ORIGINAL RESEARCH

Variation in Practice Regarding Pretreatment With Dual Antiplatelet Therapy for Patients With Non–ST Elevation Myocardial Infarction

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***Background*—**Despite guideline recommendations, a significant number of patients with non–ST elevation myocardial infarction (NSTEMI) do not receive dual antiplatelet therapy (DAPT) before angiography "pretreatment." While there may be valid clinical reasons to not pretreat, such as concern for bleeding or multivessel disease warranting coronary artery bypass graft surgery, the degree of variability and factors associated with DAPT pretreatment are unknown.

***Methods and Results*—**From the multicenter TRIUMPH registry, 1632 NSTEMI patients were not taking DAPT on admission and were included in the study cohort. Among the study patients, only 22% patients received DAPT pretreatment. A multivariable logistic regression model showed that race other than white or black (odds ratio [OR] 0.41, 95% CI 0.21–0.83), hemoglobin level (OR 1.18, 95% CI 1.08–1.29), patients' bleeding risk (assessed with NCDR CathPCI Bleeding Risk Score) (OR 0.85, 95% CI 0.74–0.99), and severe left ventricular dysfunction (OR 0.3, 95% CI 0.13–0.65) were the main predictors of pretreatment with DAPT, whereas likelihood of needing coronary artery bypass graft surgery (GRACE prediction model) was not (OR 1.09, 95% CI 0.88–1.35). Median ORs were calculated to assess variability of receiving DAPT pretreatment across sites after adjustment for patient characteristics. Receiving DAPT pretreatment varied substantially across sites (range 0–100%, mean OR 3.94, $P<0.0001$).

***Conclusions*—**While deviating from guideline-recommended DAPT pretreatment in patients with NSTEMI was associated with patient factors (eg, bleeding risk), marked variation was present across sites after accounting for patient-level characteristics. This suggests that site-level interventions are needed to improve concordance with current guidelines. **(*J Am Heart Assoc*. 2016;5: e003576 doi: 10.1161/JAHA.116.003576)**

Key Words: dual antiplatelet therapy • non–ST-elevation myocardial infarction • variation in care

Although early administration of dual antiplatelet therapy (DAPT) with aspirin and a platelet adenosine diphosphate receptor (P2Y-12) inhibitor is recommended by current American Heart Association/American College of Cardiology guidelines,[1] recent data have demonstrated that up to half of patients presenting with non–ST-elevation myocardial infarction (NSTEMI) do not receive DAPT before coronary angiography ("pretreatment").[2,3] Defining whether the variation in DAPT pretreatment is attributable to patient- or provider-level factors can identify the importance and strategy for quality improvement.

Many clinical considerations might support not using DAPT pretreatment, such as concerns for increased bleeding risk (eg, patients with low baseline hemoglobin, with low platelet counts, or taking long-term anticoagulants) or the expectation that the patients with NSTEMI might have underlying severe coronary vessel disease requiring coronary artery bypass graft surgery (CABG).[4–9] Prediction models to detect the risk of bleeding after percutaneous coronary intervention (PCI), as well as to estimate the probability of undergoing CABG after a NSTEMI,[10–13] have been developed to support such decisions, but whether avoiding DAPT pretreatment is associated with patient-centered risks is unknown. Moreover, the variability across hospitals in DAPT pretreatment for patients with NSTEMI, after accounting for patient-level considerations in its use can identify an important opportunity to increase the consistency of guideline concordant care across centers.

We used the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients'

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/6/e003576/DC1/embed/inline-supplementary-material-1.pdf

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Health Status (TRIUMPH) registry of patients with acute myocardial infarction (AMI) to examine practice pattern variations of DAPT pretreatment in NSTEMI patients. To illuminate patient-centered reasons for not using DAPT pretreatment, we examined the association of patient-level factors, including the recently validated[14] Global Risk of Acute Coronary Events (GRACE) model[10] and the National Cardiovascular Data Registry (NCDR) CathPCI Bleeding Risk Score,[15] with the use of DAPT before PCI. After adjusting for these patient-level factors, we then examined site-level variations in DAPT pretreatment.

