Prescription Patterns of Clopidogrel, Prasugrel, and Ticagrelor After Percutaneous Coronary Intervention With Stent Implantation (from the NCDR PINNACLE Registry)

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The use of prasugrel and ticagrelor as part of dual antiplatelet therapy is increasing in patients after percutaneous coronary intervention (PCI). Accordingly, we aimed to evaluate their prescription patterns in the National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) registry. We analyzed patients enrolled in NCDR PINNACLE registry from January 2013 to March 2015 who underwent PCI with drug-eluting stent and were prescribed dual antiplatelet therapy. All patients received aspirin. The primary study outcome was a 3-level variable denoting the second antiplatelet agent prescribed: (1) clopidogrel, (2) prasugrel, or (3) ticagrelor. Baseline characteristics were compared among the 3 groups. Odds ratios and 95% credible intervals were calculated from a nested hierarchical Bayesian logistic regression models to identify independent predictors of prescription of antiplatelet medications, incorporating practice and provider as random effects. Our study cohort consisted of 26,710 patients during our study period January 2013 to March 2015. Seventy nine percent of patients were prescribed clopidogrel, 12% prasugrel, and 11% ticagrelor. Patients aged ≥75 years, women, history of tobacco use, Peripheral Arterial Disease (PAD), hypertension, diabetes, previous vascular complication, heart failure, and stroke/transient ischemic attack were more likely to be on clopidogrel than prasugrel or ticagrelor. The relative percentages of ticagrelor and prasugrel were higher in patients with history of myocardial infarction, compared with those without myocardial infarction. In summary, our study highlights the prescription patterns associated with prescription of antiplatelet agents after PCI. We found that both ticagrelor and prasugrel were mostly prescribed per the current practice guidelines, thus reflecting appropriate guideline adherence by practices in NCDR PINNACLE registry. **(Am J Cardiol 2019;124:1807−1812)**

The last decade has seen the development and increasing use of newer and more potent antiplatelet drugs, including prasugrel and ticagrelor.[1,2] They were approved by the US Food and Drug Administration in 2009 and 2011, respectively,[3] and are currently indicated as alternatives to clopidogrel in patients with acute coronary syndrome.[4] In fact, the 2016 American College of Cardiology (ACC)/American Heart Association (AHA) and 2017 European guidelines recommend using ticagrelor over clopidogrel in acute coronary syndrome.[5,6] Moreover, prasugrel[7] and ticagrelor[8] are also being used as an off-label indication in patients who underwent elective percutaneous coronary intervention (PCI). Accordingly, we aimed to evaluate various patient characteristics and provider/practice factors associated with the prescription of newer antiplatelet agents in patients who underwent stent placement for myocardial infarction (MI) in the National Cardiovascular Data Registry (NCDR) PINNACLE registry, including off-label indication in patients who underwent elective PCI.

Methods

We analyzed data from 4,963,664 patients aged ≥18 years in the PINNACLE registry between January 2013 and March 2015. Of these, 42,489 had received a drug-eluting stent. Out of these, 32,778 patients had an encounter within 12 months of PCI. After excluding patients with no documented prescription and those with inconsistent data our final study cohort consisted of 26,710 patients (Figure 1). For patients with multiple qualifying encounters, the first available encounter in the study time frame was used.

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See page 1811 for disclosure information.

