Prevention of Stroke with Ticagrelor in Patients with Prior Myocardial Infarction

Insights from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54)

BACKGROUND: In the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54), ticagrelor reduced the risk of major adverse cardiovascular events when added to low-dose aspirin in stable patients with prior myocardial infarction, resulting in the approval of ticagrelor 60 mg twice daily for long-term secondary prevention. We investigated the incidence of stroke, outcomes after stroke, and the efficacy of ticagrelor focusing on the approved 60 mg twice daily dose for reducing stroke in this population.

METHODS: Patients were followed for a median of 33 months. Stroke events were adjudicated by a central committee. Data from similar trials were combined using meta-analysis.

RESULTS: Of 14,112 patients randomly assigned to placebo or ticagrelor 60 mg, 213 experienced a stroke; 85% of these strokes were ischemic. A total of 18% of strokes were fatal and another 15% led to either moderate or severe disability at 30 days. Ticagrelor significantly reduced the risk of stroke (hazard ratio, 0.75; 95% confidence interval, 0.57–0.98; P=0.034), driven by a reduction in ischemic stroke (hazard ratio, 0.76; 95% confidence interval, 0.56–1.02). Hemorrhagic stroke occurred in 9 patients on placebo and 8 patients on ticagrelor. A meta-analysis across 4 placebo-controlled trials of more intensive antiplatelet therapy in 44,816 patients with coronary disease confirmed a marked reduction in ischemic stroke (hazard ratio, 0.66; 95% confidence interval, 0.54–0.81; P=0.0001).

CONCLUSIONS: High-risk patients with prior myocardial infarction are at risk for stroke, approximately one-third of which are fatal or lead to moderate-to-severe disability. The addition of ticagrelor 60 mg twice daily significantly reduced this risk without an excess of hemorrhagic stroke but with more major bleeding. In high-risk patients with coronary disease, more intensive antiplatelet therapy should be considered not only to reduce the risk of coronary events, but also of stroke.

Clinical Perspective

What Is New?
- Intensive antiplatelet therapy as long-term secondary prevention in patients with prior myocardial infarction is anticipated to reduce the risk of coronary events.
- This study demonstrates that long-term ticagrelor reduced stroke through a reduction in ischemic stroke and did not increase hemorrhagic stroke.
- When pooled with other studies investigating potent antiplatelet therapy for long-term secondary prevention after myocardial infarction, results show a consistent reduction in ischemic stroke.

What Are the Clinical Implications?
- When considering intensive antiplatelet regimens for long-term secondary prevention, clinicians and patients must weigh benefits and risks.
- Although these therapies are anticipated to reduce both de novo and stent-related coronary events, this analysis highlights broader benefits in reducing ischemic stroke. These data may be useful in clinical decision making.
- Overall, for 1000 patients initiated on ticagrelor 60 mg twice daily for 3 years, 13 primary end-point events would be prevented, including $\approx$5 ischemic strokes. This benefit would come at a cost of 9 TIMI major bleeds but no hemorrhagic strokes or fatal bleeds.

Stroke remains one of the most feared adverse cardiovascular events because it is a leading cause of long-term disability and remains within the top 5 causes of death in the United States. Each year $\approx$800,000 people in the United States experience a stroke with ischemic stroke being the most common type (87%). It is estimated that in 2010, 11.6 million incident ischemic strokes occurred globally.1

Although patients who have experienced a stroke are at heightened risk of recurrence, the majority of strokes ($\approx$80%) are first events rather than recurrent events.1 To reduce stroke rates, vulnerable populations must therefore be identified for preventive interventions. Patients with uncontrolled hypertension and atrial fibrillation are clearly at heightened risk. Among the remaining vulnerable groups, patients with symptomatic atherosclerosis in any territory, including prior myocardial infarction (MI), are at heightened risk of atherothrombotic stroke.2,3

Whereas the benefits of more intensive antiplatelet strategies in patients with prior MI would be expected to be reduced and indeed are driven by reductions in recurrent coronary events, the observation of an additional benefit in reducing stroke may have important implications for patients and clinicians weighing the overall risks and benefits of therapy.

The PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) was designed to test prospectively the hypothesis that the addition of ticagrelor to aspirin would reduce cardiovascular risk in patients with prior MI. Overall, both ticagrelor 60 mg twice daily and ticagrelor 90 mg twice daily reduced the composite of cardiovascular death, MI, or stroke by $\approx$15% over long-term follow-up. Although both doses were efficacious, the 60-mg dose was to be better tolerated, leading to the approval of this dose as long-term secondary prevention.

In this analysis, we investigate the incidence, predictors, and subsequent outcomes of stroke. We also evaluate the effect of the approved ticagrelor 60-mg dose added to aspirin on the risk of stroke, specifically both ischemic and hemorrhagic stroke. Last, we examine whether the effects of ticagrelor 60 mg in PEGASUS-TIMI 54 were consistent with observations from other trials evaluating more intensive antiplatelet therapy in long-term trials of secondary prevention in patients with coronary disease.

METHODS

Study Population
PEGASUS-TIMI 54 randomly assigned patients with prior MI to ticagrelor 60 mg twice daily, ticagrelor 90 mg twice daily, or placebo, all on a background of low-dose aspirin. The protocol was approved by the relevant ethics committee at each participating site. Written informed consent was obtained from all the patients. The design and primary results of the trial have been published. A total of 21,162 patients were enrolled, with 14,112 allocated to either placebo or ticagrelor 60 mg twice daily. Patients aged at least 50 years were enrolled with a spontaneous MI occurring 1 to 3 years before enrollment and at least one of the following additional high-risk features: age of $\geq$65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as a creatinine clearance $<60$ mL/min as estimated by the Cockcroft-Gault equation. Patients were ineligible if there was planned use of a P2Y$_12$ receptor antagonist or anticoagulant therapy during the study period; if they had a bleeding disorder, a history of intracranial bleeding, a central nervous system tumor, or an intracranial vascular abnormality; or if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous month. Early in the course of the trial, observations of bleeding risks in other trials of different antiplatelet therapies in patients with known prior stroke resulted in an amendment to the protocol excluding these patients from PEGASUS-TIMI 54. Therefore, few patients with prior stroke were enrolled, and those that were randomized were discontinued from therapy early in the course of the trial.