Methods

Study Design

The study was designed as a retrospective analysis of patients enrolled in the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH) registry. Details regarding the TRIUMPH registry have been described previously.[16] In brief, TRIUMPH is a large prospective multicenter registry that successively enrolled patients across 24 sites with a diagnosis of AMI from April 2005 through December 2008, a time when there was broad consensus about the importance of DAPT pretreatment. Patients 18 years and older who had elevated cardiac enzymes (creatinine kinase-MB or troponin-I) on hospital admission and characteristics of ischemia (chest pain or electrocardiographic (ECG) abnormalities consistent with a diagnosis of AMI) were eligible. Incarcerated patients were not eligible; patients were also excluded if they refused to participate in the registry, were unable to undergo informed consent, had prolonged transfer periods from nonparticipating facilities (>24 hours), or did not speak either English or Spanish. Trained study coordinators abstracted data from the medical records and performed baseline interviews within 24 to 72 hours of presentation to assess patients' demographic, clinical, socioeconomic,[17,18] health, and psychological status. At each participating site, institutional review boards approved the study protocol and each patient provided signed informed consent.

Analytic Cohort

Given the focus of the guidelines on patients with NSTEMI, we excluded patients with ST-elevation MI (STEMI) and those who were already taking DAPT as outpatients before admission. At the time of this study, DAPT consisted of aspirin and a P2Y-12 inhibitor (ie, clopidogrel or ticlopidine). We also excluded patients enrolled at 2 sites in the TRIUMPH registry that did not offer on-site CABG, where delays in CABG might be more common and concerns about more extensive coronary disease might be less relevant. The study cohort was then assessed to determine which patients received pretreatment with DAPT.

Statistical Analysis

Baseline characteristics of NSTEMI patients who did and did not receive DAPT pretreatment were compared by using Student t test for continuous variables and χ^2 tests for categorical variables (Table). Based on literature review and clinical criteria, we attempted to capture all patient and clinical characteristics that we thought might be associated with DAPT pretreatment. For example, we have previously validated the GRACE model[10] as the best method for identifying the risk of patients for needing CABG in the setting of NSTEMI.[14] Thus, to best capture this important reason for not pretreating with DAPT before angiography, we calculated the risk score by using the GRACE model for each patient on the basis of their sex; history of CABG, angina, congestive heart failure, dyslipidemia, hypertension, atrial fibrillation, and diabetes; and ECG findings. To assess whether the patients' risk of bleeding was associated with avoiding DAPT pretreatment, we collected data regarding patients taking coumadin or any other oral anticoagulants on admission and their preprocedural platelet counts. We also calculated each patient's NCDR CathPCI Bleeding Risk Score.[15] Finally, we collected some additional variables based on clinical judgment that we thought might be associated with DAPT pretreatment; such as race, history of smoking, stroke/transient ischemic attack, peripheral arterial disease, chronic lung disease, family history of coronary artery disease, and baseline left ventricular (LV) function.

We then used hierarchical logistic regression models, with site-centered covariates, to assess whether our collected variables had a significant association with DAPT pretreatment. The raw rates of DAPT pretreatment were assessed among all study sites. To assess the extent of variability in DAPT pretreatment across sites, we calculated the median odds ratios (MOR). The MOR estimates the difference in likelihood of receiving DAPT pretreatment at one random study site versus the other after accounting for patient-level characteristics.[19,20] SAS version 9.4 was used to perform all analyses. All analyses were prespecified, and a 2-sided P value <0.05 denoted statistical significance.

A majority of patients (93%) were not missing any covariate information, with 2% missing 1 value and 5% missing ≥2. The highest missing rate for any single variable was 4.8% (GRACE CABG Risk Score), followed by smoking status, which was missing in 0.6% of patients. To correct for any biases because of the small number of missing covariates, data were imputed by using an imputation model that contained all of the variables from the multivariable model (IVEware; Institute for Social Research).[21] Table S1 shows no significant differences

Table. Baseline Characteristics of NSTEMI Patients Undergoing DAPT Pretreatment Versus No Pretreatment

Variable	DAPT Pretreatment, n=359	No Pretreatment, n=1273	*P* Value
Mean age, y	58.3±12.4	60.5±12.7	0.003
Male	69.6%	62.7%	0.015
Race			<0.001
White/Caucasian	72.8%	58.8%	
Black/African American	22.8%	35.6%	
Other	4.5%	5.7%	
Smoking status			0.669
Current (<30 d)	37.3%	35.4%	
Former (>30 d)	32.6%	32.1%	
Never (<100 d)	30.1%	32.5%	
Medical history			
Prior angina	12.0%	13.1%	0.569
Prior CABG	6.4%	12.6%	0.001
Prior MI	15.9%	22.7%	0.005
Prior PCI	16.7%	14.8%	0.385
Prior CVA or TIA	5.0%	8.3%	0.036
Chronic kidney disease	5.8%	9.8%	0.02
Chronic heart failure	2.5%	13.7%	<0.001
Peripheral vascular disease	3.9%	4.8%	0.476
Chronic lung disease	5.3%	10.9%	0.001
Hypertension	66.0%	73.4%	0.006
Diabetes	28.7%	34.9%	0.028
Hospital presentation characteristics			
Killip Class			<0.001
I	93.5%	84.5%	
II	5.1%	12.5%	
III	1.4%	2.1%	
IV	0.0%	0.9%	
LV systolic function			<0.001
Normal	80.7%	64.3%	
Mild	10.9%	15.7%	
Moderate	5.9%	9.3%	
Severe	2.5%	10.7%	
ECG findings			
ST depression	23.7%	26.6%	0.278
ST elevation	9.4%	11.6%	0.265
LBBB	2.5%	5.5%	0.02
Family history of CAD	75.8%	71.0%	0.075
Medications on arrival or before cardiac catheterization			
Warfarin	2.5%	7.6%	<0.001
GP IIb/IIIa inhibitors	41.2%	28.5%	<0.001
Baseline laboratory values			
Initial hemoglobin, g/dL	14.3±1.7	13.5±2.2	<0.001
Initial platelet count	250.6±77.2	253.4±86.5	0.583
Risk scores			
GRACE CABG Risk Score	10.0±1.6	9.7±1.8	0.002
NCDR CathPCI Bleeding Risk Score	50.6±14.9	55.2±18.3	<0.001

Data are reported as mean±SD or %. CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; GP IIb/IIIa, glycoprotein IIb/IIIa; GRACE, Global Risk of Acute Coronary Events; LBBB, left bundle-branch block; LV, left ventricular; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NSTEMI, non–ST elevation myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

when comparing the output of logistic regression models with and without missing data.

Results

Study Population

There were 4340 patients with an AMI enrolled in the TRIUMPH registry. We excluded patients with STEMI (n=1860), those who were already taking DAPT on admission (n=387), and patients who did not have information regarding their pretreatment with DAPT (n=390). We further excluded 71 patients who were enrolled at 2 sites in the TRIUMPH registry that did not perform on-site CABG. The final study cohort consisted of 1632 NSTEMI patients across 22 study sites (Figure 1).

Unadjusted Association of Patient Factors With DAPT Pretreatment

Among the study cohort, 359 (22%) patients received pretreatment with DAPT. Table shows the overall demographic and clinical characteristics of patients who did and did not receive pretreatment with DAPT. Patients in the pretreatment group were younger and more likely to be male and white, with a lower prevalence of prior CABG, MI, heart failure, hypertension, and diabetes. The pretreatment group was also more likely to have a higher hemoglobin level, to not be taking warfarin, and to have normal LV systolic function. Paradoxically, the likelihood of having multivessel coronary disease

