ORIGINAL RESEARCH

Antiplatelet Therapy Changes for Patients With Myocardial Infarction With Recurrent Ischemic Events: Insights Into Contemporary Practice From the TRANSLATE-ACS (Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) Study

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***Background*—**Guidelines recommend $P2Y_{12}$ inhibitor therapy for 1 year after myocardial infarction (MI), yet little guidance is provided on antiplatelet management for patients with recurrent ischemic events during that year. We describe changes in $P2Y_{12}$ inhibitor type among patients with recurrent ischemic events in the first year after MI.

***Methods and Results*—**The TRANSLATE-ACS (Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) study enrolled 12 365 patients with MI treated with percutaneous coronary intervention. We examined whether $P2Y_{12}$ inhibitor choice changed among patients with recurrent MI, stent thrombosis, and/or unplanned revascularization during the first year after MI, and modeled factors associated with $P2Y_{12}$ inhibitor intensification (changing clopidogrel to prasugrel or ticagrelor). In the first year after MI, 1414 patients (11%) had a total of 1740 recurrent ischemic events (771 recurrent MIs, 969 unplanned revascularizations, and 165 stent thromboses). Median time to the first recurrent ischemic event was 154 days (25th–75th percentiles, 55–287 days). Of those with recurrent ischemic events, 101 of 1092 (9.3%) occurring in clopidogrel-treated patients led to $P2Y_{12}$ inhibitor intensification. Recurrent events involving stent thrombosis or MI were the strongest factors associated with $P2Y_{12}$ inhibitor intensification, yet only 40% of patients with stent thrombosis and 14% of patients with recurrent MI had $P2Y_{12}$ inhibitor intensification. Increasing age and longer time from the index MI were associated with lower likelihood for intensification.

***Conclusions*—**Few patients after MI with a recurrent ischemic event who were taking clopidogrel switched to a more potent $P2Y_{12}$ inhibitor, even after stent thrombosis events. Specific guidance is needed for patients who have recurrent ischemic events, particularly when closely spaced.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01088503. **(*J Am Heart Assoc*. 2018;7: e007982. DOI: 10.1161/JAHA.117.007982.)**

Key Words: clopidogrel • coronary revascularization • myocardial infarction • secondary prevention • stent thrombosis

Guidelines recommend 1 year of $P2Y_{12}$ inhibitor therapy in combination with aspirin after acute coronary syndrome (ACS).[1–4] Compared with clopidogrel, the higher-potency $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, reduce the incidence of recurrent cardiovascular events in patients with ACS undergoing percutaneous coronary intervention (PCI), but uptake of these agents into clinical practice in the United States has been tempered by concerns about increased bleeding risk and higher out-of-pocket patient costs.[5–8]

Among clopidogrel-treated patients with high on-treatment platelet activity, prasugrel and ticagrelor have been shown to effectively inhibit platelet aggregation,[9–11] but randomized

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An accompanying Data S1 is available at http://jaha.ahajournals.org/content/7/4/e007982/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Less than 10% of patients after myocardial infarction who have a recurrent ischemic event while taking clopidogrel are switched to a more potent $P2Y_{12}$ inhibitor at the time of the recurrent event.
- Recurrent events involving stent thrombosis or ST-segment–elevation myocardial infarction were strongly associated with switching to a more potent $P2Y_{12}$ inhibitor, yet only 40% of patients with stent thrombosis and 37% of patients with ST-segment–elevation myocardial infarction were switched.

What Are the Clinical Implications?

- Specific evidence and guidance for the management of patients with closely spaced ischemic events is lacking, and a clinical trial in patients after myocardial infarction with recurrent ischemic events while taking clopidogrel may help clarify the optimal management strategy for these patients.

controlled trials switching patients with high on-clopidogrel platelet reactivity to prasugrel or ticagrelor have failed to show clinical benefit.[12–16] Recurrent ischemic events while receiving clopidogrel therapy may affect physician decision making because of perceived clopidogrel "failure," although these events may not necessarily reflect inadequate platelet inhibition. In patients with ACS, in-hospital reinfarction while taking clopidogrel is associated with a higher likelihood of a switch to prasugrel.[17] Postdischarge switching is rare, and most switches are from prasugrel or ticagrelor to clopidogrel, driven by cost considerations.[18] However, antiplatelet management of patients with recurrent ischemic events after hospital discharge has not been previously described, and consensus guidelines offer no specific recommendations.

The TRANSLATE-ACS (Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) study enrolled patients with myocardial infarction (MI) undergoing PCI and treated with a $P2Y_{12}$ inhibitor.[15,18,19] Patients were observed longitudinally after discharge, with independent adjudication of recurrent MI and revascularization events, core laboratory adjudication of stent thrombosis, and patient-reported medication adherence. Therefore, the TRANSLATE-ACS study provided the opportunity to evaluate antiplatelet therapy changes after recurrent ischemic events.

Methods

Study Population

The design of the TRANSLATE-ACS study has been previously reported.[19] Briefly, the TRANSLATE-ACS study was a multicenter observational study that examined longitudinal antiplatelet use and outcomes among 12 365 patients with MI who were treated with PCI. Patients were enrolled from April 4, 2010 through October 31, 2012. Eligible patients were ≥18 years old, diagnosed as having ST-segment–elevation MI (STEMI) or non-STEMI, treated with PCI and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticlopidine, or ticagrelor), and able to provide consent for long-term follow-up. Patients enrolled in another research study that dictated antiplatelet treatment in the 1 year after MI were excluded.