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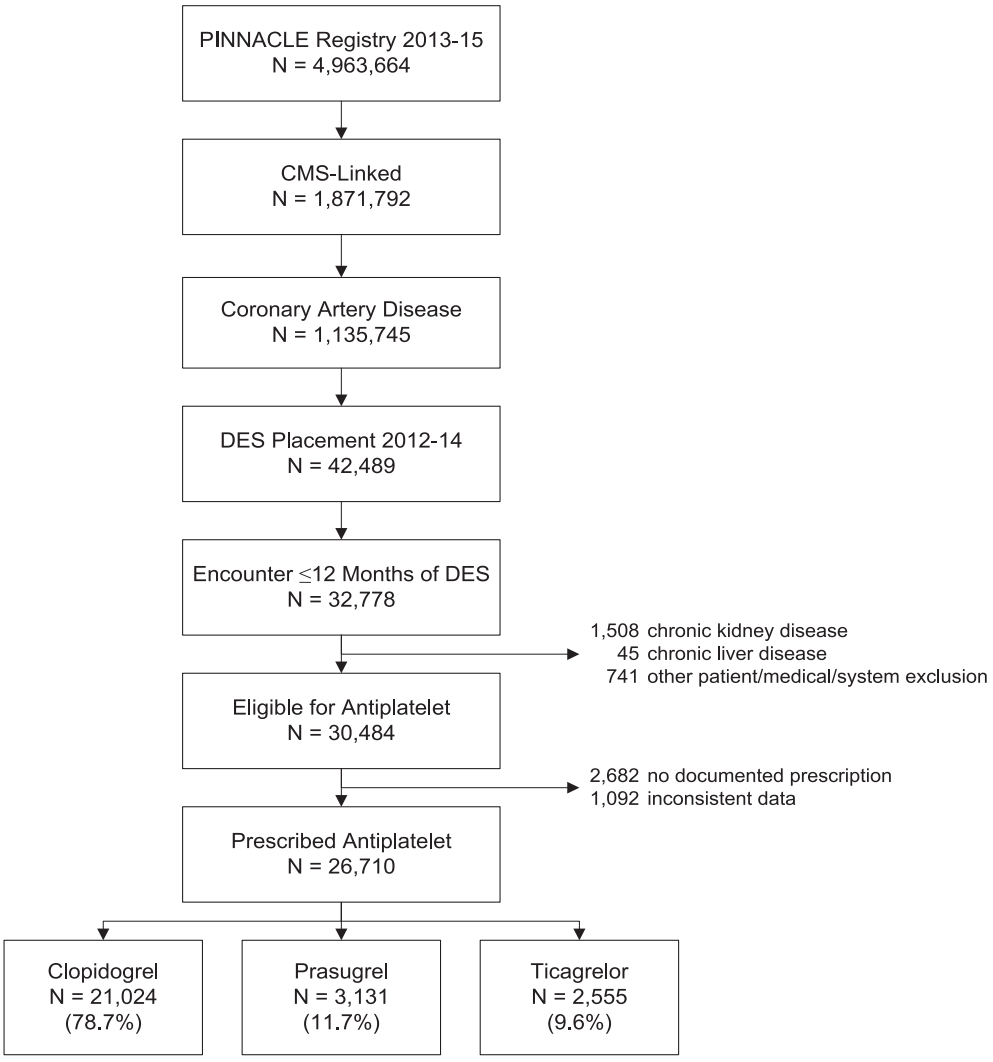

Figure 1. Flowchart of the patients from the PINNACLE registry included in the study.

Patients were classified per the dual antiplatelet therapy regimen, that is, aspirin with clopidogrel, prasugrel, or ticagrelor. Patient characteristics were compared between the 3 groups using 1-way analysis of variance for continuous variables and chi-square tests for categorical variables. Predictors of antiplatelet agent choice were identified using 2 nested hierarchical logistic regression models, one for selection of a newer agent versus clopidogrel, and one for selection of ticagrelor versus clopidogrel, among those using a newer agent. Models included fixed effects for all patient characteristics listed in Table 1, as well as random intercepts office practice and for provider within practice. The variance estimates for the provider and practice effects were converted to median odds ratios, which have the interpretation of estimating the median relative odds in selection of an antiplatelet agent for 2 random providers (or practices), for patients with the same covariates. For example, an Median Odds Ratio (MOR) of 2.0 would denote that, roughly "on average" any 2 providers selected at random would have a twofold difference in odds of selecting a particular agent for similar patients.

A secondary analysis was performed to study the off-label use of prasugrel and ticagrelor, by repeating the above analysis stratified by history of MI. All models were fit using Bayesian methods with weak priors on all parameters. Model-estimated effects (odds ratios) were summarized by posterior mean and 95% credible intervals. Analyses were conducted in using SAS version 9.4[9] (SAS Institute, Inc., Cary, North Carolina) and R version 3.1.1.[10]

Results

Of the 26,710 patients treated with a drug-eluting stent and on dual antiplatelet therapy, 21,024 (79%) were on clopidogrel, 3,131 (12%) on prasugrel, and 2,555 (10%) on ticagrelor. Baseline characteristics of patients in the 3 groups are summarized in Table 1. Mean age for the cohort was 74.5 ± 7.0 years. Approximately 46% (n = 12,203) patients were aged ≥75 years. Patients in the clopidogrel group (75.2 ± 7.0 years) were older than those in prasugrel (70.7 ± 4.9 years) and ticagrelor (73.9 ± 6.7 years) groups. Clopidogrel group had a higher percentage of patients aged

Table 1
Baseline characteristics of patients in the 3 antiplatelet groups (clopidogrel, prasugrel, and ticagrelor)