End Points
The primary efficacy end point for PEGASUS-TIMI 54 was the composite of cardiovascular death, MI, or stroke, and the
primary safety end point was TIMI major bleeding. For the current analysis, stroke was the primary efficacy outcome. Stroke was a prespecified component of the overall trial primary end point. A stroke end point was defined as the new onset of focal neurological symptoms lasting >24 hours or evidence of new infarct on brain imaging even if symptoms were <24 hours in duration. Stroke events were further classified as ischemic or primary hemorrhagic. Ischemic strokes that were associated with hemorrhagic conversion were also identified. Nonhemorrhagic infarction with hemorrhagic conversion was defined as evidence of cerebral infarction with blood thought to represent hemorrhagic conversion and not a primary hemorrhage based on location and imaging characteristics. All potential stroke events were adjudicated by a clinical events committee composed of specialists in neurology who were blinded to treatment allocation. Site investigators were trained in the assessment of disability after stroke by using the modified Rankin scale (mRS). Investigators were instructed to complete an assessment at 30 days after discharge. Scores on the mRS increase with greater disability and range from 0 (no symptoms at all) to a maximum of 6 (death) with a score of 3 indicating moderate disability.\(^7\)

**Statistical Considerations**

Baseline characteristics were summarized using either medians and quartiles for continuous variables or frequencies and percentages for categorical variables. Differences were tested with the Wilcoxon rank-sum test for continuous variables and with the Pearson \(\chi^2\) test for categorical data. Cumulative event rates at 3 years were calculated by the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated with the use of a Cox proportional-hazards model, and all reported \(P\) values are 2-sided. Efficacy analyses were performed on an intention-to-treat basis. Safety analyses included all the patients who received at least 1 dose of study drug and included all the events occurring after receipt of the first dose and within 7 days of the last dose of study drug. The primary analysis focused on the efficacy and safety of the ticagrelor 60 mg dose that is approved for long-term use. Results for the 90-mg ticagrelor dose are presented in the online-only Data Supplement. Subgroup analyses were done to evaluate the consistency of effects. A 2-sided \(P\) value of <0.05 was considered significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc.).

To put these data in the context of the totality of evidence, data from other large, long-term placebo-controlled trials of more intensive antiplatelet therapy in patients with coronary artery disease were combined into a meta-analysis.\(^8-11\) Detailed methodology is presented in the online-only Data Supplement. Trials meeting the criteria were combined by using a random-effects model with weighting based on the inverse variance (Comprehensive Meta-Analysis version 3.3.070, Biostat Inc).

**RESULTS**

**Baseline Characteristics**

Of the 14,112 patients randomly assigned to either placebo or ticagrelor 60 mg twice daily, a total of 213 patients experienced a stroke during a median of 33 months of follow-up. The majority of first strokes were ischemic (181, 85%). Of these 181 strokes, 173 subjects had ischemic stroke event, and a subset of 8 patients had an ischemic stroke with hemorrhagic conversion in addition. The other types of strokes include 16 strokes hemorrhagic (16, 8%), and unknown (16, 8%, online-only Data Supplement Figure 1). The baseline characteristics of patients who did and did not experience a stroke during follow-up are shown in Table 1. Patients who experienced a stroke were older, had higher systolic blood pressure at randomization, and more frequently had comorbidities including a history of hypertension, diabetes mellitus, and impaired renal function. Patients with stroke were more likely to have more extensive cardiovascular disease, including a history of congestive heart failure, and a history of atrial fibrillation. Because of the early modification of the protocol excluding these patients, the number of patients with a history of stroke was small (n=62, <1% of the analysis cohort).

**Outcomes After Stroke**

Of those patients that experienced a stroke, 180 (85%) were hospitalized for a median duration of 8 days (interquartile range, 5–14). A total of 87% of patients with strokes had residual disability at or beyond 24 hours, whereas 13% were asymptomatic at 24 hours but had brain-imaging data documenting a stroke. Of patients hospitalized for a stroke, 26 (14%) died in hospital. Of the patients who were discharged alive, 19 (12%) were unable to return home and required a higher level of care at either a nursing home or another acute care facility. At 6 months after discharge, another 14 (9%) of the patients that survived the index hospitalization for stroke had died. Sites were asked to collect a mRS at 30 days from the stroke event. In addition to the 18% (39/213) of strokes that were fatal, another 15% (33/213) led to either moderate or severe disability (mRS, 3–5).

**Reduction of Stroke With Ticagrelor**

Stroke of any kind was significantly reduced with ticagrelor 60 mg twice daily relative to placebo (HR, 0.75; 95% CI, 0.57–0.98; \(P=0.034\); Table 2, Figure 1). This reduction in stroke was driven by a reduction in ischemic stroke (HR, 0.76; 95% CI, 0.56–1.02; Table 2). Hemorrhagic stroke was infrequent overall and not statistically different between treatment groups (placebo=9, ticagrelor 60 mg=8; Table 3) as was ischemic stroke with hemorrhagic conversion (placebo=5, ticagrelor 60 mg=4; Table 3). The reduction in stroke in ticagrelor 60 mg versus placebo appeared largely consistent across relevant subgroups at heightened risk of stroke based on demographics and comorbidities (online-only Data Supplement Table I). Data for the efficacy and safety of the ticagrelor 90 mg twice daily dose were generally similar (online-only Data Supplement Tables I and II).
The efficacy of ticagrelor in reducing strokes that resulted in at least moderate disability or death (mRS, 3–6; HR, 0.57; 95% CI, 0.33–0.99;  \( P = 0.045 \)) seemed, if anything, even greater than its effect on less severe strokes resulting in no or minimal disability (mRS, 0–2; HR, 0.81; 95% CI, 0.56–1.17;  \( P = 0.26 \); Figure 2, online-only Data Supplement Figure II).

**Overall Safety and Efficacy of Ticagrelor**

Ticagrelor 60 mg twice daily increased TIMI major bleeding (HR, 2.32; 95% CI, 1.68–3.21;  \( P < 0.001 \)) but with no statistically significant increase in intracranial hemorrhage (HR, 1.33; 95% CI, 0.77–2.31;  \( P = 0.31 \)) or fatal bleeding (HR, 1.00; 95% CI, 0.44–2.27;  \( P = 1.00 \); Tables 4 and 5). Ticagrelor 60 mg twice daily reduced the composite of cardiovascular death, MI, or stroke (HR, 0.84; 95% CI, 0.74–0.95;  \( P = 0.0043 \)) and did not result in any excess of all-cause mortality (HR, 0.89; 9% CI, 0.76–1.04;  \( P = 0.14 \); Table 4). Considering absolute risk, for 1000 patients initiated on ticagrelor 60 mg twice daily for 3 years, 13 primary end-point events would be prevented including ≈5 ischemic strokes. This benefit would come at a cost of 9 TIMI major bleeds but no hemorrhagic strokes or fatal bleeds.

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke n=13889</th>
<th>Stroke n=213</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>65 (59–71)</td>
<td>67 (60–74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>3318 (24)</td>
<td>60 (28)</td>
<td>0.14</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>12024 (87)</td>
<td>177 (83)</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight in kg, median (IQR)</td>
<td>81 (70–91)</td>
<td>78 (68–91)</td>
<td>0.061</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>28 (25–31)</td>
<td>27 (25–31)</td>
<td>0.53</td>
</tr>
<tr>
<td>SBP (mm Hg), median (IQR)</td>
<td>130 (120–142)</td>
<td>138 (122–150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mm Hg), median (IQR)</td>
<td>80 (70–84)</td>
<td>80 (70–86)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

**Comorbidities**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke n=13889</th>
<th>Stroke n=213</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension, n (%)</td>
<td>10757 (77)</td>
<td>188 (88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>10670 (77)</td>
<td>161 (76)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>2317 (17)</td>
<td>32 (15)</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4476 (32)</td>
<td>89 (42)</td>
<td>0.003</td>
</tr>
<tr>
<td>eGFR &lt;60, n (%)</td>
<td>3116 (23)</td>
<td>80 (39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Cardiovascular history**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke n=13889</th>
<th>Stroke n=213</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of second prior MI, n (%)</td>
<td>2320 (17)</td>
<td>36 (17)</td>
<td>0.94</td>
</tr>
<tr>
<td>Multivessel CAD, n (%)</td>
<td>8296 (60)</td>
<td>107 (50)</td>
<td>0.0052</td>
</tr>
<tr>
<td>History of CABG, n (%)</td>
<td>661 (5)</td>
<td>11 (5)</td>
<td>0.74</td>
</tr>
<tr>
<td>History of PCI, n (%)</td>
<td>11560 (83)</td>
<td>156 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qualifying NSTEMI, n (%)</td>
<td>5594 (40)</td>
<td>91 (43)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of CHF, n (%)</td>
<td>2747 (20)</td>
<td>73 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of atrial fibrillation, n (%)</td>
<td>540 (4)</td>
<td>33 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of TIA, n (%)</td>
<td>173 (1)</td>
<td>5 (2)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>59 (0)</td>
<td>3 (1)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

**Medical therapies**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke n=13889</th>
<th>Stroke n=213</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, n (%)</td>
<td>13873 (100)</td>
<td>213 (100)</td>
<td>0.53</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>12886 (93)</td>
<td>192 (90)</td>
<td>0.15</td>
</tr>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>8048 (58)</td>
<td>119 (56)</td>
<td>0.55</td>
</tr>
<tr>
<td>ARB, n (%)</td>
<td>3229 (23)</td>
<td>61 (29)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and TIA, transient ischemic attack.
Meta-analysis of Reduction of Stroke With More Intensive Antiplatelet Strategies

Combining data from a total of 4 randomized, long-term placebo-controlled trials of more versus less intensive antiplatelet therapy in 44,816 patients with coronary disease who experienced a total of 532 strokes (online-only Data Supplement Table III) demonstrated a significant 28% reduction in stroke in patients treated with more intensive therapy (HR, 0.72; 95% CI, 0.60–0.85; P<0.001, Figure 3A) with no evidence of heterogeneity (P value for heterogeneity, 0.76; I², 0%). As expected, the effects of more intensive antiplatelet therapy on ischemic stroke (Figure 3B) were more pronounced with a 34% reduction (HR, 0.66; 95% CI, 0.54–0.81; P=0.0001). There was no significant effect on hemorrhagic stroke (HR, 1.29; P=0.48; Figure 3C), but with broad 95% CIs (0.64–2.59) because of the smaller number of events. There was some evidence for moderate heterogeneity (I², 29%). When the data from TRA2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events [TRA 2P]–Thrombolysis in Myocardial Infarction [TIMI] 50 trial) were limited to patients only on background aspirin monotherapy (ie, excluding patients on background aspirin + thienopyridine, in whom vorapaxar would be the third antiplatelet agent), then the meta-analytic HR for hemorrhagic stroke was 1.04 (95% CI, 0.58–1.84; Figure 3D) with no evidence of heterogeneity (I², 0%).

