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The Clinical Outcomes of Percutaneous Coronary Intervention Performed Without Pre-Procedural Aspirin

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Objectives The purpose of this study was to examine the incidence and outcomes of percutaneous coronary intervention (PCI) performed in patients who had not received pre-procedural aspirin.

Background Aspirin is an essential component of peri-PCI pharmacotherapy. Previous studies suggest that pre-procedural aspirin is not administered to a clinically significant number of patients undergoing PCI.

Methods We evaluated the incidence of PCIs performed without pre-procedural aspirin use among patients undergoing PCI from January 2010 through December 2011 at 44 hospitals in Michigan. Propensity-matched multivariate analysis was used to adjust for the nonrandom use of aspirin.

Results Our study population comprised 65,175 patients, of whom 4,640 (7.1%) did not receive aspirin within 24 h before undergoing PCI. Aspirin nonreceivers were more likely to have had previous gastrointestinal bleeding or to present with cardiogenic shock or after cardiac arrest. In the propensity-matched analysis, absence of aspirin before PCI was associated with a higher rate of death (3.9% vs. 2.8%; odds ratio: 1.89 [95% confidence interval: 1.32 to 2.71], $p < 0.001$) and stroke (0.5% vs. 0.1%; odds ratio: 4.24 [95% confidence interval: 1.49 to 12.11], $p = 0.007$) with no difference in need for transfusions. This association was consistent across multiple pre-specified subgroups.

Conclusions A significant number of patients do not receive aspirin before undergoing PCI. Lack of aspirin before PCI was associated with significantly increased in-hospital mortality and stroke. Our study results support the need for quality efforts focused on optimizing aspirin use before PCI. (J Am Coll Cardiol 2013;62:2083–9) © 2013 by the American College of Cardiology Foundation

Aspirin (ASA) has been the cornerstone of procedural and post-procedural therapy in patients undergoing percutaneous coronary intervention (PCI) since the early days of the procedure (1–4). The benefits of pre-PCI ASA are related to its antiplatelet effects and the modulation of vascular inflammation in response to vascular injury after PCI (5). Even though the impact of pre-procedural ASA on PCI outcomes has never been studied in large randomized controlled trials, there is significant evidence to support its benefit in this population (6–8).

Multiple studies, including data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative, suggest that a small but clinically important subgroup of patients undergo PCI without receiving pre-procedural ASA (9,10). Although ASA is relatively safe, widely available, and inexpensive (11,12), there are a number of reasons for which ASA might be withheld before a procedure. These include but are not limited to: the inability to take oral ASA, omission of ASA therapy while the patient is being rushed to the catheterization laboratory, true contraindications such as ASA-induced anaphylaxis, as well as perceived or relative contraindications such as previous bleeding, gastritis, peptic ulcer disease, renal dysfunction, ASA-exacerbated respiratory tract disease, and ASA-induced urticaria (13,14). To

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Abbreviations and Acronyms

ASA = aspirin

BMC2 = Blue Cross Blue Shield of Michigan Cardiovascular Consortium

CABG = coronary artery bypass grafting

CI = confidence interval

CIN = contrast-induced nephropathy

OR = odds ratio

PCI = percutaneous coronary intervention

the best of our knowledge, there have been no studies that specifically addressed the association between ASA nonuse before PCI and in-hospital outcomes in the contemporary era. A better understanding of the incidence and clinical implications of pre-PCI ASA nonuse might be helpful in shaping a strategy to manage such patients, including the use of desensitization therapy, provision of alternative dual antiplatelet regimens, or considerations for surgical revascularization.

Accordingly, we evaluated the frequency and implications of pre-procedural ASA nonuse in patients undergoing PCI. We used data from a large statewide quality improvement initiative, The Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) registry.

Methods

Patient population and data collection. BMC2 is a prospective, multicenter registry that collects demographic, clinical, and procedural data from consecutive PCI cases at all nonfederal hospitals in the state of Michigan. The details of the BMC2 registry and its data collection and auditing process have been described previously (15,16). Briefly, procedural data on all patients undergoing PCI at participating hospitals are collected by using standardized data collection forms. Baseline data include clinical, demographic, procedural, and angiographic characteristics as well as medications used before, during, and after the procedure; information on in-hospital outcomes is also collected.