Variable		Antiplatelet agent			p Value
	Total (n = 26,710)	Clopidogrel (n = 21,024)	Prasugrel (n = 3,131)	Ticagrelor (n = 2,555)	
Age (years)	74.5 ± 7.0	75.2 ± 7.0	70.7 ± 4.9	73.9 ± 6.7	<0.001
Age ≥ 75 years	12,203 (45.7%)	10,514 (50.0%)	594 (19.0%)	1,095 (42.9%)	
Women	10,112 (37.9%)	8,166 (38.8%)	993 (31.7%)	953 (37.3%)	<0.001
BMI (kg/m2)	29.0 ± 5.8	28.9 ± 5.8	29.6 ± 5.5	28.8 ± 5.7	<0.001
Tobacco use					0.004
Former	10,767 (45.3%)	8,508 (45.6%)	1,241 (45.3%)	1,018 (43.7%)	
Current	3,124 (13.2%)	2,507 (13.4%)	348 (12.7%)	269 (11.5%)	
Dyslipidemia	20,974 (78.5%)	16,458 (78.3%)	2,507 (80.1%)	2,009 (78.6%)	0.074
Hypertension	20,821 (78.0%)	16,622 (79.1%)	2,300 (73.5%)	1,899 (74.3%)	<0.001
Diabetes mellitus	7,466 (28.0%)	5,982 (28.5%)	837 (26.7%)	647 (25.3%)	0.001
Stable angina pectoris	5,603 (21.0%)	4,647 (22.1%)	558 (17.8%)	398 (15.6%)	<0.001
Unstable angina pectoris	3,591 (13.4%)	2,964 (14.1%)	363 (11.6%)	264 (10.3%)	<0.001
Prior myocardial infarction	12,153 (45.5%)	9,325 (44.4%)	1,543 (49.3%)	1,285 (50.3%)	<0.001
Peripheral arterial disease	4,490 (16.8%)	3,800 (18.1%)	396 (12.6%)	294 (11.5%)	<0.001
Prior stroke/TIA	2,756 (10.3%)	2,340 (11.1%)	215 (6.9%)	201 (7.9%)	<0.001
Heart failure	6,700 (25.1%)	5,498 (26.2%)	624 (19.9%)	578 (22.6%)	<0.001
Prior nonintracranial major hemorrhage	81 (0.3%)	75 (0.4%)	4 (0.1%)	2 (0.1%)	0.008
Prior vascular complication	1,070 (4.0%)	901 (4.3%)	110 (3.5%)	59 (2.3%)	<0.001
Currently on anticoagulant	3,066 (11.5%)	2,685 (12.8%)	205 (6.5%)	176 (6.9%)	<0.001

BMI = body mass index, TIA = transient ischemic attack.

≥75 years, women, history of tobacco use, Peripheral Arterial Disease (PAD), hypertension, diabetes, previous vascular complication, heart failure, and stroke/transient ischemic attack (TIA), when compared with prasugrel and ticagrelor groups. Nineteen percent (n = 594 of 3,131) of patients who were on prasugrel were aged ≥75 years. Patients on clopidogrel (22.1%) had a higher prevalence of stable angina pectoris compared with those on prasugrel (17.8%) and ticagrelor (15.6%). The relative percentages of ticagrelor and prasugrel were higher in patients with history of MI, compared with those without MI. Clopidogrel group had a higher percentage of patients on oral anticoagulants, compared with prasugrel and ticagrelor groups.

Figure 2 summarizes the predictors of prescription of the 3 antiplatelet agents in patients who had PCI with a drug-eluting stent after adjusting for baseline variables. As shown in the figure, patients with age ≥75 years, women and those with PAD, previous stroke/TIA, hypertension, chronic heart failure, use of oral anticoagulant, and cigarette smoking were more likely to be prescribed clopidogrel compared with prasugrel and ticagrelor. Patients with a history of MI were more likely to be prescribed prasugrel or ticagrelor after stent implantation when compared with those without MI. Among the new agents, ticagrelor was more likely to be prescribed in patients aged ≥75 years and with history of MI whereas it was less likely to be prescribed in patients with body mass index (BMI) >25kg/m^2 when compared with prasugrel.

We also studied the off-label use of new antiplatelet agents in patient who underwent percutaneous intervention for stable or unstable angina, by stratifying the multivariable model by previous versus no previous MI. We assessed whether any effects differed by MI history by performing a global interaction assessment, comparing model fit statistics (widely available information criteria; lower values denote better fit) between the primary main-effects only model and a model including all 2-way interactions with previous MI. The difference in model widely available information criteria (main-effects only minus interaction model) was −24.8 (95% confidence interval −41.8, −7.7) for prediction of use of a newer agent and −23.0 (95% confidence interval −40.1, −5.9) for prediction of ticagrelor versus prasugrel, in both cases indicating that the main-effects only model fit the data better than one with interactions. Supplemental Table also shows that the estimated odds ratios were broadly similar for those with versus without a previous MI. Significant differences in prescribing patterns between practices and between providers were noted in our analysis.