All patients enrolled in the TRANSLATE-ACS study provided written informed consent, and the study protocol was approved by the ethics committee or institutional review board of each participating site. The Duke University Medical Center Institutional Review Board (Durham, NC) approved use of TRANSLATE-ACS study data for this analysis. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The analysis population for this study began with patients who were discharged alive after their index PCI event (Figure 1). The analysis then further focused on the patients who had a recurrent MI, an unplanned revascularization, or both during the following 1 year, as defined later.

Data Collection and Definitions

During each patient's index MI admission, hospitals collected baseline demographic and clinical characteristics, processes of care, discharge medications, and in-hospital outcomes using data elements and definitions modified from the National Cardiovascular Data Registry CathPCI Registry. Patients reported current medications and recurrent hospitalizations during telephone interviews at 6 weeks, 6 months, 12 months, and 15 months after MI. Patients were queried on how often they missed taking a dose of their $P2Y_{12}$ inhibitor; nonadherence was defined as missing >1 dose per week. Rehospitalizations were verified by the collection of medical bills. Medical records for hospitalizations involving death, recurrent MI, coronary revascularization (PCI or coronary artery bypass grafting), or stent thrombosis were collected, and events were centrally validated using standardized criteria.[19] The diagnosis of MI was validated using a definition consistent with the Third Universal Definition of Myocardial Infarction.[20] Unplanned coronary revascularizations included both PCI and coronary artery bypass grafting, but excluded staged revascularizations, defined as those performed within 60 days of the index PCI in the absence of new symptoms. When stent thrombosis was suspected, coronary angiograms were independently reviewed by an angiographic core laboratory, and stent thrombosis was validated using Academic Research Consortium criteria.[21] For each event, data were

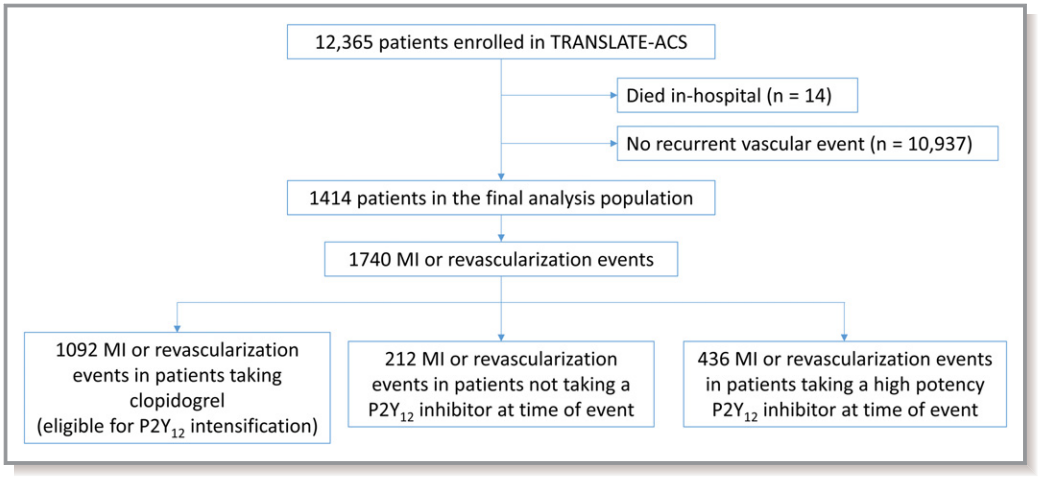

Figure 1. Study flow diagram. MI indicates myocardial infarction; and TRANSLATE-ACS, Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome.

abstracted regarding $P2Y_{12}$ inhibitor therapy use at the time of readmission and at discharge.

The primary outcome of our analysis was $P2Y_{12}$ inhibitor intensification in response to MI or revascularization, which we defined as a switch from a lower-potency $P2Y_{12}$ inhibitor (either clopidogrel or ticlopidine, because some patients discharged with another agent were switched to ticlopidine during follow-up) to a higher-potency $P2Y_{12}$ inhibitor (either prasugrel or ticagrelor). A switch occurred when the admission and discharge $P2Y_{12}$ inhibitors for the hospitalization involving the recurrent coronary ischemic event were different. Patients who were not taking a $P2Y_{12}$ inhibitor at the time of their recurrent event were not eligible for intensification, because patients in whom $P2Y_{12}$ inhibitors are stopped early are likely to differ substantially from patients who continue to use $P2Y_{12}$ inhibitors up to the time of their event. Increasing clopidogrel dosage to 150 mg/d was also not considered $P2Y_{12}$ inhibitor intensification because the TRANSLATE-ACS study did not collect medication dosages; moreover, the 150-mg/d dose of clopidogrel is off label.

Statistical Analysis

Patients were grouped first according to $P2Y_{12}$ inhibitor therapy at the time of their recurrent coronary ischemic event, and then according to whether they had $P2Y_{12}$ inhibitor intensification. Descriptive statistics were reported as median (25th–75th percentile) for continuous variables and frequency (percentage) for categorical variables. For continuous variables, differences between groups were compared using the Wilcoxon rank-sum test. For categorical variables, differences between groups were assessed using the χ^2 test when sample size was sufficient and the Fisher exact test when it was not sufficient. All analyses were performed at the event level to enable us to evaluate the effect of multiple recurrent events on $P2Y_{12}$ inhibitor intensification.

