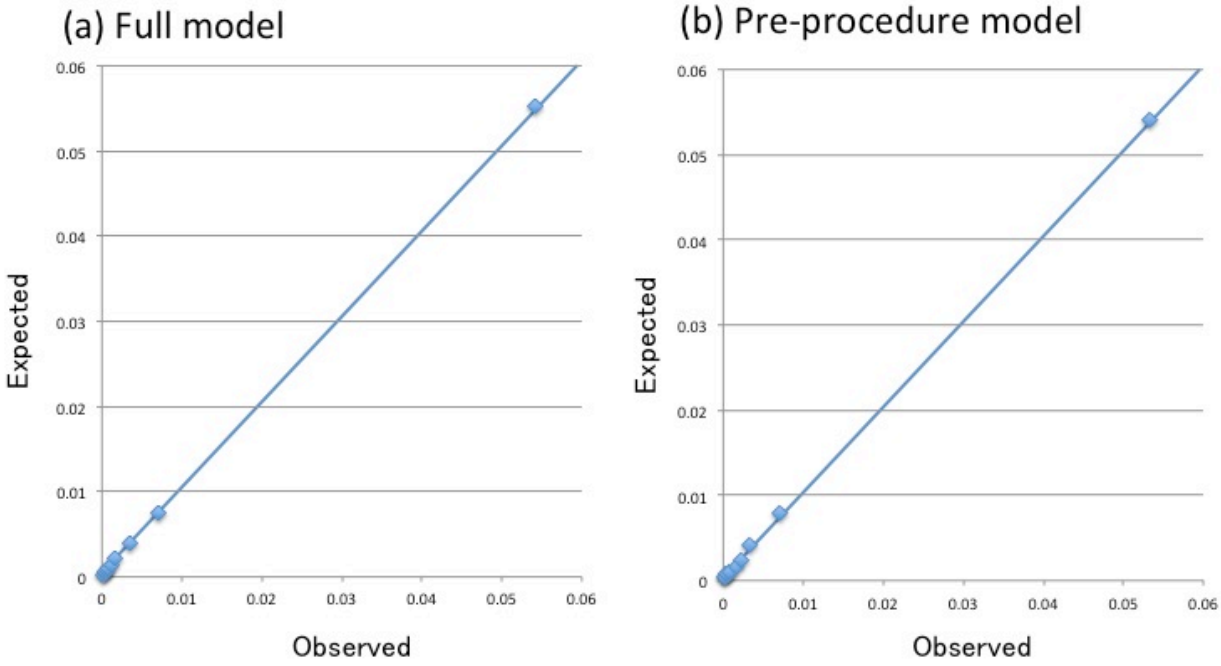
eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort



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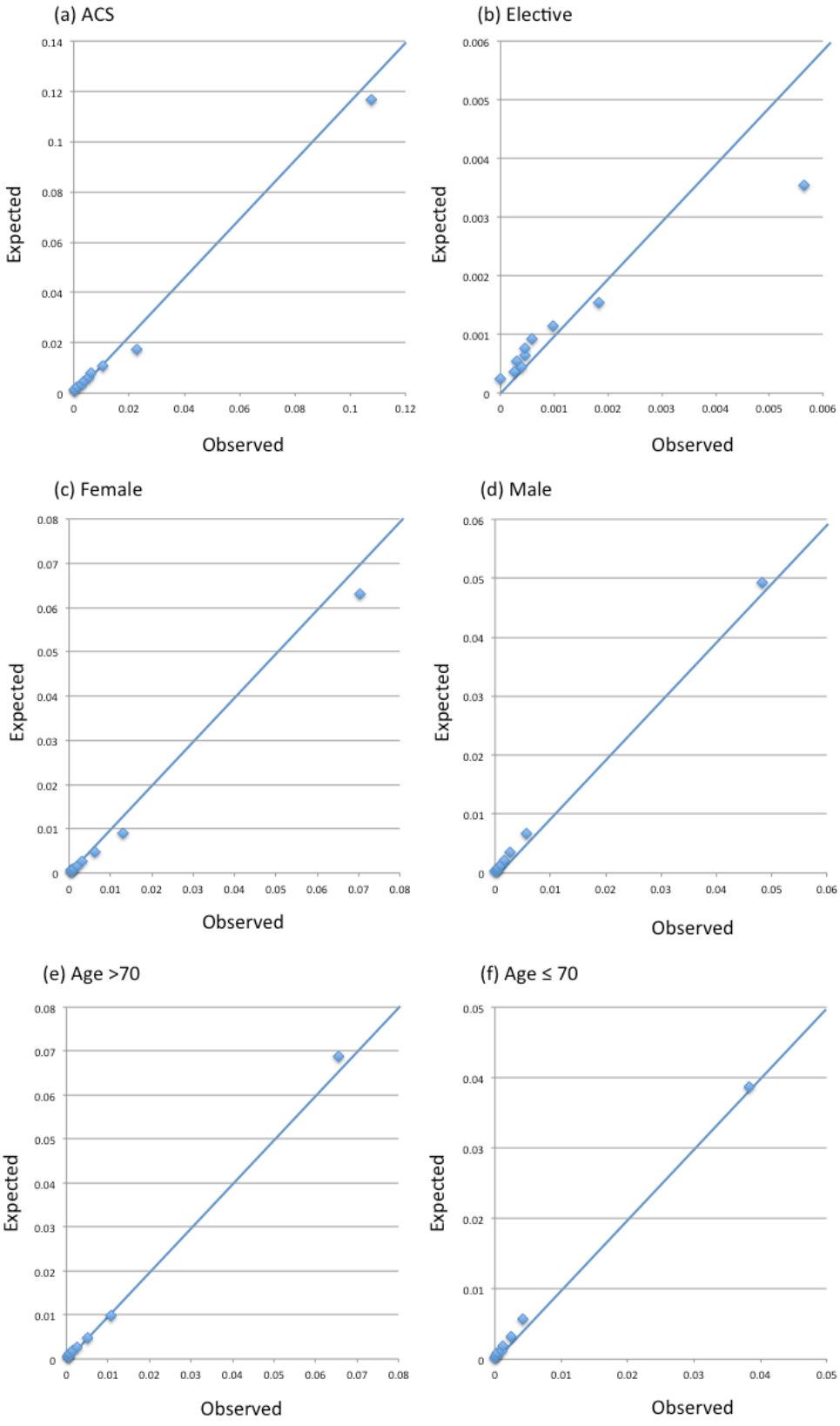
eFigure 2. Calibration plots of full model in subgroups



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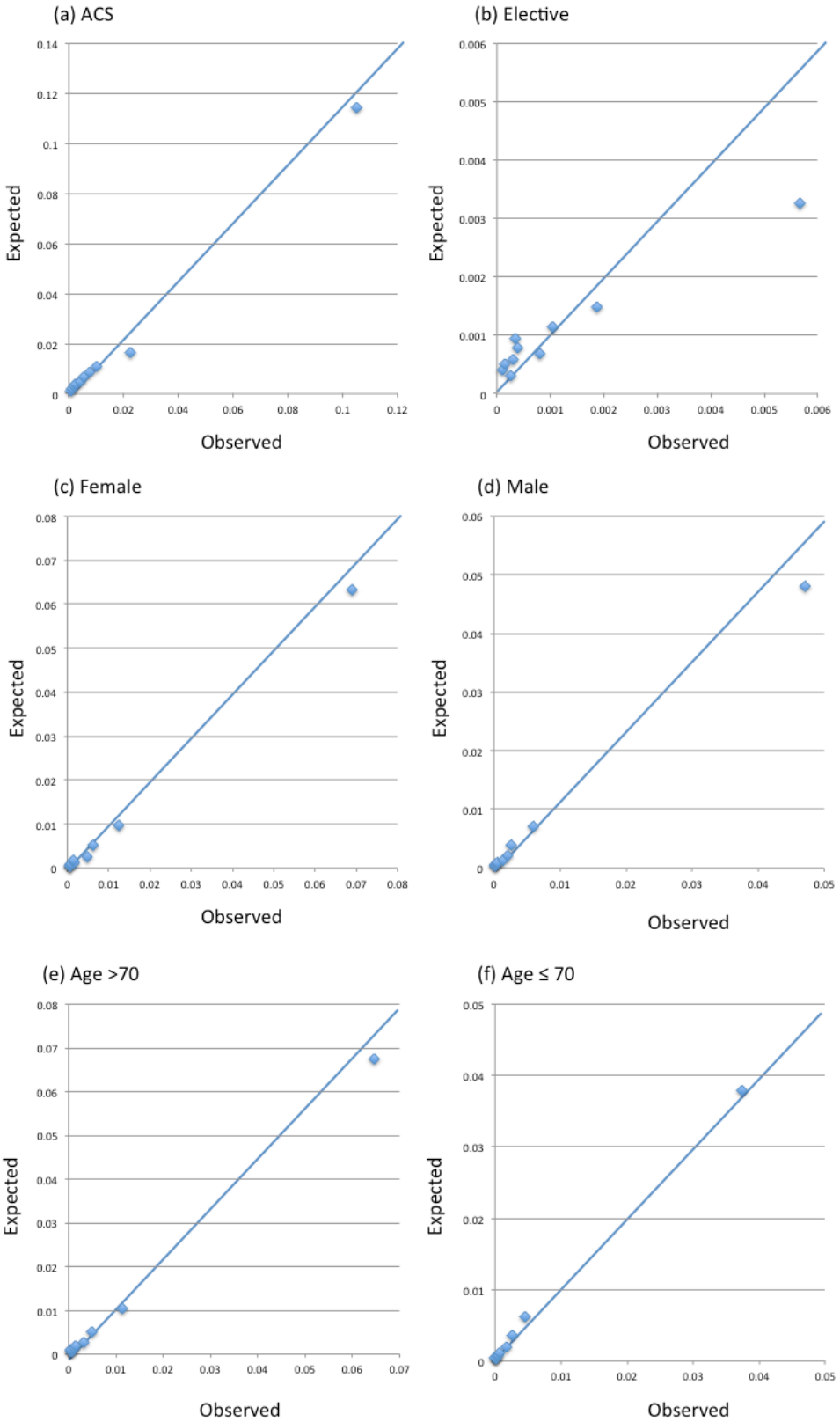
eFigure 3. Calibration plots of pre-procedure model in subgroups



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STROBE Statement: Checklist

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, page 7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes, page 7
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, pages 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, pages 7-9
Bias	9	Describe any efforts to address potential sources of bias	Yes, pages 8-9
Study size	10	Explain how the study size was arrived at	Yes, page 9

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, pages 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, page 9
		(*c*) Explain how missing data were addressed	Yes, page 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Only in-hospital outcomes were evaluated. Patients with missing for outcomes were excluded from the analysis. Page 9
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	Yes, page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, pages 9-10
		(b) Give reasons for non-participation at each stage	Yes, pages 9-10
		(c) Consider use of a flow diagram	Yes, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Although precise numbers of missingness are not presented, the percentages are described. Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Only in-hospital outcomes were evaluated. Pages 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Yes, Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Yes, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No. Only adjusted odds ratios are presented.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, eTable 3, eFigure 2, eFigure 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, page 11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, throughout the Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, page 2

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BMJ Open

Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Report from the Japanese Nationwide Registry

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Risk model, Percutaneous coronary intervention, In-hospital mortality

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1

Title: Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Report from the Japanese Nationwide Registry

Running Title: Mortality risk model after PCI in Japan

Authors:

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Conflict of Interest: None declared.

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Abstract (290 words)

Objectives— Percutaneous coronary intervention (PCI) is applied in broad spectrum of coronary artery disease and accurate risk stratification is required to support clinical decision-making, and must be performed in the acute setting. We sought to develop and validate the risk model predicting in-hospital mortality in broad spectrum of patients after in Japan.

Design— Retrospective cohort study.

Setting— The Japanese PCI (J-PCI) registry includes a nationally representative retrospective sample of patients underwent PCI and covers approximately 88% of all PCIs in Japan.

Participants— A total of 669,181 patients who underwent PCI between January 2014 and December 2016 in 1018 institutes.

Main outcome measures— In-hospital death.

Results— Study population (N=669,181; mean [SD] age, 70.1 [11.0] years; female, 24.0%) was divided into a 50% sample for model derivation (N=334,591), with the remaining 50% used for model validation (N=334,590). Form derivation cohort, both "full" and "pre-procedure" risk models were developed using logistic regression. Using validation cohort, developed risk models were internally validated. In-hospital mortality rate was 0.7%. Pre-procedure model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoking, renal dysfunction, dialysis, peripheral vascular disease, previous heart failure, cardiogenic shock. Angiographic information, such as number of diseased vessel and location of target lesion was also included in the full model. Both models performed well in the entire validation cohort (C-indexes: 0.929 for full model and 0.926 for pre-procedure model, respectively) and among pre-specified subgroups, with good calibration, although both models underestimated the risk of mortality in high-risk patients with elective procedure.

Conclusions—These simple models from a nationwide Japanese PCI registry, easily applicable in clinical practice, and readily available directly at the patients' presentation, is a valid tool for pre-procedural risk stratification in patients undergoing

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PCI in contemporary Japanese practice.

Key Words: Risk model; Percutaneous coronary intervention; In-hospital mortality

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Article Summary

Strengths and limitations of this study

- We developed and internally validated the risk model predicting in-hospital mortality using a nationally representative sample of >650,000 patients underwent PCI in Japan, which enables to provide risk-adjusted mortality in benchmark report.
- For the clinical use, "pre-procedure" risk model that does not require procedure-related variables and a simplified integer risk score based on the pre-procedure model were also developed and internally validated, aiding in stratifying patients at risk of death pre-procedurally.
- Several variables selected in other risk models were not included in the J-PCI registry and may further refine risk prediction.
- The models underestimated the risk of mortality and could not provide an accurate estimation in elective procedure, mainly due to the small number of in-hospital deaths.

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Background

In Japan, percutaneous coronary interventions (PCIs) are widely available for both elective and acute settings, and >200,000 procedures are performed annually in >1000 hospitals. On the advent of technology and technique in interventional cardiology, the current in-hospital mortality rate is about 1%.(1,2) However, PCI is applied onto wide spectrum of coronary artery disease, and its indication varies substantially across hospitals, especially between low and high volume centers, suggesting an opportunity for improvement.(1,2) Adjusted risk mortality is a core component of performance measures and used even for public reporting;(3) therefore, adjustment for the variation in patient risk across hospitals is critically important to enable an accurate assessment of each hospital's performance and opportunity to improve.

A number of risk prediction models for short-term mortality after PCI were developed within the last decade.(4-9) However, almost all of them share certain limitations: 1) they were not validated; 2) they were derived from small studies; and 3) the parameters used cannot be easily assessed directly in the catheterization lab. Furthermore, given favorable patient and laboratory profile (e.g. lesser risk of bleeding) for percutaneous procedures amongst the East Asian patients, PCI is applied onto significantly complex and 'sicker' group of patients in Japan. Hence, there remains a challenge to use these existing models for the risk adjustment due to the differences in biological responses for medication or procedure among ethnicities and practice pattern among counties.(10-12)

The risk prediction model from its own dataset is mandatory, especially when considering the adjustment for mortality in benchmark, eventually leading to improve quality of care in PCIs. The aims of this study were, using the nationwide Japanese PCI registry (J-PCI), 1) to develop two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings, one based on all available variables including both pre-procedure– and procedure-related variables, and the other based on pre-procedural variables only, 2) to internally validate the developed risk models, and 3) to develop and validate a clinician-friendly simplified integer risk score to enable pre-PCI risk stratification in clinical care.

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Methods

Data source

We analyzed patients who underwent PCI between January 2014 and December 2016 (n = 680,947) and were registered in the J-PCI. The J-PCI was established in 2007 and is a prospective Japanese nationwide multicenter registry of the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) designed to collect clinical variables and in-hospital outcome data on PCI patients.(1,13-15) Variables regarding patient background, clinical presentation, angiographic and procedure-related information, and in-hospital outcomes were collected for each patient. The CVIT registry subcommittee designed the software for the web-based data collection system, and each data manager in the participating hospitals submits data through this system annually. Because registration in the J-PCI database is mandatory for the application for board certification and renewal, although participation in the J-PCI is voluntary, data completeness is high. According to the annual reports of the Japanese Registry Of All cardiac and vascular Disease (JROAD), 773,359 PCIs (209,920 PCIs for acute indications and 563,439 PCIs for non-acute indications) were performed during the current study period (http://www.j-circ.or.jp/jittai_chosa/, accessed on February 14, 2018). Since we included a total of 680,947 PCIs, approximately 88% of all procedures in Japan were estimated to be registered in our registry. The accuracy of submitted data is maintained by data auditing (20 institutions annually), which is operated by members of the CVIT registry subcommittee.

The study protocol of the J-PCI registry was approved by the Institutional Review Board Committee at the Network for Promotion of Clinical Studies (a specified nonprofit organization affiliated with Osaka University Graduate School of Medicine, Osaka, Japan) and complied with the principles contained within the Declaration of Helsinki. Written informed consent was waived due to the retrospective study design.

Data Definitions

The primary outcome measure of the J-PCI analysis was in-hospital mortality, which

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was defined as all-cause mortality during hospitalization. Cardiogenic shock was defined as a sustained episode of systolic blood pressure <80 mmHg and/or a cardiac index of <1.8 L/min/m^2 (regardless of the measurement methods) despite the maximum treatment determined to be secondary to cardiac dysfunction; and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support including an intra-aortic balloon pump to maintain blood pressure and cardiac index above the specified levels within 24 hour prior to the PCI procedures. Renal dysfunction in this registry was defined as the presence of proteinuria including microalbuminuria, serum creatinine ≥1.3 mg/dL, or estimated glomerular filtration rate ≤60 mL/min/1.73m^2 according to guidelines from the Japanese Society of Nephrology.(16) The other definitions of J-PCI variables are available online (http://www.cvit.jp/registry/jpci_definition.pdf, accessed on February 14, 2018).

Statistical Analysis

The study cohort was randomly divided in a 1:1 ratio into derivation (n = 334,591) and validation (n = 334,590) cohorts, respectively. The demographics and clinical patient characteristics were summarized by enrollment year, and the data are presented as mean ± SD or as proportion (%), depending on the variables. Trend tests were performed using the Cochrane-Armitage test for trend.

All variables in **Table 1** except for procedure details were listed as initial candidate variables. Age was treated as continuous variable and the others were as dichotomous variables. For diagnosis, unstable angina, ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI) were included in the list of candidate variables from clinical judgment. After accounting for multicollinearity among candidate variables, final candidates for inclusion in the multivariable model were selected as follows: age, sex, clinical presentation (unstable angina, STEMI, NSTEMI), previous PCI, previous coronary artery bypass grafting, previous myocardial infarction (MI), diabetes, hypertension, dyslipidemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis, renal dysfunction on dialysis), chronic lung disease, peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure, number of diseased vessel (two vessel disease, three vessel disease, left main trunk lesion), and involvement of left

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anterior descending artery or left main trunk as a target lesion. Age was treated as a continuous variable, and other variables were treated dichotomously. Multivariable logistic regression with a backward selection method was then performed to identify independent predictors of in-hospital death. Package "step" in R was used for backward selection, in which elimination process was based on Akaike's Information Criterion.

From the derivation cohort, we developed two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings, one based on all available variables including both pre-procedure– and procedure-related variables ("full" model), and the other based on pre-procedural variables only (pre-procedure model). In addition, an integer score was assigned to each variable selected in the pre-procedure model in proportion to the estimated regression coefficient (0.23) defined from an incremental risk ratio per 10 years of age. The regression coefficient for each level of every risk factor was subsequently divided by this reference value (0.23) to compute its weights for the risk score.(17,18)

Using the validation cohort, the performance of the developed models was examined by using C-statistics to assess discrimination and by demonstrating calibration plots to evaluate calibration. After assessing discrimination and calibration across the entire validation cohort, we examined model performance for clinically distinct patient populations. These included acute coronary syndrome (ACS) vs. non-ACS, female vs. male, and advanced age (>70) vs. younger age (≤70).

All variables had less than 3% missingness. To account for missing data, single imputation was used for each variable; "STEMI" for type of MI, "transradial" for access site, and "No" for others. Data were analyzed using R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). All P-values are 2-sided with $P<0.05$ being considered statistically significant.

Patient and Public Involvement

Lack of the risk model predicting in-hospital mortality in patients undergoing PCI at hospitals participating in the J-PCI registry was the motivation to conduct this study.

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The development of the risk model enables to provide risk-adjusted mortality in benchmark report to each institute, leading to the improvement in quality of care and patient outcome in the field of PCI.

Results

Population Characteristics

After excluding patients with missing information regarding age and/or sex (n = 3410), patients outside the age range of 20 to 100 years (n = 281), missing information regarding outcomes (n = 647), and missing information regarding diagnosis (n = 43), a total of 669,181 patients from 1018 institutes were included in the analysis (**Figure 1**). The baseline demographics, lesion characteristics, and procedure details are summarized in **Table 1**, and in-hospital outcomes are shown in **Table 2**, stratified by enrollment year. About 40% of PCIs were performed for ACS and 3% of patients were complicated with cardiogenic shock within 24 hours prior to PCI. During the indexed hospitalization, a total of 4788 (0.7%) experienced death after PCI. The bivariate relationships between patient characteristics and in-hospital mortality are shown in the supplement (**eTable 1** for the derivation cohort and **eTable 2** for the validation cohort).

Between 2014 and 2016, demographics and risk factors of patients undergoing PCI did not change in terms of clinically meaningful difference. Regarding diagnosis at the time of PCI, the proportion of silent ischemic heart disease was slightly increased over time from 15.9% in 2014 to 17.4% in 2016, whereas PCIs for STEMI were decreasing from 18.6% to 17.3% (P values for trend <0.001). Procedures significantly changed during the study period. The rate of transradial approach increased significantly from 60.6% to 66.9%, in parallel with the decreasing trend of transfemoral approach (P values for trend <0.001). Similarly, the use of drug eluting balloon and drug eluting stent showed an increasing trend, whereas the use of bare metal stent decreased significantly (all P values for trend <0.001). In patients with STEMI, the use of thrombus aspiration remained stable during the study period, although its trend demonstrated the statistically significant increase (P value for trend =0.011).

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Development of Full and Pre-procedure Models

Table 3 shows the results of the multivariable logistic regression analyses. Pre-procedure variables selected in the final models were age, sex (female), STEMI, NSTEMI, unstable angina, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis, renal dysfunction on dialysis), peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure. All angiographic information, such as three-vessel disease, left main trunk lesion, and involvement of left anterior descending artery or left main trunk as a target lesion, were retained in the full model.

Discrimination and Calibration Performance of Full and Pre-procedure Models

In the entire validation cohort, discrimination performance of the full model was excellent, with C-index of 0.929 (95% confidence interval [CI], 0.924 – 0.935). The exclusion of the angiographic information from the full model resulted in only a slight decrement in the overall model discriminatory performance, and the C-index of the pre-procedure model was 0.926 (95% CI, 0.920 – 0.931). Both full and pre-procedure models performed well even in the pre-specified sub-groups, and C-index were ranging from 0.829 to 0.933 for the full model and from 0.820 to 0.926 for the pre-procedure model, respectively (**eTable 3 in the supplement**). There was excellent calibration performance of both models in the entire validation cohort (**eFigure 1 in the supplement)**. The calibration performance was also acceptable in the pre-specified subgroups, although both models were likely to underestimate the risk of mortality in high-risk patients with elective procedure (**eFigure 2 and eFigure 3 in the supplement**).

Development and Validation of Integer Simple Risk Score

The integer point for each variable derived from beta coefficients in the multivariable models are listed in **Figure 2**. The highest number of points was 12 for cardiogenic shock, whereas the lowest was −3 for dyslipidemia. The possible total points ranged

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from −6 to 43. The agreements between the observed and estimated risks of mortality with the developed risk-scoring methods were assessed across 5 groups in the entire validation cohort (**Figure 2**). Overall, the agreements were acceptable, although the integer score underestimated mortality risk in the higher risk patients, where the observed and predicted mortalities were 1.2% and 0.9% in the second highest risk group, 6.9% and 6.6% in the highest-risk group, respectively.

Discussion

Using the nationally representative cohort of Japanese patients undergoing PCI with >660,000 procedures from 1018 institutes, we developed and internally validated risk models predicting in-hospital mortality in patients after PCI. The final full model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidemia, smoker, renal dysfunction, peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours before procedure, and angiographic information. The model performed very well in an independent validation cohort, as well as in various subgroups stratified by age, sex, and clinical presentation. The model performance was retained even after excluding angiographic information, and a simplified integer risk score based on the pre-procedure model also performed well. These developed risk prediction models enable to provide risk-adjusted mortality in benchmark report, compare an institution's performance with that of national experience, and stratify patient at risk pre-procedurally.

For the purpose of risk adjustment for benchmarking and comparing institutional performances, rigorous adjustment is warranted. It is well known that there are significant differences in patient demographics, biological response to medication or procedure, and practice pattern in PCI between Japan and the Western countries.(10,19) For example, patients are likely to be more advanced age and have lower body mass weight, and more frequently experienced bleeding complications. Furthermore, the proportion of PCIs for elective indications in Japan is greater than those in other countries. Regarding practice patterns, thrombus aspiration is still widely performed for treating patients with STEMI despite the recent downgrade of the relevant recommendations in the US and European guidelines.(20,21) In spite of

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these significant differences, some risk models or clinical scores that are derived from the Western countries have been externally validated and proved to be useful in Japanese patients.(10,22,23) Kohsaka et al. applied the in-hospital mortality risk model derived from the National Cardiovascular Data Registry CathPCI Registry, which is the nationwide PCI registry in the US, to the regional PCI registry from 15 Japanese institutes near Tokyo area, and demonstrated that the US model was clinically applicable in Japanese population with excellent discrimination and acceptable calibration performances.(10) However, given its limited calibration performance in high-risk patients, the risk model derived from its own dataset is preferable to provide an accurate adjusted mortality.

A number of risk models were developed from various registries to predict risk of mortality in patients undergoing PCI. Individual components varied among risk models, but the several components, such as age, clinical presentation or urgency, renal dysfunction, cardiogenic shock were consistently included in the model.(4-9) Our developed risk models also allied with the previous ones and included these core variables. Although angiographic information was also serving as a component of our full model, its incremental predictive value may be limited, given the sufficient performance of the pre-procedure model. This finding is consistent with the work of others and Peterson et al. showed that in-hospital mortality was driven primarily by pre-existing patient comorbidities and makers of clinical instability.(4) It has important clinical implications in that it allows patients and physicians to obtain a reasonable estimate of mortality pre-procedurally.

Few studies reported the risk model predicting mortality after PCI derived from Japanese population. Tanaka et al. developed the Kyoto Model using the CREDO-Kyoto Registry, which is one of the most established PCI registries in Japan.(24) However, the Kyoto Model intended to predict long-term mortality after revascularization and was not applicable to patients undergoing PCI for MI, because the dataset excluded the patients with acute MI within 1 week of the index procedure. Furthermore, the dataset included patients with revascularization between 2000 and 2002, and could not be directly applied to current practice. Our study is the first to report the risk model predicting in-hospital mortality in Japan using the nationwide

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PCI registry in the contemporary PCI practice. Thus, it will enable the Japanese cardiovascular society to provide an instrument for the pre-PCI risk stratification and to distribute the risk-adjusted mortality in benchmark reports, leading to improve quality of care and clinical outcome in PCI.

Several variables, such as prior PCI, hypertension, dyslipidemia, and current smoker, were identified as independent factors associated with reduction in mortality. Although some controversies remain and they may be attributed to confounding, their associations with improved mortality are consistent with the previous reports.(4,5,25-27) Smoker's paradox is a well-known phenomenon and has been reported in patients undergoing PCI.(26,27) Recent data have demonstrated a specific pharmacodynamic enhancement of platelet inhibition by clopidogrel among smokers,(28) which may hold important implications for patients treated with PCI, given that clopidogrel is still widely used for patients treated with PCI in Japan.(19) The protective effect of dyslipidemia may be related to statin use before PCI, which our database does not collect as a separate variable. The diagnosis for dyslipidemia may have acted as a proxy for statin use, which has been shown to reduce the risk of post-procedural MI and mortality in previous meta-analysis studies. Meta-analysis demonstrated that statin administration before PCI significantly reduced the risk of post-procedural MI, resulting in the reduction in mortality.(29,30) The impact of pre-existing hypertension on in-hospital mortality is controversial; however, a recent study from the Acute Myocardial Infarction in Switzerland Plus Registry reported that pre-existing hypertension was associated with increased risk of in-hospital mortality in patients presenting with ACS. (31) Although the exact mechanism is unknown, pre-treatment for hypertension through the use of beta-blockers and renin–angiotensin aldosterone inhibitors could have led to the favorable outcome. Previous studies have consistently demonstrated the protective effect of prior PCI in terms of reduction in in-hospital mortality in patients undergoing PCI. (4,5) This may be attributed to the fact that patients with prior PCI were more likely to undergo subsequent "low-risk" PCI, such as staged PCI. In contrast, those with prior CABG were more likely to undergo subsequent "high-risk" PCI, such as PCI for multivessel lesion, left main trunk lesion, and severely calcified lesion, resulting in increased risk of in-hospital

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mortality.

