Time-Varying Effects of Prasugrel Versus Clopidogrel on the Long-Term Risks of Stroke After Acute Coronary Syndromes

Results From the TRILOGY ACS Trial

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Background and Purpose—The role of more intense, sustained platelet inhibition in preventing stroke after acute coronary syndrome (ACS) is unclear. We observed a signal for reduced stroke risk in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial after 12 months of treatment with prasugrel versus clopidogrel in medically managed patients with ACS.

Methods—We examined 7243 patients with ACS, aged <75 years and without prior stroke, analyzing differences in baseline characteristics between patients with and without a stroke event through 30 months with a Cox proportional hazards model. We also assessed the effect of prasugrel versus clopidogrel (plus aspirin) on risk of all stroke events and ischemic stroke over time with an extended Cox proportional hazards model.

Results—Stroke events were infrequent through 30 months (ischemic stroke=62; hemorrhagic stroke=15). Patients with stroke were older, had more comorbidities, and had a higher Global Registry of Acute Coronary Events (GRACE) risk score. There was a trend for a lower unadjusted frequency of all stroke events through 30 months for prasugrel versus clopidogrel: 31 (1.5%) versus 46 (2.2%); P=0.08. There was a significant treatment-by-time interaction for those with ischemic stroke (P=0.03), consistent with the 12-month landmarked Kaplan–Meier log-rank test showing a reduced hazard of ischemic stroke after 12 months with prasugrel (P=0.04). No significant interactions between treatment effect of prasugrel versus clopidogrel and time were observed for all stroke events.

Conclusions—We observed a potential late treatment effect for prasugrel versus clopidogrel for a reduced risk of ischemic stroke in medically managed patients with ACS aged <75 years. These hypothesis-generating findings suggest that longer duration and more potent platelet inhibition with prasugrel may be associated with lower risk of ischemic stroke after 12 months.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00699998.

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Key Words: acute coronary syndrome ■ adenosine diphosphate ■ clopidogrel ■ prasugrel ■ stroke
Methods

Study Design and Procedures

TRILOGY ACS enrolled patients from >950 international sites. The trial eligibility criteria, design, and primary results have been reported.\(^2\)\(^3\) TRILOGY ACS was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Patients with prior stroke or transient ischemic attack and already taking or about to start chronic oral anticoagulation were

<table>
<thead>
<tr>
<th>Table. Baseline Patient Characteristics by Stroke Versus No Stroke</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td><strong>Age, y</strong> 65.0 (61.0–69.0) 62.0 (66.0–68.0) 1.05 (1.02–1.08) 0.003</td>
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<tr>
<td><strong>Female sex, %</strong> 29.9 36.0 1.43 (0.91–2.24) 0.12</td>
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<tr>
<td><strong>White race, %</strong> 61.0 65.4 0.81 (0.51–1.28) 0.37</td>
</tr>
<tr>
<td><strong>Weight, kg</strong> 75.1 (65.0–84.0) 77.0 (65.8–89.0) 1.00 (0.98–1.01) 0.60</td>
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<tr>
<td><strong>Presentation</strong></td>
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<tr>
<td><strong>NSTEMI, %</strong> 81.6% 67.2% 2.87 (1.52–5.44) 0.001</td>
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<tr>
<td><strong>Medical history</strong></td>
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<tr>
<td><strong>Family history of CAD</strong> 32.4 31.8 0.99 (0.59–1.64) 0.96</td>
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<td><strong>Hypertension</strong> 90.9 80.3 2.46 (1.13–5.35) 0.02</td>
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<tr>
<td><strong>Hyperlipidemia</strong> 69.9 58.8 1.52 (0.92–2.51) 0.10</td>
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<td><strong>Diabetes mellitus</strong> 55.8 38.7 2.03 (1.30–3.19) 0.002</td>
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<td><strong>Current/recent smoking</strong> 20.8 21.8 0.96 (0.55–1.67) 0.89</td>
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<tr>
<td><strong>Prior peptic ulcer disease</strong> 3.9 5.4 0.76 (0.24–2.40) 0.64</td>
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<tr>
<td><strong>Prior MI</strong> 48.1 44.0 1.15 (0.74–1.80) 0.53</td>
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<tr>
<td><strong>Prior PCI</strong> 23.7 28.1 0.78 (0.46–1.32) 0.35</td>
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<tr>
<td><strong>Prior CABG</strong> 19.5 15.4 1.31 (0.74–2.30) 0.35</td>
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<tr>
<td><strong>Prior PAD</strong> 8.0 6.6 1.21 (0.53–2.80) 0.65</td>
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<tr>
<td><strong>Prior AF</strong> 13.2 6.0 2.43 (1.25–4.73) 0.009</td>
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<tr>
<td><strong>Prior chronic heart failure</strong> 20.8 17.1 1.37 (0.79–2.37) 0.27</td>
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<tr>
<td><em><em>Baseline laboratories, measurements,</em> procedures</em>*</td>
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<tr>
<td><strong>GRACE risk score</strong> 122.0 (74.0–188.0) 114.0 (41.0–196.0) 1.02 (1.01–1.03) 0.0001</td>
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<tr>
<td><strong>Creatinine, g/dL</strong> 1.1 (0.9–1.4) 1.0 (0.8–1.2) 1.28 (1.03–1.59) 0.03</td>
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<tr>
<td><strong>Creatinine clearance, mL/min</strong> 66.1 (49.8–98.8) 80.8 (62.7–103.0) 0.99 (0.98–0.99) 0.0007</td>
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<tr>
<td><strong>Systolic BP, mmHg</strong> 130.0 (119.0–140.0) 128.0 (119.0–138.0) 1.01 (1.00–1.03) 0.03</td>
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<tr>
<td><strong>Heart rate, bpm</strong> 65.0 (60.0–78.0) 70.0 (62.0–76.0) 0.99 (0.97–1.02) 0.62</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/dL</strong> 13.4 (12.5–14.6) 13.8 (12.7–14.9) 0.89 (0.78–1.03) 0.12</td>
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<tr>
<td><strong>Angiography performed before randomization, %</strong> 39.0 42.6 0.84 (0.53–1.33) 0.47</td>
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<td><strong>Concomitant medications at randomization</strong></td>
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<td><strong>Aspirin, daily dose, mg</strong></td>
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<td><strong>&lt;100</strong> 29.9 34.1 0.83 (0.51–1.35) 0.44</td>
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<td><strong>100–250</strong> 53.2 52.2 1.04 (0.66–1.62) 0.87</td>
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<tr>
<td><strong>&gt;250</strong> 6.5 7.6 0.83 (0.33–2.04) 0.68</td>
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<td><strong>Beta-blocker</strong> 74.0 77.9 0.77 (0.46–1.28) 0.31</td>
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<td><strong>ACE-I/ARB</strong> 77.9 75.0 1.18 (0.69–2.02) 0.55</td>
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<td><strong>Statin</strong> 83.1 83.9 0.92 (0.51–1.67) 0.78</td>
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<tr>
<td><strong>Proton-pump inhibitor</strong> 22.1 23.0 0.96 (0.56–1.64) 0.87</td>
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ACE-I indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CAD, cerebrovascular disease; CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