To identify factors associated with $P2Y_{12}$ inhibitor intensification, we used logistic regression to create a multivariable model, assessing candidate variables listed in Data S1. The logistic regression model used generalized estimating equations to account for within-patient clustering; discrimination was assessed by calculating a C-statistic.

Results

$P2Y_{12}$ Inhibitor Use at Time of Recurrent Ischemic Events

Among 12 279 patients with MI who were treated with PCI and discharged alive on a $P2Y_{12}$ inhibitor, 1414 (11.5%) had 1740 recurrent coronary ischemic events during the first year after MI. These included 771 recurrent MI events (432 treated with revascularization and 339 treated without revascularization) and 969 unplanned coronary revascularizations performed in the absence of a recurrent MI. Of MI events, 165 (21.4%) involved stent thrombosis. Median time to the first recurrent ischemic event was 154 days (25th–75th percentile, 54–287 days). At the time of the recurrent ischemic event, 1087 patients (62.5%) were taking clopidogrel, 5 patients (0.3%) were taking ticlopidine, 381 patients (21.9%) were taking prasugrel, and 55 patients (3.2%) were taking ticagrelor. Only 5% of recurrent ischemic events occurred in patients who were prescribed $P2Y_{12}$ inhibitors at the time of the event but reported nonadherence to therapy. Although all recurrent ischemic events occurred within 1 year of the index MI, 212 patients (12.2%) were no longer taking a $P2Y_{12}$ inhibitor at the time of the recurrent event.

Table 1. Baseline Patient Characteristics by $P2Y_{12}$ Inhibitor at the Time of the Recurrent Ischemic Event

Characteristics	Overall (N=1740)	Clopidogrel/ Ticlopidine (n=1092)	None (n=212)	Prasugrel/ Ticagrelor (n=436)	*P* Value
Demographics					
Age, y	61 (52–69)	61 (53–70)	61 (51–69)	57 (50–65)	<0.001
Male sex	1168 (67.1)	736 (67.4)	133 (62.7)	299 (68.6)	0.32
White race	1472 (84.6)	928 (85.0)	165 (77.8)	379 (86.9)	0.007
Health insurance					
Private	1000 (57.5)	630 (57.7)	93 (43.9)	277 (63.5)	<0.001
Medicare	731 (42.0)	501 (45.9)	98 (46.2)	132 (30.3)	<0.001
Medicaid	184 (10.6)	116 (10.6)	29 (13.7)	39 (8.9)	0.21
None	234 (13.5)	133 (12.2)	43 (20.3)	58 (13.3)	0.007
Financial hardship of paying for medications	429 (26.8)	270 (26.6)	62 (33.9)	97 (24.2)	0.05
Married	1027 (59.0)	649 (59.4)	92 (43.4)	286 (65.6)	<0.001
High school graduate or beyond	1449 (83.3)	903 (82.7)	166 (78.3)	380 (87.2)	0.01
Employed	689 (39.6)	395 (36.2)	61 (28.8)	233 (53.4)	<0.001
Medical history at the time of index event					
Prior CABG	348 (20.0)	250 (22.9)	30 (14.2)	68 (15.6)	<0.001
Prior stroke or TIA	132 (7.6)	94 (8.6)	28 (13.2)	10 (2.3)	<0.001
PAD	233 (13.4)	164 (15.0)	35 (16.5)	34 (7.8)	<0.001
Prior heart failure	230 (13.2)	157 (14.4)	33 (15.6)	40 (9.2)	0.02
Atrial fibrillation/flutter	124 (7.1)	84 (7.7)	18 (8.5)	22 (5.1)	0.14
Diabetes mellitus	725 (41.7)	452 (41.4)	90 (42.5)	183 (42.0)	0.94
Chronic lung disease	249 (14.3)	173 (15.8)	32 (15.1)	44 (10.1)	0.01
Features of index admission					
STEMI	791 (45.5)	448 (41.0)	112 (52.8)	231 (53.0)	<0.001
Multivessel disease	1151 (66.2)	736 (67.4)	132 (62.3)	283 (64.9)	0.24
Platelet function testing performed	246 (14.1)	143 (13.1)	28 (13.2)	75 (17.2)	0.11
LVEF ≤40%	387 (25.2)	242 (25.4)	47 (25.4)	98 (24.8)	0.97
BMI, kg/m^2	29 (26–34)	29 (26–34)	29 (26–33)	30 (27–34)	0.13
GFR, mL/min	73 (57–91)	71 (55–91)	74 (51–92)	77 (60–93)	0.02
Platelet function testing performed	246 (14.1)	28 (13.2)	143 (13.1)	75 (17.2)	0.11
Features of index PCI					
Location					0.05
Left main	22 (1.3)	10 (0.9)	4 (1.9)	8 (1.8)	
LAD	578 (33.2)	360 (33.0)	74 (34.9)	144 (33.0)	
LCX	429 (24.7)	295 (27.1)	47 (22.2)	87 (20.0)	
RCA	695 (40.0)	419 (38.4)	84 (39.6)	192 (44.0)	
Lesion involved stent thrombosis	80 (4.6)	35 (3.2)	15 (7.1)	30 (6.9)	0.01
Lesion involved vein graft	174 (10.0)	137 (12.6)	9 (4.3)	28 (6.4)	<0.001
Drug-eluting stent implanted	1097 (63.1)	676 (61.9)	104 (49.1)	317 (72.7)	<0.001