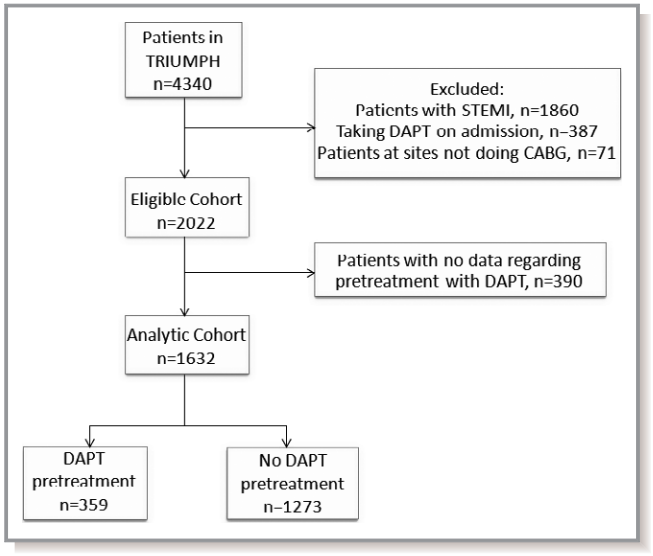

Figure 1. Flow chart of patient selection. CABG indicates coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; STEMI, ST elevation myocardial infarction; TRIUMPH, Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status.

requiring CABG, the GRACE CABG Risk Scores, were slightly higher for those pretreated with DAPT compared with those who were not (10.0±1.6 versus 9.7±1.8, P=0.002), but the risk of bleeding, as assessed with NCDR CathPCI Bleeding Risk Scores, was lower in those pretreated with DAPT (50.6±14.9 versus 55.2±18.3, P<0.001).

Adjusted Association of Patient Factors With DAPT Pretreatment

Independent predictors of pretreatment with DAPT included higher hemoglobin levels (odds ratio [OR] per 1 g/dL 1.18, 95% CI 1.08–1.29 per 1 g/dL), race other than white or black (OR 0.41, 95% CI 0.21–0.83), and mild (OR 0.55, 95% CI 0.36–0.84), moderate (OR 0.60, 95% CI 0.35–1.03), and severe LV dysfunction (OR 0.3, 95% CI 0.13–0.65). Patients' bleeding risk (assessed with NCDR CathPCI Bleeding Risk Scores for an increase by 10 points) (OR 0.85, 95% CI 0.74–0.99) was also significantly associated with DAPT pretreatment. The patients' risk for needing CABG (as assessed with the GRACE CABG Risk Score for 1-point increase in total score [OR 1.09, 95% CI 0.88–1.35]) was not associated with DAPT pretreatment. The main predictors in the regression model are shown in Figure 2. The final model had a c-statistic of 0.83.

Variability in DAPT Pretreatment Across Centers

Marked variability in DAPT pretreatment was observed across sites ranging, from 0% to 100% (Figure 3). After adjusting for