DISCUSSION

Stroke remains a frequent cardiovascular complication impacting >10 million people globally each year. It is a major cause of disability and a leading cause of mortality. A significant proportion of strokes occur in the setting of arterial disease such as large vessel atherothrombosis. To that end, antiplatelet therapy with aspirin reduces the risk of recurrent stroke by ≈15%. Although substituting clopidogrel or ticagrelor for aspirin has not been shown to result in statistically significant reductions in stroke, trends toward a reduction in ischemic stroke on the order of 5% to 10% have been observed. More
intensive antiplatelet therapy with >1 agent does reduce the risk of ischemic stroke, but typically at the cost of intracranial bleeding in these patients with prior infarction of brain tissue.15–20

Although patients with a prior stroke are at heightened risk, >80% of strokes occur as first strokes.1 Patients with atrial fibrillation and hypertension are at clearly heightened risk. Other vulnerable populations for stroke include those with symptomatic atherosclerosis characterized by prior MI. Registries estimate that the annual risk of stroke in a post-MI population is ≈1.4% per year.2 It is estimated that as many as 1 in 10 patients who experience an MI will have a stroke within the next 5 years.1 Importantly, because of their underlying atherosclerosis, the post-MI population is one which may be particularly likely to experience large vessel atherothrombotic stroke and therefore to potentially benefit from intensive antithrombotic strategy.

In the present patient population, at high risk for stroke but largely without a history of prior stroke, long-term secondary prevention with ticagrelor 60 mg twice daily added to low-dose aspirin reduced all stroke. This benefit for stroke was driven by a reduction in ischemic stroke with, in this selected population, no counterbalancing increase in hemorrhagic stroke or ischemic stroke with hemorrhagic conversion. The reduction in stroke observed with ticagrelor 60 mg twice daily was consistent across the severity scale including a significant reduction in strokes resulting in at least moderate persistent disability or death within 30 days after discharge. The benefit of ticagrelor was consistent across key clinical subgroups.

Table 3. Safety Outcomes of Stroke With Ticagrelor 60 mg Twice Daily

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=6996</th>
<th>Ticagrelor 60 mg n=6958</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>3-y KM Rate</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic stroke with hemorrhagic conversion</td>
<td>5</td>
<td>0.11</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and KM, Kaplan-Meier.

Figure 2. Modified Rankin scale of strokes occurring on placebo and ticagrelor 60 mg.

CI indicates confidence interval; HR, hazard ratio; and mRS, modified Rankin scale.
When combined with other data sets evaluating more intensive antiplatelet strategies for long-term secondary prevention, we observed a consistent association between more intensive antiplatelet strategy and a reduction in stroke driven by a 34% reduction in ischemic stroke. When restricting to cohorts that examined aspirin and an additional agent versus aspirin alone, this benefit was not associated with a significant increase in hemorrhagic stroke or hemorrhagic conversion of ischemic stroke. Although these findings support the hypothesis that more intensive antiplatelet strategies are effective for not only MI, but also stroke prevention in appropriately selected populations, they should be considered within the limitations of the meta-analysis presented. In addition, the effect observed should not be extended to other populations. For example, dual antiplatelet therapy did not prove superior to aspirin monotherapy in high-risk asymptomatic patients, including those with asymptomatic carotid disease.21 Similarly, although dual-antiplatelet therapy is superior to aspirin monotherapy in patients with atrial fibrillation, both are inferior to anticoagulation.22,23

It is important to distinguish our findings from data in a patient population we did not study, namely patients with prior stroke, in whom data suggest either lack of benefit or an increased risk of intracranial hemorrhage.15–19 Differences in efficacy may be explained by the heterogeneous etiologies of stroke (eg, lacunar, cardioembolic, atherothrombotic) and the possibility that not all stroke risk is modified by antiplatelet therapy. For example, cohorts selected for specific types of stroke such as lacunar stroke have been shown clearly not to benefit from long-term dual-antiplatelet therapy. It is possible, however, that long-term dual-antiplatelet therapy does reduce atherothrombotic stroke in the same way it reduces atherothrombotic MI and that prior-MI are most vulnerable to atherothrombotic stroke. And in terms of safety, we deliberately excluded patients with prior stroke because of the increased risk of intracranial hemorrhage with more intensive antiplatelet therapy that has been seen in other trials.15–20

These observations should be taken within the context of the overall efficacy and safety of long-term ticagrelor. Overall, ticagrelor reduced the composite of cardiovascular death, myocardial infarction, and stroke at the cost of increased TIMI major bleeding. For 1000 patients initiated on ticagrelor 60 mg twice daily for 3 years, ≈5 ischemic strokes would be prevented with no excess of hemorrhagic stroke. When evaluating the broader efficacy and safety of long-term ticagrelor in this population, for 1000 patients initiated on ticagrelor 60 mg twice daily for 3 years, 13 cardiovascular death, MI, or stroke events would be prevented at a cost of 9 TIMI major bleeds but no fatal bleeds.

### Limitations

There are several limitations to this analysis that should be considered. Patients included in PEGASUS-TIMI 54...
were selected in that they were required to have at least 1 high-risk feature for ischemic complications (age >65 years, diabetes mellitus, multivessel coronary disease, multiple prior MIs, chronic kidney disease) and were excluded if they were at heightened bleeding risk (eg, recent bleeding, need for anticoagulation, prior intracranial bleeding). The findings should not be generalized to other populations, in particular, those at lower ischemic risk or at higher bleeding risk. The pathogenesis of stroke was not ascertained and therefore the events reported

### A Stroke Reduction with More Intensive Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>0.750</td>
<td>0.476</td>
<td>1.161</td>
<td>-1.242</td>
<td>0.214</td>
</tr>
<tr>
<td>TRAP-TIMI 50</td>
<td>0.620</td>
<td>0.451</td>
<td>0.852</td>
<td>-2.946</td>
<td>0.003</td>
</tr>
<tr>
<td>DAPT</td>
<td>0.800</td>
<td>0.511</td>
<td>1.262</td>
<td>-0.976</td>
<td>0.329</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>0.760</td>
<td>0.572</td>
<td>0.983</td>
<td>-2.061</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>0.716</td>
<td>0.603</td>
<td>0.851</td>
<td>-3.786</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Favors More Intensive Antiplatelet Therapy
Favors Less Intensive Antiplatelet Therapy