Continued

Table 1. Continued

Characteristics	Overall (N=1740)	Clopidogrel/ Ticlopidine (n=1092)	None (n=212)	Prasugrel/ Ticagrelor (n=436)	*P* Value
Discharge medications after index MI					
$P2Y_{12}$ inhibitor					
Clopidogrel	1254 (72.1)	1026 (94.0)	153 (72.5)	75 (17.2)	<0.001
Prasugrel	414 (23.8)	51 (4.7)	48 (22.8)	315 (72.3)	<0.001
Ticlopidine	8 (0.5)	8 (0.7)	0 (0)	0 (0)	0.09
Ticagrelor	55 (3.2)	4 (0.4)	5 (2.4)	46 (10.6)	<0.001
None	8 (0.5)	3 (0.3)	5 (2.4)	0 (0)	<0.001
Anticoagulant	114 (6.6)	72 (6.6)	25 (11.8)	17 (3.9)	<0.001
Bleeding between index and follow-up event					
Moderate-severe >30 d before	34 (2.0)	9 (0.8)	17 (8.0)	8 (1.8)	<0.001
Moderate-severe ≤30 d before	51 (2.9)	34 (3.1)	10 (4.7)	7 (1.6)	0.07
Mild >30 d before	39 (2.2)	22 (2.0)	9 (4.3)	8 (1.8)	0.11
Mild ≤30 d before	44 (2.5)	30 (2.8)	8 (3.8)	6 (1.4)	0.14
Features of recurrent ischemic event					
Time to event, d	154 (55–287)	148 (52–279)	193 (74–323)	157 (52–288)	0.03
Type of event					<0.001
MI with revascularization	432 (24.8)	253 (23.2)	90 (42.5)	89 (20.4)	
MI without revascularization	339 (19.5)	201 (18.4)	68 (32.1)	70 (16.1)	
Revascularization without MI	969 (55.7)	638 (58.4)	54 (25.5)	277 (63.5)	
Stent thrombosis adjudicated	165 (9.5)	91 (8.3)	45 (21.2)	29 (6.7)	<0.001

Categorical variables are presented as frequency (percentage); continuous variables are presented as median (25th–75th percentile). Generation 1 $P2Y_{12}$ inhibitors are defined as clopidogrel or ticlopidine; generation 2 $P2Y_{12}$ inhibitors are defined as prasugrel or ticagrelor. BMI indicates body mass index; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment–elevation MI; and TIA, transient ischemic attack.

Compared with patients no longer taking a $P2Y_{12}$ inhibitor, patients taking clopidogrel had a shorter time from their index event to the recurrent event (148 versus 193 days; P=0.003) (Table 1). Patients taking clopidogrel were less likely to have a recurrent MI or stent thrombosis and more likely to have an unplanned revascularization alone compared with patients no longer taking a $P2Y_{12}$ inhibitor. In patients with recurrent ischemic events after $P2Y_{12}$ inhibitor discontinuation, these events occurred at a median of 92 days (25th–75th percentiles, 37–191 days) after $P2Y_{12}$ inhibitor discontinuation.

Compared with patients taking a higher-potency $P2Y_{12}$ inhibitor at the time of the recurrent ischemic event, patients taking clopidogrel were older and more often had prior coronary artery bypass grafting, prior stroke/transient ischemic attack, and peripheral artery disease. Among patients taking clopidogrel at the time of the recurrent event, 51 (5%) were discharged on a higher-potency $P2Y_{12}$ inhibitor and then switched to clopidogrel; the recurrent ischemic event occurred at a median of 218 days (25th–75th percentile, 131–301 days) after $P2Y_{12}$ inhibitor switching. Time from index to recurrent event and type of recurrent event were similar between patients still taking lower- versus higher-potency $P2Y_{12}$ inhibitors. Stent thrombosis was observed in 21.8% of patients no longer taking a $P2Y_{12}$ inhibitor, 8.3% of patients taking clopidogrel or ticlopidine, and 6.7% of patients taking a higher-potency $P2Y_{12}$ inhibitor (P<0.0001).

Changes in $P2Y_{12}$ Inhibitor Therapy After Recurrent Ischemic Events

Overall, 353 patients (20.3%) changed $P2Y_{12}$ inhibitors at the time of their recurrent ischemic event (Figure 2). Among patients with MI, 178 (23.2%) changed; 116 patients (11.8%) with revascularization only changed, and 85 patients (51.5%) with stent thrombosis changed.

Of the 212 patients no longer taking a $P2Y_{12}$ inhibitor at the time of the recurrent ischemic events, 117 (55.2%) were reinitiated on a $P2Y_{12}$ inhibitor (74 [34.9%] started taking clopidogrel, and 42 [19.8%] started taking a higher-potency $P2Y_{12}$ inhibitor). Among the 436 patients taking prasugrel or ticagrelor at the time of the recurrent ischemic event, 13 (3.0%)