All data elements have been prospectively defined, and the protocol was approved by local institutional review boards at each of the participating hospitals. In addition to a random audit of 2% of all cases, medical records of all patients undergoing multiple procedures or coronary artery bypass grafting (CABG) and of patients who died in the hospital are reviewed routinely to ensure data accuracy. ASA nonreceivers were defined as patients who did not take or receive ASA within the 24 h before the procedure. Contraindication to ASA was as per physician documentation and assumed to be present if the treating physician made a notation in the patient chart that the risk of ASA therapy outweighed any potential benefit due to the presence of an allergy or a medical condition.

Statistical analysis and study endpoints. The key study endpoints were in-hospital mortality (defined as death from any cause before discharge) and need for transfusion. Secondary endpoints include post-procedure myocardial infarction, stroke, repeat target lesion PCI, emergent CABG, any CABG, vascular complications, contrast-induced nephropathy (CIN), and new renal dysfunction requiring dialysis.

Statistical comparisons of baseline characteristics between ASA receivers and nonreceivers were performed by using Fisher exact tests for categorical variables and Student *t* tests for continuous variables. We used propensity matching to adjust for the nonrandom absence of ASA before PCI. A generalized propensity score was estimated by using logistic regression models, with pre-procedural administration of ASA as the outcome, and including baseline clinical history and presentation characteristics as predictors (covariates are listed in Table 1). The propensity score was estimated based on reduced logistic regression models for cases with missing covariate data in which <3 covariate values were missing (17). A propensity-matched cohort was constructed with ASA receivers and nonreceivers matched on a 1:1 basis within a caliper 0.05 SD of the propensity score. After propensity matching, 4,008 patients were selected for each group for a total analysis population of 8,016.

To assess the adequacy of matching and covariate balance between the 2 groups, we examined the standardized differences for the included baseline covariates in the matched cohort. After matching, none of the covariates had a standardized difference that exceeded 10% (Online Fig. 1). For further confirmation of balanced matching, we assessed for the differences in an unrelated outcome (CIN) that would not be expected to be influenced by ASA use. Presence of a differing outcome between the 2 groups in the absence of biological plausibility would be suggestive of residual confounding. Finally, we performed a sensitivity analysis to examine the sensitivity of the results, particularly the primary outcome of in-hospital mortality, to unmeasured confounders (18). Multivariate logistic regression models were fitted in the propensity-matched cohort with a number of in-hospital outcomes as dependent variables and pre-procedural ASA as the covariate of interest, adjusting for baseline clinical and presentation covariates used for matching.

We further tested the impact of ASA nonuse on mortality in multiple pre-specified subgroups: age, sex, presentation of coronary artery disease (ST-segment elevation myocardial infarction, non–ST-segment elevation acute coronary syndrome, and stable angina), and presence or absence of shock, cardiac arrest, and diabetes. Subgroup analysis was performed both by using the Fisher exact test for the univariate analysis and by adjusting for significant baseline covariates through multivariate logistic regression models fitted separately within each subgroup. Multivariate subgroup analysis was performed within the propensity-matched cohort, with the covariates chosen for inclusion in the models based on their significance in the overall multivariate mortality model at a significance level of alpha = 0.1. For all other analyses, a nominal p value <0.05 was considered statistically significant, and no adjustments were made for multiple comparisons. All analyses were performed by using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline Characteristics of Unmatched and Propensity-Matched Cohorts

