Antiplatelet Use and Ischemic Stroke Risk in Minor Stroke or Transient Ischemic Attack: A Post Hoc Analysis of the POINT Trial

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BACKGROUND AND PURPOSE: Dual antiplatelet therapy has been shown to reduce the risk of recurrent stroke in patients with minor stroke or transient ischemic attack. However, whether the effect of dual antiplatelet therapy is modified by pretreatment antiplatelet status is unclear.

METHODS: This is a post hoc analysis of the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke). Patients were divided into 2 groups based on pretreatment antiplatelet use. The primary outcome was ischemic stroke within 90 days of randomization.

RESULTS: We included 4881 patients of whom 41% belonged to the no pretreatment antiplatelet. Ischemic stroke occurred in 6% and 5% in the antiplatelet pretreatment and no antiplatelet pretreatment, respectively. Antiplatelet pretreatment was not associated with the risk of ischemic stroke (adjusted hazard ratio, 1.05 [95% CI, 0.81–1.37]) or risk of major hemorrhage (hazard ratio, 1.10 [95% CI, 0.55–2.21]; \(P=0.794\)). The effect of dual antiplatelet therapy on recurrent ischemic stroke risk was not different in patients who were on antiplatelet before randomization (adjusted hazard ratio, 0.69 [95% CI, 0.50–0.94]) as opposed to those who were not (adjusted hazard ratio, 0.75 [95% CI, 0.50–1.12]), \(P\) for interaction = 0.685.

CONCLUSIONS: In patients with minor stroke and high-risk transient ischemic attack, dual antiplatelet therapy reduces the risk of ischemic stroke regardless of premorbid antiplatelet use.

Key Words: blood platelets □ brain ischemia □ ischemic attack, transient □ ischemic stroke □ stroke

Dual antiplatelet therapy (DAPT) has been shown to reduce the risk of recurrent stroke in patients with minor stroke and high-risk transient ischemic attack (TIA) compared with monotherapy.1–3 Around a third of patients presenting with TIA or minor ischemic stroke are on antiplatelet before the index event.4 An important question to address is whether antiplatelet monotherapy may be sufficient in patients who have a cerebrovascular ischemic event and are antiplatelet naïve.

In this post hoc analysis of the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke), we sought to determine whether antiplatelet therapy status before randomization modified the effect of DAPT on the risk of recurrent stroke. We aim to provide more detailed analyses than what was provided in the original POINT trial prespecified subgroup analyses results.

METHODS

This study was exempt from the institutional review board review because only preexisting, deidentified data were used.
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Data from this study are available upon request to the National Institute of Neurological Disorder and Stroke. This study was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (see the Data Supplement).

Cohort
This was a post hoc analysis of data from the POINT trial. The protocol of the trial has been published previously.1 For the purpose of the study, we included all patients enrolled in POINT with data available on antiplatelet medication use before randomization, as well as aspirin treatment during the trial.

Primary Predictors
The primary predictor was antiplatelet pretreatment, which was defined as patient’s reported use of antiplatelet therapy (aspirin, clopidogrel, dipyridamole, or ticlopidine) at the time of the qualifying index event and was determined by patient or proxy interview at the time of trial enrollment.

Outcomes
Patients in POINT were followed for 90 days from randomization. The primary outcome was ischemic stroke during follow-up. Ischemic stroke during follow-up was based on a new or rapid worsening of focal neurological deficit with clinical or imaging evidence of infarction. The secondary outcome is the risk of major hemorrhage (defined as symptomatic intracranial hemorrhage, intraocular bleeding causing visual acuity loss, transfusion of ≥2 units of red blood cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death attributable to bleeding).

Table. Baseline Characteristics and Outcomes of Patients On Versus Off Antiplatelet Before Enrollment

<table>
<thead>
<tr>
<th></th>
<th>Antiplatelet pretreatment (n=2849)</th>
<th>No antiplatelet pretreatment (n=2032)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y; mean±SD</td>
<td>66.3±12.8</td>
<td>62.2±13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>1547 (54%)</td>
<td>1139 (56%)</td>
<td>0.225</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>White</td>
<td>2083 (75%)</td>
<td>1472 (75%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>592 (21%)</td>
<td>374 (19%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>77 (3%)</td>
<td>67 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity, n (%)</td>
<td>200 (7%)</td>
<td>187 (10%)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>2141 (75%)</td>
<td>1232 (61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>920 (32%)</td>
<td>420 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of coronary artery disease, n (%)</td>
<td>443 (16%)</td>
<td>54 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of congestive heart failure, n (%)</td>
<td>108 (4%)</td>
<td>18 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active smoking</td>
<td>522 (18%)</td>
<td>482 (24%)</td>
<td></td>
</tr>
<tr>
<td>Past smoking history</td>
<td>875 (31%)</td>
<td>457 (23%)</td>
<td></td>
</tr>
<tr>
<td>Randomized to clopidogrel, n (%)</td>
<td>1434 (50%)</td>
<td>998 (49%)</td>
<td>0.401</td>
</tr>
<tr>
<td>Ischemic stroke within 90 d, n (%)</td>
<td>164 (6%)</td>
<td>103 (5%)</td>
<td>0.298</td>
</tr>
</tbody>
</table>

Figure 1. Ischemic stroke outcome according to antiplatelet pretreatment.
This Figure shows the cumulative incidence of ischemic stroke outcomes in the no antiplatelet pretreatment group (A) and antiplatelet pretreatment group (B). Inset graphs show the same data on an expanded y axis.
Statistical Analysis
We report descriptive statistics using means (SD) and medians (interquartile range) for normally and non-normally distributed continuous variables, respectively. Discrete variables are reported using counts (percentage [%]). Unadjusted comparisons were conducted using t-tests for continuous variables and \( \chi^2 \) tests for categorical variables. We fit Cox proportional hazards models to the outcome of recurrent ischemic stroke events and report unadjusted and adjusted hazard ratios (HRs). In all adjusted models, we adjusted for the following covariates: age, sex, ethnicity, Black race, history of hypertension, history of diabetes, history of coronary artery disease, history of congestive heart failure, and active smoking. We used Schoenfeld residuals to confirm the proportional hazards assumption of the adjusted Cox models. We also performed subgroup analyses to determine whether the effect of clopidogrel (versus placebo) on recurrent ischemic stroke risk was modified by prerandomization antiplatelet therapy. All analyses were conducted using SPSS 25.0 (Chicago, IL), and \( P<0.05 \) was considered statistically significant.

RESULTS
Univariate Analyses
We included a total of 4881 patients in the final analysis. Baseline characteristics of both no antiplatelet pretreatment and antiplatelet pretreatment groups are depicted in the Table. Pretreatment antiplatelet included aspirin (2737 patients), clopidogrel (32 patients), dipyridamole (3 patients), and DAPT (77 patients).

Ischemic stroke outcomes occurred in 6% in the antiplatelet pretreatment group and 5% in the no antiplatelet pretreatment group (\( P=0.29 \)).

Antiplatelet Therapy Before Randomization and Ischemic Stroke Risk
Antiplatelet pretreatment was not associated with the risk of ischemic stroke in both unadjusted (HR, 1.13 [95% CI, 0.89–1.45]; \( P=0.317 \)) and adjusted models (HR, 1.05 [95% CI, 0.81–1.37]; \( P=0.701 \)). Results were similar regardless of the index event (TIA versus minor stroke). Moreover, antiplatelet pretreatment was not associated with significantly increased risk of major hemorrhage (HR, 1.10 [95% CI, 0.55–2.21]; \( P=0.794 \)).

In adjusted models, the effect of adding clopidogrel (versus placebo) on recurrent ischemic stroke risk was not different in patients who were on antiplatelet before randomization (adjusted HR, 0.68 [95% CI, 0.50–0.94]; \( P=0.809 \)) as opposed to those who were not (adjusted HR, 0.75 [95% CI, 0.50–1.12]; \( P=0.895 \); \( P \) for interaction, 0.685; Figures 1 and 2).

DISCUSSION
In this post hoc analysis of the POINT trial, we demonstrated that the effect of DAPT on reducing ischemic stroke risk was not different between patients with versus without antiplatelet therapy before randomization.

There is growing evidence supporting the benefit of DAPT after minor stroke or TIA.\(^1,5,6\) Three randomized trials demonstrated reduction of ischemic events with DAPT compared with monotherapy.\(^1,3,6\) Based on the results of these trials, DAPT has become the standard of care for patients with minor stroke or TIA.

Pretreatment antiplatelet therapy is common among patients presenting with ischemic strokes, and the existing literature reported conflicting results regarding the interaction between pretreatment antiplatelet therapy and the effect of DAPT on ischemic stroke outcome. In the THALES trial (Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA), the results differed according to aspirin treatment and DAPT was associated with stroke reduction only in patients with no pretreatment antiplatelet.\(^3\) Conversely, there was no interaction between pretreatment aspirin and DAPT in the CHANCE trial (Clopidogrel With Aspirin in Acute Minor Stroke or TIA).\(^6\) In this study, we found that pretreatment antiplatelet therapy was not associated with the risk of recurrent ischemic stroke. More importantly, the effect of DAPT appeared to be consistent regardless of pretreatment antiplatelet therapy. Our study adds additional evidence that patients with minor stroke...
or TIA should be started on DAPT irrespective of their pretreatment antiplatelet status.

Limitations
Limitations include imbalances between the antiplatelet pretreatment and no antiplatelet pretreatment groups, which could have affected our results in an unpredictable manner despite adjustment for possible confounders.

Conclusions
This study indicates that in patients with minor stroke and high-risk TIA, DAPT reduces the risk of ischemic stroke regardless of premorbid antiplatelet use.

ARTICLE INFORMATION
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Disclosures
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Supplemental Materials
STROBE Checklist

REFERENCES