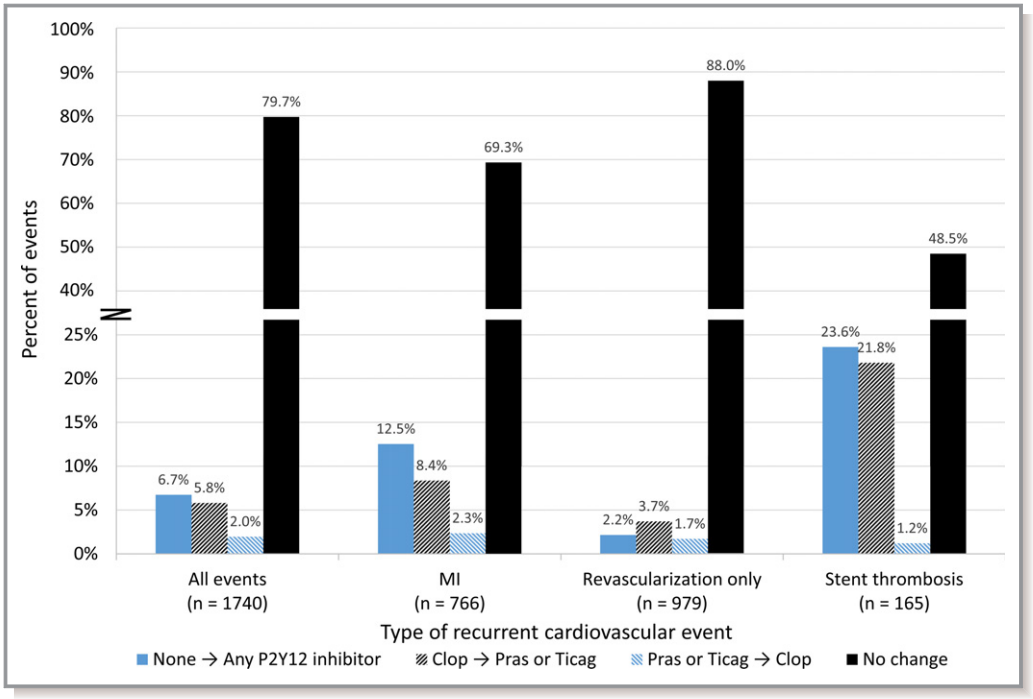

Figure 2. Percentage of patients with escalation and deescalation of antiplatelet therapy. Clop indicates clopidogrel; MI, myocardial infarction; Pras, prasugrel; and Ticag, ticagrelor.

switched to the other high-potency $P2Y_{12}$ inhibitor (10 after recurrent MI and 3 after unplanned revascularization without MI) and 34 (7.8%) switched to clopidogrel (18 after recurrent MI and 16 after unplanned revascularization without MI).

Of the 1092 patients taking clopidogrel or ticlopidine at the time of their event, 101 (9.3%) switched to a higher-potency $P2Y_{12}$ inhibitor, defined as $P2Y_{12}$ inhibitor intensification. Patients with MI were more likely to have $P2Y_{12}$ inhibitor intensification than those with revascularization only. Of 450 patients with a recurrent MI while taking clopidogrel, 65 (14.4%) were switched to prasugrel or ticagrelor; 36 of 637 patients (5.7%) were switched to a higher-potency $P2Y_{12}$ inhibitor after an unplanned revascularization event without MI ($P<0.001$). Among 175 patients who were taking clopidogrel at the time of a second or higher recurrent ischemic event, 20 (11.4%) had $P2Y_{12}$ inhibitor intensification.

$P2Y_{12}$ Inhibitor Intensification

Patients with $P2Y_{12}$ inhibitor intensification (n=101) at the time of their recurrent coronary ischemic event were younger than those without intensification (n=991) (57 versus 62 years; $P<0.001$). They less often had prior coronary artery bypass grafting, peripheral artery disease, multivessel coronary artery disease, and atrial fibrillation/flutter. Bleeding events between index and recurrent events were rare and did not differ significantly between those with and without intensification (Table 2). Patients with $P2Y_{12}$ inhibitor intensification had their recurrent events sooner after the index event than patients without intensification (83 versus 154 days; $P<0.001$), more often had MIs rather than revascularization alone (64.3 versus 39.3%; $P<0.001$), and more often had STEMI (33.7% versus 5.7%; $P<0.001$) and stent thrombosis (35.6% versus 5.6%; $P<0.001$).

On multivariable modeling, 4 patient features were significantly associated with intensification of antiplatelet therapy (Figure 3). Stent thrombosis was the strongest feature (odds ratio, 4.45; 95% confidence interval, 2.37–8.34), and presentation with MI rather than revascularization alone also had a positive association with $P2Y_{12}$ inhibitor intensification. Younger age and shorter duration from index MI event were also associated with a higher incidence of intensification (odds ratio, 1.12 per 1-month decrease in duration from index to recurrent event [95% confidence interval, 1.05–1.19]; odds ratio, 1.39 per 10-year decrease in age [95% confidence interval, 1.14–1.69]). Financial hardship of paying for medications, diabetes mellitus, and moderate/severe bleeding between the index MI and the time of the recurrent ischemic event each had no significant association with the likelihood of intensifying $P2Y_{12}$ inhibitor therapy. The C-statistic for the multivariable model was 0.77.

Although stent thrombosis was the strongest factor associated with $P2Y_{12}$ inhibitor intensification, only 36 of 91 patients (40%) with stent thrombosis while taking clopidogrel were switched to either prasugrel or ticagrelor. Of 90 patients with STEMI, 34 (37%) had $P2Y_{12}$ inhibitor intensification.

