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 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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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 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 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 laboratory, 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.

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 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 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...
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 $\chi^2$ 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 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 P2Y<sub>12</sub> 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<sup>2</sup>                | 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
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, 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 events, 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.
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 coronary ischemic 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.¹⁷ 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.¹⁸ 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 antiplatelet 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 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 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 antiplatelet therapy appears to be more common with STEMI and stent thrombosis, it

![Figure 3](https://example.com/figure3.png)
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,12,25 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 high-potency P2Y12 inhibitor therapy,26,27 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,28–30 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,31 no randomized controlled trial has demonstrated that intensifying P2Y12 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 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.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 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.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 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.6,38,39 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 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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References
1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Makhary HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2012;127:e261–e426.
2. O’Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, Ettinger SM, Fang JC, Faxon DP, Franklin BA, Granger CB, Granger-Kobatz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of STElevation myocardial infarction. Circulation. 2012;127:e261–e426.
3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigi M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016;37:267–315.
4. Ibanez B, James SK, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Creai F, Cuzdevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lemoine ML, Prescott E, Roffi M, Valgimigi M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;39:119–177.
5. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Mayo J, Husted S, Steg PG, Cornel JH, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J. 2014;35:2083–2093.
6. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Stieg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–1057.
7. Vividost BD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gofftlib S, Neumann FJ, Ardissino D, Defierv S, Murphy SA, Riesmeyer J, Weraakody G, Gibson CM. A patient EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–2015.
8. Kim K, Lee TA, Touchette DR, DiDomenico RJ, Ardati AK, Walton SM. Contemporary trends in oral antplatelet agent use in patients treated with percutaneous coronary intervention for acute coronary syndrome. J Manag Care Pharm. 2017;23:57–63.
9. Gurbel PA, Bldin KP, Buer K, Antonini MJ, Wei C, Teng R, Rasmussen L, Storey RF, Nielsen T, Eikelboom JWW. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies. Circulation. 2010;121:1188–1199.
10. Alexopoulos D, Dimitropoulos G, Davlouros P, Xanthopoulou I, Kassimis G, Stavrou HA, Hahalis G, Athanasiadou A. Prasugrel achieves higher on high-potency compared with low-potency clopidogrel. JACC Cardiovasc Interv. 2011;4:403–410.
11. Alexopoulos D, Xanthopoulou I, Davlouros P, Plakomtis T-E, Panagioutou A, Mavronasiou E, Hahalis G. Prasugrel achieves higher on high-potency platelet reactivity in chronic coronary artery disease patients more effectively than high-dose (150-mg) clopidogrel. JACC Cardiovasc Interv. 2011;4:403–410.
12. Collet JP, Cuisset T, Rangé G, Gayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z. Bedside monitoring to adjust antithrombotic therapy for coronary stenting. N Engl J Med. 2012;367:2100–2109.
13. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Muller U, Richard G, Jakubowski JA, Neumann FJ. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Strategy With Prasugrel) study. J Am Coll Cardiol. 2012;59:2159–2164.
14. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Standard vs high-dose clopidogrel as a basis for platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. J Am Med Assoc. 2011;305:1097–1105.
15. Wang TY, Henry TD, Effron MB, Honeycutt E, Hess CN, Zettler ME, Cohen DJ, Baker BA, Berger PB, Anastrom KJ. Cluster-randomized clinical trial examining the impact of platelet function testing on patient treatment with adenosine diphosphate receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome prospective open-label antithrombotic therapy study. Circ Cardiovasc Interv. 2015;8:e001712.
16. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delacrene N, Bellemain-Apaxa A, Range G, El Mahmoud R. Platelet function monitoring to adjust antithrombotic therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388:2015–2022.
17. Bagai A, Wang Y, Wang TY, Curtis JP, Gurum HS, Shah B, Cheema AN, Peterson ED, Saucedo F, Granger CB. In-hospital switching between prasugrel and clopidogrel among patients with acute myocardial infarction treated with percutaneous coronary intervention insights into contemporary practice from the national cardiovascular data registry. Circ Cardiovasc Interv. 2014;7:585–593.
18. Zettler ME, Peterson ED, McCoy LA, Effron MB, Anastrom KJ, Henry TD, Baker BA, Messinger JC, Cohen DJ, Wang TY. Switching of adenosine diphosphate

doi:10.1161/JAHA.117.007982
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.