*Continuous variables expressed as medians (25th, 75th percentiles).
excluded. Eligible patients were randomized to receive clopidogrel (75 mg/d) or prasugrel (10 mg/d for those aged <75 years; 5 mg/d for those with body weight <60 kg or aged ≥75 years), plus low-dose aspirin, for 6 to 30 months. All patients requiring oral anticoagulation after trial inclusion had study drug discontinued but were followed-up in the study and had end points collected and adjudicated. Median treatment and follow-up durations were 15 and 17 months, respectively.

All end points were independently adjudicated. Study treatment was discontinued permanently once a patient had a stroke event.

### Statistical Analysis

In this prespecified analysis, we examined the primary efficacy population (7243 patients with ACS aged <75 years) and compared baseline demographics between patients with and without stroke through 30 months. Differences in baseline characteristics were analyzed with a Cox proportional hazards model.

Using Kaplan–Meier curves, we examined the risk of stroke (all strokes and ischemic strokes only) by treatment over time. We used a global test (an extended Cox proportional hazards model and a standardized score process test) to determine whether there was evidence of a randomized treatment time-varying effect on all stroke events and ischemic stroke. Then, using landmark analyses at 3 and 12 months, we tested for differences in survival functions at 3 and 12 months postbaseline. The 3-month landmark was chosen as previous studies indicated events rates were highest during the first 3 months after an ACS event; thus, excluding these events would provide a measure of the long-term risk of events and any potential treatment effect.4,5 We performed the second landmark analysis at 12 months because of the signal of a difference in stroke risk after 12 months in TRILOGY ACS.

The analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.0.2 (R Project for Statistical Computing; http://www.r-project.org/).

### Results

Of 7243 patients analyzed, 77 (1.1%) experienced a stroke event (62 ischemic; 15 hemorrhagic; Table). These patients were older; had more comorbidities, including atrial fibrillation; and had a higher Global Registry of Acute Coronary Events (GRACE) long-term mortality risk score.
We observed a trend for a lower unadjusted frequency of all stroke events through 30 months for patients treated with prasugrel versus clopidogrel: 31 (1.5%) versus 46 (2.2%); \( P = 0.08 \) (Figure 1A). This relationship was markedly less with regard to ischemic strokes for prasugrel versus clopidogrel: 27 (1.0%) versus 35 (1.8%); \( P = 0.30 \) (Figure 1B).