Table 2. Baseline Patient Characteristics by Intensification Status Among Patients Taking Clopidogrel or Ticlopidine at the Time of Follow-Up Event

Variable	Intensification (n=101)	No Intensification (n=991)	*P* Value
Demographics			
Age, y	57 (49–68)	62 (54–70)	<0.001
Male sex	63 (62.4)	673 (67.9)	0.26
White race	82 (81.2)	846 (85.4)	0.32
Health insurance			
Private	54 (53.5)	576 (58.1)	0.36
Medicare	38 (37.6)	463 (46.7)	0.08
Medicaid	12 (11.9)	104 (10.5)	0.67
None	12 (11.9)	121 (12.2)	0.91
Financial hardship of paying for medications	32 (33.7)	238 (25.8)	0.10
Married	57 (56.4)	592 (59.7)	0.56
High school graduate or beyond	86 (85.2)	817 (82.4)	0.39
Employed	48 (47.5)	347 (35.0)	0.01
Weight, kg	84 (74–102)	86 (75–102)	0.31
BMI, kg/m^2	29 (26–33)	29 (26–34)	0.75
GFR, mL/min	79 (60–95)	71 (55–90)	0.07
Medical history at the time of index event			
Prior CABG	10 (9.9)	240 (24.2)	0.001
Prior stroke or TIA	11 (10.9)	83 (8.4)	0.39
PAD	8 (7.9)	156 (15.8)	0.04
Prior heart failure	10 (9.9)	147 (14.8)	0.19
Atrial fibrillation/flutter	2 (2.0)	82 (8.3)	0.03
Diabetes mellitus	41 (40.6)	411 (41.5)	0.91
Smoker	43 (42.6)	330 (33.3)	0.06
Chronic lung disease	13 (12.9)	160 (16.2)	0.40
Features of index admission			
Multivessel disease	55 (54.5)	681 (68.7)	0.008
LVEF ≤40%	23 (26.7)	219 (25.3)	0.69
Culprit lesion location			0.12
Left main	0 (0)	10 (1.0)	
LAD	43 (42.6)	317 (32.0)	
LCX	23 (22.8)	272 (27.5)	
RCA	33 (32.7)	386 (39.0)	
Drug-eluting stent implanted	55 (54.5)	621 (62.7)	0.12
Platelet function testing performed	11 (10.9)	132 (13.3)	0.49
Discharge medications			
$P2Y_{12}$ inhibitor			
Clopidogrel	88 (87.1)	938 (94.7)	0.003
Prasugrel	10 (9.9)	41 (4.1)	0.009
Ticlopidine	0 (0)	8 (0.8)	0.37
Ticagrelor	1 (1.0)	3 (0.3)	0.28
None	2 (2.0)	1 (0.1)	<0.001
Anticoagulant	4 (4.0)	68 (6.9)	0.26
Bleeding between index and follow-up event			
Moderate-severe >30 d before	1 (1.0)	8 (0.8)	0.85
Moderate-severe ≤30 d before	1 (1.0)	33 (3.3)	0.20
Mild >30 d before	0 (0)	22 (2.2)	0.13
Mild ≤30 d before	0 (0)	30 (3.0)	0.08
Features of follow-up event			
Time to event, d	83 (9–178)	154 (57–285)	<0.001
Type of event			<0.001
MI with revascularization	52 (51.5)	201 (20.3)	
MI without revascularization	13 (12.9)	188 (19.0)	
Revascularization without MI	36 (35.7)	602 (60.8)	
MI type: STEMI	34 (33.6)	56 (5.6)	<0.001
Stent thrombosis	36 (35.6)	55 (5.6)	<0.001
Nonadherent to $P2Y_{12}$ inhibitor	8 (7.9)	54 (5.5)	0.31
Culprit vessel previously stented lesion	55 (62.5)	282 (35.1)	<0.001

Categorical variables are presented as frequency (percentage); continuous variables are presented as median (25th–75th percentile). Intensification defined as switch from clopidogrel to prasugrel or ticagrelor within 7 days after the recurrent event. BMI indicates body mass index; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; RCA, right coronary artery; STEMI, ST-segment–elevation MI; and TIA, transient ischemic attack.

Discussion

Within 1 year after MI treated with PCI, 11% of patients experienced a recurrent ischemic event; most occurred while the patient was still taking guideline-recommended $P2Y_{12}$ inhibitor therapy. Time from index to recurrent event and type of recurrent event were similar between patients taking lower- versus higher-potency $P2Y_{12}$ inhibitors. Among patients taking a lower-potency $P2Y_{12}$ inhibitor, only 9% intensified