19. Chin CT, Wang TY, Anstrom KJ, Zhu B, Maaf JJ, Messenger JC, Ryan KA, Davidson-Ray L, Zettler M, Effron MB, Mark DB, Peterson ED. Treatment with adenosine diphosphate receptor inhibitors-longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study design: expanding the paradigm of longitudinal observational research. Am Heart J. 2011;162:844–851.

20. Thygessen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Liborio B, Morrow DA, Clemenensen PM, Johnson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atr A, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nijemine MS, Gheorghiadie M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Thistle R, Lopez-Sendón JL, Robertson WM, Weisberg D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction: insights into the TReatment with ADP receptor iNhibitorS: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) study. Circulation. 2012;126:2020–2035.

21. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344–2351.

22. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Therox P, Ruda M, Ham H, Got D, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791–1800.

23. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes JR, Krucoff MW, Hermiller J, Dauerman H, Simon DJ, Kandzari DE, Geratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371:2155–2166.

24. Kohli P, Wallentin L, Reyes E, Horow J, Husted S, Angiolillo DJ, Ardissino D, Maurer G, Moraja M, Nicolau JC. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO Study. Circulation. 2013;127:257–265.

25. Windecker S, Koh P, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jun P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Lauffer G, Neumann F, Richter DJ, Schauerte P, Sousa U, Stefanini GG, Taggart DP, Torracca L, Vargimigli M, Wijns W, Witkowska A. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014;35:2541–2619.

26. James S, Angiolillo DJ, Cornel JH, Erling J, Husted S, Kontny F, Maya Y, Nicolau JC, Spinar J, Storey RF. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010;31:3006–3016.

27. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby JJ, Verheugt FW, Goodman SG, Corbalan R, Purdy DA, Murphy SA. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation. 2008;118:1626–1636.

28. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–362.

29. Aradi D, Storey RF, Komacić A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet J-P. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur Heart J. 2014;35:215–219.

30. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferrri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicenter registry study. J Am Coll Cardiol. 2013;62:614–624.

31. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. Nat Rev Cardiol. 2016;13:11.

32. Wang TY, Henry TD, McCoy LA, Berger PB, Cohen DJ, Effron MB, Zettler M, Baker BA, Messenger JC, Peterson ED. Contemporary use of platelet function and pharmacogenomic testing among patients with acute myocardial infarction undergoing percutaneous coronary intervention in the United States. Am Heart J. 2015;170:706–714.

33. Bagai A, Peterson ED, McCoy LA, Effron MB, Zettler ME, Stone GW, Henry TD, Cohen DJ, Schulte PJ, Anstrom KJ. Association of measured platelet reactivity with changes in P2Y12 receptor inhibitor therapy and outcomes after myocardial infarction: insights into routine clinical practice from the TReatment with ADP receptor iNhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) study. Am Heart J. 2017;187:19–28.

34. Garber MG, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Med Care. 2004;42:649–652.

35. Green A, Pottégard A, Broe A, Dines D, Emmeus M, Hasvold P, Gislason GH. Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction: a Danish nationwide population-based cohort study. BMJ Open. 2016;6:e010860.

36. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet. 2013;382:1714–1722.

37. Fosbl EL, Ju C, Anstrom KJ, Zettler ME, Messinger JC, Waksman R, Effron MB, Baker BA, Cohen DJ, Peterson ED. Early cessation of adenosine diphosphate receptor inhibitors among acute myocardial infarction patients treated with percutaneous coronary intervention. Circ Cardiovasc Interv. 2016;9:e003402.

38. Basra SS, Wang TY, Simon DN, Chiswell K, Virani SS, Alam M, Nambi V, Denktas AE, Deswal A, Ballantyne CM. Contemporary patterns of use of antiplatelet agents in patients with acute myocardial infarction: insights from the national cardiovascular data registry (NCDR). Circ Cardiovasc Qual Outcomes. 2016;9:A138.

39. Kim K, Lee TA, Ardati AK, D’Iendrio RJ, Touchette DR, Walton SM. Comparative effectiveness of oral antiplatelet agents in patients with acute coronary syndrome. Pharmacotherapy. 2017;37:877–887.

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11
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
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