### B Ischemic Stroke Reduction with More Intensive Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>0.764</td>
<td>0.4677</td>
<td>1.2481</td>
<td>-1.074</td>
<td>0.282</td>
</tr>
<tr>
<td>TRAP-TIMI 50</td>
<td>0.510</td>
<td>0.3606</td>
<td>0.7212</td>
<td>-3.607</td>
<td>0.0001</td>
</tr>
<tr>
<td>DAPT</td>
<td>0.680</td>
<td>0.3976</td>
<td>1.1630</td>
<td>-1.406</td>
<td>0.159</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>0.760</td>
<td>0.5931</td>
<td>1.0527</td>
<td>-1.794</td>
<td>0.0726</td>
</tr>
<tr>
<td></td>
<td>0.6929</td>
<td>0.5399</td>
<td>0.8139</td>
<td>-3.928</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Favors More Intensive Antiplatelet Therapy
Favors Less Intensive Antiplatelet Therapy

### C Hemorrhagic Stroke with More Intensive Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>0.340</td>
<td>0.035</td>
<td>3.286</td>
<td>-0.932</td>
<td>0.351</td>
</tr>
<tr>
<td>TRAP-TIMI 50</td>
<td>3.650</td>
<td>1.019</td>
<td>13.071</td>
<td>1.989</td>
<td>0.047</td>
</tr>
<tr>
<td>DAPT</td>
<td>1.200</td>
<td>0.497</td>
<td>2.895</td>
<td>0.406</td>
<td>0.685</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>0.970</td>
<td>0.372</td>
<td>2.526</td>
<td>-0.062</td>
<td>0.950</td>
</tr>
<tr>
<td></td>
<td>1.267</td>
<td>0.639</td>
<td>2.952</td>
<td>0.705</td>
<td>0.481</td>
</tr>
</tbody>
</table>

Favors More Intensive Antiplatelet Therapy
Favors Less Intensive Antiplatelet Therapy

### D Hemorrhagic Stroke with Dual versus Mono Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>0.340</td>
<td>0.025</td>
<td>3.286</td>
<td>-0.932</td>
<td>0.351</td>
</tr>
<tr>
<td>TRAP-TIMI 50 ASA*</td>
<td>3.000</td>
<td>0.250</td>
<td>5.899</td>
<td>0.343</td>
<td>0.726</td>
</tr>
<tr>
<td>DAPT</td>
<td>1.200</td>
<td>0.497</td>
<td>2.895</td>
<td>0.406</td>
<td>0.685</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>0.970</td>
<td>0.372</td>
<td>2.526</td>
<td>-0.062</td>
<td>0.950</td>
</tr>
<tr>
<td></td>
<td>1.037</td>
<td>0.583</td>
<td>1.983</td>
<td>0.123</td>
<td>0.902</td>
</tr>
</tbody>
</table>

Favors Dual Antiplatelet Therapy
Favors Antiplatelet Monotherapy

*Restricting to dual with vorapaxar+aspirin vs. aspirin alone

Figure 3. The effect of potent antiplatelet therapy versus placebo for all stroke (A), ischemic stroke (B), hemorrhagic stroke (C), and hemorrhagic stroke limiting to subgroups comparing dual-antiplatelet therapy (aspirin and a P2Y12 inhibitor or aspirin and a PAR-1 inhibitor) to aspirin alone (D).
may represent several etiologies, including atherosclerotic stroke, cardioembolic stroke, and lacunar stroke. It is also possible that the benefit of ticagrelor for reducing stroke was not homogenous across these etiologies. Because the population was one of patients with prior MI largely without history of stroke, it is likely that the majority of strokes were atherosclerotic in etiology. To that end, in patients presenting with a stroke, the use of more intensive antplatelet therapy tended to reduce atherosclerotic ischemic stroke with no benefit for non-thrombotic strokes such as lacunar stroke. Although no significant differences in efficacy were observed in the subgroups evaluated, there were trends for slightly greater magnitude of effect in patients with risk factors for stroke. Future analyses of other large data sets will be needed to examine this issue further. In addition, it should be noted that the meta-analysis included patients with coronary disease, which includes a spectrum of disease, included antplatelet agents with differing mechanisms of action, and that background therapies were not identical in all trials. Combining the trials as a meta-analysis was intended to show the consistency of ischemic stroke reduction with more intensive antplatelet strategies in patients with coronary disease and predominantly prior MI.

CONCLUSIONS
High-risk patients with prior MI are at long-term risk of stroke, primarily because of ischemic stroke. Outcomes in patients with stroke are poor with >30% resulting in moderate to severe disability or death. The addition of a second antplatelet agent to aspirin as long-term secondary prevention in patients with coronary disease reduces the risk of stroke by =34% without a counterbalancing risk of hemorrhagic stroke or hemorrhagic conversion after ischemic stroke but with more major bleeding. Stroke prevention should be considered when weighing the risks and benefits of long-term antplatelet therapy in high-risk patients with coronary disease.

SOURCES OF FUNDING
This study was supported by a grant from AstraZeneca.

DISCLOSURES
Dr Bonaca reports research grant support from AstraZeneca and Medimmune and consulting for AstraZeneca, Merck, and Bayer. Dr Goto received honoraria from Eisai, Sanofi-Aventis, Otsuka, Bayer, Novartis, Astra-Zeneca, Astros, Pfizer, Medtronics-Japan, Tanabe-Mitsubishi, Takeda, Daiichi-Sankyo, Mochida, MSD. Dr Goto also received research grants from Sanofi-Aventis, Berlinger-Ingelheim, Otsuka, and Daiichi-Sankyo. Dr Bhatt reports the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology, Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda. Dr Steg reports significant research grants from Merck, Sanofi, and Servier; other personal fees and nonfinancial support from AstraZeneca, Sanofi, Servier; personal fees from Amarin, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL-Behring, Daiichi-Sankyo, Lilly, Merck, Janssen, Novartis, Medtronic, Pfizer, The Medicines Company, GSK, Regeneron. Dr Storey reports grants and personal fees from AstraZeneca, and personal fees from Aspen, PlaqueTec, The Medicines Company, Medscape, and ThermoFisher Scientific. Dr Cohen reports grants and personal fees from AstraZeneca, during the conduct of the study; personal fees from Merck, personal fees from Janssen, personal fees from Maquet, personal fees from malpractice attorneys, grants from Janssen, grants from Edwards, personal fees from Merck, personal fees from BMS/Pfizer, personal fees from Janssen, personal fees from Bi, personal fees from Lilly, outside the submitted work. Erica Goodrich reports no disclosures. Dr Mauri reports grants (to her institution) from Abbott, Boston Scientific, Cordis, Medtronic, Eli Lilly and Company, Daiichi Sankyo, Sanofi, Bristol-Myers Squibb, Boehringer Ingelheim, and Biotronik; and is a consultant for Medtronic, Eli Lilly and Company, Boehringer Ingelheim, Biotronik, Amgen, Recor, and St. Jude, and receives honoraria from Astra Zeneca and Sanofi. Dr Ophus reports grants and personal fees from Astra Zeneca, personal fees from Merck, personal fees from BMS, personal fees from Abbott, personal fees from Boston, personal fees from VRN, personal fees from WCN. Drs Ruda, Spinari, Seung, and Hu report no disclosures. Dr Dalby reports serving on South African advisory boards for the following: Aspen, AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Sanofi, and Servier. He also reports receiving honoraria from AstraZeneca and Servier and travel sponsorship from Bayer, Boehringer-Ingelheim, Novartis, and Sanofi. Drs Jensen Held are employed by AstraZeneca. Dr Morrow is a member of the TIMI Study Group and reports consulting fees from Abbott Laboratories, AstraZeneca, diaDexus, Gilead, GlaxoSmithKline, and Medtronic.

Prevention of Ischemic Stroke with Ticagrelor

Circulation. 2016;134:00-00. DOI: 10.1161/CIRCULATIONAHA.116.024637

September 20, 2016 9
Merck, Novartis, and Roche Diagnostics. Dr Braunwald reports
grant support to his institution from AstraZeneca. Dr Sabatine
reports research grant support through Brigham and Women’s
Hospital from: Abbott Laboratories, Amgen, AstraZeneca, Criti-
cal Diagnostics, Daiichi-Sankyo, Eisai, Gilead, GlaxoSmithKline,
Intarcia, Janssen Research Development, MedImmune, Merck,
Novartis Roche Diagnostics, Sanofi-aventis, and Takeda and
consulting for: Alnylam, Amgen, AstraZeneca, Cubist, CVS
Caremark, Intarcia, Ionis, and Merck.

AFFILIATIONS
From TIMI Study Group, Brigham and Women’s Hospital, Har-
vard Medical School, Boston, MA (M.P.B., D.L.B., E.G., D.A.M.,
E.B., M.S.); Tokai University School of Medicine; Institute of
Medical Science, Isehara, Japan (S.G.); FACT, DHU-FIRE IN-
SERM Unité 1148, Assistance Publique–Hôpitaux de Paris and
Université Paris Diderot, Paris, France, and NHLI Imperial
College, Royal Brompton Hospital, London, UK (P.G.S.); University
of Sheffield, United Kingdom (R.F.S.); Division of Cardiology,
Newark Beth Israel Medical Center, Rutgers-New Jersey Medi-
cal School, Newark (M.C.); Brigham and Women’s Hospital and
Harvard Clinical Research Institute, Harvard Medical School,
Boston, MA (L.M.); CWZ Hospital, Nijmegen, The Netherlands
(T.O.O.); Cardiology Research and Production complex MH
Fr, Moscow, Russia (M.R.); Internal Cardiology Department,
KCMU, Seoul, South Korea (K.-B.S.); Heart Institute, Interven-
tion Center, People Hospital of Peking University, China (D.H.);
Catholic University of Korea (K.-B.S.); Heart Institute, Interven-
tion Center, People Hospital of Peking University, China (D.H.);
Life Fourways Hospital, Randburg, South Africa (A.J.D.); and
AstraZeneca, Mölndal, Sweden (E.J., P.H.).

FOOTNOTES
Guest Editor for this article was Mariell Jessup, MD.
Received July 25, 2016; accepted August 2, 2016.
The online-only Data Supplement is available with this arti-
cle at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/
CIRCULATIONAHA.116.024637/-/DC1.
Circulation is available at http://circ.ahajournals.org.

REFERENCES
1. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett
   DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Ful-
   berton HJ, Howard VJ, Huffman MD, Jais PR, Jimenez MC, Judd SE,
   Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magnen
   M, Balsilis S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A,
   RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS;
   PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term
   use of ticagrelor compared to placebo on a Background of Aspirin-
   Thrombolyis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.

   J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S; REACH
   Registry Investigators. One-year cardiovascular event rates in out-

3. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM,
   Wilson PW, Alberts MJ, D’Agostino R, Liau CS, Mas JL, Röther J,
   Smith SC Jr, Salette G, Contant CF, Massaro JM, Steg PG; REGA-
   Registry Investigators. Comparative determinants of 4-year car-
   diovascular event rates in stable outpatients at risk of or with
jama.2010.1322.

   RF, Held P, Jensen EC, Sabatine MS. Design and rationale for the
   Prevention of Cardiovascular Events in Patients With Prior Heart
   Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-
   Thrombolyis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.

5. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Mag-
   nani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T,
   Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC,
   Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS;
   PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term
   use of ticagrelor in patients with prior myocardial infarction. N Engl

6. Depicted in proof.

7. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn
   J. Interobserver agreement for the assessment of handicap in

8. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE,
   Cabouc P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey
   GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA,
   EJ, Fox KA; CHARISMA Investigators. Patients with prior myocar-
   dial infarction, stroke, or symptomatic peripheral arterial disease
   doi: 10.1016/j.jacc.2007.03.025.

9. Scirica BM, Bonaca MP, Braunwald E, De Ferrari GM, Iszasa D,
   Lewis BS, Mehrhof F, Merlani PA, Murphy SA, Sabatine MS, Ten-
   dera M, Van de Werf F, Wilcox R, Morrow DA; TRA 2P-TIMI 50
   Steering Committee Investigators. Vorapaxar for secondary pre-
   vention of thrombotic events for patients with previous myocardial
   infarction: a prespecified subgroup analysis of the TRA 2P-TIMI 50
   6736(12)6269-0.

10. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg
    PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes
    DR Jr, Krucowff MW, Hermiller J, Dauerman HL, Simon DJ, Kanz-
    dazi DE, Garrant KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ,
    Massaro JM; DAPT Study Investigators. Twelve or 30 months of

11. Udel RA, Bonaca MP, Collet JP, Lincock AM, Kereiakes DJ, Costa F,
    Lee CW, Mauri L, Valgimigli M, Park SJ, Montalescot G, Sabatine
    MS, Braunwald E, Bhatt DL. Long-term dual antiplatelet therapy for
    secondary prevention of cardiovascular events in the subgroup of
    patients with previous myocardial infarction: a collaborative meta-

    C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti
    A. Aspirin in the primary and secondary prevention of vascular
disease: collaborative meta-analysis of individual participant data

13. CAPRIE Investigators. A randomised, blinded, trial of clopidogrel
    versus aspirin in patients at risk of ischaemic events (CAPRIE).

    Y, Wong KS; SOCRATES Steering Committee and Investigators.


Prevention of Stroke with Ticagrelor in Patients with Prior Myocardial Infarction: Insights from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54)


Circulation. published online August 30, 2016; Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2016 American Heart Association, Inc. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2016/08/29/CIRCULATIONAHA.116.024637

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/08/29/CIRCULATIONAHA.116.024637.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
Prevention of Stroke with Ticagrelor in Patients with Prior Myocardial Infarction:

Insights from PEGASUS-TIMI 54

SUPPLEMENTAL MATERIAL
Supplemental Methods for the Meta-Analysis

We undertook a systematic review and meta-analysis in accordance with the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Randomized placebo-controlled trials investigating more intensive antiplatelet therapy in stable patients with coronary artery disease were considered eligible if they followed patients for at least 1 year and they observed at least 50 stroke events among the treatment arms. We excluded trials of secondary prevention in patients with prior stroke and trials of anticoagulants.

We conducted a search of Medline (1950 through May 2, 2016) and the Cochrane databases, using the search terms listed on the following page. A total of 89 trials met the criteria and were reviewed. Data including eligibility criteria, randomized intervention, duration of follow up, sample size, and number of events were extracted by two investigators (M.P.B and M.S.S.) independently. Results were compared and any disagreements were resolved by consensus. If published data were not available, we contacted the study principal investigator (PI) for input to maximize contribution to, and harmonize outcomes. After excluding trials based on the aforementioned exclusion criteria, 4 trials remained (Supplemental Table 3).

The primary outcome was the incidence of stroke with secondary outcomes of stroke subtypes including ischemic and hemorrhagic. When available, we used the hazard ratios or risk ratios reported in the original manuscript for the meta-analysis.
Search Strategy and Results

1. (((((((((((Antiplatelet[Title/Abstract]) OR Dual antiplatelet therapy[Title/Abstract]) OR DAPT[Title/Abstract]) OR Thienopyridine[Title/Abstract]) OR ADP receptor antagonist[Title/Abstract]) OR purinergic P2Y receptor antagonists[Title/Abstract]) OR clopidogrel[Title/Abstract]) OR prasugrel[Title/Abstract]) OR ticlopidine[Title/Abstract]) OR ticagrelor[Title/Abstract]) OR cilostazol[Title/Abstract]) OR dipyridamole[Title/Abstract]) OR vorapaxar[Title/Abstract] = 34773

2. Search (((coronary artery disease) OR coronary stenting) OR secondary prevention) OR atherothrombosis = 232,681

3. Search stroke = 252106

4. Search placebo controlled = 154435

5. Search Randomized controlled trial = 529091

1 AND 2 AND 3 AND 4 AND 5 and limited to “Clinical Trial” = 89

57 excluded because they did not include patients with stable coronary artery disease
14 excluded because they were not a randomized clinical trial
11 excluded because they were secondary analyses of a trial that was included
2 excluded due to insufficient number of stroke events/ insufficient duration of follow up
1 excluded because it was not placebo controlled

4 met all criteria and were included in the meta-analysis
## Supplemental Table 1 – Reduction in Stroke with Ticagrelor in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of Patients</th>
<th>Ticagrelor 90 mg 3 yr KM%</th>
<th>Ticagrelor 60 mg 3 yr KM%</th>
<th>Placebo 3 yr KM%</th>
<th>Ticagrelor 90 mg vs. Placebo HR (95% CI)</th>
<th>p-interaction</th>
<th>Ticagrelor 60 mg vs. Placebo HR (95% CI)</th>
<th>p-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Diabetes</td>
<td>14,355</td>
<td>1.52</td>
<td>1.32</td>
<td>1.70</td>
<td>0.91 (0.65 - 1.28)</td>
<td>0.32</td>
<td>0.78 (0.55 - 1.11)</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6,806</td>
<td>1.82</td>
<td>1.77</td>
<td>2.46</td>
<td>0.69 (0.45 - 1.06)</td>
<td>0.69</td>
<td>0.80 (0.56 - 1.13)</td>
<td>0.68</td>
</tr>
<tr>
<td>No renal dysfunction</td>
<td>16,649</td>
<td>1.45</td>
<td>1.20</td>
<td>1.40</td>
<td>0.93 (0.66 - 1.30)</td>
<td>0.29</td>
<td>0.80 (0.56 - 1.13)</td>
<td>0.68</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>4,849</td>
<td>2.09</td>
<td>2.38</td>
<td>3.50</td>
<td>0.69 (0.44 - 1.07)</td>
<td>0.71</td>
<td>0.82 (0.59 - 1.16)</td>
<td>0.44</td>
</tr>
<tr>
<td>No history of CHF</td>
<td>16,933</td>
<td>1.47</td>
<td>1.25</td>
<td>1.52</td>
<td>0.96 (0.69 - 1.33)</td>
<td>0.14</td>
<td>0.82 (0.59 - 1.16)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of CHF</td>
<td>4,226</td>
<td>2.21</td>
<td>2.37</td>
<td>3.45</td>
<td>0.63 (0.40 - 1.00)</td>
<td>0.66</td>
<td>0.78 (0.58 - 1.05)</td>
<td>0.35</td>
</tr>
<tr>
<td>No history of AF</td>
<td>20,293</td>
<td>1.51</td>
<td>1.33</td>
<td>1.68</td>
<td>0.89 (0.67 - 1.19)</td>
<td>0.09</td>
<td>0.78 (0.58 - 1.05)</td>
<td>0.35</td>
</tr>
<tr>
<td>History of AF</td>
<td>867</td>
<td>3.87</td>
<td>4.80</td>
<td>8.26</td>
<td>0.44 (0.21 - 0.94)</td>
<td>0.55</td>
<td>0.55 (0.27 - 1.11)</td>
<td>0.79</td>
</tr>
<tr>
<td>No prior stroke/TIA</td>
<td>20,813</td>
<td>1.53</td>
<td>1.45</td>
<td>1.89</td>
<td>0.80 (0.61 - 1.04)</td>
<td>0.36</td>
<td>0.75 (0.57 - 0.99)</td>
<td>0.79</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>347</td>
<td>6.51</td>
<td>2.94</td>
<td>5.00</td>
<td>1.40 (0.45 - 4.42)</td>
<td>0.63</td>
<td>0.63 (0.15 - 2.62)</td>
<td></td>
</tr>
</tbody>
</table>
**Supplemental Table 2 – Stroke Outcomes with Ticagrelor 90 mg Twice Daily**

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Placebo N=7067 n (3 yr KM%)</th>
<th>Ticagrelor 90 mg N=7067 n (3 yr KM%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>122 (1.94)</td>
<td>100 (1.61)</td>
<td>0.82</td>
<td>P=0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.63 – 1.07)</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>103 (1.65)</td>
<td>88 (1.41)</td>
<td>0.85</td>
<td>P=0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.64 – 1.14)</td>
<td></td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>21 (0.34)</td>
<td>18 (0.33)</td>
<td>0.86</td>
<td>P=0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.46 – 1.61)</td>
<td></td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
<td>17 (0.29)</td>
<td>17 (0.27)</td>
<td>1.00</td>
<td>P=1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.51 – 1.96)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Placebo N=6996 n (3 yr KM%)</th>
<th>Ticagrelor 90 mg N=6988 n (3 yr KM%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Stroke</td>
<td>9 (0.19)</td>
<td>4 (0.07)</td>
<td>0.51</td>
<td>P=0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.16 – 1.64)</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke with Hemorrhagic Conversion</td>
<td>5 (0.11)</td>
<td>4 (0.08)</td>
<td>0.92</td>
<td>P=0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (0.25 – 3.43)</td>
<td></td>
</tr>
</tbody>
</table>
### Supplemental Table 3 – Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population for this Analysis</th>
<th>Intervention</th>
<th>Patients in this Analysis</th>
<th>Strokes in this Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA⁸</td>
<td>Patients with prior MI</td>
<td>Clopidogrel vs. placebo on a background of ASA</td>
<td>3,846</td>
<td>75</td>
</tr>
<tr>
<td>TRA2P-TIMI 50⁹</td>
<td>Patients randomized in the MI stratum with no history of stroke/TIA</td>
<td>Vorapaxar vs. placebo on a background of ASA monotherapy or DAPT (ASA and clopidogrel)</td>
<td>16,897</td>
<td>164</td>
</tr>
<tr>
<td>DAPT¹⁰</td>
<td>Patients with coronary disease undergoing stenting</td>
<td>Withdrawal vs. continuation of P2Y₁₂ inhibition in patients tolerating therapy at 12 months after coronary stenting</td>
<td>9,961</td>
<td>80</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>Patients with an MI 1-3 years prior</td>
<td>Ticagrelor 60 mg twice daily, placebo</td>
<td>14,112</td>
<td>213</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>44,816</strong></td>
<td><strong>532</strong></td>
</tr>
</tbody>
</table>
Supplemental Figure Legends

Supplemental Figure 1
Distribution of stroke types occurring during follow up

Supplemental Figure 2
Distribution of Modified Rankin Score by treatment shown as a proportion of total stroke events
Supplemental Figure 1 – Distribution of Stroke Events by Type

N= 14,112 Patients
Randomized to ticagrelor 60 mg twice daily or placebo
Supplemental Figure 2 – Distribution of Modified Rankin Score by Treatment

Rankin Score at 30 Days by Treatment

Placebo
Strokes with MRS at 30 Days = 99

Ticagrelor 60 mg
Strokes with MRS at 30 Days = 72

Percent (%)