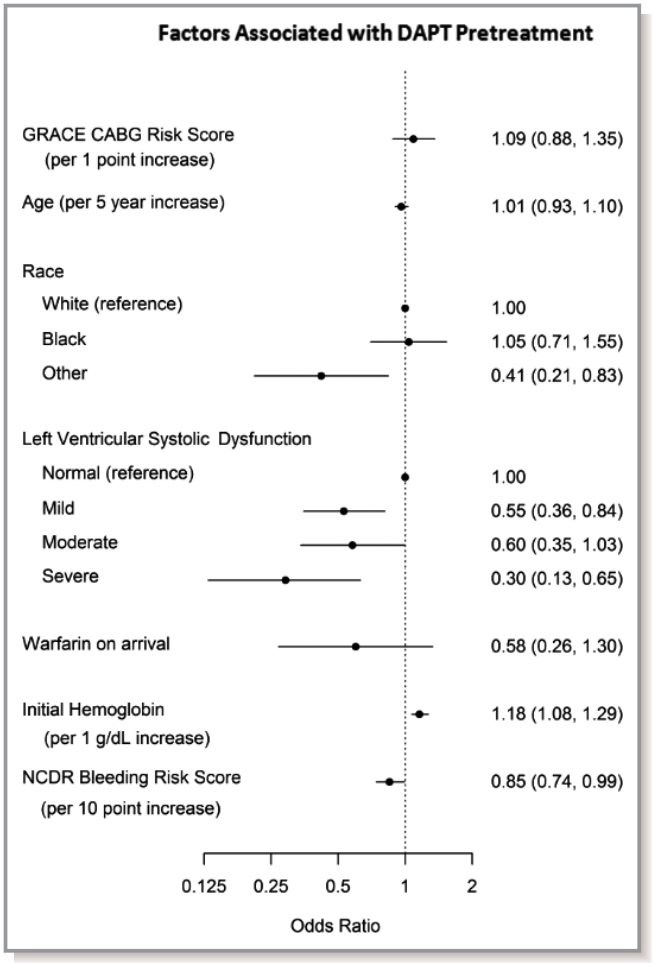

Figure 2. Patient predictors of dual antiplatelet therapy (DAPT) pretreatment. Forest plot depicting the odds ratios of patient level that are associated with odds of receiving DAPT treatment. CABG indicates coronary artery bypass graft surgery; GRACE, Global Risk of Acute Coronary Events; NCDR, National Cardiovascular Data Registry; TRIUMPH, Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status.

patient characteristics in a hierarchical model, the MOR was 3.94 (95% CI 2.04–6.09) with P<0.0001. This suggests an almost 4-fold mean variation in the likelihood that a patient with NSTEMI presenting at 1 random site in the TRIUMPH study would be treated with DAPT before PCI versus another.

Discussion

As the United States transitions to value-based healthcare reimbursement, the importance of delivering consistent, guideline-concordant care grows ever more important and insights into the source of treatment variability become a priority. In this multicenter registry of patients with NSTEMI, we found marked variability in the rates of DAPT pretreatment across sites, ranging from 0% to 100%. Importantly, we observed an independent association between a number of

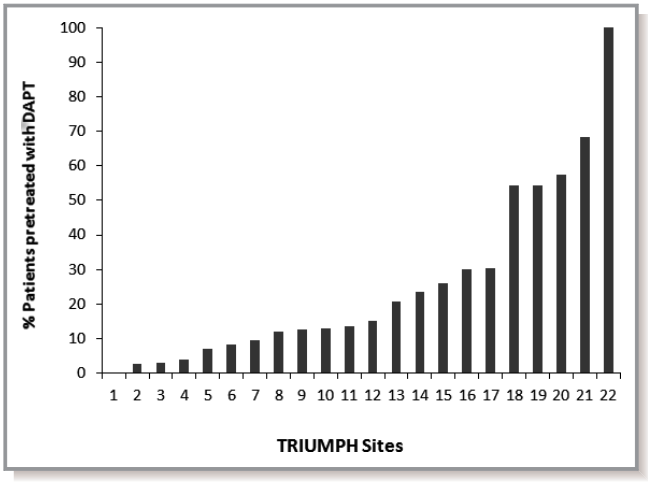

Figure 3. Graph of site-level variation for receiving dual antiplatelet therapy (DAPT) pretreatment. The *x*-axis shows sites that were included in the TRIUMPH registry from 1 to 23. The *y*-axis shows percentages of patients as a function of each site that received DAPT pretreatment. TRIUMPH indicates Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status.

variables suggesting increased risk from DAPT and the avoidance of DAPT pretreatment, such as lower hemoglobin levels, taking anticoagulants on admission, and bleeding risk. However, we found no independent association between patients' likelihood of needing CABG and the avoidance of DAPT pretreatment. After adjusting for all patient characteristics independently associated with DAPT pretreatment, we still found marked variability in treatment across hospitals. On average, a given patient with NSTEMI presenting at one TRIUMPH site versus another would be almost 4 times more likely to be pretreated with DAPT. This large degree of variation across sites suggests that site-level interventions are needed to improve the consistency of DAPT pretreatment for patients with NSTEMI undergoing PCI across hospitals.

Our work expands on the current understanding of practice patterns surrounding pretreatment with DAPT. We found that the majority of patients with NSTEMI in our study cohort did not receive DAPT pretreatment, which is similar to previous studies.[2,3] A retrospective analysis published in 2010, assessing 6253 patients who underwent PCI, showed that 56% of patients with NSTEMI or unstable angina did not receive pretreatment with DAPT.[22] Also, in a randomized controlled trial of 9492 patients with high-risk acute coronary syndromes, conducted in 29 countries, Giugliano et al showed that the rate of intended early use of clopidogrel as a part of DAPT was lower in North America than elsewhere (50.8% versus 85.8%).[23] The most common reasons cited by previous studies for physicians not pretreating patients with DAPT are the risk of increased bleeding and the likelihood that patients may need to undergo CABG and will be susceptible to prolonged hospital stays.[4] In our study, we studied in detail how strongly the risk of bleeding or other clinical factors may be associated with DAPT pretreatment. Our analyses showed that patients taking oral anticoagulants or who had high NCDR CathPCI Bleeding Risk Scores with any degree of LV dysfunction were less likely to receive DAPT pretreatment. On the other hand, patients with a higher hemoglobin level had higher odds of being pretreated. These observations suggest that providers may be rationally considering the risk of bleeding as well as how stable patients are with regard to their cardiac function when deciding whether to pretreat patients with DAPT. Our study further showed that patients who were not black or white were less likely to receive DAPT. A potential reason for this is that despite being underrepresented in major clinical trials, there is evidence to suggest that minority groups, especially Asian patients, are more prone to bleeding complications following PCI, compared with white patients.[24] Therefore, providers might be considering this risk of bleeding in these minority patients and be less likely to pretreat them with DAPT. However, further research is needed to evaluate this relationship. More importantly, we found that DAPT pretreatment was not significantly associated with the patients' GRACE model risk score, leading us to believe that providers may not be considering the risk of CABG as an important factor to give or delay DAPT. The significant variability in rates of pretreatment with DAPT across facilities that was present even after accounting for patient-level factors shows that providers are not using a standardized approach to risk-stratify patients for purposes of administering or delaying DAPT pretreatment.

American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommend initiating DAPT at the earliest time after presentation to the hospital and before angiography (pretreatment).[1,24] These recommendations are mainly based on evidence from the Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE)[5] and the Clopidogrel for the Reduction of Events During Observation (CREDO) trials,[25] which were conducted more than a decade ago and may not represent contemporary practice trends. In these studies, most of the patients had their PCIs postponed for up to several days after pretreatment, whereas current practice often leads to invasive treatment within hours of first medical contact. Also, recent studies suggest that DAPT pretreatment may not necessarily improve cardiovascular outcomes.[17,19] A recent meta-analysis showed that 32 383 NSTEMI patients who received pretreatment with aspirin and clopidogrel did not have a significantly lower risk of mortality.[19] Another randomized trial (the Comparison of Prasugrel at the Time of PCI or Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction [ACCOAST]) enrolled 4033 NSTEMI patients and found that

pretreatment with prasugrel (a more potent antiplatelet agent than clopidogrel) did not decrease adverse cardiac outcomes but rather was associated with increased bleeding.[18] Therefore, if patient-centered reasons (like risk of bleeding) are the cause of the low DAPT pretreatment, then deviating from guidelines may not necessarily provide poor care, especially in light of new emerging evidence.[26] In contrast, if site-level variability accounts for the use of DAPT before coronary angiography independent of patient-level factors, then it would underscore the importance of quality improvement efforts to improve guideline concordance and improve the consistency of care.[27] Previously proposed models that either predict the likelihood for CABG or estimate the bleeding risk for patients presenting with NSTEMI may not be perfect.[10–14] However, these prediction models could provide clinicians with evidence-based guidance for the selection of DAPT pretreatment, thereby providing a more standardized approach to treating patients with NSTEMI, potentially reducing practice variations and helping to increase adherence to the guidelines.