A time-varying reduced hazard of ischemic stroke with prasugrel versus clopidogrel was demonstrated in the treatment-by-time interaction analysis \( (P = 0.03) \) and the supremum test \( (P = 0.03) \). However, no significant interactions between treatment effect and time were observed when all stroke events were analyzed \( (P = 0.09) \). Figure 2A and 2B shows the instantaneous hazard for all strokes and ischemic strokes for patients taking prasugrel versus clopidogrel. The curve trajectories are different and consistent with the treatment-by-time interaction results.

For ischemic stroke, the 3-month landmark analysis did not show any difference in treatment effect between prasugrel and clopidogrel \( (P = 0.11) \). However, the 12-month landmark Kaplan–Meier log-rank test demonstrated a significantly reduced hazard of ischemic stroke in patients taking prasugrel \( (P = 0.04) \).

**Discussion**

Several important observations emerge. First, among patients with ACS, the frequency of the first stroke in patients taking prolonged dual antiplatelet therapy was relatively low. Second, although we observed a trend for fewer stroke events among patients who received more potent antiplatelet inhibition with prasugrel, this difference was not statistically significant. Third, we observed a treatment-by-time interaction, whereby patients randomized to prasugrel appeared to have a lower hazard of ischemic stroke versus patients receiving clopidogrel 12 months after the index ACS event.

We observed a 1.1% rate of stroke events over a median follow-up period of 17 months. A recent meta-analysis reported an overall stroke rate of 1.8% over 12 months for patients receiving clopidogrel and aspirin.\(^6\) However, because it included trials enrolling patients with a history of stroke, it would be expected to have a higher event rate.

There are considerably fewer data addressing the effect of more potent P2Y12 inhibition on stroke, with inconsistent

**Figure 2.** Treatment-by-time interaction for all stroke and ischemic only stroke events. **A**, Instantaneous hazard for all stroke events stratified by treatment. **B**, Instantaneous hazard for ischemic stroke events stratified by treatment.
results. In Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), ACS patients scheduled for coronary revascularization were randomized to prasugrel or clopidogrel. Patients with prior ischemic stroke were included unless the stroke occurred within 3 months of enrollment. Among patients with prior ischemic stroke, there were significantly more stroke events among those treated with prasugrel (6.5% versus 1.2%; P=0.002). However, among patients without a prior stroke, there was no difference in stroke incidence (0.9% prasugrel versus 1.0% clopidogrel).7 Furthermore, in Study of Platelet Inhibition and Patient Outcomes (PLATO), which compared another potent P2Y12 inhibitor (ticagrelor) with clopidogrel in patients with ACS, no difference was seen in the rate of stroke in the overall study population or among patients receiving only medical management.5,9

Therefore, to date, few data support a role for more potent P2Y12 inhibition versus clopidogrel in reducing stroke events. As such, our observation of a possible time-dependent effect whereby prolonged potent P2Y12 inhibition may provide protection from stroke is interesting and novel. Furthermore, this time-dependent effect seems to be absent after 3 months after the ACS event although it was detectable after 12 months in our analysis. We may have been able to detect this effect because, unlike TRITON-TIMI 38 and PLATO that followed patients for maximums of 15 and 12 months, respectively, TRILOGY ACS followed patients for a median of 17 months.

Nevertheless, because stroke has multiple underlying causes and because more potent P2Y12 inhibition targets only one possible pathophysiological cause, additional study is warranted to identify patients who may benefit from prolonged potent P2Y12 inhibition.9

Limitations
Our study represents a subgroup analysis of a trial with an overall neutral outcome. The number of strokes observed was low, so this study is an exploratory, underpowered, hypothesis-generating analysis whose findings should be interpreted cautiously. Atrial fibrillation is known to be associated with an increased risk of ischemic stroke, but we were unable to evaluate the impact of concomitant oral anticoagulants on the reduced late risk of ischemic stroke observed with prasugrel versus clopidogrel because oral anticoagulants were not permitted to be used together with the randomized treatments at the time of randomization and during follow-up. Finally, because the protocol mandated that patients discontinue study drug after any type of stroke event was reported, the effect of long-term platelet inhibition on recurrent strokes is unknown.

Conclusions
Our results suggest that a longer duration of more intense platelet inhibition with prasugrel (versus clopidogrel) in patients without prior stroke or transient ischemic attack may be associated with a lower risk of ischemic stroke after 12 months. These hypothesis-generating results merit study in larger populations.

Sources of Funding
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Disclosures
C.T. Chin obtained grant funding from AstraZeneca and Boston Scientific. All conflicts of M.T. Roe are listed at https://www.dcri.org/about-us/conflict-of-interest. B. Neely and R. Corbalán have no conflict of interest to disclose.

References
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