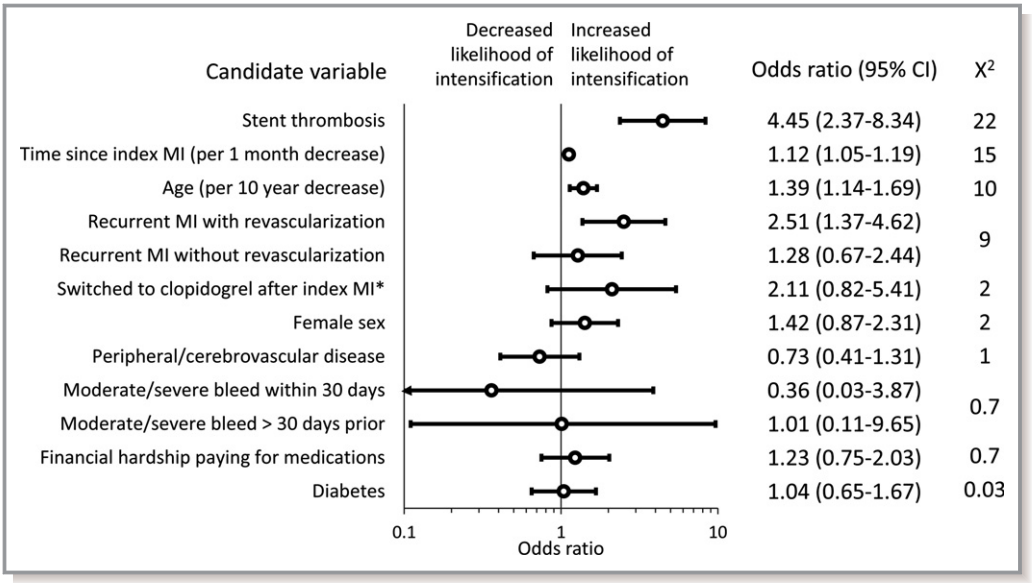

Figure 3. Multivariable model of antiplatelet intensification (defined as switching from clopidogrel to prasugrel or ticagrelor) for patients taking clopidogrel at the time of a recurrent vascular event. The asterisk indicates discharged on prasugrel after index myocardial infarction (MI), and switched to clopidogrel before follow-up event. CI indicates confidence interval.

to prasugrel or ticagrelor after their recurrent ischemic event. Switching between higher-potency $P2Y_{12}$ inhibitors (ticagrelor to prasugrel, or vice versa) was infrequent (3.0%). Recurrent MI (compared with revascularization without MI) and stent thrombosis were strongly associated with $P2Y_{12}$ inhibitor intensification; yet, only 40% of patients with stent thrombosis and 14% of patients with recurrent MI had $P2Y_{12}$ inhibitor intensification. Increasing age and longer time from the index MI were also associated with lower likelihood for intensification.

No prior study has evaluated the incidence and predictors of intensifying $P2Y_{12}$ inhibitor therapy in response to recurrent coronary ischemic events in patients with recent MI treated with PCI. A previous analysis examined switching from clopidogrel to a higher-potency $P2Y_{12}$ inhibitor during the index MI hospitalization; younger age, private health insurance, and presentation with STEMI were associated with intensification of $P2Y_{12}$ inhibitor therapy, whereas prior history of atrial fibrillation, stroke, peripheral artery disease, or heart failure were associated with clopidogrel continuation.[17] Patients switched to a higher-potency $P2Y_{12}$ inhibitor were more likely to have had a recurrent MI during their index hospitalization than patients continued on clopidogrel. In another TRANSLATE-ACS analysis, 7.6% of patients switched $P2Y_{12}$ inhibitors in the year after their ACS event; two thirds of these switches were from prasugrel or ticagrelor to clopidogrel, and many switches cited cost as the primary motivating factor.[18] Of patients switching from clopidogrel to a higher-potency $P2Y_{12}$ inhibitor, 18.5% had an ischemic event in the 7 days before the switch, including 5.6% with a stent thrombosis.

Younger age remained associated with $P2Y_{12}$ inhibitor intensification after a postdischarge recurrent ischemic event. The negative association between increasing age and $P2Y_{12}$ inhibitor intensification may reflect clinician wariness of bleeding with higher-potency $P2Y_{12}$ inhibitor use in older patients, as seen in the pivotal clinical trials evaluating these agents.[7] Bleeding risk is likely further exacerbated by extending antiplatelet treatment duration as a result of the recurrent ischemic event.[22,23] On-treatment recurrent MI events were strongly associated with $P2Y_{12}$ inhibitor intensification both during the index MI hospitalization and postdischarge, presumably reflecting clinicians' acceptance of the benefit of higher-potency platelet inhibition in patients with recurrent MI.[24] Surprisingly, shorter duration of time between the index and recurrent ischemic events was a predictor of $P2Y_{12}$ inhibitor intensification. Longer duration of antiplatelet treatment from index to the later recurrent event may indicate patients better able to persist with antiplatelet therapy without bleeding, which we had expected would increase the likelihood of $P2Y_{12}$ inhibitor intensification. However, clinicians may view a period of clinical stability after the index MI as a positive prognostic indicator. When the patient had a recurrent event soon after the prior event while taking a lower-potency $P2Y_{12}$ inhibitor, it may be interpreted as a sign of "treatment failure."

Although intensification of antiplatelet therapy appears to be more common with STEMI and stent thrombosis, it

remains infrequent. Less than 10% of patients with a recurrent ischemic event while taking clopidogrel switched to a higher-potency $P2Y_{12}$ inhibitor. Guideline updates in 2014 provided a class IIa recommendation for higher-potency $P2Y_{12}$ inhibitors in preference to clopidogrel,[1,25] but there is no direct evidence specific to patients with recurrent ischemic events while taking $P2Y_{12}$ inhibitor therapy. In routine clinical practice, physician decisions about antiplatelet therapy choice may be based on several factors unique to the individual patient, including predicted risk of recurrent events, predicted safety, and cost of treatment. Although patients with diabetes mellitus have been shown to benefit from higher-potency $P2Y_{12}$ inhibitor therapy,[26,27] diabetes mellitus was not a significant factor associated with $P2Y_{12}$ inhibitor intensification. Bleeding before the recurrent ischemic event was rare, and its rarity likely explains its lack of statistically significant association with $P2Y_{12}$ inhibitor intensification. The point estimate for the association between recent moderate/severe bleeding and $P2Y_{12}$ inhibitor intensification was 0.36, trending toward lower likelihood of $P2Y_{12}$ inhibitor intensification. There was a trend toward $P2Y_{12}$ inhibitor intensification among patients initially discharged on a higher-potency $P2Y_{12}$ inhibitor after their index event who switched to clopidogrel after discharge and then developed a recurrent ischemic event. It is perhaps reassuring that patient financial hardship paying for medications did not affect physician decision making in the setting of a recurrent ischemic event.

