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

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Abstract

Background and Purpose: Dual antiplatelet therapy (DAPT) has been shown to reduce the risk of recurrent stroke in patients with minor stroke or transient ischemic attack (TIA). However, whether the effect of DAPT is modified by pre-treatment antiplatelet status is unclear.

Methods: This is a post-hoc analysis of the POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial. Patients were divided into two groups based on pre-treatment 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 pre-treatment antiplatelet. Ischemic stroke occurred in 6% and 5% in the antiplatelet pre-treatment and no antiplatelet pre-treatment, respectively. Antiplatelet pre-treatment was not associated with the risk of ischemic stroke (adjusted HR 1.05; 95% CI 0.81–137) or risk of major hemorrhage (HR 1.10 95% CI 0.55 – 2.21, p = 0.794). The effect of DAPT on recurrent ischemic stroke risk was not different in patients who were on antiplatelet prior to randomization (adjusted HR, 0.69; 95% CI 0.50–0.94) as opposed to those who were not (adjusted HR, 0.75; 95% CI 0.50–1.12), p-value for interaction = 0.685.

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Supplemental Materials: STROBE Checklist

Conclusion: In patients with minor stroke and high-risk TIA, DAPT reduces the risk of ischemic stroke regardless of pre-morbid antiplatelet use.

Keywords

stroke; transient ischemic attack; antiplatelet

Introduction

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 to monotherapy. [1–3] Around a third of patients presenting with TIA or minor ischemic stroke are on antiplatelet prior to 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 (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial, we sought to determine whether antiplatelet therapy status prior to 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 institutional review board review because only pre-existing, de-identified data were used. 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 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 previously published.[1] For the purpose of the study, we included all patients enrolled in POINT with data available on antiplatelet medication use prior to randomization as well as aspirin treatment during the trial.

Primary Predictors—The primary predictor was antiplatelet pre-treatment, 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 a new or rapidly 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 or more units of red blood cells or an equivalent amount of whole

blood, hospitalization or prolongation of an existing hospitalization, or death attributable to bleeding).

Statistical Analysis: see Data Supplement.

Results

Univariate analyses

We included a total of 4881 patients in the final analysis. Baseline characteristics of both no antiplatelet pre-treatment and antiplatelet pre-treatment groups are depicted in Table 1. 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 pre-treatment group and 5% in the no- antiplatelet pre-treatment group (p=0.29).

Antiplatelet therapy prior to randomization and ischemic stroke risk

Antiplatelet pre-treatment 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 pre-treatment 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 prior to 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-value for interaction = 0.685 (Figures 1 & 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 prior to randomization. Furthermore, treatment with aspirin during the trial was associated with a lower risk of ischemic stroke and this effect was not different between patients randomized to clopidogrel versus placebo.

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 to 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.

Pre-treatment antiplatelet therapy is common among patients presenting with ischemic strokes and the existing literature reported conflicting results regarding the interaction between pre-treatment antiplatelet therapy and the effect of DAPT on ischemic stroke outcome. In the ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA (THALES) trial, the results differed according to aspirin treatment and DAPT was associated with stroke reduction only in patients with no pre-treatment antiplatelet.[3]

Conversely, there was no interaction between pre-treatment aspirin and DAPT in the clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial.[6] In this study, we found that pre-treatment antiplatelet therapy was not associated with the risk of recurrent ischemic stroke. More importantly, the effect of DAPT appeared to be consistent regardless of pre-treatment antiplatelet therapy. Our study adds additional evidence that patients with minor stroke or TIA should be started on DAPT irrespective of their pre-treatment antiplatelet status.