Discussion

In this large registry-based study, we examined and compared the factors influencing prescription of prasugrel, ticagrelor, and clopidogrel. Clopidogrel was the only P2Y12-receptor blocker available in generic form at the time of data collection. Since the TRITON-TIMI-38[1] and PLATO[2] trials, prescription rates of prasugrel and ticagrelor have been on the rise.[11] As of now, there has been only one randomized head-to-head comparison of ticagrelor versus prasugrel,[12] which showed no difference in outcomes at 1-year follow-up.

The use of prasugrel and ticagrelor was lower compared with that in other parts of the world during our study period. The ticagrelor prescription rate sky-rocketed immediately after the PLATO trial in Europe,[2,13,14] compared with United states where it took time.[15] In a large Swedish study, the percentage of patients with acute coronary syndrome discharged on ticagrelor increased from 34% in January 2012 to 55% in January 2013.[14] Prasugrel prescription rate continued to rise after its approval in late 2000s, but only until the PLATO trial, after which ticagrelor use increased markedly.[16] In another European study reporting data

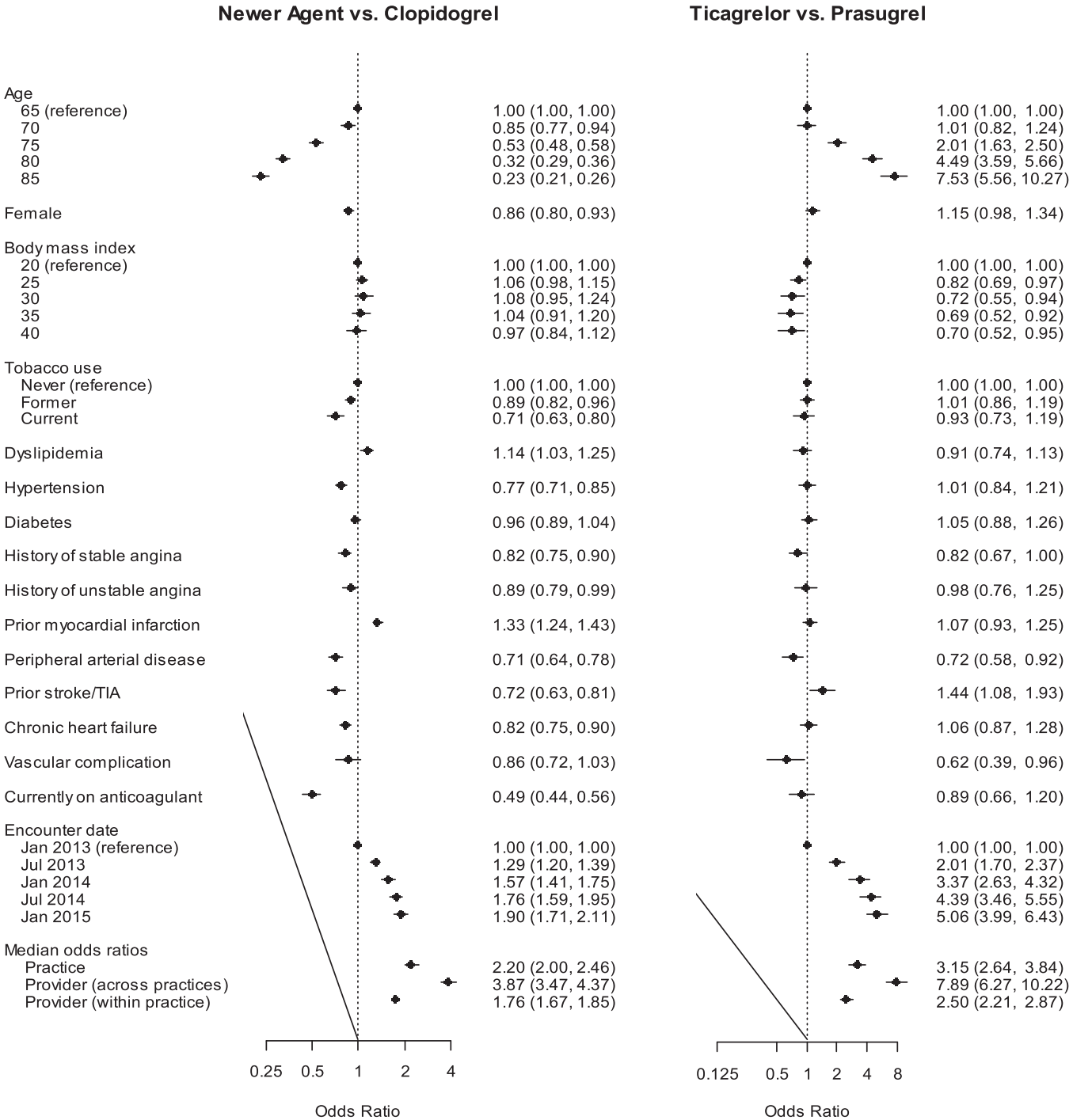

Figure 2. Predictors of prescription of antiplatelet agents in patients undergoing drug-eluting stent placement in practices enrolled in the PINNACLE registry.

during 2010 to 2011, 92% of patients received clopidogrel compared with 8% for prasugrel as part of the dual antiplatelet therapy regimen.[17]

Our study showed that older patients (≥75 years) were more likely to be prescribed clopidogrel compared with prasugrel and ticagrelor, also consistent with previous studies.[14,15] Providers may be more comfortable prescribing clopidogrel in the high-risk elderly population with increased bleeding risk, than the newer, more potent drugs. Prasugrel is not recommended in patients aged ≥75 years anyway.[5] However, 19% of all patients who were prescribed prasugrel were ≥75 years old in our study. In an analysis of 27,533 patients receiving prasugrel between July 2009 and June 2013, 4.4% had a "nonrecommended" indication, which was defined as prasugrel use in patients aged ≥75 years without previous MI or diabetes.[18] When the covariates of PAD, previous stroke/TIA, hypertension, and chronic heart failure were compared, the prescription patterns of the 3 antiplatelet agents were

identical: clopidogrel was more likely be prescribed compared with newer antiplatelet agents. Unlike prasugrel and ticagrelor, clopidogrel use in PAD is approved by the Food and Drug Administration,[19] as well as supported by AHA/ACC guidelines.[20]