Although high on-clopidogrel platelet reactivity is prevalent and associated with a higher risk of recurrent ischemic events,[28–30] and several studies have shown that switching between $P2Y_{12}$ inhibitors is safe and effectively reduces platelet reactivity in patients with high on-clopidogrel platelet reactivity,[31] no randomized controlled trial has demonstrated that intensifying $P2Y_{12}$ inhibition reduces clinical end points in patients with high on-clopidogrel platelet reactivity.[12–16] Platelet function testing is infrequently performed in current practice,[15] and recurrent ischemic events while taking clopidogrel may not necessarily reflect inadequate platelet inhibition. The low rates of $P2Y_{12}$ inhibitor intensification observed, 37% of patients with STEMI and 40% of patients with stent thrombosis, underscore clinical inertia in the absence of data and guideline recommendations. A clinical trial that tests $P2Y_{12}$ inhibitor intensification for patients with recurrent ischemic events taking clopidogrel (≈10% of patients with ACS) may help clarify optimal management for this patient population and provide evidence to guide physician decision making.

Limitations

This is a secondary analysis of observational data and is subject to unmeasured confounding and selection bias. Because of the limited number of patients with $P2Y_{12}$ inhibitor intensification, the number of variables tested in the multivariable model was limited to prevent overfitting. Variables were chosen on the basis of clinical reasoning, but other variables not included in the model may be important to physician decision making. Furthermore, the results of platelet function testing may play a role in decisions about $P2Y_{12}$ inhibitor intensification; however, the TRANSLATE-ACS study did not collect data on platelet function testing at the time of recurrent ischemic events. There was no association between platelet function testing at the time of the index admission and $P2Y_{12}$ inhibitor intensification in response to recurrent events. Routine platelet function testing is not recommended by consensus guidelines and is rare in clinical practice, and physicians infrequently change antiplatelet therapy in response to its results.[1,3,32,33] Medication nonadherence may play a role in physician decision making and is often underestimated with patient self-reporting,[34] but it was reported in only 5% of patients with recurrent ischemic events in our study. Approximately 12% of patients were not taking a $P2Y_{12}$ inhibitor at the time of their recurrent event, even though guidelines recommend 1 year of $P2Y_{12}$ inhibitor therapy after MI. Adherence to guidelines is not perfect in clinical practice, and patients and physicians may have opted to stop $P2Y_{12}$ inhibitor therapy early for several reasons. Persistence with $P2Y_{12}$ inhibitor therapy in our cohort is in line with other published reports.[35–37] TRANSLATE-ACS study event adjudication did not differentiate between type I and type II recurrent MIs, which may also affect clinician decision making with respect to prescription of antiplatelet therapy. Nearly 45% of recurrent MIs in the TRANSLATE-ACS study were treated without revascularization, and physicians may be more likely to intensify $P2Y_{12}$ inhibitor therapy in patients with invasively managed MI. Our results may, therefore, underestimate the rate of $P2Y_{12}$ inhibitor intensification in response to a type I MI in clinical practice, although distinguishing between type I and II MIs is difficult in both the clinical and research setting. In addition, ticagrelor was released in the United States during the conduct of the TRANSLATE-ACS study, and was used infrequently by patients enrolled in the study; only 2.1% of patients in the TRANSLATE-ACS study were treated with ticagrelor at the time of their index event. Practice changes since the TRANSLATE-ACS study period show a small, but significant, increase in uptake of higher-potency $P2Y_{12}$ inhibitors in the United States, and these data may not fully reflect current practices; however, >50% of patients with ACS are still treated with clopidogrel in many contemporary US registries.[8,38,39] Last, because patients in the TRANSLATE-ACS study were only observed for 15 months after the index MI event, we are unable to report outcomes for patients with $P2Y_{12}$ inhibitor intensification in response to recurrent events compared with those without intensification.

Conclusion

Within 1 year after MI treated with PCI, 11% of patients experienced a recurrent ischemic event; most occurred while the patient was still taking guideline-recommended $P2Y_{12}$ inhibitor therapy. Among patients taking a lower-potency $P2Y_{12}$ inhibitor, few intensified to a higher-potency $P2Y_{12}$ inhibitor at the time of a recurrent ischemic event, even among those with STEMI or stent thrombosis. Physicians are more likely to intensify $P2Y_{12}$ inhibitor therapy in response to a recurrent MI or stent thrombosis and in patients of younger age or those who develop the recurrent ischemic event sooner after the index event. Whether intensification reduces further cardiovascular events in this high-risk population warrants further investigation to generate specific guideline recommendations.

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Supplemental Material

Data S1.

Variables evaluated for their association with antiplatelet intensification

Variables collected at the time of the index event: age, sex, financial hardship of paying for medications, prior stroke/TIA or prior peripheral arterial disease, diabetes

Variables related to the follow-up event: Type of event (MI with revascularization, MI without revascularization, revascularization without MI), stent thrombosis, time from index discharge to recurrent event, bleeding event between index discharge and follow-up event