	Unmatched Cohort			Propensity-Matched Cohort		
Variable	ASA Nonreceivers (n = 4,640)	ASA Receivers (n = 60,535)	p Value	ASA Nonreceivers (n = 4,008)	ASA Receivers (n = 4,008)	p Value
Mean age (yrs)	65.3	65.9	<0.001	65.9	66.0	0.73
Male	61.3%	66.4%	<0.001	61.3%	60.3%	0.37
No insurance coverage	4.9%	5.2%	<0.001	5.1%	5.8%	0.13
Current smoker	30.0%	29.3%	0.33	30.9%	31.3%	0.74
Body mass index (kg/m^2)	30.3	30.6	0.02	30.3	30.3	0.98
Hypertension	82.8%	85.2%	<0.001	83.8%	83.3%	0.57
Diabetes mellitus	36.6%	37.2%	0.38	36.5%	35.9%	0.56
Previous myocardial infarction	36.4%	35.7%	<0.001	28.0%	28.0%	1.00
Previous PCI	37.5%	45.4%	<0.001	36.9%	36.6%	0.87
Previous cardiac arrest	3.7%	2.4%	<0.001	3.6%	4.3%	0.11
Congestive heart failure	13.9%	15.6%	0.003	15.0%	14.6%	0.57
Gastrointestinal bleeding	1.7%	1.1%	<0.001	1.9%	2.2%	0.34
Valve disease	3.9%	5.5%	<0.001	4.3%	4.5%	0.83
Extracardiac vascular disease	26.4%	26.4%	0.99	26.8%	27.6%	0.44
Atrial fibrillation	8.5%	10.7%	<0.001	9.4%	9.3%	0.91
Chronic obstructive pulmonary disease	20.5%	18.3%	<0.001	21.7%	21.4%	0.83
End-stage renal disease	2.6%	2.2%	0.13	2.6%	2.5%	0.72
Left ventricular ejection fraction	50.6%	51.7%	<0.001	50.6%	50.2%	0.20
Baseline creatinine (mg/dl)	1.2	1.1	0.005	1.2	1.2	0.77
Baseline glomerular filtration rate (ml/min)	76.5	78.7	<0.001	76.6	76.7	0.97
Baseline hemoglobin (g/dl)	13.3	13.4	<0.001	13.3	13.3	0.21
STEMI <12 h	15.3%	13.1%	<0.001	15.0%	15.3%	0.78
STEMI (unstable, >12 h)	0.9%	0.7%	0.06	0.9%	0.9%	1.00
STEMI (stable, >12 h)	0.4%	0.4%	0.90	0.4%	0.3%	0.56
STEMI (after thrombolysis)	0.6%	0.3%	0.05	0.7%	0.9%	0.53
Rescue PCI for STEMI	0.7%	0.6%	0.42	0.6%	0.7%	1.00
Non–ST-segment elevation acute coronary syndrome	40.2%	46.8%	<0.001	44.1%	44.3%	0.93
Staged PCI	4.8%	6.9%	<0.001	4.8%	5.2%	1.00
Cardiogenic shock	4.0%	1.4%	<0.001	3.9%	4.5%	0.16
Cardiac arrest	5.1%	1.5%	<0.001	5.1%	5.5%	0.45

Baseline demographic, clinical characteristics, and clinical presentations of both the unmatched patients and the propensity-matched cohort of patients receiving aspirin (ASA) compared with ASA nonusers.
PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Results

Patient population. Among a total of 65,175 PCIs performed in 44 institutions in Michigan between January 2010 and December 2011, ASA was not administered to 4,640 (7.1%) of the patients before PCI. Of those patients who did not receive ASA, only 495 (10.7%) had a documented contraindication to ASA use. Among the ASA nonreceivers, ST-segment elevation myocardial infarction was the presenting diagnosis in 830 (17.9%) and non–ST-segment elevation acute coronary syndrome in 1,866 (40.2%) patients; 1,447 (31.2%) patients underwent PCI for stable coronary artery disease, with the remainder undergoing PCI for multiple other indications. A significant number of patients who did not receive ASA before PCI were started on ASA after the procedure (n = 2,111 [45.5%]).

Baseline demographic, clinical, and presentation characteristics of the 2 groups are presented in Table 1. Most of the baseline demographic and clinical characteristics were statistically different for the unmatched groups given the large sample size. The most notable clinically significant differences included previous PCI, which was more common in ASA receivers, and previous gastrointestinal bleeding, which was more frequent in ASA nonreceivers. Moreover, ASA nonreceivers were more likely to undergo primary PCI and to present in cardiogenic shock or after a cardiac arrest. There was no difference in baseline renal function or hemoglobin levels between the 2 groups.

Unadjusted outcomes of ASA receivers compared with nonreceivers are summarized in Table 2. Patients who did not receive ASA were more likely to die, have a stroke, or undergo CABG. Similarly, the transfusion rate was higher in those who did not receive ASA.

Propensity score-matched data. A total of 8,016 patients were selected in 1:1 propensity score matching, with 4,008 patients in the group receiving ASA before PCI and an equal number in the group of ASA nonusers. The C-statistic for the propensity score model was 0.69. The 2 groups were well matched, with no statistically significant difference in the baseline demographic and clinical characteristics, including clinical presentation (Table 1, Online Fig. 1).

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Table 2 Unmatched Data on In-Hospital Outcomes

In-Hospital Outcome	ASA Nonreceivers (%)	ASA Receivers (%)	p Value
Death	3.9	1.2	<0.001
Transfusion	5.3	3.3	<0.001
Post-procedural myocardial infarction	0.7	0.5	0.18
CABG	1.5	0.9	0.00044
Emergent CABG	0.2	0.2	1.00
Stroke	0.5	0.2	0.02
Repeat PCI to the same lesion	0.5	0.6	0.41
Vascular complications	3.4	2.9	0.06
Contrast-induced nephropathy	4.0	2.5	<0.001
New renal dysfunction requiring dialysis	0.5	0.2	0.0047

Unadjusted in-hospital outcomes of patients receiving ASA compared with those not receiving ASA before PCI.

CABG = coronary artery bypass grafting; other abbreviations as in Table 1.

Although procedural medications were not included in the covariates used for propensity matching, no major differences were noted in the use of procedural antiplatelet and anticoagulation agents (Online Table 1). Most notably, the use of glycoprotein IIb/IIIa inhibitors within the 24 h before and during the procedure was not different between the 2 groups. ASA nonusers were more likely to be treated with prasugrel and ticagrelor, whereas clopidogrel use was more common in ASA receivers.

Adjusted outcomes in the propensity-matched cohort are displayed in Table 3 and Figure 1. After adjusting for baseline confounders, patients who underwent PCI without receipt of ASA were more likely to die (3.9% vs. 2.8%; odds ratio [OR]: 1.89 [95% confidence interval (CI): 1.32 to 2.71], $p < 0.001$) or have a stroke (0.5% vs. 0.1%; OR: 4.24 [95% CI: 1.49 to 12.11], $p = 0.007$). Death adjudicated with a cardiovascular primary cause occurred in 93 (2.32%) patients receiving ASA and 121 (3.02%) ASA nonreceivers (OR: 1.31 [95% CI: 0.99 to 1.74], $p = 0.06$). There was also a trend toward an increased risk for CABG (OR: 1.52, $p = 0.07$) that did not reach statistical significance. No difference in the need for transfusions, post-procedural myocardial infarction, repeat PCI to the same lesion, or vascular complications was observed between the 2 groups. These results were preserved in multiple pre-specified subgroups (Fig. 2).

Table 3 Propensity-Matched Data on In-Hospital Outcomes

In-Hospital Outcome	ASA Nonreceivers (%)	ASA Receivers (%)	p Value
Death	3.87	2.79	0.0005
Transfusion	5.71	5.54	0.53
Post-procedural myocardial infarction	0.70	0.50	0.22
CABG	1.65	1.00	0.07
Emergent CABG	0.20	0.20	0.93
Stroke	0.52	0.15	0.007
Repeat PCI to the same lesion	0.50	0.47	0.73
Vascular complications	3.47	4.07	0.40
Contrast-induced nephropathy	4.37	4.14	0.25
New renal dysfunction requiring dialysis	0.47	0.60	0.52

Comparison of in-hospital outcomes in propensity-matched groups of ASA receivers versus ASA nonreceivers.

Abbreviations as in Table 1.

To assess whether disparities in the baseline health status not captured by the covariates included in the dataset might have confounded our analysis, the incidence of CIN, which is presumed to be physiologically unrelated to ASA use, was evaluated in the matched cohort. No difference in the unrelated outcome of CIN (OR: 1.17 [95% CI: 0.89 to 1.54]) was observed.

Furthermore, on sensitivity analysis, our results were robust to the effect of an unmeasured confounder. A number of scenarios were evaluated assuming unmeasured confounders varying in both the extent of disparity in the prevalence between the 2 groups of ASA receivers and nonreceivers and in the effect size (OR) on outcomes. Only in the most extreme scenarios (i.e., those assuming both very large effect size and disparity in prevalence) was the association between mortality and nonreceipt of ASA rendered statistically insignificant after accounting for confounder effects (Online Table 2).

Discussion

The key finding of our study is that a significant number of patients do not receive ASA before undergoing PCI despite the Class I recommendations for pre-procedural ASA in both the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for PCI (19–21). This finding seems to occur across all presentations, including stable coronary artery disease. Absence of ASA before PCI seems to be associated with an increased risk of mortality and stroke.

The underuse of ASA before PCI is especially surprising because only a small proportion of ASA nonreceivers (10.7%) had a documented contraindication. It is possible that some patients did not receive ASA due to the severity of their illness and presence of factors such as cardiac arrest or shock that would prevent oral administration of ASA and in whom rectal administration was not considered. These and other factors, such as the failure to recognize the importance of pre-procedural ASA by the primary caregivers, may account for the lack of ASA administration in patients being rushed to the catheterization laboratory for emergent procedures. Inappropriate reasons for withholding ASA, such as a distant history of gastrointestinal bleeding, are also likely to contribute, as suggested in previous studies (14).

Furthermore, we observed an increased risk of all-cause in-hospital mortality and stroke in association with the

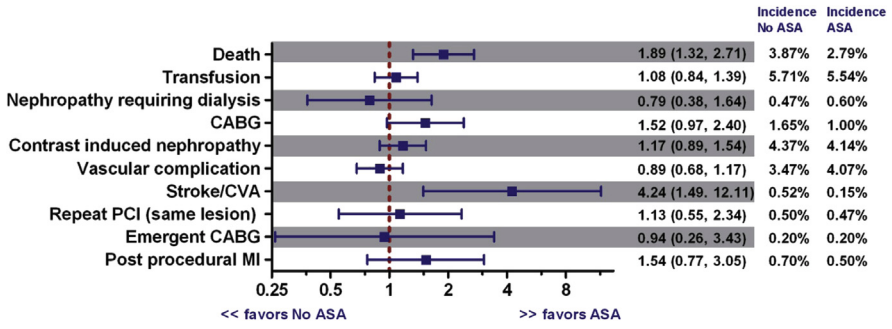

Figure 1 **Propensity-Matched In-Hospital Outcomes**

Forest plot of the odds ratios and their 95% confidence intervals for the major in-hospital outcomes among propensity-matched groups of aspirin (ASA) nonreceivers compared with ASA receivers before percutaneous coronary intervention (PCI). CABG = coronary artery bypass grafting; CVA = cardiovascular accident; MI = myocardial infarction.

absence of ASA use before PCI. Although part of this increased rate of death in the cohort of ASA nonreceivers could be driven by the more acute and critical clinical presentation, adjusting for these differences did not eliminate the risk associated with the absence of ASA use. This was further demonstrated in the subgroup analysis, in which the higher risk of death in ASA nonreceivers persisted in patients presenting without cardiogenic shock and who did not have a cardiac arrest before presentation. Although the number of deaths in the stable angina population was too low for an adjusted analysis, the signal of increased unadjusted mortality in this cohort in association with ASA nonuse is noteworthy. It is likely that the absence of ASA before PCI increases the risk of ischemic events, and this is the most probable reason for the higher rate of in-hospital mortality and stroke that was observed in our study. This association could be further supported by the strong signal for increased in-hospital cardiovascular death in the ASA nonusers group, which could be explained by the possibility that patients who did not receive ASA were more prone to local platelet activation and thrombosis that could have led to acute closure or stent thrombosis (events that are often fatal). Furthermore, suboptimal results may have manifested as a greater degree of myocardial injury and larger infarctions, with a resulting increase in the risk of arrhythmic events. Moreover, almost one-half of the patients who did not receive ASA before the procedure received it thereafter, which is likely to have negated part of the deleterious impact of nonreceipt of ASA before the procedure.

The findings of our study add to and significantly extend previous, similar work (3,6,9,11). We identified a clinically significant proportion of patients not receiving ASA before undergoing contemporary PCI, a finding that is especially striking because all hospitals included in the study participate in an active, multicenter quality improvement collaborative. It also confirms previous findings that associate not receiving pre-procedural ASA with worse outcomes, most notably in-hospital death. Our results gain further

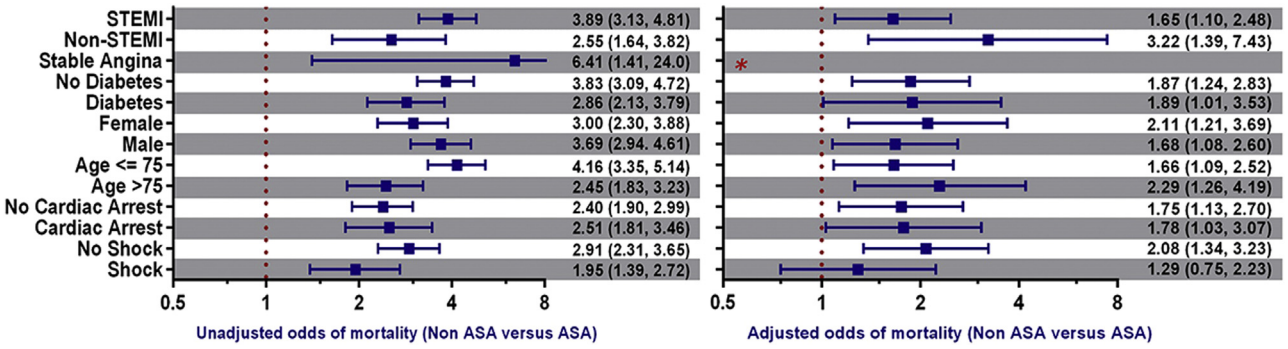

Figure 2 **Primary Outcome Subgroup Analysis**

Forest plot of the odds ratios and their 95% confidence intervals of in-hospital mortality in key subgroups. The **left panel** reflects the unadjusted outcomes, and the **right panel** reflects the risk adjusted outcomes in the propensity-matched subsets. *Adjusted analysis was not performed for stable angina population due to an exceedingly low event rate. ASA = aspirin; STEMI = ST-segment elevation myocardial infarction.

significance in the face of recent data from the WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) study, which suggested that omitting ASA from dual chronic antiplatelet therapy in patients on oral anticoagulant agents undergoing PCI is associated with less bleeding and no increase in the risk of thrombotic events compared with triple therapy (22). Our study predated the WOEST trial, and thus its findings could not have been influenced by this trial. More importantly, establishing an association between lack of pre-procedural ASA and worse in-hospital outcomes re-emphasizes the role of pre-PCI ASA and serves as a reminder not to apply the results of the WOEST study liberally across all patients undergoing PCI. It is important to recognize that our study focused on pre-procedural ASA, whereas the WOEST trial explored the utility of chronic post-PCI ASA in patients who were treated with long-term clopidogrel and warfarin.

Study limitations. The specific reasons for the contraindication to receiving ASA are unavailable in the BMC2 database. Moreover, not receiving ASA before the procedure, as was defined in the study, might have been difficult to confirm in patients presenting in critical conditions such as after cardiac arrest or in cardiogenic shock. Similarly, the dose and exact timing of ASA administration might have been difficult to confirm in patients who self-administered ASA before presentation. However, these factors would have likely biased our findings toward the null. Moreover, the records of all patients who died were audited, and it is unlikely that there was a systematic error in abstracting ASA data. In addition, our findings are subject to unmeasured confounders that may skew the observed associations.

We believe that our data should be considered hypothesis generating. Triggered by our findings, similar studies to further test our hypothesis, as well as others to analyze the long-term outcomes associated with ASA nonuse before and after PCI, should be considered. If our results are replicated, this would justify more focused efforts to optimize ASA use and shape a strategy to manage patients with true contraindications or intolerances to ASA therapy, including the need for desensitization therapy, consideration of other options for dual antiplatelet therapy, or possible surgical revascularization, which would not require ASA pre-treatment.

Conclusions

A significant number of patients do not receive ASA before undergoing PCI. ASA nonreceivers in our study were more likely to experience adverse outcomes, including a higher rate of in-hospital death and stroke. Further studies are needed to confirm our findings and motivate quality efforts focused on optimizing ASA use before PCI, as recommended in the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for PCI (19–21).

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APPENDIX

For supplemental tables and a figure, please see the online version of this article.