Limitations

This study has several limitations. First, J-PCI is a voluntary registry; the contributing hospitals may have larger procedure volume than the average institutes in Japan. However, J-PCI included >85% of all PCIs performed in Japan and assured high participation rate by linking to the application for board certification and renewal. Second, improving the quality of the database is a continuing issue in J-PCI. For data accuracy, not only is data auditing important but also the education of persons inputting data at each site to enable adherence to correct data definitions. Third, the candidate variables for the risk models were limited to those available in J-PCI. Actually, several variables selected in other risk models were not included in our dataset and may further refine risk prediction. Fourth, the models underestimated the risk of mortality in high-risk patients who underwent elective procedure, although their discrimination and calibration performances were acceptable. Although the exact reason remains unknown, lack of granularity for variables representing the complexity of PCI, such as SINTAX score, chronic total occlusion, and severity of calcification, may have led to the suboptimal calibration performance in this particular population. Since the developed risk models cover patients with a broad range of mortality risk, providing an accurate estimation for all patients is challenging, especially in low-risk patients, mainly owing to the small number of in-hospital deaths. Further studies may be required to generate separate models for patients with specific clinical presentations for improved risk prediction. Fifth, the models have been validated using only J-PCI data; it has not been validated on an external dataset. Finally, J-PCI captured in-hospital outcomes that occurred only during hospitalizations where PCIs were performed; therefore, data on the subsequent outcomes once patients were transferred to outside hospitals and facilities were lacking. This may have led to the underestimation of mortality in J-PCI. We have recently launched a project involving selected institutes participating in J-PCI, aiming to obtain long-term follow-up data, which may provide additional insights.

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Conclusion

Using the nationwide Japanese PCI registry, we have developed and internally validated the risk models for predicting in-hospital mortality after PCI. The models performed very well in broad spectrum of patients undergoing PCI as well as in clinically important subgroups. These models should enable to improve patient mortality after PCI by facilitating pre-PCI risk stratification, improving hospital quality assessment, and providing an accurate adjusted risk in benchmark reports.

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Author Contributions

T Inohara and S Kohsaka had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: **T Inohara and S Kohsaka**

Acquisition, analysis, or interpretation of data: **T Inohara, S Kohsaka, K Yamaji, H Ishii, T Amano, S Uemura, K Kadota, H Kumamaru, H Miyata, and M Nakamura**

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Administrative, technical, or material support: **S Kohsaka, T Amano, and M Nakamura**

Study supervision: **S Kohsaka, H Kumamaru, H Miyata, and M Nakamura**

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Data Sharing Statement

In addition to data in this manuscript, all data in the J-PCI registry are available to investigators from >1000 sites participating in the J-PCI registry. The dataset are stored in servers of the National Clinical Database (NCD). Local investigators can submit proposal for data use for research purposes.

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Figure Legends

Figure 1. Study cohort creation
Abbreviations: PCI, percutaneous coronary intervention

Figure 2. Integer score and its calibration performance
The agreements between the observed and expected risks of mortality with the developed integer score were assessed across 5 groups of the total points in the validation cohort.
Abbreviations: Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort

eFigure 2. Calibration plots of full model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

eFigure 3. Calibration plots of pre-procedure model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

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Table 1. Baseline characteristics by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	*P*
Demographics				
Age, yrs, mean (SD)	69.97 (10.99)	70.08 (11.04)	70.26 (11.07)	<0.001
Female	50747 (24.1)	52048 (23.9)	57677 (24.0)	0.218
Diagnosis				<0.001
Elective setting				
Stable angina	80244 (38.1)	83258 (38.2)	91894 (38.2)	
Silent ischemic heart disease	33550 (15.9)	36431 (16.7)	41764 (17.4)	
Old myocardial infarction	12528 (6.0)	13034 (6.0)	14152 (5.9)	
Acute setting				
Unstable angina	33985 (16.1)	33582 (15.4)	37599 (15.6)	
Myocardial infarction	50237 (23.9)	51684 (23.7)	55239 (23.0)	
STEMI	39140 (18.6)	40050 (18.4)	41740 (17.3)	
NSTEMI	9217 (4.4)	9844 (4.5)	11452 (4.8)	
Risk Factors				
Previous PCI	96877 (46.2)	99896 (46.6)	110161 (46.5)	0.022
Previous CABG	8871 (4.2)	8525 (4.0)	8949 (3.8)	<0.001
Previous MI	48620 (23.4)	49547 (23.3)	54073 (22.9)	0.001
Diabetes Mellitus	90152 (42.8)	94250 (43.2)	105066 (43.7)	<0.001
Hypertension	155985 (74.1)	162075 (74.4)	178888 (74.3)	0.083

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Hypercholesterolemia	130740 (62.1)	137264 (63.0)	153059 (63.6)	<0.001
Current smoker	64368 (30.6)	67385 (30.9)	74027 (30.8)	0.054
Renal Insufficiency	35366 (16.8)	37857 (17.4)	43460 (18.1)	<0.001
On dialysis	13099 (6.2)	13649 (6.3)	15602 (6.5)	<0.001
Chronic lung disease	3347 (1.6)	4039 (1.9)	5336 (2.2)	<0.001
Peripheral Vascular Disease	13273 (6.3)	15169 (7.0)	18064 (7.5)	<0.001
Previous heart failure	26105 (12.8)	27667 (13.1)	31478 (13.4)	<0.001
Cardiopulmonary arrest on arrival	3285 (1.6)	3311 (1.6)	4137 (1.7)	<0.001
Cardiogenic shock within 24 hrs	6023 (2.9)	6307 (3.0)	7429 (3.1)	<0.001
Acute heart failure within 24 hrs	8217 (4.0)	8082 (3.8)	9347 (4.0)	0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	126593 (60.1)	133649 (61.3)	150471 (62.5)	<0.001
Two vessel disease	55997 (26.6)	56117 (25.7)	60936 (25.3)	<0.001
Three vessel disease	27205 (12.9)	27371 (12.6)	28424 (11.8)	<0.001
Left main trunk	8322 (4.0)	9129 (4.2)	9688 (4.0)	<0.001
Lesion Location:				
RCA	73309 (34.8)	74356 (34.1)	81482 (33.9)	<0.001
LAD/Left Main	106996 (50.8)	111132 (51.0)	123788 (51.4)	<0.001
LCX	54314 (25.8)	55638 (25.5)	60444 (25.1)	<0.001
Bypass graft	2163 (1.0)	1189 (0.5)	1202 (0.5)	<0.001
Procedure details				
Approach				<0.001

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Transradial	127686 (60.6)	138397 (63.5)	161104 (66.9)	
Transfemoral	71473 (33.9)	67668 (31.0)	67166 (27.9)	
Others (e.g. brachial)	11376 (5.4)	11924 (5.5)	12378 (5.1)	
Device				
Thrombus aspiration[a]	21551/39140 (55.1)	21640/40050 (54.0)	22605/41740 (54.2)	<0.001
Distal protection	7392 (3.5)	8077 (3.7)	7519 (3.1)	<0.001
Rotablader	7294 (3.5)	7686 (3.5)	8910 (3.7)	<0.001
Drug eluting balloon	12922 (6.1)	15769 (7.2)	22916 (9.5)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	166194 (78.9)	184327 (84.6)	206323 (85.7)	<0.001
Bare metal stent	14854 (7.1)	7807 (3.6)	4966 (2.1)	<0.001
TIMI flow post-procedure				
Flow 3	205978 (97.8)	213709 (98.0)	235969 (98.1)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; TIMI, Thrombolysis in Myocardial Infarction.

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Table 2. Crude outcomes by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	P
In-hospital death	1523 (0.7)	1479 (0.7)	1786 (0.7)	0.033
Bleeding complication	546 (0.3)	701 (0.3)	779 (0.3)	<0.001
Access site bleeding	334 (0.2)	429 (0.2)	460 (0.2)	0.007
Non-access site bleeding	223 (0.1)	287 (0.1)	341 (0.1)	0.003
Periprocedural MI	875 (0.4)	921 (0.4)	1140 (0.5)	0.005
Tamponade	317 (0.2)	287 (0.1)	350 (0.1)	0.234
Post-procedure shock	1920 (0.9)	1927 (0.9)	2145 (0.9)	0.603
Acute stent thrombosis	407 (0.2)	331 (0.2)	297 (0.1)	<0.001
Emergent operation	206 (0.1)	213 (0.1)	204 (0.1)	0.246

Abbreviations: MI, myocardial infarction.

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Table 3. Full and pre-procedure risk model

	Full Model				Pre-procedure Model			
	Coefficient	OR	95% CI	*P*	Coefficient	OR	95% CI	*P*
Intercept	-8.878621				-8.472575			
Demographics								
Age, per 1 year	0.023744	1.02	1.02 - 1.03	<0.001	0.023608	1.02	1.02 - 1.03	<0.001
Female	0.177372	1.19	1.08 - 1.32	<0.001	0.155252	1.17	1.06 - 1.29	0.002
Diagnosis								
STEMI	2.528622	12.5	10.7 - 14.7	<0.001	2.530134	12.6	10.7 - 14.7	<0.001
NSTEMI	2.170769	8.77	7.24 - 10.6	<0.001	2.260405	9.59	7.93 - 11.6	<0.001
Unstable angina	1.108935	3.03	2.50 - 3.68	<0.001	1.163039	3.2	2.64 - 3.88	<0.001
Risk Factors								
Previous PCI	-0.121767	0.89	0.79 - 0.99	0.029	-0.170187	0.84	0.76 - 0.94	0.002
Previous CABG	0.371319	1.45	1.17 - 1.79	<0.001	0.38463	1.47	1.19 - 1.81	<0.001
Hypertension	-0.181962	0.83	0.76 - 0.91	<0.001	-0.175804	0.84	0.77 - 0.92	<0.001
Hypercholesterolemia	-0.55876	0.57	0.52 - 0.63	<0.001	-0.540335	0.58	0.53 - 0.64	<0.001
Current smoker	-0.19942	0.82	0.74 - 0.91	<0.001	-0.210492	0.81	0.73 - 0.90	<0.001
Renal Insufficiency without Dialysis	0.522425	1.69	1.51 - 1.88	<0.001	0.552934	1.74	1.56 - 1.93	<0.001
Renal Insufficiency on Dialysis	0.827209	2.29	1.95 - 2.69	<0.001	0.821163	2.27	1.94 - 2.67	<0.001
Peripheral Vascular Disease	0.457832	1.58	1.35 - 1.85	<0.001	0.498317	1.65	1.41 - 1.92	<0.001
Previous heart failure	0.451346	1.57	1.40 - 1.77	<0.001	0.491731	1.64	1.45 - 1.84	<0.001

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Cardiogenic shock within 24 hrs	2.540633	12.7	11.6 - 13.9	<0.001	2.67607	14.5	13.3 - 15.9	<0.001
Number of Diseased Vessels								
Three vessel disease	0.368771	1.45	1.31 - 1.60	<0.001				
Left main trunk	0.680996	1.98	1.75 - 2.23	<0.001				
Lesion Location								
LAD/Left Main	0.527633	1.69	1.55 - 1.86	<0.001				

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LAD, left anterior descending.

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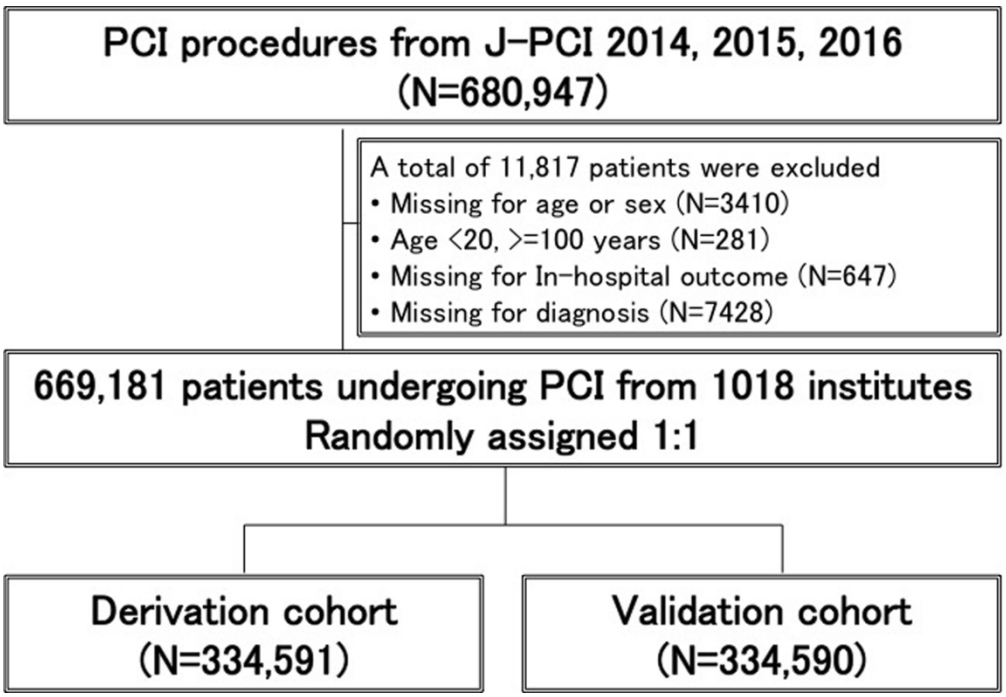

Figure 1. Study cohort creation

233x160mm (300 x 300 DPI)

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	Beta Coefficient	Score
Demograohics		
Age	0.023608	
20-29		0
30-39		1
40-49		2
50-59		3
60-69		4
70-79		5
80-89		6
90-99		7
Female	0.155252	1
Diagnosis		
STEMI	2.530134	11
NSTEMI	2.260405	10
Unstable angina	1.163039	5
Risk Factors		
Previous PCI	-0.170187	-1
Previous CABG	0.38463	2
Hypertension	-0.175804	-1
Hypercholesterolemia	-0.540339	-3
Current smoker	-0.210493	-1
Renal Insufficiency without Dialysis	0.552934	3
Renal Insufficiency on Dialysis	0.821163	4
Peripheral Vascular Disease	0.498317	3
Previous heart failure	0.491731	3
Cardiogenic shock within 24 hrs	2.67607	12

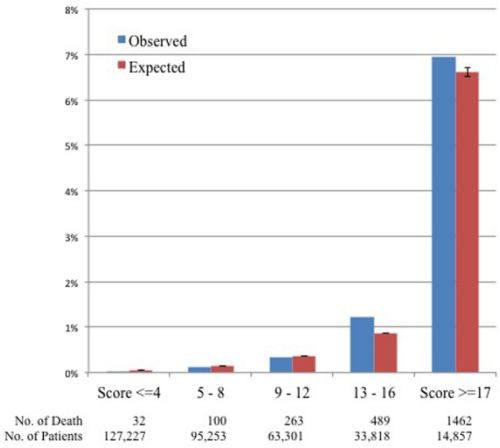

Figure 2. Integer score and its calibration performance

324x147mm (300 x 300 DPI)

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Supplemental Material

eTable 1. Derivation cohort

	Overall N=334591	Death, No N=332130	Death, Yes N=2461	*P*
Demographics				
Age, yrs, mean (SD)	70.09 (11.03)	70.06 (11.02)	74.15 (12.13)	<0.001
Female	79981 (23.9)	79196 (23.8)	785 (31.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127639 (38.1)	127544 (38.4)	95 (3.9)	
Silent ischemic heart disease	55975 (16.7)	55894 (16.8)	81 (3.3)	
Old myocardial infarction	19862 (5.9)	19831 (6.0)	31 (1.3)	
Acute setting				
Unstable angina	52703 (15.8)	52490 (15.8)	213 (8.7)	
Myocardial infarction	78412 (23.4)	76371 (23.0)	2041 (82.9)	
STEMI	60408 (18.1)	58837 (17.7)	1571 (63.8)	
NSTEMI	15145 (4.5)	14850 (4.5)	295 (12.0)	
Risk Factors				
Previous PCI	153791 (46.5)	153216 (46.7)	575 (23.9)	<0.001
Previous CABG	13310 (4.0)	13192 (4.0)	118 (4.9)	0.041
Previous MI	75965 (23.1)	75499 (23.2)	466 (19.7)	<0.001
Diabetes Mellitus	144880 (43.3)	143857 (43.3)	1023 (41.6)	0.085
Hypertension	248534 (74.3)	246954 (74.4)	1580 (64.2)	<0.001
Hypercholesterolemia	210860 (63.0)	209898 (63.2)	962 (39.1)	<0.001
Current smoker	103072 (30.8)	102456 (30.8)	616 (25.0)	<0.001
Renal Insufficiency	58278 (17.4)	57455 (17.3)	823 (33.4)	<0.001
On dialysis	21174 (6.3)	20939 (6.3)	235 (9.5)	<0.001
Chronic lung disease	6383 (1.9)	6311 (1.9)	72 (2.9)	<0.001
Peripheral Vascular Disease	23270 (7.0)	23033 (6.9)	237 (9.6)	<0.001
Previous heart failure	42743 (13.2)	42249 (13.1)	494 (21.0)	<0.001
Cardiopulmonary arrest on arrival	5450 (1.7)	4476 (1.4)	974 (40.0)	<0.001
Cardiogenic shock within 24 hrs	9903 (3.0)	8512 (2.6)	1391 (57.3)	<0.001
Acute heart failure within 24 hrs	12952 (4.0)	11761 (3.6)	1191 (49.5)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	204905 (61.2)	203905 (61.4)	1000 (40.6)	<0.001
Two vessel disease	86917 (26.0)	86253 (26.0)	664 (27.0)	0.264
Three vessel disease	41600 (12.4)	40927 (12.3)	673 (27.3)	<0.001
Left main trunk	13483 (4.0)	13040 (3.9)	443 (18.0)	<0.001
Lesion Location:				

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RCA	114891 (34.3)	114069 (34.3)	822 (33.4)	0.337
LAD/Left Main	170823 (51.1)	169149 (50.9)	1674 (68.0)	<0.001
LCX	85244 (25.5)	84583 (25.5)	661 (26.9)	0.12
Bypass graft	2261 (0.7)	2234 (0.7)	27 (1.1)	0.015
Procedure details				
Approach				<0.001
Transradial	213314 (63.8)	212740 (64.1)	574 (23.3)	
Transfemoral	103410 (30.9)	101690 (30.6)	1720 (69.9)	
Others (e.g. brachial)	17864 (5.3)	17697 (5.3)	167 (6.8)	
Device				
Thrombus aspiration[a]	33067/60408 (54.7)	32264/58837 (54.8)	803/1571 (51.1)	<0.001
Distal protection	11468 (3.4)	11354 (3.4)	114 (4.6)	0.001
Rotablader	11937 (3.6)	11865 (3.6)	72 (2.9)	0.095
Drug eluting balloon	25907 (7.7)	25851 (7.8)	56 (2.3)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278173 (83.1)	276424 (83.2)	1749 (71.1)	<0.001
Bare metal stent	13927 (4.2)	13697 (4.1)	230 (9.3)	<0.001
TIMI flow post-procedure				
Flow 3	327771 (98.0)	325613 (98.0)	2158 (87.7)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 2. Validation cohort

	Overall N=334590	Death, No N=332263	Death, Yes N=2327	*P*
Demographics				
Age, yrs, mean (SD)	70.13 (11.04)	70.09 (11.03)	74.78 (11.95)	<0.001
Female	80491 (24.1)	79702 (24.0)	789 (33.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127757 (38.2)	127673 (38.4)	84 (3.6)	
Silent ischemic heart disease	55770 (16.7)	55680 (16.8)	90 (3.9)	
Old myocardial infarction	19852 (5.9)	19805 (6.0)	47 (2.0)	
Acute setting				
Unstable angina	52463 (15.7)	52243 (15.7)	220 (9.5)	
Myocardial infarction	78748 (23.5)	76862 (23.1)	1886 (81.0)	
STEMI	60522 (18.1)	59085 (17.8)	1437 (61.8)	
NSTEMI	15369 (4.6)	15083 (4.5)	286 (12.3)	
Risk Factors				
Previous PCI	153145 (46.3)	152590 (46.5)	555 (24.3)	<0.001
Previous CABG	13035 (3.9)	12931 (3.9)	104 (4.5)	0.175
Previous MI	76275 (23.2)	75832 (23.3)	443 (19.7)	<0.001
Diabetes Mellitus	144588 (43.2)	143595 (43.2)	993 (42.7)	0.612
Hypertension	248415 (74.2)	246933 (74.3)	1482 (63.7)	<0.001
Hypercholesterolemia	210203 (62.8)	209296 (63.0)	907 (39.0)	<0.001
Current smoker	102708 (30.7)	102209 (30.8)	499 (21.4)	<0.001
Renal Insufficiency	58405 (17.5)	57666 (17.4)	739 (31.8)	<0.001
On dialysis	21175 (6.3)	20959 (6.3)	216 (9.3)	<0.001
Chronic lung disease	6339 (1.9)	6259 (1.9)	80 (3.4)	<0.001
Peripheral Vascular Disease	23236 (6.9)	23027 (6.9)	209 (9.0)	<0.001
Previous heart failure	42507 (13.1)	42024 (13.0)	483 (21.8)	<0.001
Cardiopulmonary arrest on arrival	5283 (1.6)	4442 (1.4)	841 (36.5)	<0.001
Cardiogenic shock within 24 hrs	9856 (3.0)	8603 (2.6)	1253 (54.6)	<0.001
Acute heart failure within 24 hrs	12694 (3.9)	11605 (3.6)	1089 (48.0)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	205814 (61.5)	204889 (61.7)	925 (39.8)	<0.001
Two vessel disease	86133 (25.7)	85477 (25.7)	656 (28.2)	0.007
Three vessel disease	41400 (12.4)	40748 (12.3)	652 (28.0)	<0.001
Left main trunk	13656 (4.1)	13247 (4.0)	409 (17.6)	<0.001
Lesion Location:				
RCA	114256 (34.1)	113461 (34.1)	795 (34.2)	1
LAD/Left Main	171093 (51.1)	169519 (51.0)	1574 (67.6)	<0.001
LCX	85152 (25.4)	84496 (25.4)	656 (28.2)	0.003

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Bypass graft	2293 (0.7)	2276 (0.7)	17 (0.7)	0.889
Procedure details				
Approach				<0.001
Transradial	213873 (63.9)	213341 (64.2)	532 (22.9)	
Transfemoral	102897 (30.8)	101265 (30.5)	1632 (70.1)	
Others (e.g. brachial)	17814 (5.3)	17651 (5.3)	163 (7.0)	
Device				
Thrombus aspiration[a]	32729/60522 (54.1)	31993/59085 (54.1)	736/1437 (51.2)	<0.001
Distal protection	11520 (3.4)	11430 (3.4)	90 (3.9)	0.284
Rotablader	11953 (3.6)	11874 (3.6)	79 (3.4)	0.684
Drug eluting balloon	25700 (7.7)	25637 (7.7)	63 (2.7)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278671 (83.3)	277032 (83.4)	1639 (70.4)	<0.001
Bare metal stent	13700 (4.1)	13451 (4.0)	249 (10.7)	<0.001
TIMI flow post-procedure				
Flow 3	327885 (98.0)	325799 (98.1)	2086 (89.6)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 3. Discrimination performance of full and pre-procedure models

			Full Model		Pre-procedure Model	
	Sample, n	Death, n	C-index	95% CI	C-index	95% CI
Derivation cohort	334591	2461	0.929	0.924 - 0.935	0.926	0.920 - 0.931
Validation cohort	334590	2327	0.923	0.917 - 0.928	0.918	0.912 - 0.923
Subgroups (in validation cohort)						
ACS	131211	2106	0.886	0.879 - 0.893	0.876	0.868 - 0.883
Elective	203379	221	0.829	0.800 - 0.858	0.82	0.790 - 0.850
Female	80491	789	0.907	0.897 - 0.918	0.901	0.890 - 0.912
Male	254099	1538	0.927	0.920 - 0.934	0.922	0.915 - 0.929
Age >70	176629	1570	0.912	0.905 - 0.920	0.908	0.900 - 0.915
Age <=70	157204	757	0.933	0.924 - 0.942	0.926	0.916 - 0.935

Abbreviations: ACS, acute coronary syndrome.

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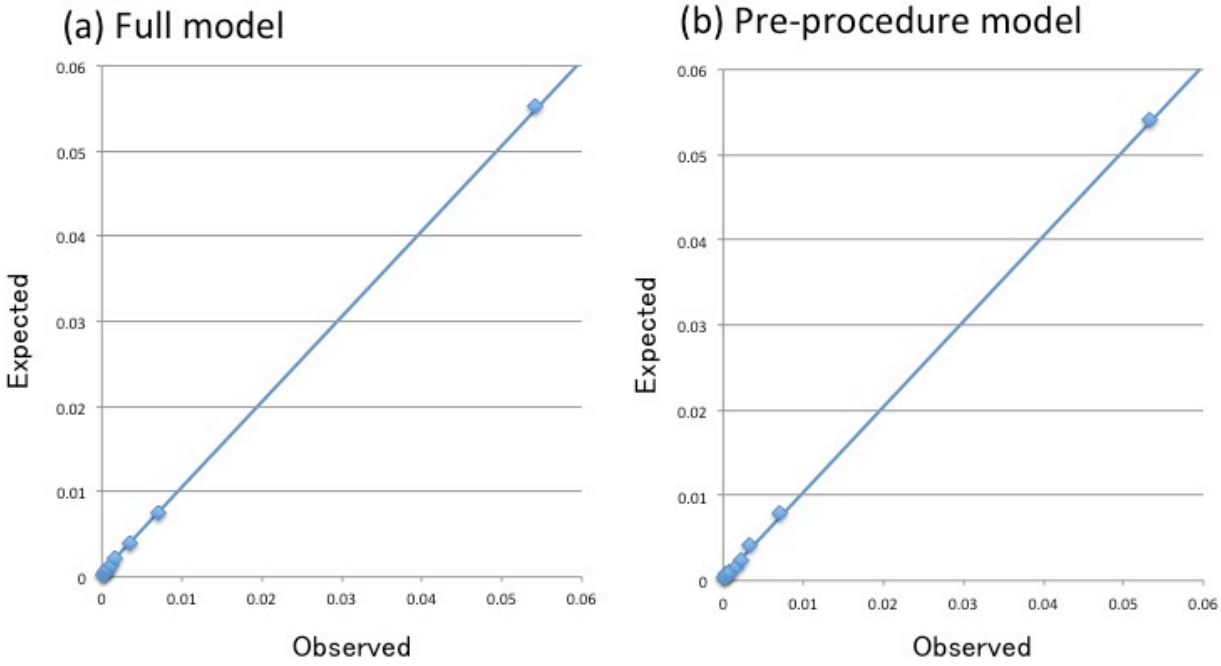
eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort



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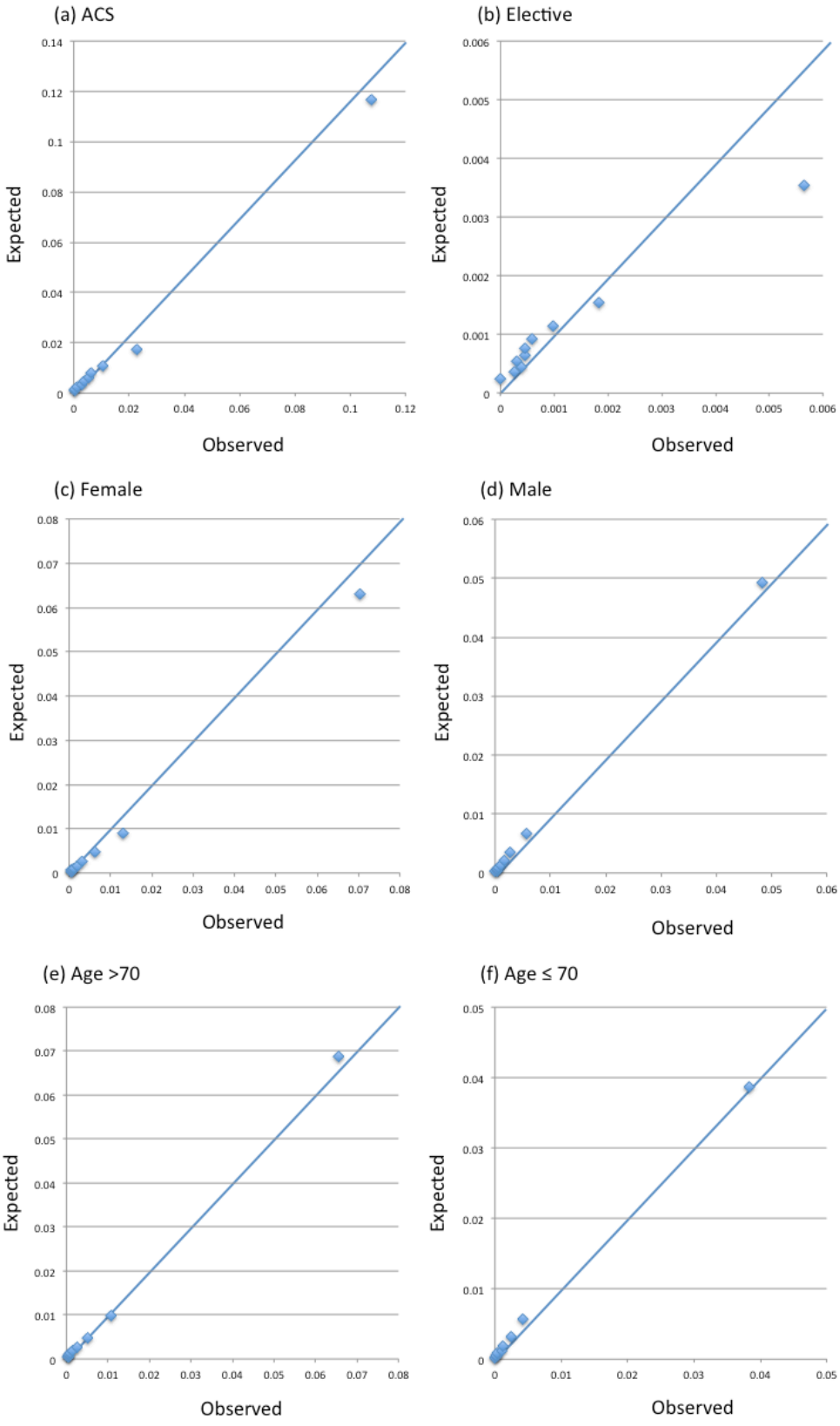
eFigure 2. Calibration plots of full model in subgroups



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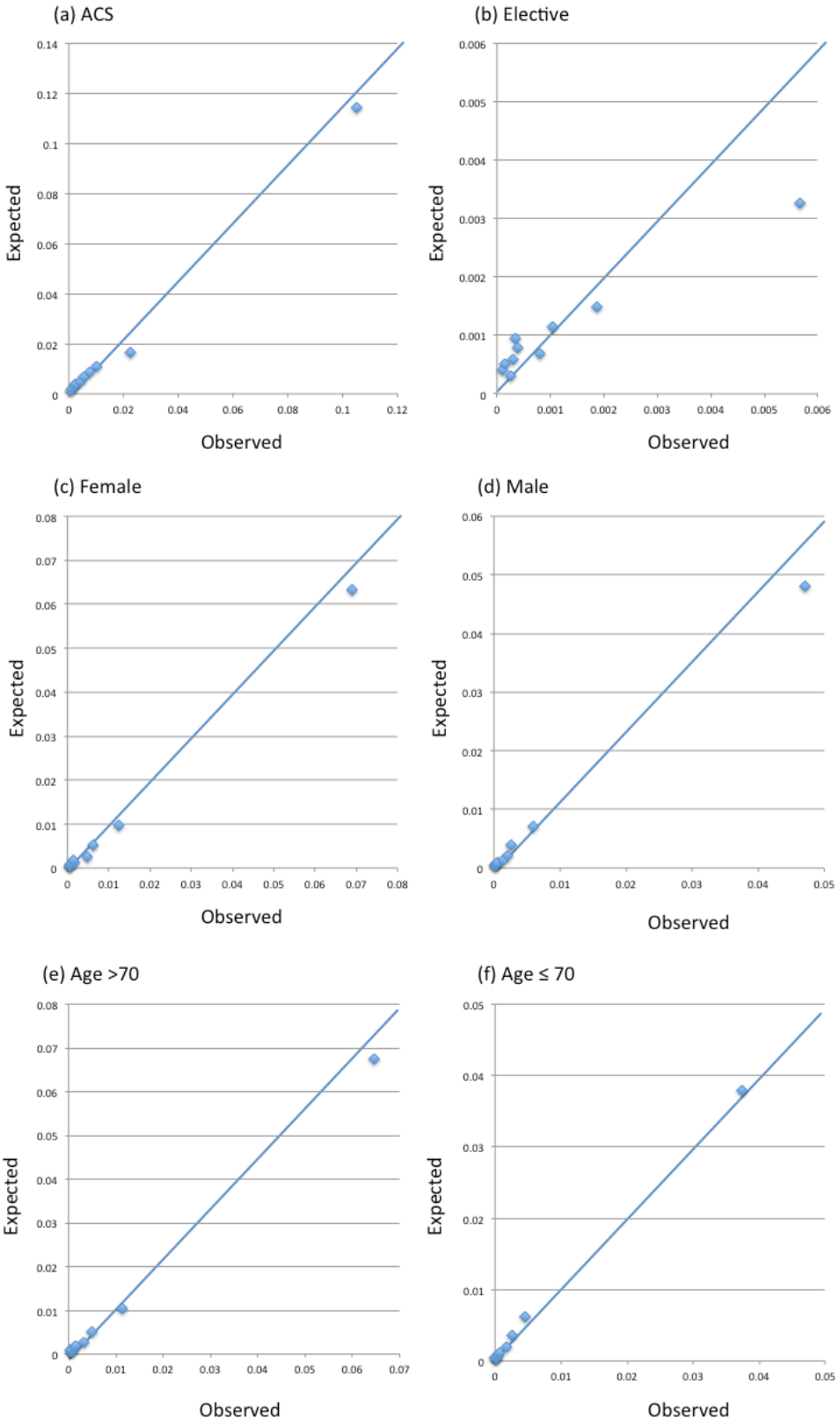
eFigure 3. Calibration plots of pre-procedure model in subgroups



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STROBE Statement: Checklist

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, page 7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes, page 7
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, pages 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, pages 7-9
Bias	9	Describe any efforts to address potential sources of bias	Yes, pages 8-9
Study size	10	Explain how the study size was arrived at	Yes, page 9

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, pages 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, page 9
		(*c*) Explain how missing data were addressed	Yes, page 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Only in-hospital outcomes were evaluated. Patients with missing for outcomes were excluded from the analysis. Page 9
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	Yes, page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, pages 9-10
		(b) Give reasons for non-participation at each stage	Yes, pages 9-10
		(c) Consider use of a flow diagram	Yes, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Although precise numbers of missingness are not presented, the percentages are described. Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Only in-hospital outcomes were evaluated. Pages 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Yes, Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Yes, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No. Only adjusted odds ratios are presented.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, eTable 3, eFigure 2, eFigure 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, page 11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, throughout the Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, page 2

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BMJ Open

Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Nationwide Retrospective Cohort Study in Japan

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Risk model, Percutaneous coronary intervention, In-hospital mortality

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1

Title: Risk Stratification Model for In-Hospital Death in Patients Undergoing Percutaneous Coronary Intervention: A Nationwide Retrospective Cohort Study in Japan

Running Title: Mortality risk model after PCI in Japan

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Conflict of Interest: Dr Inohara has a research grant from Boston Scientific. Dr Kohsaka reports investigator-initiated grant funding from Bayer and Daiichi Sankyo, and personal fees from Bayer and Bristol-Myers Squibb. Dr Ishii receives lecture fees from Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, and MSD. Dr Amano receives lecture fees from Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. Dr Nakamura receives remuneration for lecture from Daiichi Sankyo, Sanofi, Bayer, Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Terumo, Japan Lifeline, Abbott, Boston Scientific, Medtronic, and Nipro, and

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Abstract (300 words)

Objectives: To provide an accurate adjustment for mortality in benchmark, developing a risk prediction model from its own dataset is mandatory. We aimed to develop and validate a risk model predicting in-hospital mortality in a broad spectrum of Japanese patients after percutaneous coronary intervention (PCI).

Design: A retrospective cohort study was conducted.

Setting: The Japanese PCI (J-PCI) registry includes a nationally representative retrospective sample of patients who underwent PCI and covers approximately 88% of all PCIs in Japan.

Participants: Overall, 669,181 patients who underwent PCI between January 2014 and December 2016 in 1018 institutes.

Main outcome measures: In-hospital death.

Results: The study population (N=669,181; mean [SD] age, 70.1 [11.0] years; women, 24.0%) was divided into two groups: 50% of the sample was used for model derivation (N=334,591), while the remaining 50% was used for model validation (N=334,590). Using the derivation cohort, both 'full' and 'pre-procedure' risk models were developed using logistic regression analysis. Using the validation cohort, the developed risk models were internally validated. The in-hospital mortality rate was 0.7%. the pre-procedure model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidaemia, smoking, renal dysfunction, dialysis, peripheral vascular disease, previous heart failure, and cardiogenic shock. Angiographic information, such as the number of diseased vessel and location of target lesion, was also included in the full model. Both models performed well in the entire validation cohort (C-indexes: 0.929 and 0.926 for full and pre-procedure models, respectively) and amongst pre-specified subgroups with good calibration, although both models underestimated the risk of mortality in high-risk patients with elective procedure.

Conclusions: These simple models from a nationwide J-PCI registry, which is easily applicable in clinical practice and readily available directly at the patients' presentation, are valid tools for pre-procedural risk stratification of patients

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undergoing PCI in contemporary Japanese practice.

Keywords: Risk model; Percutaneous coronary intervention; In-hospital mortality

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Article summary

Strengths and limitations of this study

- We developed and internally validated a risk model predicting in-hospital mortality using a nationally representative sample of >650,000 patients who underwent PCI in Japan to provide risk-adjusted mortality in benchmark reports.
- For clinical use, the 'pre-procedure' risk model that did not require procedure-related variables and a simplified integer risk score based on the pre-procedure model were also developed and internally validated, aiding in stratifying patients at risk of death pre-procedurally.
- Several variables selected in other risk models were not included in the J-PCI registry and could further refine risk prediction.
- The models underestimated the risk of mortality and could not provide an accurate estimation in elective procedure, mainly owing to the small number of in-hospital deaths.

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Background

In Japan, percutaneous coronary interventions (PCIs) are widely available for both elective and acute settings, and >200,000 procedures are performed annually in >1,000 hospitals. On the advent of technology and technique in interventional cardiology, the current in-hospital mortality rate is about 1%.(1,2) However, PCI is applied onto wide spectrum of coronary artery disease, and its indication varies substantially across hospitals, especially between low- and high-volume centres, suggesting an opportunity for improvement.(1,2) Adjusted risk mortality is a core component of performance measures and used even for public reporting (3); therefore, adjustment for the variation in patient risk across hospitals is critically important to enable an accurate assessment of each hospital's performance and opportunity to improve.

A number of risk prediction models for short-term mortality after PCI were developed within the last decade.(4-9) However, almost all of them share certain limitations: 1) they were not validated, 2) they were derived from small studies, and 3) the parameters used cannot be easily assessed directly in the catheterisation laboratory. Furthermore, given the favourable patient and laboratory profile (e.g. lesser risk of bleeding) for percutaneous procedures amongst the East Asian patients, PCI is performed onto significantly complex and 'sicker' group of patients in Japan. Hence, it remains a challenge for clinicians to use these existing models for the risk adjustment due to the differences in biological responses to medication or procedure amongst ethnicities and practice pattern amongst counties.(10-12)

The risk prediction model from its own dataset is mandatory, especially when considering the adjustment for mortality in benchmark, eventually leading to improve quality of care in PCIs. Using the nationwide Japanese PCI registry (J-PCI), this study aimed 1) to develop two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings, one based on all available variables including both pre-procedure- and procedure-related variables, and the other based on pre-procedural variables only; 2) to internally validate the developed risk models; and 3) to develop and validate a clinician-friendly simplified integer risk score to enable pre-PCI risk stratification in

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clinical care.

Methods

Data source

We analysed patients who underwent PCI between January 2014 and December 2016 (N=680,947) and were registered in the J-PCI. The J-PCI was established in 2007 and is a prospective Japanese nationwide multicentre registry of the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) designed to collect clinical variables and in-hospital outcome data on PCI patients.(1,13-15) Variables regarding patient background, clinical presentation, angiographic and procedure-related information, and in-hospital outcomes were collected from each patient. The CVIT registry subcommittee designed the software for the web-based data collection system, and each data manager in the participating hospitals submits data through this system annually. As registration in the J-PCI database is mandatory for the application for board certification and renewal, although participation in the J-PCI is voluntary, there is high degree of data completeness. According to the annual reports of the Japanese Registry of All Cardiac and Vascular Disease (JROAD), 773,359 PCIs (209,920 PCIs for acute indications and 563,439 PCIs for non-acute indications) were performed during the current study period (http://www.j-circ.or.jp/jittai_chosa/, accessed on February 14, 2018). Since we included a total of 680,947 PCIs, approximately 88% of all procedures in Japan were estimated to be registered in our registry. The accuracy of submitted data is maintained by data auditing (20 institutions annually), which is operated by members of the CVIT registry subcommittee.

The study protocol of the J-PCI registry was approved by the Institutional Review Board Committee at the Network for Promotion of Clinical Studies (a specified non-profit organisation affiliated with Osaka University Graduate School of Medicine, Osaka, Japan) and complied with the principles contained within the Declaration of Helsinki. Written informed consent was waived due to the retrospective nature of the study.

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Data definitions

The primary outcome measure of the J-PCI analysis was in-hospital mortality, which was defined as all-cause mortality during hospitalisation. Cardiogenic shock was defined as a sustained episode of systolic blood pressure <80 mmHg and/or a cardiac index of <1.8 L/min/m^2 (regardless of the measurement methods) despite the maximum treatment determined to be secondary to cardiac dysfunction, and/or the need for parenteral inotropic or vasopressor agents or mechanical support, including an intra-aortic balloon pump to maintain blood pressure and cardiac index above the specified levels within 24 hours prior to the initiation of PCI. In this registry, renal dysfunction was defined as the presence of proteinuria including microalbuminuria, serum creatinine ≥1.3 mg/dL, or estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 according to the Japanese Society of Nephrology guidelines.(16) The other definitions of J-PCI variables are available online (http://www.cvit.jp/registry/jpci_definition.pdf, accessed on February 14, 2018).

Statistical analysis

The study cohort was randomly divided in a 1:1 ratio into derivation (N=334,591) and validation (N=334,590) cohorts. The demographic data and clinical patient characteristics were summarised by enrolment year, and the data were presented as mean ± SD or as proportion (%), depending on the variables. Trend tests were performed using the Cochrane-Armitage test for trend.

All variables in **Table 1** except for procedure details were listed as initial candidate variables. Age was considered as a continuous variable, while the others were considered as dichotomous variables. With regard to diagnosis, unstable angina, ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI) were included in the list of candidate variables based on clinical judgement. After accounting for multicollinearity amongst candidate variables, final candidates for inclusion in the multivariable model were selected as follows: age, sex, clinical presentation (unstable angina, STEMI, and NSTEMI), previous PCI, previous coronary artery bypass grafting, previous myocardial infarction (MI), diabetes, hypertension, dyslipidaemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis and renal dysfunction on dialysis), chronic lung disease, peripheral

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vascular disease, previous heart failure, cardiogenic shock within 24 hours prior to the procedure, number of diseased vessel (two-vessel disease, three-vessel disease, and left main trunk lesion), and involvement of the left anterior descending artery or left main trunk as a target lesion. Age was considered as a continuous variable, while the others were considered as dichotomous variables. Multivariable logistic regression with a backward selection method was then performed to identify independent predictors of in-hospital death. Package 'step' in R was used for backward selection, in which elimination process was based on Akaike's Information Criterion.

From the derivation cohort, we developed two separate PCI risk prediction models for estimating in-hospital mortality that can be applied to both acute and elective clinical settings: one based on all available variables including both pre-procedure- and procedure-related variables (full model) and the other based on pre-procedural variables only (pre-procedure model). In addition, an integer score was assigned to each variable selected in the pre-procedure model in proportion to the estimated regression coefficient (0.23) defined from an incremental risk ratio by age (10 years) The regression coefficient for each level of every risk factor was subsequently divided by this reference value (0.23) to compute its weights for the risk score.(17,18)

Using the validation cohort, the performance of the developed models was examined by using C-statistics to assess discrimination and by demonstrating calibration plots to evaluate calibration. After assessing discrimination and calibration across the entire validation cohort, we examined the model performance for clinically distinct patient populations. These included acute coronary syndrome (ACS) vs. non-ACS, female vs. male, and advanced age (>70) vs. younger age (≤70).

All variables had less than 3% missingness. To account for missing data, single imputation was used for each variable; 'STEMI' for type of MI, 'transradial' for access site, and 'No' for others. Data were analysed using R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). All P values were two sided, and P values <0.05 were considered significant.

Patient and public involvement

Patients and public were not involved in this study.

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Results

Population characteristics

After excluding patients with missing data on age and/or sex (N=3410), outside the age range of 20–100 years (N=281), with missing data on outcomes (N=647), and with missing data on diagnosis (N=43), 669,181 patients from 1,018 institutes were included in the analysis (**Figure 1**). The baseline demographic data, lesion characteristics, and procedure details are summarised in **Table 1**, while in-hospital outcomes are shown in **Table 2**, stratified by enrolment year. About 40% of PCIs were performed in patients with ACS, while 3% of patients developed cardiogenic shock within 24 hours prior to PCI. During the index hospitalisation, 4,788 (0.7%) patients died after PCI. The bivariate relationships between patient characteristics and in-hospital mortality are shown in the Supplementary Tables (**eTable 1** for the derivation cohort and **eTable 2** for the validation cohort).

Between 2014 and 2016, demographics and risk factors of patients undergoing PCI did not change in terms of clinically meaningful difference. With regard to the diagnosis at the time of PCI, the proportion of patients with silent ischaemic heart disease slightly increased from 15.9% in 2014 to 17.4% in 2016, whereas the proportion of patients who underwent PCIs as treatment for STEMI decreased from 18.6% to 17.3% (P values for trend <0.001). Procedures significantly changed during the study period. The rate of transradial approach increased significantly from 60.6% to 66.9%, in parallel with the decreasing trend of transfemoral approach (P values for trend <0.001). Similarly, the use of drug-eluting balloon and drug-eluting stent showed an increasing trend, whereas the use of bare metal stent decreased significantly (all P values for trend <0.001). In patients with STEMI, the use of thrombus aspiration remained stable during the study period, although its trend demonstrated a significant increase (P value for trend =0.011).

Development of full and pre-procedure models

Table 3 shows the results of the multivariable logistic regression analyses. Pre-procedure variables selected in the final models were age, sex (female), STEMI,

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NSTEMI, unstable angina, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidaemia, smoker, renal dysfunction (renal dysfunction without requiring dialysis and renal dysfunction on dialysis), peripheral vascular disease, previous heart failure, and cardiogenic shock within 24 hours prior to the procedure. All angiographic information, such as three-vessel disease, left main trunk lesion, and involvement of left anterior descending artery or left main trunk as a target lesion, were retained in the full model.

Discrimination and calibration performance of full and pre-procedure models

In the entire validation cohort, discrimination performance of the full model was excellent, with C-index of 0.929 (95% confidence interval [CI], 0.924–0.935). The exclusion of the angiographic information from the full model resulted in only a slight decrement in the overall model discriminatory performance, and the C-index of the pre-procedure model was 0.926 (95% CI, 0.920–0.931). Both full and pre-procedure models performed well even in the pre-specified subgroups, and C-indexes ranged from 0.829 to 0.933 for the full model and from 0.820 to 0.926 for the pre-procedure model, respectively (**eTable 3 in the supplement**). There was excellent calibration performance of both models in the entire validation cohort (**eFigure 1 in the supplement)**. The calibration performance was also acceptable in the pre-specified subgroups, although both models were likely to underestimate the risk of mortality in high-risk patients who underwent elective procedure (**eFigure 2 and eFigure 3 in the supplement**).

Development and validation of integer simple risk score

The integer points for each variable derived from beta coefficients in the multivariable models are listed in **Figure 2**. The highest number of points was 12 (cardiogenic shock), whereas the lowest was −3 (dyslipidaemia). The possible total points ranged from −6 to 43. The agreements between the observed and estimated risks of mortality with the developed risk-scoring methods were assessed across five groups in the entire validation cohort (**Figure 2**). Overall, the agreements were acceptable, although the integer score underestimated mortality risk in the higher-risk

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patients, where the observed and predicted mortalities were 1.2% and 0.9% in the second highest risk group, and 6.9% and 6.6% in the highest-risk group, respectively.

Discussion

Using the nationally representative cohort of Japanese patients who underwent PCI with >660,000 procedures from 1,018 institutes, we developed and internally validated risk models predicting in-hospital mortality in patients after PCI. The final full model included age, sex, clinical presentation, previous PCI, previous coronary artery bypass grafting, hypertension, dyslipidaemia, smoker, renal dysfunction, peripheral vascular disease, previous heart failure, cardiogenic shock within 24 hours prior to the procedure, and angiographic information. The model performed very well in an independent validation cohort, as well as in various subgroups stratified by age, sex, and clinical presentation. The model performance was retained even after excluding angiographic information, and a simplified integer risk score based on the pre-procedure model also performed well. These developed risk prediction models provided the risk-adjusted mortality in benchmark report, compared an institution's performance with that of national experience, and stratified patients who were at risk pre-procedurally.

For the purpose of risk adjustment for benchmarking and comparing institutional performances, rigorous adjustment is warranted. Significant differences were observed in patient demographics, biological response to medication or procedure, and practice pattern in PCI between Japan and the Western countries.(10,19) For example, patients in Japan are likely to have more advanced age, have lower body mass weight, and experience bleeding complications than those in Western countries. Furthermore, the proportion of elective PCIs performed in Japan is greater than those in other countries. With regard to practice patterns, thrombus aspiration is still widely performed as treatment for patients with STEMI despite the recent downgrade of the relevant recommendations in the US and European guidelines.(20,21) In spite of these significant differences, some risk models or clinical scores that are derived from the Western countries have been externally validated and were proven useful in Japanese patients.(10,22,23) Kohsaka

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et al. applied the in-hospital mortality risk model derived from the National Cardiovascular Data Registry CathPCI Registry, which is the nationwide PCI registry in the US, to the regional PCI registry from 15 Japanese institutes near Tokyo area and demonstrated that the US model was clinically applicable in Japanese population with excellent discrimination and acceptable calibration performances.(10) However, given its limited calibration performance in high-risk patients, the risk model derived from its own dataset can provides an accurate adjusted mortality.

A number of risk models were developed from various registries to predict risk of mortality in patients undergoing PCI. Individual components varied amongst risk models, but several components, such as age, clinical presentation or urgency, renal dysfunction, and cardiogenic shock, were consistently included in the model.(4-9) Our developed risk models also allied with the previous models and included these core variables. Although angiographic information also served as a component of our full model, its incremental predictive value may be limited, given the sufficient performance of the pre-procedure model. This finding is consistent with those of previous studies, and Peterson et al. showed that in-hospital mortality was driven primarily by pre-existing patient comorbidities and makers of clinical instability.(4) It allows patients and physicians to obtain a reasonable estimate of mortality pre-procedurally.

Few studies reported the risk model predicting mortality after PCI derived from Japanese population. Tanaka et al. developed the Kyoto Model using the CREDO-Kyoto Registry, which is one of the most established PCI registries in Japan.(24) However, the Kyoto Model intended to predict long-term mortality after revascularisation and was not applicable to patients undergoing PCI for MI, because the dataset excluded patients who experienced acute MI 1 week prior to the index procedure. Furthermore, the dataset included patients who underwent revascularisation between 2000 and 2002 and could not be directly applied to current practice. Our study is the first to report the risk model predicting in-hospital mortality in Japan using the nationwide PCI registry in the contemporary PCI practice. Thus, the Japanese cardiovascular society can use this model as an instrument for the pre-PCI risk stratification and to distribute the risk-adjusted mortality in benchmark

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reports, leading to improve quality of care and clinical outcomes in PCI.

Several variables, such as prior PCI, hypertension, dyslipidaemia, and current smoker, were identified as independent factors associated with reduction in mortality. Although some controversies remain and they may be attributed to the confounding factors, their associations with improved mortality were consistent with those of previous studies.(4,5,25-27) Smoker's paradox is a well-known phenomenon and has been reported in patients undergoing PCI.(26,27) Recent data have demonstrated a specific pharmacodynamic enhancement of platelet inhibition by clopidogrel amongst smokers,(28) which may hold important implications for patients treated with PCI, given that clopidogrel is still widely used for patients treated with PCI in Japan.(19) The protective effect of dyslipidaemia may be related to statin use before PCI, which our database does not collect as a separate variable. The diagnosis for dyslipidaemia may have acted as a proxy for statin use, which has been shown to reduce the risk of post-procedural MI and mortality in previous meta-analysis studies. Meta-analysis demonstrated that statin administration before PCI significantly reduced the risk of post-procedural MI, resulting in the reduction in mortality.(29,30) The impact of pre-existing hypertension on in-hospital mortality remains controversial; however, a recent study from the Acute Myocardial Infarction in Switzerland Plus Registry reported that pre-existing hypertension was associated with increased risk of in-hospital mortality in patients presenting with ACS. (31) Although the exact mechanism is unknown, pre-treatment of hypertension with beta-blockers and renin-angiotensin aldosterone inhibitors could have led to a favourable outcome. Previous studies have consistently demonstrated the protective effect of prior PCI in terms of reduction in in-hospital mortality in patients undergoing PCI. (4,5) This may be attributed to the fact that patients with prior PCI were more likely to undergo subsequent 'low-risk' PCI, such as staged PCI. In contrast, those with prior CABG were more likely to undergo subsequent 'high-risk' PCI, such as PCI for multivessel lesion, left main trunk lesion, and severely calcified lesion, resulting in increased risk of in-hospital mortality.

Limitations

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This study had several limitations. First, J-PCI is a voluntary registry; the contributing hospitals may have larger procedure volume than the average institutes in Japan. However, J-PCI included >85% of all PCIs performed in Japan and assured high participation rate by linking to the application for board certification and renewal. Second, improving the quality of the database is a continuing issue in J-PCI. With regard to data accuracy, not only is data auditing important but also the education of persons inputting data at each site as it enables adherence to correct data definitions. Third, the candidate variables for the risk models were limited to those available in J-PCI. Actually, several variables selected in other risk models were not included in our dataset and may further refine risk prediction.

Fourth, the models underestimated the risk of mortality in high-risk patients who underwent elective procedure, although their discrimination and calibration performances were acceptable. Although the exact reason remains unknown, lack of granularity for variables representing the complexity of PCI, such as SYNTAX score, chronic total occlusion, and severity of calcification, may have led to the suboptimal calibration performance in this particular population. Since the developed risk models cover patients with a broad range of mortality risk, providing an accurate estimation for all patients is challenging, especially in low-risk patients, mainly owing to the small number of in-hospital deaths. Further studies may be required to generate separate models for patients with specific clinical presentations to improve risk prediction.

Fifth, the models have been validated using only J-PCI data; it has not been validated on an external dataset. Finally, J-PCI captured in-hospital outcomes that occurred only during hospitalizations where PCIs were performed; therefore, data on the subsequent outcomes when the patients were transferred to other hospitals and facilities were lacking. This may have led to the underestimation of mortality in J-PCI. We have recently launched a project involving selected institutes participating in J-PCI, aiming to obtain long-term follow-up data, which may provide additional insights.

Conclusion

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Using the nationwide Japanese PCI registry, we have developed and internally validated the risk models for predicting in-hospital mortality after PCI. The models performed very well in a broad spectrum of patients undergoing PCI as well as in clinically important subgroups. These models are expected to help improve the rate of patient mortality after PCI by facilitating pre-PCI risk stratification, improving hospital quality assessment, and providing an accurate adjusted risk in benchmark reports.

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Author Contributions

T Inohara and S Kohsaka had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: **T Inohara and S Kohsaka**

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Administrative, technical, or material support: **S Kohsaka, T Amano, and M Nakamura**

Study supervision: **S Kohsaka, H Kumamaru, H Miyata, and M Nakamura**

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Data Sharing Statement

In addition to data in this manuscript, all data in the J-PCI registry are available to investigators from >1000 sites participating in the J-PCI registry. The dataset are stored in servers of the National Clinical Database (NCD). Local investigators can submit proposal for data use for research purposes.

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Figure Legends

Figure 1. Study cohort creation
Abbreviations: PCI, percutaneous coronary intervention

Figure 2. Integer score and its calibration performance
The agreements between the observed and expected risks of mortality with the developed integer score were assessed across 5 groups of the total points in the validation cohort.
Abbreviations: Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort

eFigure 2. Calibration plots of full model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

eFigure 3. Calibration plots of pre-procedure model in subgroups including clinical presentation (a, b), sex (c, d), and age (e, f).

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Table 1. Baseline characteristics by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	*P*
Demographics				
Age, yrs, mean (SD)	69.97 (10.99)	70.08 (11.04)	70.26 (11.07)	<0.001
Female	50747 (24.1)	52048 (23.9)	57677 (24.0)	0.218
Diagnosis				<0.001
Elective setting				
Stable angina	80244 (38.1)	83258 (38.2)	91894 (38.2)	
Silent ischemic heart disease	33550 (15.9)	36431 (16.7)	41764 (17.4)	
Old myocardial infarction	12528 (6.0)	13034 (6.0)	14153 (5.9)	
Acute setting				
Unstable angina	33985 (16.1)	33582 (15.4)	37599 (15.6)	
Myocardial infarction	50237 (23.9)	51684 (23.7)	55239 (23.0)	
STEMI	39140 (18.6)	40050 (18.4)	41740 (17.3)	
NSTEMI	9217 (4.4)	9844 (4.5)	11453 (4.8)	
Risk Factors				
Previous PCI	96877 (46.2)	99896 (46.6)	110163 (46.5)	0.022
Previous CABG	8871 (4.2)	8525 (4.0)	8949 (3.8)	<0.001
Previous MI	48620 (23.4)	49547 (23.3)	54073 (22.9)	0.001
Diabetes Mellitus	90152 (42.8)	94250 (43.2)	105066 (43.7)	<0.001
Hypertension	155985 (74.1)	162075 (74.4)	178889 (74.3)	0.083
Dyslipidaemia	130740 (62.1)	137264 (63.0)	153059 (63.6)	<0.001
Current smoker	64368 (30.6)	67385 (30.9)	74027 (30.8)	0.054
Renal Insufficiency	35366 (16.8)	37857 (17.4)	43460 (18.1)	<0.001
On dialysis	13099 (6.2)	13649 (6.3)	15601 (6.5)	<0.001
Chronic lung disease	3347 (1.6)	4039 (1.9)	5336 (2.2)	<0.001

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Peripheral Vascular Disease	13273 (6.3)	15169 (7.0)	18064 (7.5)	<0.001
Previous heart failure	26105 (12.8)	27667 (13.1)	31478 (13.4)	<0.001
Cardiopulmonary arrest on arrival	3285 (1.6)	3311 (1.6)	4137 (1.7)	<0.001
Cardiogenic shock within 24 hrs	6023 (2.9)	6307 (3.0)	7429 (3.1)	<0.001
Acute heart failure within 24 hrs	8217 (4.0)	8082 (3.8)	9347 (4.0)	0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	126593 (60.1)	133649 (61.3)	150477 (62.5)	<0.001
Two vessel disease	55997 (26.6)	56117 (25.7)	60936 (25.3)	<0.001
Three vessel disease	27205 (12.9)	27371 (12.6)	28424 (11.8)	<0.001
Left main trunk	8322 (4.0)	9129 (4.2)	9688 (4.0)	<0.001
Lesion Location:				
RCA	73309 (34.8)	74356 (34.1)	81482 (33.9)	<0.001
LAD/Left Main	106996 (50.8)	111132 (51.0)	123788 (51.4)	<0.001
LCX	54314 (25.8)	55638 (25.5)	60444 (25.1)	<0.001
Bypass graft	2163 (1.0)	1189 (0.5)	1202 (0.5)	<0.001
Procedure details				
Approach				<0.001
Transradial	127686 (60.6)	138397 (63.5)	161104 (66.9)	
Transfemoral	71473 (33.9)	67668 (31.0)	67166 (27.9)	
Others (e.g. brachial)	11376 (5.4)	11924 (5.5)	12378 (5.1)	
Device				
Thrombus aspiration[a]	21551/39140 (55.1)	21640/40050 (54.0)	22605/41740 (54.2)	<0.001
Distal protection	7392 (3.5)	8077 (3.7)	7519 (3.1)	<0.001
Rotablader	7294 (3.5)	7686 (3.5)	8910 (3.7)	<0.001
Drug eluting balloon	12922 (6.1)	15769 (7.2)	22916 (9.5)	<0.001
Stent characteristics				
Type of stent				

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Drug eluting stent	166194 (78.9)	184327 (84.6)	206323 (85.7)	<0.001
Bare metal stent	14854 (7.1)	7807 (3.6)	4966 (2.1)	<0.001
TIMI flow post-procedure				
Flow 3	205978 (97.8)	213709 (98.0)	235969 (98.1)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; TIMI, Thrombolysis in Myocardial Infarction.

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Table 2. Crude outcomes by enrollment year

	J-PCI 2014 N=210544	J-PCI 2015 N=217989	J-PCI 2016 N=240648	P
In-hospital death	1523 (0.7)	1479 (0.7)	1786 (0.7)	0.033
Bleeding complication	546 (0.3)	701 (0.3)	779 (0.3)	<0.001
Access site bleeding	334 (0.2)	429 (0.2)	460 (0.2)	0.007
Non-access site bleeding	223 (0.1)	287 (0.1)	341 (0.1)	0.003
Periprocedural MI	875 (0.4)	921 (0.4)	1140 (0.5)	0.005
Tamponade	317 (0.2)	287 (0.1)	350 (0.1)	0.234
Post-procedure shock	1920 (0.9)	1927 (0.9)	2145 (0.9)	0.603
Acute stent thrombosis	407 (0.2)	331 (0.2)	297 (0.1)	<0.001
Emergent operation	206 (0.1)	213 (0.1)	204 (0.1)	0.246

Abbreviations: MI, myocardial infarction.

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Table 3. Full and pre-procedure risk model

	Full Model				Pre-procedure Model			
	Coefficient	OR	95% CI	*P*	Coefficient	OR	95% CI	*P*
Intercept	-8.878621				-8.472575			
Demographics								
Age, per 1 year	0.023744	1.02	1.02 - 1.03	<0.001	0.023608	1.02	1.02 - 1.03	<0.001
Female	0.177372	1.19	1.08 - 1.32	<0.001	0.155252	1.17	1.06 - 1.29	0.002
Diagnosis								
STEMI	2.528622	12.5	10.7 - 14.7	<0.001	2.530134	12.6	10.7 - 14.7	<0.001
NSTEMI	2.170769	8.77	7.24 - 10.6	<0.001	2.260405	9.59	7.93 - 11.6	<0.001
Unstable angina	1.108935	3.03	2.50 - 3.68	<0.001	1.163039	3.2	2.64 - 3.88	<0.001
Risk Factors								
Previous PCI	-0.121767	0.89	0.79 - 0.99	0.029	-0.170187	0.84	0.76 - 0.94	0.002
Previous CABG	0.371319	1.45	1.17 - 1.79	<0.001	0.38463	1.47	1.19 - 1.81	<0.001
Hypertension	-0.181962	0.83	0.76 - 0.91	<0.001	-0.175804	0.84	0.77 - 0.92	<0.001
Dyslipidaemia	-0.55876	0.57	0.52 - 0.63	<0.001	-0.540339	0.58	0.53 - 0.64	<0.001
Current smoker	-0.19942	0.82	0.74 - 0.91	<0.001	-0.210493	0.81	0.73 - 0.90	<0.001
Renal Insufficiency without Dialysis	0.522425	1.69	1.51 - 1.88	<0.001	0.552934	1.74	1.56 - 1.93	<0.001
Renal Insufficiency on Dialysis	0.827209	2.29	1.95 - 2.69	<0.001	0.821163	2.27	1.94 - 2.67	<0.001
Peripheral Vascular Disease	0.457832	1.58	1.35 - 1.85	<0.001	0.498317	1.65	1.41 - 1.92	<0.001
Previous heart failure	0.451346	1.57	1.40 - 1.77	<0.001	0.491731	1.64	1.45 - 1.84	<0.001
Cardiogenic shock within 24 hrs	2.540633	12.7	11.6 - 13.9	<0.001	2.67607	14.5	13.3 - 15.9	<0.001
Number of Diseased Vessels								
Three vessel disease	0.368771	1.45	1.31 - 1.60	<0.001				
Left main trunk	0.680996	1.98	1.75 - 2.23	<0.001				
Lesion Location								
LAD/Left Main	0.527633	1.69	1.55 - 1.86	<0.001				

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Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LAD, left anterior descending.

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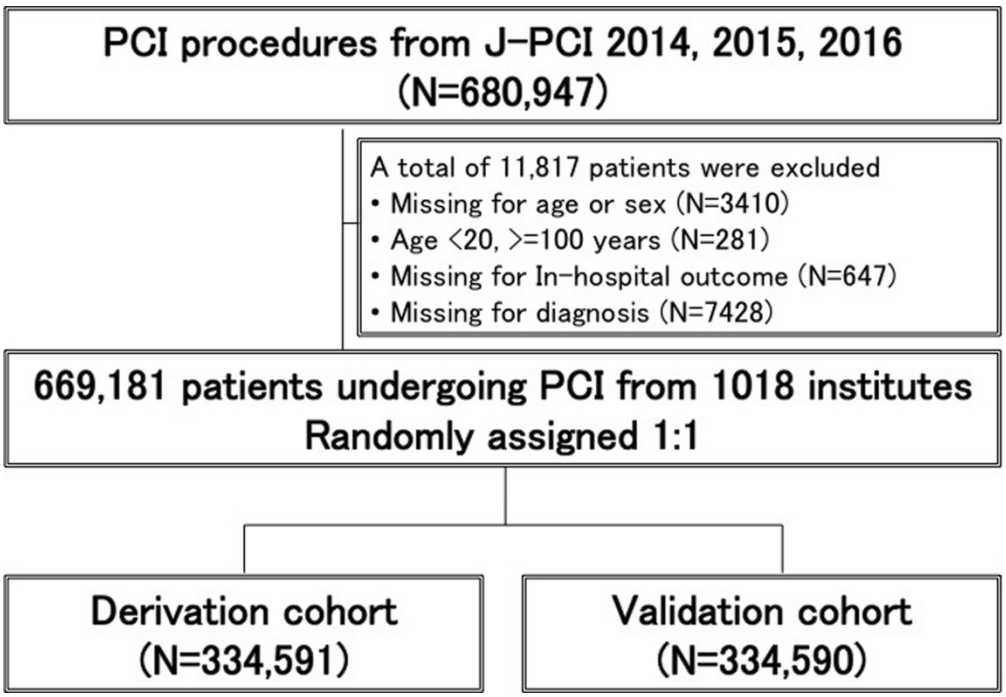

Figure 1. Study cohort creation

233x160mm (300 x 300 DPI)

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	Beta Coefficient	Score
Demograohics		
Age	0.023608	
20-29		0
30-39		1
40-49		2
50-59		3
60-69		4
70-79		5
80-89		6
90-99		7
Female	0.155252	1
Diagnosis		
STEMI	2.530134	11
NSTEMI	2.260405	10
Unstable angina	1.163039	5
Risk Factors		
Previous PCI	-0.170187	-1
Previous CABG	0.38463	2
Hypertension	-0.175804	-1
Dyslipidaemia	-0.540339	-3
Current smoker	-0.210493	-1
Renal Insufficiency without Dialysis	0.552934	3
Renal Insufficiency on Dialysis	0.821163	4
Peripheral Vascular Disease	0.498317	3
Previous heart failure	0.491731	3
Cardiogenic shock within 24 hrs	2.67607	12

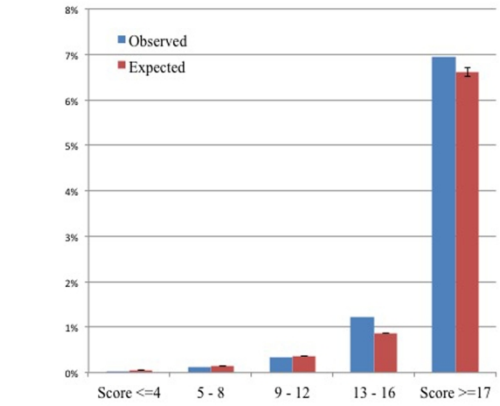

Figure 2. Integer score and its calibration performance

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Supplemental Material

eTable 1. Derivation cohort

	Overall N=334591	Death, No N=332130	Death, Yes N=2461	*P*
Demographics				
Age, yrs, mean (SD)	70.09 (11.03)	70.06 (11.02)	74.15 (12.13)	<0.001
Female	79981 (23.9)	79196 (23.8)	785 (31.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127639 (38.1)	127544 (38.4)	95 (3.9)	
Silent ischemic heart disease	55975 (16.7)	55894 (16.8)	81 (3.3)	
Old myocardial infarction	19862 (5.9)	19831 (6.0)	31 (1.3)	
Acute setting				
Unstable angina	52703 (15.8)	52490 (15.8)	213 (8.7)	
Myocardial infarction	78412 (23.4)	76371 (23.0)	2041 (82.9)	
STEMI	60408 (18.1)	58837 (17.7)	1571 (63.8)	
NSTEMI	15145 (4.5)	14850 (4.5)	295 (12.0)	
Risk Factors				
Previous PCI	153791 (46.5)	153216 (46.7)	575 (23.9)	<0.001
Previous CABG	13310 (4.0)	13192 (4.0)	118 (4.9)	0.041
Previous MI	75965 (23.1)	75499 (23.2)	466 (19.7)	<0.001
Diabetes Mellitus	144880 (43.3)	143857 (43.3)	1023 (41.6)	0.085
Hypertension	248534 (74.3)	246954 (74.4)	1580 (64.2)	<0.001
Hypercholesterolemia	210860 (63.0)	209898 (63.2)	962 (39.1)	<0.001
Current smoker	103072 (30.8)	102456 (30.8)	616 (25.0)	<0.001
Renal Insufficiency	58278 (17.4)	57455 (17.3)	823 (33.4)	<0.001
On dialysis	21174 (6.3)	20939 (6.3)	235 (9.5)	<0.001
Chronic lung disease	6383 (1.9)	6311 (1.9)	72 (2.9)	<0.001
Peripheral Vascular Disease	23270 (7.0)	23033 (6.9)	237 (9.6)	<0.001
Previous heart failure	42743 (13.2)	42249 (13.1)	494 (21.0)	<0.001
Cardiopulmonary arrest on arrival	5450 (1.7)	4476 (1.4)	974 (40.0)	<0.001
Cardiogenic shock within 24 hrs	9903 (3.0)	8512 (2.6)	1391 (57.3)	<0.001
Acute heart failure within 24 hrs	12952 (4.0)	11761 (3.6)	1191 (49.5)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	204905 (61.2)	203905 (61.4)	1000 (40.6)	<0.001
Two vessel disease	86917 (26.0)	86253 (26.0)	664 (27.0)	0.264
Three vessel disease	41600 (12.4)	40927 (12.3)	673 (27.3)	<0.001
Left main trunk	13483 (4.0)	13040 (3.9)	443 (18.0)	<0.001
Lesion Location:				

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RCA	114891 (34.3)	114069 (34.3)	822 (33.4)	0.337
LAD/Left Main	170823 (51.1)	169149 (50.9)	1674 (68.0)	<0.001
LCX	85244 (25.5)	84583 (25.5)	661 (26.9)	0.12
Bypass graft	2261 (0.7)	2234 (0.7)	27 (1.1)	0.015
Procedure details				
Approach				<0.001
Transradial	213314 (63.8)	212740 (64.1)	574 (23.3)	
Transfemoral	103410 (30.9)	101690 (30.6)	1720 (69.9)	
Others (e.g. brachial)	17864 (5.3)	17697 (5.3)	167 (6.8)	
Device				
Thrombus aspiration[a]	33067/60408 (54.7)	32264/58837 (54.8)	803/1571 (51.1)	<0.001
Distal protection	11468 (3.4)	11354 (3.4)	114 (4.6)	0.001
Rotablader	11937 (3.6)	11865 (3.6)	72 (2.9)	0.095
Drug eluting balloon	25907 (7.7)	25851 (7.8)	56 (2.3)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278173 (83.1)	276424 (83.2)	1749 (71.1)	<0.001
Bare metal stent	13927 (4.2)	13697 (4.1)	230 (9.3)	<0.001
TIMI flow post-procedure				
Flow 3	327771 (98.0)	325613 (98.0)	2158 (87.7)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 2. Validation cohort

	Overall N=334590	Death, No N=332263	Death, Yes N=2327	*P*
Demographics				
Age, yrs, mean (SD)	70.13 (11.04)	70.09 (11.03)	74.78 (11.95)	<0.001
Female	80491 (24.1)	79702 (24.0)	789 (33.9)	<0.001
Diagnosis				<0.001
Elective setting				
Stable angina	127757 (38.2)	127673 (38.4)	84 (3.6)	
Silent ischemic heart disease	55770 (16.7)	55680 (16.8)	90 (3.9)	
Old myocardial infarction	19852 (5.9)	19805 (6.0)	47 (2.0)	
Acute setting				
Unstable angina	52463 (15.7)	52243 (15.7)	220 (9.5)	
Myocardial infarction	78748 (23.5)	76862 (23.1)	1886 (81.0)	
STEMI	60522 (18.1)	59085 (17.8)	1437 (61.8)	
NSTEMI	15369 (4.6)	15083 (4.5)	286 (12.3)	
Risk Factors				
Previous PCI	153145 (46.3)	152590 (46.5)	555 (24.3)	<0.001
Previous CABG	13035 (3.9)	12931 (3.9)	104 (4.5)	0.175
Previous MI	76275 (23.2)	75832 (23.3)	443 (19.7)	<0.001
Diabetes Mellitus	144588 (43.2)	143595 (43.2)	993 (42.7)	0.612
Hypertension	248415 (74.2)	246933 (74.3)	1482 (63.7)	<0.001
Hypercholesterolemia	210203 (62.8)	209296 (63.0)	907 (39.0)	<0.001
Current smoker	102708 (30.7)	102209 (30.8)	499 (21.4)	<0.001
Renal Insufficiency	58405 (17.5)	57666 (17.4)	739 (31.8)	<0.001
On dialysis	21175 (6.3)	20959 (6.3)	216 (9.3)	<0.001
Chronic lung disease	6339 (1.9)	6259 (1.9)	80 (3.4)	<0.001
Peripheral Vascular Disease	23236 (6.9)	23027 (6.9)	209 (9.0)	<0.001
Previous heart failure	42507 (13.1)	42024 (13.0)	483 (21.8)	<0.001
Cardiopulmonary arrest on arrival	5283 (1.6)	4442 (1.4)	841 (36.5)	<0.001
Cardiogenic shock within 24 hrs	9856 (3.0)	8603 (2.6)	1253 (54.6)	<0.001
Acute heart failure within 24 hrs	12694 (3.9)	11605 (3.6)	1089 (48.0)	<0.001
Lesion characteristics				
Number of Diseased Vessels				
One vessel disease	205814 (61.5)	204889 (61.7)	925 (39.8)	<0.001
Two vessel disease	86133 (25.7)	85477 (25.7)	656 (28.2)	0.007
Three vessel disease	41400 (12.4)	40748 (12.3)	652 (28.0)	<0.001
Left main trunk	13656 (4.1)	13247 (4.0)	409 (17.6)	<0.001
Lesion Location:				
RCA	114256 (34.1)	113461 (34.1)	795 (34.2)	1
LAD/Left Main	171093 (51.1)	169519 (51.0)	1574 (67.6)	<0.001
LCX	85152 (25.4)	84496 (25.4)	656 (28.2)	0.003

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Bypass graft	2293 (0.7)	2276 (0.7)	17 (0.7)	0.889
Procedure details				
Approach				<0.001
Transradial	213873 (63.9)	213341 (64.2)	532 (22.9)	
Transfemoral	102897 (30.8)	101265 (30.5)	1632 (70.1)	
Others (e.g. brachial)	17814 (5.3)	17651 (5.3)	163 (7.0)	
Device				
Thrombus aspiration[a]	32729/60522 (54.1)	31993/59085 (54.1)	736/1437 (51.2)	<0.001
Distal protection	11520 (3.4)	11430 (3.4)	90 (3.9)	0.284
Rotablader	11953 (3.6)	11874 (3.6)	79 (3.4)	0.684
Drug eluting balloon	25700 (7.7)	25637 (7.7)	63 (2.7)	<0.001
Stent characteristics				
Type of stent				
Drug eluting stent	278671 (83.3)	277032 (83.4)	1639 (70.4)	<0.001
Bare metal stent	13700 (4.1)	13451 (4.0)	249 (10.7)	<0.001
TIMI flow post-procedure				
Flow 3	327885 (98.0)	325799 (98.1)	2086 (89.6)	<0.001

a. Confined to patients with STEMI

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; DES, drug eluting stent; BMS, bare metal stent; TIMI, Thrombolysis in Myocardial Infarction.

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eTable 3. Discrimination performance of full and pre-procedure models

			Full Model		Pre-procedure Model	
	Sample, n	Death, n	C-index	95% CI	C-index	95% CI
Derivation cohort	334591	2461	0.929	0.924 - 0.935	0.926	0.920 - 0.931
Validation cohort	334590	2327	0.923	0.917 - 0.928	0.918	0.912 - 0.923
Subgroups (in validation cohort)						
ACS	131211	2106	0.886	0.879 - 0.893	0.876	0.868 - 0.883
Elective	203379	221	0.829	0.800 - 0.858	0.82	0.790 - 0.850
Female	80491	789	0.907	0.897 - 0.918	0.901	0.890 - 0.912
Male	254099	1538	0.927	0.920 - 0.934	0.922	0.915 - 0.929
Age >70	176629	1570	0.912	0.905 - 0.920	0.908	0.900 - 0.915
Age <=70	157204	757	0.933	0.924 - 0.942	0.926	0.916 - 0.935

Abbreviations: ACS, acute coronary syndrome.

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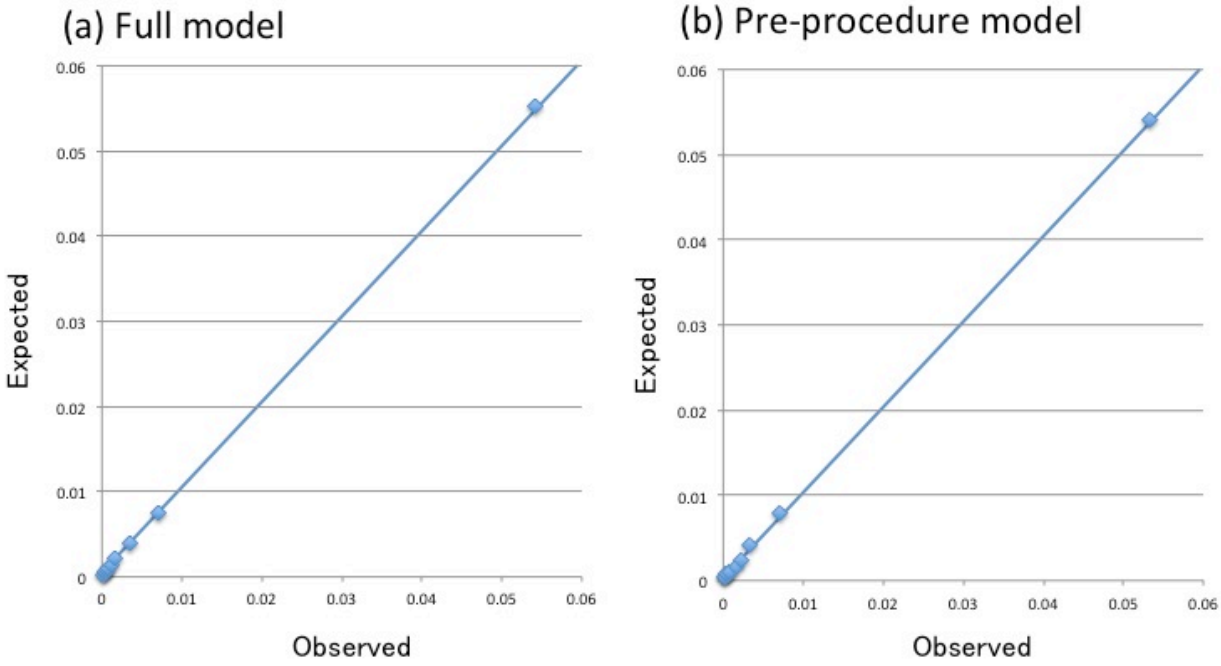
eFigure 1. Calibration plots of (a) full model and (b) pre-procedure model in entire validation cohort



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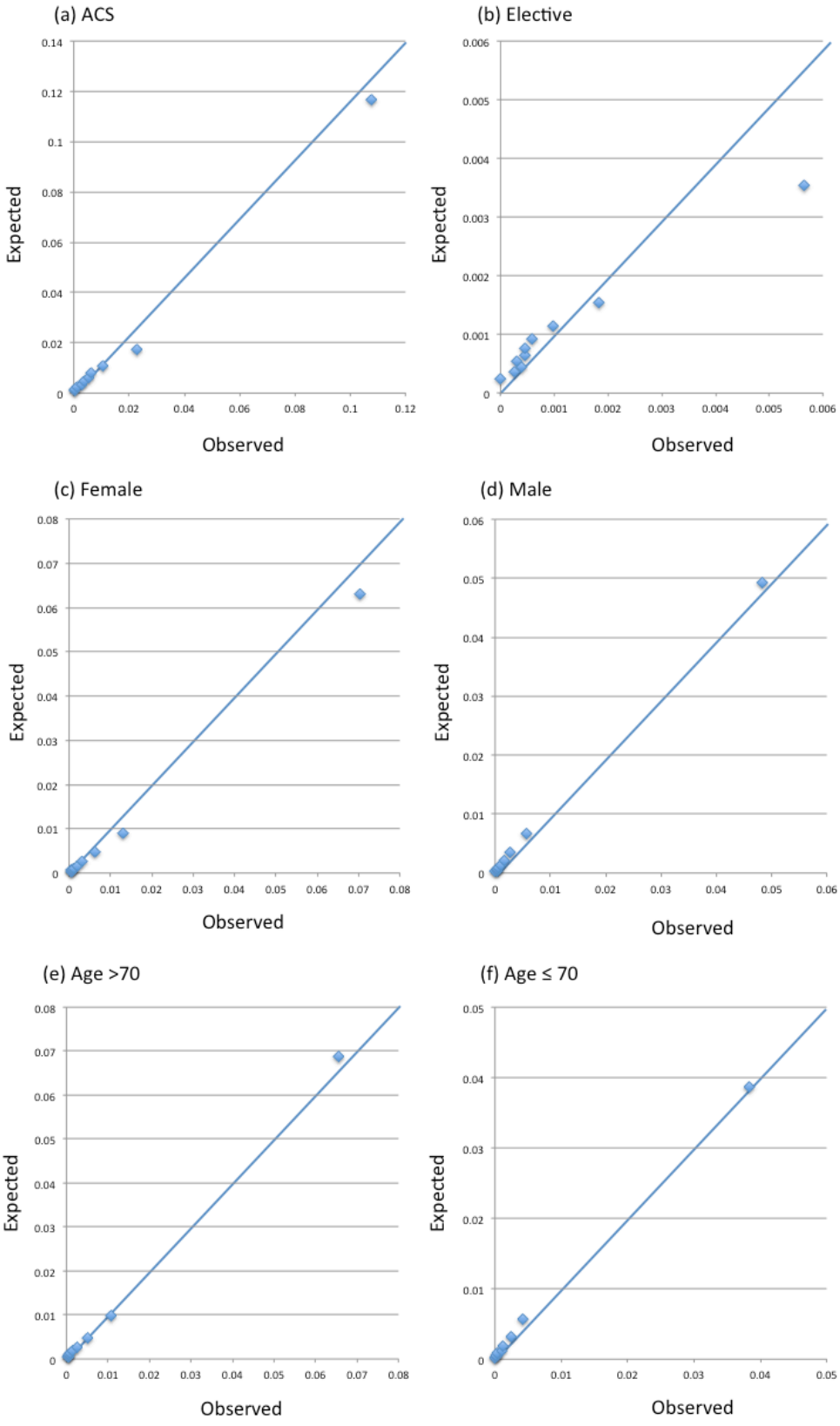
eFigure 2. Calibration plots of full model in subgroups



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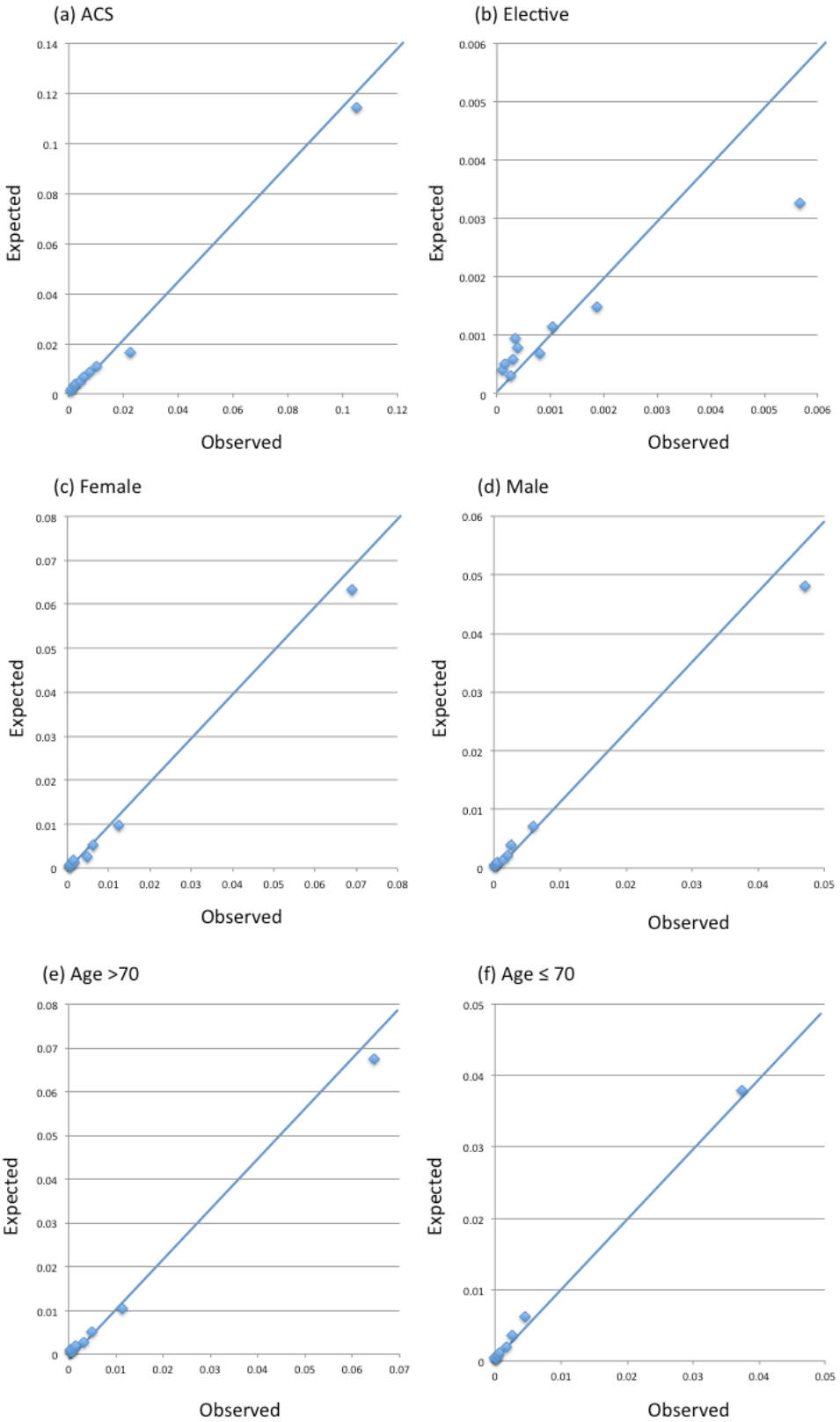
eFigure 3. Calibration plots of pre-procedure model in subgroups



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STROBE Statement: Checklist

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes, page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Yes, page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, page 7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes, page 7
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes, pages 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, pages 7-9
Bias	9	Describe any efforts to address potential sources of bias	Yes, pages 8-9
Study size	10	Explain how the study size was arrived at	Yes, page 9

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes, pages 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Yes, page 9
		(*c*) Explain how missing data were addressed	Yes, page 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Only in-hospital outcomes were evaluated. Patients with missing for outcomes were excluded from the analysis. Page 9
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	Yes, page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes, pages 9-10
		(b) Give reasons for non-participation at each stage	Yes, pages 9-10
		(c) Consider use of a flow diagram	Yes, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Although precise numbers of missingness are not presented, the percentages are described. Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Only in-hospital outcomes were evaluated. Pages 7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Yes, Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Yes, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No. Only adjusted odds ratios are presented.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes, eTable 3, eFigure 2, eFigure 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes, page 11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, throughout the Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes, page 2

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