Our findings should be considered in the context of several potential limitations. At the time of our study (2005–2008), there was little controversy regarding giving DAPT pretreatment. However, the addition of newer P2Y-12 inhibitors with a more rapid onset of action and conflicting data, such as those from ACCOAST, may suggest that pretreatment is less important now than at the time of this study. Nevertheless, insights separating patient-level from site-level variability are important and whatever practice patterns are eventually adopted would likely require site-level interventions to support the consistency of care across hospitals. In addition, although we attempted to look at a comprehensive list of patient-level factors that were potentially associated with DAPT pretreatment, we could have missed important variables, which could have influenced/confounded our results, but our logistic regression model had a good discrimination with c-statistic of 0.83 providing us with reasonable confidence in the results. Also, glycoprotein IIb/IIIa inhibitors are a form of antiplatelet therapy that can also be administered upstream of angiography and influence DAPT pretreatment, but as we did not have data regarding the exact time of administration of these medications (whether patients received them before or after getting DAPT), we did not include them as a "predictor variable" in our logistic regression analyses. Finally, we only explored practice trends of DAPT pretreatment and did not examine outcomes, as previous large-scale trials have already explored this.

In our multicenter MI registry, less than one-fourth of NSTEMI patients were pretreated with DAPT, and while patient characteristics associated with increased bleeding risk were also associated with less DAPT pretreatment, there remained marked variation across sites even after adjusting for these patient factors. These findings suggest that the use of DAPT before angiography in NSTEMI patients is more influenced by site-level protocols, rather than personalized care to individual patients. Efforts to improve the quality of DAPT pretreatment should focus on site-level interventions, which seem more important than any patient-level considerations in current practice.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of Logistic Regression Models with and without Missing Data

Variables	Model with Missing Data O.R (95% C.I)	Model with Imputed Data O.R (95% C.I)
Age (yrs)	1.00 (0.92-1.09)	1.01 (0.93-1.10)
Male versus female	0.67 (0.40-1.11)	0.68 (0.41-1.11)
Race (reference = white)		
Black	1.02 (0.68-1.52)	1.05 (0.71-1.55)
Other	0.45 (0.22-0.91)	0.41 (0.20-0.83)
Angina	1.12 (0.58-2.16)	1.00 (0.53-1.88)
Prior bypass graft surgery	0.79 (0.33-1.88)	0.89 (0.39-2.03)
Prior AMI	0.86 (0.55-1.36)	0.86 (0.55-1.32)
Prior PCI	1.00 (0.62-1.61)	1.01 (0.63-1.60)
CVA/TIA	0.93 (0.50-1.71)	0.95 (0.52-1.72)
Chronic kidney disease	1.37 (0.73-2.58)	1.44 (0.77-2.6)
Congestive heart failure	0.51 (0.22-1.15)	0.51 (0.22-1.14)
Peripheral vascular disease	1.05 (0.51-2.16)	0.98 (0.48-1.99)
Chronic lung disease	0.73 (0.40-1.33)	0.73 (0.40-1.31)
Hypertension	1.02 (0.67-1.54)	0.94 (0.63-1.40)
Diabetes	0.91 (0.59-1.39)	0.86 (0.57-1.30)
Family history of CAD	1.21 (0.86-1.70)	1.18 (0.85-1.64)
LV Function (reference=normal)		
Mild	0.59 (0.38-0.90)	0.55 (0.36-0.84)
Moderate	0.59 (0.34-1.05)	0.60 (0.34-1.03)
Severe	0.36 (0.15-0.83)	0.29 (0.13-0.65)
Smoking status (reference=current smoker)		
Former	1.09 (0.75-1.59)	1.08 (0.75-1.56)
Never	0.98 (0.68-1.42)	0.96 (0.67-1.38)
Warfarin	0.56 (0.24-1.32)	0.58 (0.26-1.29)
Hemoglobin	1.19 (1.09-1.31)	1.18 (1.08-1.29)
Platelet count (per 25 units)	0.97 (0.93-1.02)	0.98 (0.94-1.03)
EKG		
ST depression	0.95 (0.67-1.36)	0.88 (0.62-1.24)
ST elevation	0.92 (0.46-1.83)	1.06 (0.55-2.06)
NCDR Bleeding Risk Score (per 10 points	0.85 (0.73-0.99)	0.85 (0.73-0.98)
GRACE CABG Score (per 1 point increase)	1.04 (0.83-1.30)	1.08 (0.87-1.34)

AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular disease; LV, left ventricular; NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention;