

Disparity in the Application of Guideline-Based Medical Therapy after Percutaneous Coronary Intervention: Analysis from the Japanese Prospective Multicenter Registry

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Abstract

Background Despite the known benefits of evidence-based medical care in patients with coronary artery disease, disparities exist in the application of guideline-based medical therapy (GBMT) after percutaneous coronary intervention (PCI), particularly in patients who have undergone revascularization procedures. Underestimation of risk, overestimation of side effects, and preference of the treating physician to prioritize invasive procedures may all affect the prescription pattern.

Objective We sought to describe how GBMT is prescribed after PCI in Japan.

Methods From September 2008 to 2010, 1,612 patients underwent PCI with stenting at 14 Japanese hospitals

participating in the Japanese Cardiovascular Database Registry. GBMT was defined as treatment including dual antiplatelet therapy, beta-adrenoceptor antagonists (beta-blockers) and/or calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and statins.

Results Overall, 749 patients (46.5 %) were discharged on GBMT. Notably, the prescription rate of GBMT became lower with age (e.g. from 50.3 % [age 50–59 years] to 35.9 % [age over 80 years]). In addition, patients presenting with acute coronary syndrome (ACS) tended to receive GBMT more frequently (ST-segment elevation myocardial infarction [STEMI] 33.8 vs. 18.3 %; $p < 0.001$; non-ST-segment elevation myocardial infarction [NSTEMI] 8.5 vs. 5.9 %; $p = 0.042$), whereas patients presenting with cardiogenic shock (CS) had lower prescription rates of GBMT (2.1 vs. 4.1 %; $p = 0.032$). Overall age (odds ratio [OR] 0.647; $p = 0.020$), as well as the acute and emergent presentation (OR 3.229; $p < 0.001$ for STEMI; OR 2.122;

For the JCD-KICS Investigators. The Investigators are listed in [Appendix](#).

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$p < 0.001$ for NSTEMI; OR 0.35; $p = 0.002$ for CS) were also associated with prescription of GBMT.

Conclusion Only about half of the post-PCI patients were discharged on ideal GBMT. Elderly patients and those presenting with non-ACS status or hemodynamic compromise tended not to receive GBMT, and required more attention for optimization of their care.

1 Introduction

Secondary prevention with evidence-based care is essential for patients who undergo percutaneous coronary intervention (PCI) to reduce the risk of future cardiac events, and improve quality of life [1]. Various professional societies, such as the American Heart Association and American College of Cardiology (AHA/ACC), aim to reduce cardiovascular disease mortality, and the application of guideline-based medical therapy (GBMT) plays an important role; the strategy for secondary prevention with GBMT has been codified into the 2006 *AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease* [2]. The Japanese Circulation Society (JCS) also provides specific recommendations for secondary prevention for coronary artery disease (CAD) (see the Online Resource for the English translation, with relevant clinical studies).

Despite the known benefits of GBMT in patients with CAD, not all patients will receive GBMT, due to their comorbidities and procedural types. GBMT for the secondary prevention of cardiovascular disease is less likely to be prescribed in Japan than in the USA or Europe, particularly in patients who have undergone similar revascularization

procedures [3–5]. Underestimation of risk, overestimation of side effects, and preference of the treating physician to prioritize invasive procedures may all affect prescription patterns. However, the details of this disparity remain unclear. Further, medication prescription patterns differ strikingly between clinical trials in Japan and the USA/Europe, partially due to perception of coronary spasm.

To describe how GBMT is dispensed after PCI, we used the Japanese Cardiovascular Database (JCD) Registry to evaluate rates of secondary prevention medication prescription at hospital discharge among patients who have undergone PCI. The importance of GBMT should be fully understood, and demonstration of differences in GBMT among these CAD patients could lead to improvement in the quality of care and outcomes.

2 Methods

2.1 Study Design

The JCD is a large, ongoing, prospective, multicenter cohort study designed to collect clinical background and outcome data on PCI patients. Data, including approximately 200 variables, were collected for each patient. Participating hospitals were instructed to record data from consecutive hospital visits for PCI and to register onto the internet-based database system. This system performs checks to ensure that the reported data are complete and internally consistent. PCI with any commercially available coronary device could be included. The decision to perform PCI was made according to the investigators' clinical assessment of their patients. The study did not mandate specific interventional or surgical techniques, such as vascular access, or use of specific stents or closure devices.

The majority of clinical variables in JCD were defined according to the National Cardiovascular Data Registry (NCDR) sponsored by the ACC to conduct comparative research in order to determine the factors that led to disparities in PCI management. The NCDR is a large PCI registry system with over 1,000,000 entries of ischemic heart disease and over 500,000 entries of PCI collected from more than 500 institutions in the USA [6].

2.2 Information Disclosure

Before the launch of the JCD, information on the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network (identifier: UMIN000004736), which is recognized by the International Committee of Medical Journal Editors as an 'acceptable registry', according to a statement issued in September 2004.

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2.3 Participants

Major teaching hospitals within the metropolitan Tokyo area were selected for this study, and the study protocol was approved by the Institutional Review Board (IRB) committee at each site. Patients were enrolled at the time of the cardiovascular event; all the consecutive PCI procedures, including failure cases, during the study period were registered. Patients aged <18 years were excluded. A subgroup of patients who underwent intracoronary infusion of acetylcholine to induce coronary vasospasm was also registered, since vasospastic angina accounts for a significant portion of patients with CAD and acute coronary syndrome (ACS) in Japan [7].

2.4 Procedures and Data Collection

The JCD started enrolling patients on 1 September 2008. As of 31 August 2010, there were 14 hospitals that contributed data on 1,769 PCI and acetylcholine provocation test procedures (Fig. 1). Only patients who underwent PCI were included in the present analysis: those who underwent the acetylcholine provocation test were excluded ($n = 10$; 0.6 %). From these data, we excluded patients undergoing PCI procedures with no stent deployment ($n = 123$; 6.9 %), and those with inadequate data entry ($n = 24$; 1.4 %). Our final study cohort included 1,612 patients.

The present study was funded by the KAKENHI (Grant-in-Aid for Scientific Research; No. 21790751). The JCD Steering Committee was responsible for overall study guidance, including the study protocol, data analysis, and interpretation of the results. The Department of Healthcare

Quality Assessment of Tokyo University independently managed the database. Keio Interhospital Cardiology Study Group managed the participating sites and provided a monthly on-site monitoring service to assure data accuracy and completeness throughout the study. During the planning, implementation, and reporting of this study, there were no issues such as conflict of interest, conflict of responsibility, or intellectual property rights.

2.5 Definition of Guideline-Based Medical Therapy

Prescription rates for aspirin (acetylsalicylic acid), beta-adrenoceptor antagonists (beta-blockers), angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin II receptor blockers (ARBs) and statins and second antiplatelet agents at hospital discharge were collected from the discharge reports. The drugs for secondary prevention therapies after PCI recommended in the AHA/ACC guidelines are aspirin, beta-blockers, ACE-Is/ARBs, statins, and second antiplatelet agents [2]. AHA/ACC guidelines for ischemic heart disease strongly recommend the use of beta-blockers for the secondary prevention of all levels of ischemic heart disease from stable angina to ACS [2, 8–10]. However, due to the high incidence of vasospastic angina in Japan, the JCS guidelines also recommend calcium channel blockers (CCBs) as the first-line drug for CAD, and adds that treatment with beta-blockers alone may worsen spasm-dominant physiology, even after revascularization [11]. As Japan currently has a high rate of CCB prescriptions in patients with CAD, we included CCBs as an alternative to beta-blockers in the original definition of GBMT [11]. We also performed separate analyses based on two different definitions of GBMT: (i) one excluding ACE-Is/ARBs, and (ii) one excluding ACE-Is/ARBs and CCBs. Patients with documented contraindications for one or more of the medications ($n = 14$; 0.9 %) were excluded, and the final study population contained 1,612 patients (Fig. 1).

2.6 Statistical Analysis

Descriptive statistics were calculated on the basis of clinical characteristics and treatment information for the registered patients. When continuous variables were assumed to show a normal distribution, the data were expressed as the mean $\pm$ SD. When normality was not assumed, the data were expressed as the median with an interquartile range. Categorical data were summarized in terms of frequency and proportion. The 95 % CIs of the mean, median, and proportion values were also calculated. The baseline clinical characteristics of patients were compared using Chi-squared tests or one-way analysis of variance (ANOVA) for categorical variables and Student's *t*-test for continuous variables. A two-tailed *p*-value of <0.05 was

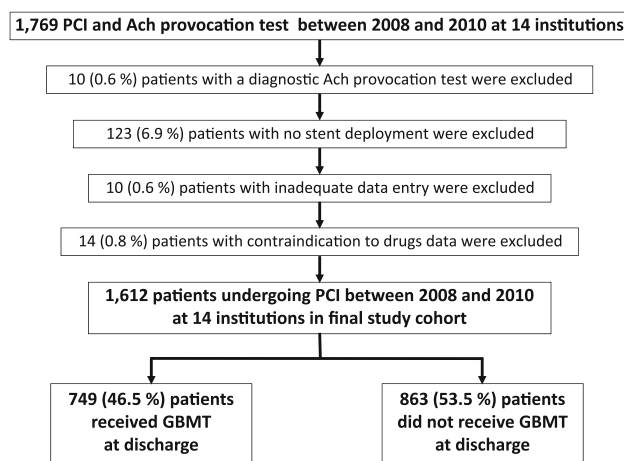


Fig. 1 Flowchart of registered patients for the present analysis. Of 1,769 patients who underwent percutaneous coronary intervention and acetylcholine provocation test during the study period, 157 patients were excluded. A total of 1,612 patients were available for the present analysis. *Ach* acetylcholine, *GBMT* guideline-based medical therapy, *PCI* percutaneous coronary intervention

considered statistically significant. Multivariable logistic regression was used to identify predictors for prescription of GBMT at discharge after adjusting for baseline demographic and clinical variables. The analysis was performed in a downward stepwise regression. The model included baseline/index hospitalization values for demographics (age and gender), clinical history (height, weight, body surface area, body mass index, obesity, prior myocardial infarction [MI], prior PCI, prior coronary artery bypass grafting [CABG], prior heart failure [HF], left ventricular ejection fraction [EF], hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, family history of young CAD, use of anti-anginal agents), admission presentation (glomerular filtration rate [GFR] at presentation, EF at presentation, symptoms, Canadian Cardiovascular Society [CCS] class, New York Heart Association [NYHA] class, ACS on admission, cardiogenic shock (CS) on admission, cardiopulmonary arrest on admission), procedure (lesion location, stage of PCI, use of device, fluoroscopy time) and all in-hospital complications (death, MI, CS, HF, cerebrovascular event, bleeding, vascular complications). We used the following patterns of GBMT as dependent variables in our models: the first model was based on a definition of GBMT as the use of all five medications (dual antiplatelet therapy, beta-blockers and/or CCBs, ACE-I/ARBs, and statins), the second model excluded the use of ACE-I/ARBs, the third model excluded the use of ACE-I/ARBs and CCBs. We also performed analyses in all models of patients, excluding an elderly group (75 years or older). All analyses were conducted with SPSS version 21.0 (SPSS Institute, Chicago, IL). IRB approval for the analyses of the JCD Registry was obtained by the Tokyo University and Keio University School of Medicine Clinical Research Institute.

3 Results

The mean age of the entire cohort was 67.62 ± 10.67 years, and 80.3 % were male. About half of the patients (805 [49.9 %]) presented with ACS. Of the 1,612 patients, 749 (46.5 %) were discharged on GBMT. Baseline characteristics by GBMT prescription are shown in Table 1, and the prescription rates of all the secondary prevention drugs are summarized in Table 2; aspirin and statins were frequently prescribed (97.1 and 82.3 %, respectively), but lower prescription rates were seen for beta-blockers, CCBs, and ACE-I/ARBs (69.2, 30.7 and 63.4 %, respectively).

The prescription rate of GBMT was inversely correlated with age. Notably, the prescription rate of GBMT became

lower with age (e.g. from 50.3 % in group aged 50–59 years to 35.9 % in those aged over 80 years). Patients with traditional coronary risk factors such as hypertension or dyslipidemia, as well as those with previous PCI or history of HF, received GBMT more frequently than those without. Similar trends were seen in patients presenting with ACS (e.g. ST-segment elevation MI [STEMI] or non-ST-segment elevation MI [NSTEMI]). On the other hand, patients with previous CABG and those presenting with CS had lower GBMT prescription rates than those without.

These variables were also associated with prescription of GBMT after adjustment for each of the other co-variables of interest as well as additional important clinical characteristics (Table 3). Hypertension, dyslipidemia, history of PCI and HF, and presentation in ACS predicted GBMT prescription, whereas age over 80 years, CABG, and presentation in CS were inversely associated with GBMT prescription.

We repeated these analyses using different definitions for GBMT (see Sect. 2.5 and Table 3). As anticipated, the majority of the predictors had similar impact, with the exception of hemodialysis. It was inversely associated with prescription of GBMT in the sub-analysis eliminating ACE-I/ARBs (OR 0.275; $p < 0.001$) and ACE-I/ARBs with CCBs (OR 0.397; $p = 0.012$). The results of all groups showed similar tendencies. The detailed demographic information is described in Appendix 3 (see the Online Resource).

Furthermore, since the evidence for use of GBMT is relatively sparse in the elderly population, we also constructed a model for a subgroup of patients excluding the elderly (75 years or older). The result of this sub-analysis also showed similar trends, with prescription of GBMT associated with more acute settings (e.g. ACS) and an inverse association with presentation of CS (Table 4).

4 Discussion

Of the Japanese post-PCI patients we analyzed, those who received GBMT accounted for approximately 50 %, presenting a significantly lower rate than in clinical studies from the USA and Europe (Table 5). We examined each medication prescription and found that aspirin and other antiplatelet agents were prescribed at a rate similar to that in other countries, but there was a striking difference in the prescription rates for beta-blockers and statins. It was of interest that the prescription rate approaches that of other countries when CCBs are added to the analysis. Statins were prescribed at a lower rate, probably because the overall low-density lipoprotein cholesterol level per person in the Japanese population is significantly lower than that in other countries [12, 13].

Table 1 Patient characteristics stratified by prescription of guideline-based medical therapy^a

	GBMT (<i>n</i> = 749)	No GBMT (<i>n</i> = 863)	<i>p</i> -value
Demographics			
Age (years) [mean ± SD]	66.74 ± 10.39	68.38 ± 10.85	0.02
50–59 (<i>n</i> = 268)	135 (50.3)	133 (49.6)	0.180
60–69 (<i>n</i> = 509)	247 (48.5)	262 (51.5)	0.260
70–79 (<i>n</i> = 568)	254 (44.7)	314 (55.3)	0.321
≥80 (<i>n</i> = 164)	59 (35.9)	105 (64.0)	0.05
Male	608 (81.2)	687 (79.6)	0.451
Clinical history			
Prior MI	185 (24.7)	174 (20.2)	0.031
Prior PCI	250 (33.4)	282 (32.7)	0.791
Prior CABG	18 (2.4)	53 (6.1)	<0.001
Prior HF	48 (6.4)	42 (4.9)	0.193
Hypertension	586 (78.2)	568 (65.8)	<0.001
Dyslipidemia	548 (73.2)	543 (62.9)	< 0.001
Diabetes mellitus	323 (43.1)	344 (39.9)	0.188
GFR (ml/min)	89.97 ± 33.97	85.95 ± 30.16	0.017
Hemodialysis	10 (1.3)	32 (3.7)	0.003
Cerebrovascular disease	57 (7.6)	56 (6.5)	0.381
Peripheral artery disease	43 (5.7)	61 (7.1)	0.310
Current smoking	274 (36.6)	256 (29.7)	0.003
Use of anti-anginal agents	191 (25.5)	229 (26.5)	0.649
Admission presentation			
Asymptomatic	123 (16.4)	179 (20.7)	0.029
Stable angina	151 (20.2)	259 (30.0)	<0.001
ACS: STEMI	253 (33.8)	158 (18.3)	< 0.001
ACS: NSTEMI	64 (8.5)	51 (5.9)	0.042
ACS: unstable angina	133 (17.8)	176 (20.4)	0.183
Cardiogenic shock	16 (2.1)	35 (4.1)	0.032
Cardiopulmonary arrest	14 (2.0)	17 (1.9)	1.000
Procedure			
Urgent PCI	154 (20.6)	157 (18.2)	0.230
Emergent PCI	229 (30.6)	144 (16.7)	<0.001
Salvage PCI	7 (0.9)	20 (2.3)	0.033
Drug-eluting stent	495 (66.1)	596 (69.1)	0.219
Bare metal stent	254 (33.9)	267 (30.9)	0.219
In-hospital adverse outcomes			
All complications	119 (15.9)	123 (14.3)	0.364
Coronary perforation	6 (0.8)	7 (0.8)	1.000
MI post PCI	31 (4.1)	28 (3.2)	0.355
Cerebral infarction	6 (0.8)	2 (0.2)	0.156
Bleeding complications within 72 h	44 (5.9)	50 (5.8)	1.000
Cardiogenic shock	14 (1.9)	24 (2.8)	0.252
In-hospital mortality	0 (0)	25 (2.9)	<0.001

^a Data are expressed as *n* (%) unless otherwise indicated

ACS acute coronary syndrome, CABG coronary artery bypass grafting, GBMT guideline-based medical therapy, GFR glomerular filtration rate, HF heart failure, MI myocardial infarction, NSTEMI non-ST-segment elevation MI, PCI percutaneous coronary intervention, SD standard deviation, STEMI ST-segment elevation MI, UA unstable angina

In the USA and Europe, many large-scale clinical studies have shown that beta-blockers offer a better prognosis and secondary prevention of ischemic heart disease [14–16]. AHA/ACC guidelines also strongly recommend the use of beta-blockers for the secondary prevention of all

levels of ischemic heart disease, from stable angina to acute MI, whereas CCBs are not strongly suggested because of the potential risk of causing a cardiovascular event [2, 8–10]. However, in Japan, approximately 40 % of ischemic heart disease is thought to be related to coronary

Table 2 Prescription rate for secondary prevention medications at discharge

Type of medication	Prescription rate [n (%)]
Aspirin	1,565 (97.1)
Clopidogrel	1,461 (90.6)
Panaldine	73 (4.5)
Cilostazol	27 (1.7)
Beta-blockers	1,116 (69.2)
ACE-Is/ARBs	1,028 (63.8)
Calcium channel blockers	495 (30.7)
Statins	1,326 (82.3)
Non-statin lipid-lowering agents	119 (7.4)

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker

spasm, and the prevalence of vasospastic angina among ischemic heart disease cases is several times higher than that in the West [11, 17]. There is a small risk of severe arrhythmia or sudden death, which worsens the prognosis. Therefore, although the efficacy of beta-blockers is well understood, CCBs are also widely used in Japan. Gaps can be clearly seen between prior large-scale studies on ischemic heart disease conducted in Japan and those conducted in other countries (Table 5) in the data on the GBMT rate at hospital discharge in each country [3–5, 18–29]. The rate of CCB prescription in Japan was approximately 60 %, as against 20–30 % in other countries. On the other hand, the rate of beta-blocker prescription in Japan was 20–30 %, while it was 80–90 % in other countries. Although our multivariate model revealed no significant differences in variables associated with the use of GBMT when CCBs were excluded from its definition, further studies are needed to directly address the efficacy of CCBs.

Analysis of patient characteristics suggested that the older the patients were, the less likely they were to receive GBMT. In subgroup of patients over the age of 80 years, only 36 % were prescribed GBMT. Older patients are likely to have a variety of co-morbidities, be already receiving multiple medications, and have lower compliance. However, age itself does not preclude the use of GBMT in this subgroup of patients, and they are likely to be a major target for performance improvement. Secondly, contrary to patients presenting with ACS, use of GBMT remains at about 40 % for non-ACS patients, and improvement is also necessary for this subgroup. We also see room for improvement in ACS patients, since a recent US registry reported the prescription rates of all secondary prevention medications as 90–98 % during the treatment of STEMI, compared with about 60 % in our data [6]. Notably, in our dataset, ACS presentation was seen in roughly 50 % of patients, consistent with the data from the

NCDR Cath-PCI registry [22]. Lastly, for patients with CS, the rate of GBMT declined, probably due to initial hemodynamic instability. However, after the initial insult, hospital survivors with CS who were treated with revascularization remain in a stable condition in the long term, and GBMT should be aggressively applied in those without contraindications [30]. We also performed sub-analyses excluding the elderly population and these models showed similar tendencies, with prescription of GBMT associated with more acute settings (e.g. ACS) and an inverse association with presentation of CS.

The in-hospital prescription rate of GBMT seems to remain low in the Japanese hospital setting according to the present analysis from the multicenter registry and there is substantial room for improvement. This aspect of inpatient care needs particular attention among individual cardiologists, and implementation of computer-based tools or programs may aid in improving the use of these medications [31]. Changing practice may be hard for some hospitals and centers, but sufficient human and/or financial resource to ensure GBMT at the time of discharge to intervening cardiologist is likely to play a key role in improving quality of care in PCI patients, and follow-up study is needed to validate its association with long-term clinical outcomes.

4.1 Limitations

Our analysis has several limitations. First, our findings are unique to Japan, where CAD patients have a better prognosis and higher incidence of vasospastic angina than those in Western countries, and may have limited generalizability. However, the use of secondary prevention medication has not been thoroughly evaluated in Asian countries, and we believe that this analysis provides a unique opportunity to improve performance among cardiovascular care in the region. Since racial and social differences are important factors in clinical decision making, it is vital to establish domestic evidence suited to each population group. Further, our variables that were associated with the use of GBMT did not differ significantly after separate modeling with definitions of GBMT that excluded CCBs.

Second, despite vigorous data management by specialized coordinators, incomplete documentation of contraindications to GBMT can lead to misclassification. Third, observational studies can be biased by baseline differences. We have attempted to nullify the effects of these data and other potential confounding variables by using multivariate analysis based on more than 200 collected variables for each patient.

Fourth, only in-hospital outcomes and treatments are available in the JCD registry, and long-term adherence and outcomes could not be assessed. However, in Japan, length

Table 3 Multivariable predictors for prescription of guideline-based medical therapy at discharge

	Odds ratio (95 % CI)	P value
Original definition of GBMT (dual antiplatelet therapy, BBs and/or CCBs, ACE-I/ARB, and statins)		
Age ≥ 80 years	0.647 (0.448–0.933)	0.020
STEMI	3.229 (2.432–4.288)	<0.001
NSTEMI	2.122 (1.398–3.220)	<0.001
Cardiogenic shock	0.349 (0.179–0.681)	0.002
Prior HF	1.681 (1.033–2.735)	0.037
Prior PCI	1.272 (0.991–1.631)	0.059
Prior CABG	0.496 (0.272–0.902)	0.022
Hypertension	2.124 (1.633–2.762)	<0.001
Dyslipidemia	1.447 (1.131–1.850)	0.003
EF 20–29 %	1.556 (1.134–2.135)	0.006
GFR	1.003 (1.000–1.007)	0.084
Definition of GBMT excluding ACE-Is/ARBs		
Age ≥ 80 years	0.504 (0.354–0.720)	<0.001
STEMI	2.034 (1.515–2.730)	<0.001
Cardiogenic shock	0.432 (0.219–0.850)	0.015
Cardiopulmonary arrest	0.447 (0.194–1.031)	0.059
Prior HF	1.656 (0.982–2.794)	0.059
Hypertension	1.273 (0.983–1.649)	0.067
Dyslipidemia	1.457 (1.136–1.867)	0.003
Hemodialysis	0.275 (0.134–0.565)	<0.001
Use of anti-anginal agents	1.708 (1.299–2.245)	< 0.001
Family history of premature CAD	0.491 (0.267–0.905)	0.023
All CAD	2.591 (1.208–5.557)	0.014
DES	0.810 (0.629–1.042)	0.101
Definition of GBMT excluding ACE-Is/ARBs and CCBs		
Age ≥ 80 years	0.548 (0.386–0.779)	0.001
STEMI	2.285 (1.735–3.008)	<0.001
Cardiogenic shock	0.377 (0.201–0.704)	0.002
Prior HF	1.542 (0.938–2.535)	0.088
Prior CABG	0.593 (0.342–1.028)	0.063
Dyslipidemia	1.412 (1.116–1.787)	0.004
Hemodialysis	0.397 (0.193–0.818)	0.012
Use of anti-anginal agents	1.553 (1.201–2.009)	0.001
EF 20–29 %	1.325 (0.959–1.830)	0.088
3 vessel disease	1.281 (0.995–1.648)	0.055
All CAD	2.225 (1.023–4.839)	0.044

ACE-I angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers, BB beta-blockers, CABG coronary artery bypass grafting, CAD coronary artery disease, CCB calcium channel blockers, CI confidence interval, DES drug-eluting stent, EF ejection fraction, GBMT guideline-based medical therapy, GFR glomerular filtration rate, HF heart failure, NSTEMI non ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction

of stay for patients who undergo PCI is generally longer (average 3–4 days) than in the USA or Europe, and allowing more time for stabilization of medication regimens. Lastly, the JCD database did not collect cost data, adverse events related to use of medications, qualitative data on cholesterol panels, or vital signs such as blood pressure, which would have enabled further stratification of GBMT.

5 Conclusion

Only about half of the post-PCI patients were discharged on ideal GBMT. Elderly patients and those presenting with non-ACS status or hemodynamic compromise tended not to receive GBMT, and require more attention for optimization of their care.

Table 4 Multivariable predictors for prescription of guideline-based medical therapy at discharge, excluding patients over 75 years of age

	Odds ratio (95 % CI)	<i>p</i> -value
Original definition of GBMT (dual antiplatelet therapy, BBs and/or CCBs, ACE-Is/ARBs and statins)		
STEMI	3.378 (2.408–4.740)	<0.001
NSTEMI	1.970 (1.218–3.188)	0.006
Cardiogenic shock	0.457 (0.202–1.034)	0.060
Prior HF	2.113 (1.063–4.199)	0.033
Prior PCI	1.297 (0.960–1.753)	0.090
Prior CABG	0.383 (0.181–0.813)	0.012
Hypertension	2.231 (1.639–3.037)	<0.001
Dyslipidemia	1.333 (0.990–1.795)	0.058
Diabetes insulin	1.537 (0.979–2.414)	0.062
EF 20–29 %	1.475 (1.009–2.155)	0.045
GFR	1.004 (0.999–1.008)	0.090
Cancer	0.390 (0.133–1.149)	0.088
Definition of GBMT excluding ACE-Is/ARBs		
STEMI	2.195 (1.571–3.067)	<0.001
Cardiogenic shock	0.379 (0.177–0.813)	0.013
Prior HF	1.927 (0.920–4.033)	0.082
Hypertension	1.308 (0.974–1.756)	0.074
Hemodialysis	0.257 (0.098–0.669)	0.005
Use of anti-anginal agents	1.614 (1.163–2.240)	0.004
Family history of premature CAD	0.442 (0.228–0.860)	0.016
All CAD	2.691 (1.060–6.834)	0.037
Definition of GBMT excluding ACE-Is/ARBs and CCBs		
Age 50–59 years	1.330 (0.978–1.808)	0.069
STEMI	2.570 (1.862–3.546)	<0.001
Cardiogenic shock	0.439 (0.203–0.947)	0.036
Prior HF	2.749 (1.319–5.726)	0.007
Dyslipidemia	1.289 (0.973–1.709)	0.077
Use of anti-anginal agents	1.549 (1.135–2.114)	0.006
Family history of premature CAD	0.540 (0.275–1.059)	0.073
GFR	1.005 (1.001–1.009)	0.026
All CAD	2.792 (1.070–7.283)	0.036

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BB* beta-blocker, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CI* confidence interval, *EF* ejection fraction, *GBMT* guideline-based medical therapy, *GFR* glomerular filtration rate, *HF* heart failure, *NSTEMI* non ST-segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

Table 5 Large-scale studies of coronary artery disease in Japan and other countries and prescription rate of secondary prevention medication

	Japan		USA		Canada and Europe		
Study name	CREDO -Kyoto	j-Cypher	PREMIER	NCDR	ACS I	ACS II	GRACE/CANRACE
Study design	Registry	Registry	Registry	Registry	Registry	Registry	Registry
Year	2000–2002	2004–2006	2003–2004	2004–2007	1999–2001	2002–2003	2004–2008
Diagnosis	CAD	ACS	ACS	ACS+CAD	ACS	ACS	ACS
Frequency of ACS (%)	0	100	100	55	100	100	100
Revascularization (PCI or CABG) (%)	100	100	100	NA	20	41	52
Patients (<i>n</i>)	3,712	910	500	1,489,745	4,518	1,956	406
ASA (%)	89	99	96	88	88	89	95
Beta-blocker (%)	22	38	93	78	76	85	81
CCB (%)	60	NA	NA	NA	28	NA	NA
Statin (%)	33	54	91	77	55 ^a	80	89 ^a
ACE-I/ARB (%)	43	76	79	57	60	66	79

^a Including non-statin lipid-lowering agents

ACE-I angiotensin-converting enzyme inhibitors, *ACS* acute coronary syndrome, *ARB* angiotensin II receptor blockers, *ASA* aspirin, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *NA* no data available, *PCI* percutaneous coronary intervention

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Appendix

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Disparity in the Application of Guideline Based Medical Therapy after Percutaneous Coronary Intervention: Analysis from the Japanese Prospective Multicenter Registry

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Electronic Supplementary Material

Appendix 1. The Japanese Circulation Society (JCS) Guidelines for Secondary Prevention of Myocardial Infarction (2011, published online only), recommendations listed by medications.

Antiplatelet Agents	1. Start aspirin (81-162mg/day) and continue indefinitely in all patients unless contraindicated. (Class I, Evidence A) 2. Start and continue thienopyridine antiplatelet agents in combination with low dose aspirin in patients after PCI with stent placement. (Class I, Evidence A)
Beta-Blockers (BB)	1. Start and continue beta-blocker indefinitely in all patients unless contraindicated, with exception of low-risk patients (successfully revascularization, normal or almost normal left ventricular function, and no severe ventricular arrhythmia),.(Class I, Evidence A) 2. For patients with moderate or severe left ventricular dysfunction, beta-blockers should be administered with gradual increase in dose. (Class I, Evidence A) 3. It is reasonable to administer beta-blockers to selected low-risk patients. (Class IIa, Evidence A) 4. For patients with suspicion of vasospastic angina, beta-blockers should not be given alone. (Class III, Evidence B)
Calcium channel blockers (CCB)	1. If patients have vasospastic angina, or MI has been confirmed to be spasm-induced, long-acting CCB should be administered to prevent ischemic event. (Class I, Evidence C) 2. It is reasonable to administer long-acting dihydropyridine CCB to MI patients if other agents have failed to control their blood pressure or angina. (Class IIa, Evidence B) 3. If patients without left ventricular dysfunction, congestive heart failure or atrioventricular block are contraindicated or intolerable to beta-blockers, it is reasonable to administer verapamil or diltiazem to manage post-MI cardiac ischemia or to control the pulse of patients with tachycardia atrial fibrillation. (Class IIa, Evidence B)

Angiotensin Converting Enzyme Inhibitors (ACE-I)	1. For high-risk MI patients with left ventricular dysfunction (LVEF<40%) or heart failure, ACE-I should be administered within 24 hours of onset. (Class I, Evidence A) 2. ACE-I should be administered to patients with post-MI left ventricular dysfunction. (Class I, Evidence A) 3. For MI patients without left ventricular dysfunction, ACE-I should be given to those who have hypertension or diabetes, or are at moderate to high risk for cardiovascular events. (Class I, Evidence A) 4. It is reasonable to administer ACE-I to all MI patients within 24 hours after onset. (Class IIa, Evidence A) 5. It is reasonable to administer ACE-I to MI patients without cardiac dysfunction who are at low risk for cardiovascular events. (Class IIa, Evidence B)
Angiotensin II Receptor Blocker (ARB)	1. For ACE-I-intolerant MI patients with symptoms of heart failure or LVEF less than 40%, ARB should be administered from the acute phase. (Class I, Evidence A) 2. Combination of ARB and ACE-I may be considered in MI patients if LV systolic dysfunction is unlikely to result in worsening of renal function. (Class IIb, Evidence B) 3. Regardless of the presence or absence of heart failure, it may be useful to administer ARB to MI patients. (Class IIb, Evidence B)
Statins	1. Start and continue in all patients with hypercholesterolemia. (Class I, Evidence A) 2. Use of statins in patients with normal LDL cholesterol levels is reasonable. (Class IIa, Evidence A)

Appendix 2. The Japanese studies referenced in JCS secondary prevention guideline.

Antiplatelet Agents

1. JAMIS : Yasue H, Ogawa H, Tanaka H, et al. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. Effects of aspirin and ticlopidine on cardiovascular events after acute myocardial infarction. *Am J Cardiol* 1999; 83: 1308-1313)
2. JPAD : Ogawa H et al: for the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial investigators: low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008; 300: 2134-41.
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Beta-Blockers (BB)

5. JBCMI : The Japanese β -blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Investigators. Comparison of the effects of beta blockers and calcium antagonists on cardiovascular events after acute myocardial infarction in Japanese subjects. *Am J Cardiol* 2004; 93: 969-973)
6. JCAD : Kohro T, Hayashi D, Yamazaki T, et al. the JCAD investigators. Beta-blocker prescription among Japanese cardiologists and its effect on various outcomes. *Circ J* 2010; 74: 962-969)

Calcium channel blockers (CCB)

7. JBCMI : The Japanese β -blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Investigators. Comparison of the effects of beta blockers and calcium antagonists on cardiovascular events after acute myocardial infarction in Japanese subjects. *Am J Cardiol* 2004; 93: 969-973)
8. CASE-J : Ogihara T, Nakao K, Fukui T, et al. the candesartan antihypertensive survival evaluation in Japan trial group: Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks. Candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; 51: 393-398.
9. JMIC-B : Yui Y, Sumiyoshi T, Kodama K, et al. Japan Multicenter Investigation for Cardiovascular Diseases-B Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004; 27: 181-191.
10. Nakagomi N, Kodani E, Takano H, et al. Secondary protective effects of Ca-antagonist for ischemic heart attack. Randomized parallel comparison with β -blocker trial. *Circ J* 2010; 74, Suppl I: 139.
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Angiotensin Converting Enzyme Inhibitors (ACE-I)

13. Shiba N, Watanabe J, Shinozaki T, et al. Poor prognosis of Japanese patients with chronic heart failure following myocardial infarction : comparison with nonischemic cardiomyopathy. *Circ J* 2005; 69: 143-149.
14. Yui Y, Sumiyoshi T, Kodama K, et al. Japan Multicenter Investigation for Cardiovascular Diseases-B Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004; 27: 181-191.

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Angiotensin II Receptor Blocker (ARB)

19. Jikei Heart Study : Mochizuki S, Dahlöf B, Shimizu M, et al. the Jikei Heart Study group. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet* 2007; 369: 1431-1439.
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22. KYOTO HEART Study : Sawada T, Yamada H, Dahlöf B, et al. the KYOTO HEART Study Group. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. *Eur Heart J* 2009; 30: 2461-2469.

Statins

23. JUST : Mizuno K, Nakamura H, Ohashi Y, et al. A randomized, open-label, comparative study of simvastatin plus diet versus diet alone angiographic retardation of coronary atherosclerosis in adult Japanese patients: Japanese Utilization of Simvastatin Therapy (JUST) Study. *Clin Ther* 2004; 26: 878-888.
24. CARS : Tamura A, Mikuriya Y, Nasu M. Effect of pravastatin (10mg/day) on progression of coronary atherosclerosis in patients with serum total cholesterol levels from 160 to 220 mg/dl and angiographically documented coronary artery disease. Coronary Artery Regression Study (CARS) Group. *Am J Cardiol* 1997; 79: 893-896.
25. PCS : Nakagawa T, Kobayashi T, Awata N, et al. Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: final 5-year angiographic follow-up of the Prevention of Coronary Sclerosis (PCS) study. *Int J Cardiol* 2004; 97: 107-114.
26. ATHEROMA : Yokoi H, Nobuyoshi M, Mitsudo K, et al. Three-year follow-up results of angiographic intervention trial using an HMG-CoA reductase inhibitor to evaluate retardation of obstructive multiple atheroma (ATHEROMA) study. *Circ J* 2005; 69: 875-883.
27. MUSASHIAMI : Sakamoto T, Kojima S, Ogawa H, et al. MUSASHI-AMI Investigators. Effects of Early Statin Treatment on Symptomatic Heart Failure and Ischemic Events After Acute Myocardial Infarction in Japanese. Acute Myocardial Infarction (MUSASHI-AMI) Investigators. *Am J Cardiol* 2006; 97: 1165-1171.
28. ESTABLISH : Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event; the ESTABLISH study. *Circulation* 2004; 110: 1061-1068.

29. JAPAN-ACS : Hiro T, Kimura T, Morimoto T, et al. JAPAN-ACS Investigators.
Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in
Patients With Acute Coronary Syndrome. A Multicenter Randomized Trial
Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus
Atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in
Acute Coronary Syndrome] Study). J Am Coll Cardiol 2009; 54: 293-302.

Appendix 3. Patient characteristics stratified by prescription of original definition (dual antiplatelet therapy, BB and/or CCB, ACE-I/ARB and statins; full GBMT), definition without ACE-I/ARB, and definition without ACE-I/ARB and CCB

	full GBMT			without ACE-I/ARB			without ACE-I/ARB and CCB		
	GBMT (n=749)	No GBMT (n=863)	P value	GBMT (n=1044)	No GBMT (n=568)	P value	GBMT (n=938)	No GBMT (n=674)	P value
<i>Demographics</i>									
Age, yrs	66.74±10.39	68.38±10.85	0.02	67.23±10.33	68.34±11.25	0.047	67.01±10.41	68.48±10.98	0.006
Male, n (%)	608 (81.2)	687 (79.6)	0.451	836 (80.1)	459 (80.8)	0.743	761 (81.1)	534 (79.2)	0.374
Body mass index, kg/m2	24.63±3.66	23.78±3.38	< 0.001	24.33±3.63	23.88±3.33	0.018	24.36±3.56	23.93±3.49	0.024
<i>Clinical history</i>									
Prior MI, n (%)	185 (24.7)	174 (20.2)	0.031	254 (24.3)	105 (18.5)	0.007	235 (25.1)	124 (18.4)	0.002
Prior PCI, n (%)	250 (33.4)	282 (32.7)	0.791	351 (33.6)	181 (31.9)	0.506	321 (34.2)	211 (31.3)	0.238
Prior CABG, n (%)	18 (2.4)	53 (6.1)	< 0.001	33 (3.2)	38 (6.7)	0.001	29 (3.1)	42 (6.2)	0.003
Prior HF, n (%)	48 (6.4)	42 (4.9)	0.193	62 (5.9)	28 (4.9)	0.429	57 (6.1)	33 (4.9)	0.324
LVEF <10%	27 (3.6)	27 (3.1)	0.678	36 (3.4)	18 (3.2)	0.885	35 (3.7)	19 (2.8)	0.33
LVEF 10-19%	29 (3.9)	26 (3.0)	0.409	37 (3.5)	18 (3.2)	0.775	36 (3.8)	19 (2.8)	0.33
LVEF 20-29%	131 (17.5)	91 (10.5)	< 0.001	157 (15.0)	65 (11.4)	0.049	146 (15.6)	76 (11.3)	0.015
Hypertension, n (%)	586 (78.2)	568 (65.8)	< 0.001	768 (73.6)	386 (68.0)	0.018	678 (72.3)	476 (70.6)	0.012
Dyslipidemia, n (%)	548 (73.2)	543 (62.9)	< 0.001	753 (72.1)	338 (59.5)	<0.001	676 (72.1)	415 (61.6)	<0.001

Diabetes mellitus, n (%)	323 (43.1)	344 (39.9)	0.188	430 (41.2)	237 (41.7)	0.833	393 (41.9)	274 (40.7)	0.645
Insulin use, n (%)	74 (9.9)	76 (8.8)	0.492	95 (9.1)	55 (9.7)	0.72	84 (9.0)	66 (9.8)	0.602
Chronic kidney disease, n (%)	26 (3.5)	43 (5.0)	0.141	32 (3.1)	37 (6.5)	0.002	29 (3.1)	40 (5.9)	0.006
GFR, ml/min	89.97±33.97	85.95±30.16	0.017	89.92±32.15	83.81±31.52	0.001	90.12±32.53	84.50±31.07	0.001
Hemodialysis, n (%)	10 (1.3)	32 (3.7)	0.003	13 (1.2)	29 (5.1)	<0.001	12 (1.3)	30 (4.5)	<0.001
Cerebrovascular disease, n (%)	57 (7.6)	56 (6.5)	0.381	67 (6.4)	46 (8.1)	0.221	59 (6.3)	54 (8.0)	0.199
Peripheral artery disease, n (%)	43 (5.7)	61 (7.1)	0.31	61 (5.8)	43 (7.6)	0.203	52 (5.5)	52 (7.7)	0.082
COPD, n (%)	25 (3.3)	22 (2.5)	0.375	32 (3.1)	15 (2.6)	0.757	24 (2.6)	23 (3.4)	0.368
Cancer, n (%)	15 (2.0)	27 (3.1)	0.163	25 (2.4)	17 (3.0)	0.514	25 (2.7)	17 (2.5)	1
Current smoking, n (%)	274 (36.6)	256 (29.7)	0.003	359 (34.4)	171 (30.1)	0.085	330 (35.29)	200 (29.7)	0.021
Family history of young CAD, n (%)	20 (2.7)	28 (3.2)	0.558	26 (2.5)	22 (3.9)	0.127	24 (2.6)	24 (3.6)	0.298
Use of antianginal agents, n (%)	191 (25.5)	229 (26.5)	0.649	298 (28.5)	122 (21.5)	0.002	265 (28.39)	155 (23.0)	0.018
<i>Admission presentation</i>									
Admission symptoms									
Asymptomatic, n (%)	123 (16.4)	179 (20.7)	0.029	169 (16.2)	133 (23.4)	<0.001	155 (16.5)	147 (21.8)	0.008
Stable angina, n (%)	151 (20.2)	259 (30.0)	< 0.001	260 (24.9)	150 (26.4)	0.511	224 (23.9)	186 (27.6)	0.093
Atypical chest pain, n (%)	25 (3.3)	36 (4.2)	0.433	41 (3.9)	20 (3.5)	0.0875	35 (3.7)	26 (3.9)	0.896
ACS: STEMI, n (%)	253 (33.8)	158 (18.3)	< 0.001	298 (28.5)	113 (19.9)	<0.001	286 (30.5)	125 (18.5)	<0.001
ACS: NSTEMI, n (%)	64 (8.5)	51 (5.9)	0.042	77 (7.4)	38 (6.7)	0.686	67 (7.1)	48 (7.1)	1
ACS: unstable angina, n (%)	133 (17.8)	176 (20.4)	0.183	196 (18.8)	113 (19.9)	0.597	168 (17.9)	141 (20.9)	0.074

CCS class3, n (%)	169 (22.6)	218 (25.3)	0.22	246 (23.6)	141 (24.8)	0.583	218 (23.2)	169 (25.1)	0.408
CCS class4, n (%)	89 (11.9)	110 (12.7)	0.649	123 (11.8)	76 (13.4)	0.383	113 (12.0)	86 (12.8)	0.701
HF on admission, n (%)	57 (7.6)	74 (8.6)	0.523	79 (7.6)	52 (9.2)	0.294	75 (8.0)	56 (8.3)	0.854
NYHA class3, n (%)	44 (5.9)	43 (5.0)	0.441	23 (2.2)	14 (2.5)	0.731	54 (5.8)	33 (4.9)	1
NYHA class4, n (%)	27 (3.6)	23 (3.6)	0.314	33 (3.2)	17 (3.0)	1	31 (3.3)	19 (2.8)	0.663
Cardiogenic shock, n (%)	16 (2.1)	35 (4.1)	0.032	22 (2.1)	29 (5.1)	0.002	21 (2.2)	30 (4.5)	0.014
Cardiopulmonary arrest, n (%)	14 (2.0)	17 (1.9)	1	14 (1.3)	17 (0.3)	0.035	14 (1.5)	17 (2.5)	0.145
All CAD, n (%)	736 (98.3)	831 (96.3)	0.022	1028 (98.5)	539 (94.9)	<0.001	924 (98.5)	643 (95.4)	<0.001
2 vessel disease, n (%)	331 (44.2)	390 (45.2)	0.688	466 (44.6)	255 (44.9)	0.958	425 (45.3)	296 (43.9)	0.612
3 vessel disease, n (%)	191 (25.5)	229 (26.5)	0.649	270 (25.9)	150 (26.4)	0.812	253 (27.0)	167 (24.8)	0.329
<i>Procedure</i>									
Urgent PCI, n (%)	154 (20.6)	157 (18.2)	0.23	206 (19.7)	105 (18.5)	0.553	186 (19.8)	125 (18.5)	0.565
Emergent PCI, n (%)	229 (30.6)	144 (16.7)	< 0.001	261 (25.0)	85 (15.0)	<0.001	247 (26.3)	99 (14.7)	<0.001
Salvage PCI, n (%)	7 (0.9)	20 (2.3)	0.033	8 (0.8)	19 (3.3)	<0.001	7 (0.7)	20 (3.0)	0.001
IABP support, n(%)	21 (2.8)	34 (3.9)	0.219	31 (3.0)	24 (4.2)	0.197	30 (3.2)	25 (3.7)	0.581
Drug eluting stent, n (%)	495 (66.1)	596 (69.1)	0.219	690 (66.1)	401 (70.6)	0.066	617 (65.8)	474 (70.3)	0.059
Bare metal stent, n (%)	254 (33.9)	267 (30.9)	0.219	354 (33.9)	167 (29.4)	0.066	321 (34.2)	200 (29.7)	0.059
Fruoro time, min	31.65±21.39	31.87±22.74	0.853	31.36±21.34	32.54±23.51	0.344	31.61±21.47	31.98±23.02	0.758
<i>In-hospital adverse outcomes</i>									
All complications, n (%)	119 (15.9)	123 (14.3)	0.364	157 (15.0)	85 (15.0)	1	146 (15.6)	96 (14.2)	0.48

Cardiac tamponade, n (%)	1 (0.1)	4 (0.5)	0.38	1 (0.1)	4 (0.7)	0.055	1 (0.1)	4 (0.6)	0.168
Cardiogenic shock, n (%)	14 (1.9)	24 (2.8)	0.252	16 (1.5)	22 (3.9)	0.005	15 (1.6)	23 (3.4)	0.02
Transfusion, n (%)	20 (2.7)	33 (3.8)	0.21	31 (3.0)	22 (3.9)	0.38	31 (3.3)	22 (3.3)	1
Bleeding complications within 72hrs, n (%)	44 (5.9)	50 (5.8)	1	63 (6.0)	31 (5.5)	0.739	63 (6.7)	31 (4.6)	0.084
Other thrombotic complication, n (%)	3 (0.4)	5 (0.6)	0.731	3 (0.3)	5 (0.9)	0.139	3 (0.3)	5 (0.7)	0.291
Introduction of new hemodialysis, n (%)	3 (0.4)	12 (1.4)	0.065	4 (0.4)	11 (1.9)	0.004	4 (0.4)	11 (1.6)	0.017
In hospital mortality, n (%)	0 (0)	25 (2.9)	<0.001	0 (0)	25 (4.4)	<0.001	0 (0.0)	25 (3.7)	<0.001

Data are expressed as mean ± SD.

GBMT = guideline based medical therapy; ASA = aspirin; BB = beta-blockers; CCB = calcium channel blockers; ACE-I =

angiotnsin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; MI = myocardial infarction; PCI = percutaneous

coronary intervention; CABG = coronary artery bypass grafting; HF = heart failure; GFR = glomerular filtration rate; COPD = chronic

obstructive pulmonary disease; CAD = coronary artery disease; ACS = acute coronary syndrome; STEMI = ST-segment elevation

myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; CCS = canadian cardiovascular society; NYHA =

new york heart association; IABP = intraaortic balloon pumping.