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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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

Alexander C. Fanaroff, MD; Lisa A. Kaltenbach, MS; Eric D. Peterson, MD, MPH; Mohammed W. Akhter, MD; Mark B. Effron, MD; Timothy D. Henry, MD; Tracy Y. Wang, MD, MHS, MSc

Background—Guidelines recommend P2Y12 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 P2Y12 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 P2Y12 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 P2Y12 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 P2Y12 inhibitor intensification. Recurrent events involving stent thrombosis or MI were the strongest factors associated with P2Y12 inhibitor intensification, yet only 40% of patients with stent thrombosis and 14% of patients with recurrent MI had P2Y12 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 P2Y12 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 P2Y12 inhibitor therapy in combination with aspirin after acute coronary syndrome (ACS).\(^1\)\(^-\)\(^4\) Compared with clopidogrel, the higher-potency P2Y12 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...
Antiplatelet Switching After Recurrent Events

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reported.19 Brie

The design of the TRANSLATE-ACS study has been previously

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 man-
gagement 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 P2Y12 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 med-
ication 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
P2Y12 inhibitor (clopidogrel, prasugrel, ticlopidine, or tica-
grelor), 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 hospi-
talizations 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 P2Y12 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 labo-
ratory, and stent thrombosis was validated using Academic
Research Consortium criteria.21 For each event, data were

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 P2Y12 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 P2Y12 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.
abstracted regarding P2Y12 inhibitor therapy use at the time of readmission and at discharge.

The primary outcome of our analysis was P2Y12 inhibitor intensification in response to MI or revascularization, which we defined as a switch from a lower-potency P2Y12 inhibitor (either clopidogrel or ticlopidine, because some patients discharged with another agent were switched to ticlopidine during follow-up) to a higher-potency P2Y12 inhibitor (either prasugrel or ticagrelor). A switch occurred when the admission and discharge P2Y12 inhibitors for the hospitalization involving the recurrent coronary ischemic event were different. Patients who were not taking a P2Y12 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 P2Y12 inhibitors up to the time of their event. Increasing clopidogrel dosage to 150 mg/d was also not considered P2Y12 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 P2Y12 inhibitor therapy at the time of their recurrent coronary ischemic event, and then according to whether they had P2Y12 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 χ² 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 P2Y12 inhibitor intensification.

To identify factors associated with P2Y12 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

P2Y12 Inhibitor Use at Time of Recurrent Ischemic Events

Among 12 279 patients with MI who were treated with PCI and discharged alive on a P2Y12 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 P2Y12 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 P2Y12 inhibitor at the time of the recurrent event.
Table 1. Baseline Patient Characteristics by P2Y12 Inhibitor at the Time of the Recurrent Ischemic Event

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N=1740)</th>
<th>Clopidogrel/Ticlopidine (n=1092)</th>
<th>None (n=212)</th>
<th>Prasugrel/Ticagrelor (n=436)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (52–69)</td>
<td>61 (53–70)</td>
<td>61 (51–69)</td>
<td>57 (50–65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1168 (67.1)</td>
<td>736 (67.4)</td>
<td>133 (62.7)</td>
<td>299 (68.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>White race</td>
<td>1472 (84.6)</td>
<td>928 (85.0)</td>
<td>165 (77.8)</td>
<td>379 (86.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>1000 (57.5)</td>
<td>630 (57.7)</td>
<td>93 (43.9)</td>
<td>277 (63.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicare</td>
<td>731 (42.0)</td>
<td>501 (45.9)</td>
<td>98 (46.2)</td>
<td>132 (30.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid</td>
<td>184 (10.6)</td>
<td>116 (10.6)</td>
<td>29 (13.7)</td>
<td>39 (8.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>None</td>
<td>234 (13.5)</td>
<td>133 (12.2)</td>
<td>43 (20.3)</td>
<td>58 (13.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Financial hardship of paying for medications</td>
<td>429 (26.8)</td>
<td>270 (26.6)</td>
<td>62 (33.9)</td>
<td>97 (24.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Married</td>
<td>1027 (59.0)</td>
<td>649 (59.4)</td>
<td>92 (43.4)</td>
<td>286 (65.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school graduate or beyond</td>
<td>1449 (83.3)</td>
<td>903 (82.7)</td>
<td>166 (78.3)</td>
<td>380 (87.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Employed</td>
<td>689 (39.6)</td>
<td>395 (36.2)</td>
<td>61 (28.8)</td>
<td>233 (53.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history at the time of index event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td>348 (20.0)</td>
<td>250 (22.9)</td>
<td>30 (14.2)</td>
<td>68 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>132 (7.6)</td>
<td>94 (8.6)</td>
<td>28 (13.2)</td>
<td>10 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD</td>
<td>233 (13.4)</td>
<td>164 (15.0)</td>
<td>35 (16.5)</td>
<td>34 (7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>230 (13.2)</td>
<td>157 (14.4)</td>
<td>33 (15.6)</td>
<td>40 (9.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>124 (7.1)</td>
<td>84 (7.7)</td>
<td>18 (8.5)</td>
<td>22 (5.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>725 (41.7)</td>
<td>452 (41.4)</td>
<td>90 (42.5)</td>
<td>183 (42.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>249 (14.3)</td>
<td>173 (15.8)</td>
<td>32 (15.1)</td>
<td>44 (10.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Features of index admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>791 (45.5)</td>
<td>448 (41.0)</td>
<td>112 (52.8)</td>
<td>231 (53.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1151 (66.2)</td>
<td>736 (67.4)</td>
<td>132 (62.3)</td>
<td>283 (64.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Platelet function testing performed</td>
<td>246 (14.1)</td>
<td>143 (13.1)</td>
<td>28 (13.2)</td>
<td>75 (17.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>387 (25.2)</td>
<td>242 (25.4)</td>
<td>47 (25.4)</td>
<td>98 (24.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (26–34)</td>
<td>29 (26–34)</td>
<td>29 (26–33)</td>
<td>30 (27–34)</td>
<td>0.13</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>73 (57–91)</td>
<td>71 (55–91)</td>
<td>74 (51–92)</td>
<td>77 (60–93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelet function testing performed</td>
<td>246 (14.1)</td>
<td>28 (13.2)</td>
<td>143 (13.1)</td>
<td>75 (17.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Features of index PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>22 (1.3)</td>
<td>10 (0.9)</td>
<td>4 (1.9)</td>
<td>8 (1.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>LAD</td>
<td>578 (33.2)</td>
<td>360 (33.0)</td>
<td>74 (34.9)</td>
<td>144 (33.0)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>429 (24.7)</td>
<td>295 (27.1)</td>
<td>47 (22.2)</td>
<td>87 (20.0)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>695 (40.0)</td>
<td>419 (38.4)</td>
<td>84 (39.6)</td>
<td>192 (44.0)</td>
<td></td>
</tr>
<tr>
<td>Lesion involved stent thrombosis</td>
<td>80 (4.6)</td>
<td>35 (3.2)</td>
<td>15 (7.1)</td>
<td>30 (6.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lesion involved vein graft</td>
<td>174 (10.0)</td>
<td>137 (12.6)</td>
<td>9 (4.3)</td>
<td>28 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-eluting stent implanted</td>
<td>1097 (63.1)</td>
<td>676 (61.9)</td>
<td>104 (49.1)</td>
<td>317 (72.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continued

DOI: 10.1161/JAHA.117.007982

Journal of the American Heart Association
Compared with patients no longer taking a P2Y12 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 P2Y12 inhibitor. In patients with recurrent ischemic events after P2Y12 inhibitor discontinuation, these events occurred at a median of 92 days (25th–75th percentiles, 37–191 days) after P2Y12 inhibitor discontinuation.

Compared with patients taking a higher-potency P2Y12 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 P2Y12 inhibitor and then switched to clopidogrel; the recurrent ischemic event occurred at a median of 218 days (25th–75th percentile, 131–301 days) after P2Y12 inhibitor switching. Time from index to recurrent event and type of recurrent event were similar between patients still taking lower-versus higher-potency P2Y12 inhibitors. Stent thrombosis was observed in 21.8% of patients no longer taking a P2Y12 inhibitor, 8.3% of patients taking clopidogrel or ticlopidine, and 6.7% of patients taking a higher-potency P2Y12 inhibitor (*P* < 0.0001).

### Changes in P2Y12 Inhibitor Therapy After Recurrent Ischemic Events

Overall, 353 patients (20.3%) changed P2Y12 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 P2Y12 inhibitor at the time of the recurrent ischemic event, 117 (55.2%) were reinitiated on a P2Y12 inhibitor (74 [34.9%] started taking clopidogrel, and 42 [19.8%] started taking a higher-potency P2Y12 inhibitor). Among the 436 patients taking prasugrel or ticagrelor at the time of the recurrent ischemic event, 13 (3.0%)...
switched to the other high-potency P2Y₁₂ 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 P2Y₁₂ inhibitor, defined as P2Y₁₂ inhibitor intensification.

Patients with MI were more likely to have P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ inhibitor intensification.

P2Y₁₂ Inhibitor Intensification

Patients with P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ inhibitor therapy. The C-statistic for the multivariable model was 0.77.

Although stent thrombosis was the strongest factor associated with P2Y₁₂ 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 P2Y₁₂ inhibitor intensification.
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 P2Y₁₂ inhibitor therapy. Time from index to recurrent event and type of recurrent event were similar between patients taking lower-versus higher-potency P2Y₁₂ inhibitors. Among patients taking a lower-potency P2Y₁₂ inhibitor, only 9% intensified

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensification (n=101)</th>
<th>No Intensification (n=991)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>57 (49–68)</td>
<td>62 (54–70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>63 (62.4)</td>
<td>673 (67.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>White race</td>
<td>82 (81.2)</td>
<td>846 (85.4)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Health insurance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>54 (53.5)</td>
<td>576 (58.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Medicare</td>
<td>38 (37.6)</td>
<td>463 (46.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Medicaid</td>
<td>12 (11.9)</td>
<td>104 (10.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>None</td>
<td>12 (11.9)</td>
<td>121 (12.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Financial hardship of paying for medications</td>
<td>32 (33.7)</td>
<td>238 (25.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Married</td>
<td>57 (56.4)</td>
<td>592 (59.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>High school graduate or beyond</td>
<td>86 (85.2)</td>
<td>817 (82.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Employed</td>
<td>48 (47.5)</td>
<td>347 (35.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84 (74–102)</td>
<td>86 (75–102)</td>
<td>0.31</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (26–33)</td>
<td>29 (26–34)</td>
<td>0.75</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>79 (60–95)</td>
<td>71 (55–90)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Medical history at the time of index event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CAGB</td>
<td>10 (9.9)</td>
<td>240 (24.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>11 (10.9)</td>
<td>83 (8.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>PAD</td>
<td>8 (7.9)</td>
<td>156 (15.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>10 (9.9)</td>
<td>147 (14.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2 (2.0)</td>
<td>82 (8.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (40.6)</td>
<td>411 (41.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoker</td>
<td>43 (42.6)</td>
<td>330 (33.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>13 (12.9)</td>
<td>160 (16.2)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Features of index admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>55 (54.5)</td>
<td>681 (68.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>23 (26.7)</td>
<td>219 (25.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Culprit lesion location</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Left main</td>
<td>0 (0)</td>
<td>10 (1.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>LAD</td>
<td>43 (42.6)</td>
<td>317 (32.0)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>23 (22.8)</td>
<td>272 (27.5)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>33 (32.7)</td>
<td>386 (39.0)</td>
<td></td>
</tr>
<tr>
<td>Drug-eluting stent implanted</td>
<td>55 (54.5)</td>
<td>621 (62.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Platelet function testing performed</td>
<td>11 (10.9)</td>
<td>132 (13.3)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Features of follow-up event

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensification (n=101)</th>
<th>No Intensification (n=991)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2Y₁₂ inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>88 (87.1)</td>
<td>938 (94.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>10 (9.9)</td>
<td>41 (4.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>0 (0)</td>
<td>8 (0.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1 (1.0)</td>
<td>3 (0.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>None</td>
<td>2 (2.0)</td>
<td>1 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Anticoagulant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (4.0)</td>
<td>68 (6.9)</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

Bleeding between index and follow-up event

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensification (n=101)</th>
<th>No Intensification (n=991)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-severe &gt;30 d before</td>
<td>1 (1.0)</td>
<td>8 (0.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Moderate-severe ≤30 d before</td>
<td>1 (1.0)</td>
<td>33 (3.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mild &gt;30 d before</td>
<td>0 (0)</td>
<td>22 (2.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Mild ≤30 d before</td>
<td>0 (0)</td>
<td>30 (3.0)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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 P2Y₁₂ inhibitor therapy. Time from index to recurrent event and type of recurrent event were similar between patients taking lower-versus higher-potency P2Y₁₂ inhibitors. Among patients taking a lower-potency P2Y₁₂ inhibitor, only 9% intensified
to prasugrel or ticagrelor after their recurrent ischemic event. Switching between higher-potency P2Y12 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 P2Y12 inhibitor intensification; yet, only 40% of patients with stent thrombosis and 14% of patients with recurrent MI had P2Y12 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 P2Y12 inhibitor therapy in response to recurrent vascular events in patients with recent MI treated with PCI. A previous analysis examined switching from clopidogrel to a higher-potency P2Y12 inhibitor during the index MI hospitalization; younger age, private health insurance, and presentation with STEMI were associated with intensification of P2Y12 inhibitor therapy, whereas prior history of atrial fibrillation, stroke, peripheral artery disease, or heart failure were associated with clopidogrel continuation. Patients switched to a higher-potency P2Y12 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 P2Y12 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. Of patients switching from clopidogrel to a higher-potency P2Y12 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 P2Y12 inhibitor intensification after a postdischarge recurrent ischemic event. The negative association between increasing age and P2Y12 inhibitor intensification may reflect clinician wariness of bleeding with higher-potency P2Y12 inhibitor use in older patients, as seen in the pivotal clinical trials evaluating these agents.7 Bleeding risk is likely further exacerbated by extending antplatelet treatment duration as a result of the recurrent ischemic event.22,23 On-treatment recurrent MI events were strongly associated with P2Y12 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 P2Y12 inhibitor intensification. Longer duration of antplatelet treatment from index to the later recurrent event may indicate patients better able to persist with antplatelet therapy without bleeding, which we had expected would increase the likelihood of P2Y12 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 P2Y12 inhibitor, it may be interpreted as a sign of “treatment failure.”

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

Figure 3. Multivariable model of antplatelet 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.
remains infrequent. Less than 10% of patients with a recurrent ischemic event while taking clopidogrel switched to a higher-potency P2Y₁₂ inhibitor. Guideline updates in 2014 provided a class IIa recommendation for higher-potency P2Y₁₂ inhibitors in preference to clopidogrel, but there is no direct evidence specific to patients with recurrent ischemic events while taking P2Y₁₂ 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 P2Y₁₂ inhibitor therapy, diabetes mellitus was not a significant factor associated with P2Y₁₂ inhibitor intensification. Bleeding before the recurrent ischemic event was rare, and its rarity likely explains its lack of statistically significant association with P2Y₁₂ inhibitor intensification. The point estimate for the association between recent moderate/severe bleeding and P2Y₁₂ inhibitor intensification was 0.36, trending toward lower likelihood of P2Y₁₂ inhibitor intensification. There was a trend toward P2Y₁₂ inhibitor intensification among patients initially discharged on a higher-potency P2Y₁₂ 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, and several studies have shown that switching between P2Y₁₂ inhibitors is safe and effectively reduces platelet reactivity in patients with high on-clopidogrel platelet reactivity, no randomized controlled trial has demonstrated that intensifying P2Y₁₂ inhibition reduces clinical end points in patients with high on-clopidogrel platelet reactivity. Platelet function testing is infrequently performed in current practice, and recurrent ischemic events while taking clopidogrel may not necessarily reflect inadequate platelet inhibition. The low rates of P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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. Medication nonadherence may play a role in physician decision making and is often underestimated with patient self-reporting, but it was reported in only 5% of patients with recurrent ischemic events in our study. Approximately 12% of patients were not taking a P2Y₁₂ inhibitor at the time of their recurrent event, even though guidelines recommend 1 year of P2Y₁₂ inhibitor therapy after MI. Adherence to guidelines is not perfect in clinical practice, and patients and physicians may have opted to stop P2Y₁₂ inhibitor therapy early for several reasons. Persistence with P2Y₁₂ inhibitor therapy in our cohort is in line with other published reports. TRANSLATE-ACS study event adjudication did not differentiate between type I and type II recurrent MIs, which may 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 P2Y₁₂ inhibitor therapy in patients with invasively managed MI. Our results may, therefore, underestimate the rate of P2Y₁₂ 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 P2Y₁₂ 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. 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 P2Y₁₂ 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 P2Y12 inhibitor therapy. Among patients taking a lower-potency P2Y12 inhibitor, few intensified to a higher-potency P2Y12 inhibitor at the time of a recurrent ischemic event, even among those with STEMI or stent thrombosis. Physicians are more likely to intensify P2Y12 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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Disclosures
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References


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receptor inhibitor after hospital discharge among myocardial infarction patients: insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study. Am Heart J. 2017;183:62–68.


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
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
Alexander C. Fanaroff, Lisa A. Kaltenbach, Eric D. Peterson, Mohammed W. Akhter, Mark B. Effron, Timothy D. Henry and Tracy Y. Wang

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