Patients with diabetes may benefit more from the newer antiplatelet agents compared with clopidogrel.[1] However, our data showed no preferential use of either clopidogrel, ticagrelor or prasugrel in diabetics, as seen in Figure 2. This finding is consistent with a study comparing clopidogrel versus ticagrelor,[14] but different from another study, where clopidogrel use was greater than prasugrel.[17] Like diabetes, patients with history of MI, having higher ischemic risk may benefit more from newer antiplatelet medications.[1,2] This trend was seen in our results. Moreover, ticagrelor was as likely to be prescribed as prasugrel in our analysis in patients with MI (Figure 2), which is consistent with another study.[16] We further conducted a sensitivity analysis to analyze patterns of prescription of these medications in patients with or without history of MI. We did not find any significant differences in the relative prescription patterns of all 3 studied antiplatelet medications with respect to history of MI (Supplement Table), except for stable angina.

With increasing BMI, ticagrelor was less likely to be prescribed compared with both clopidogrel and prasugrel. Since higher BMI is related to increased platelet reactivity,[21] one might expect greater use of more potent antiplatelet medications. However, BMI is not considered to be a predictor of stent thrombosis.[22] Future studies are needed in this regard, especially given that more than 2/3 of the adults in the United States are either overweight or obese.[23]

Our study has certain limitations. Like all retrospective studies, confounding from unmeasured variables could not be excluded. However, our results from this large, national US registry paint a "real-world" picture. The proportion of patients prescribed prasugrel or ticagrelor was significantly lower than those on clopidogrel which could have influenced the analysis. The patients included in our analysis were examined during the January 2013 to March 2015 time-frame, which is before the most guidelines recommending ticagrelor over clopidogrel in acute coronary syndrome.[5,6] Moreover, the significantly higher cost of newer antiplatelet agents compared with generic clopidogrel during our study time period could have influenced the prescription patterns. With the new medications being used more and more, the prescribing factors and preferences of practices would continue to change. Hence, our results may not accurately capture the prescription patterns of antiplatelet medications at other times. Finally, the sensitivity analysis conducted to examine off-label use of prasugrel and ticagrelor assumed the history of previous MI matching with the timing of PCI, which may not be completely accurate and hence could have influenced our results. However, given the current registry being outpatient, it is difficult to truly ascertain off-label use in all patients.

In summary, our study captured the prescription patterns associated with prescription of antiplatelet agents after PCI. We found that both ticagrelor and prasugrel were mostly prescribed per the current practice guidelines by practices in NCDR PINNACLE registry, that is, low off-label use of these newer antiplatelet medications. Nevertheless, for the time period studied, clopidogrel use remained far greater than that of the newer antiplatelet agents.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.09.003.

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