Limitations

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

Conclusion

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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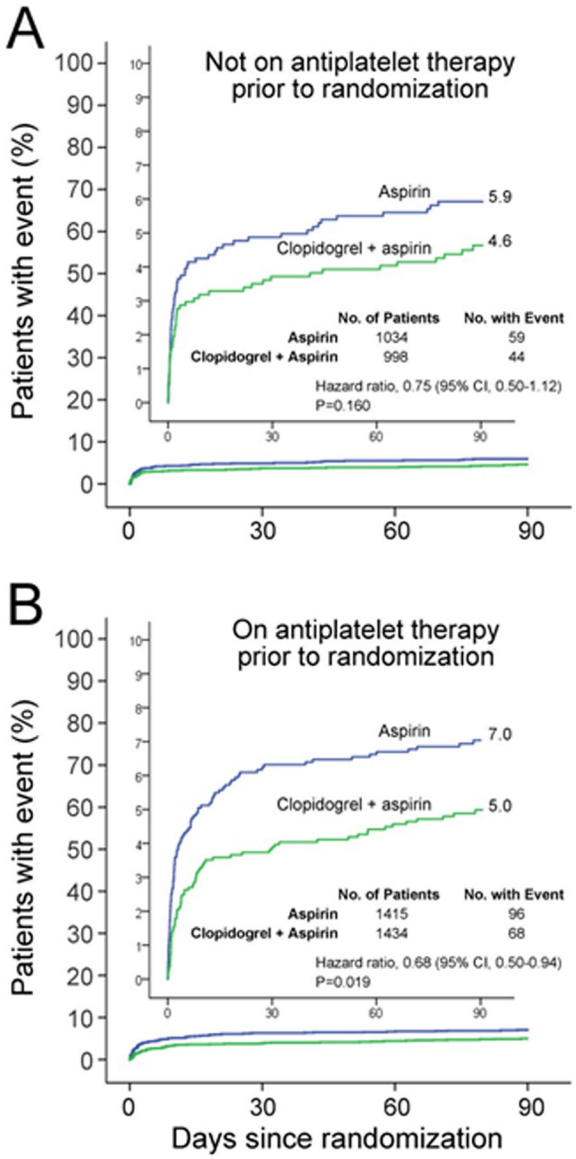

Figure 1.

Ischemic stroke outcome according to antiplatelet pre-treatment

Figure shows the cumulative incidence of ischemic stroke outcomes in the no antiplatelet pre-treatment group (A) and antiplatelet pre-treatment group (B). Inset graphs show the same data on an expanded y axis.

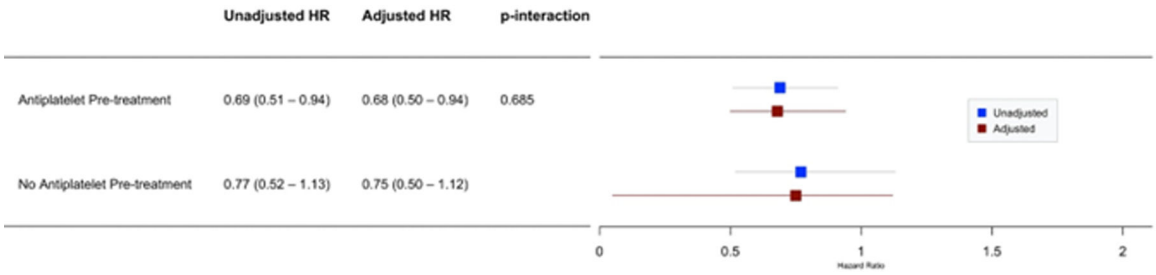

Figure 2.

Forest Plot showing unadjusted and adjusted cox regression models for the effect of clopidogrel treatment on ischemic stroke outcome stratified by antiplatelet pre-treatment status. HR indicates hazard ratio.

Table 1.

Baseline characteristics and outcomes of patients on versus off antiplatelet prior to enrollment

	Antiplatelet pre-treatment (n = 2849)	No antiplatelet pre-treatment (n = 2032)	p-value
Age (mean ± SD)	66.3 ± 12.8	62.2 ± 13.3	<0.001
Men (n (%))	1547 (54%)	1139 (56%)	0.225
Race (n (%))			0.017
White	2083 (75%)	1472 (75%)	
Black	592 (21%)	374 (19%)	
Asian	77 (3%)	67 (3%)	
Hispanic Ethnicity (n (%))	200 (7%)	187 (10%)	0.004
History of hypertension (n (%))	2141 (75%)	1232 (61%)	<0.001
History of diabetes (n (%))	920 (32%)	420 (21%)	<0.001
History of coronary artery disease (n (%))	443 (16%)	54 (3%)	<0.001
History of congestive heart failure (n (%))	108 (4%)	18 (1%)	<0.001
Smoking (n (%))			<0.001
Active smoking	522 (18%)	482 (24%)	
Past smoking history	875 (31%)	457 (23%)	
$ABCD^2$ score (median, IQR)	5 (4–6)	5 (4–6)	0.003
NIHSS score (median, IQR)	1 (0–2)	1 (0–2)	0.265
Randomized to clopidogrel (n (%))	1434 (50%)	998 (49%)	0.401
Ischemic stroke within 90 days (n (%))	164 (6%)	103 (5%)	0.298

NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation.