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Authors

Lang, Adam Edward
de Havenon, Adam
Grory, Brian Mac
et al.

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Subsequent ischemic stroke and tobacco smoking: A secondary analysis of the POINT trial

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Adam Edward Lang[1,2] (iD), Adam de Havenon[3] (iD),
Brian Mac Grory[4], Nils Henninger[5,6], Liqi Shu[7], Karen L. Furie[7],
J Donald Easton[8], Anthony Kim[8], S Claiborne Johnston[9]
and Shadi Yaghi[7]

Abstract

Background: The aim of this study was to determine the effect of smoking status on subsequent stroke risk in patients with minor ischemic stroke or TIA and to determine whether smoking modifies the effect of clopidogrel-based DAPT on subsequent stroke risk.

Methods: This was a post-hoc analysis of the Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, which had a 90-day follow-up period. We used multivariable Cox regression and subgroup interaction analysis to determine the effect of smoking on the risk of subsequent ischemic stroke and major hemorrhage, respectively.

Results: Data from 4877 participants enrolled in the POINT trial were analyzed. Among these, 1004 were current smokers and 3873 were non-smokers at the time of index event. Smoking was associated with a non-significant trend toward an increased risk of subsequent ischemic stroke during follow up (adjusted HR, 1.31 (95% CI, 0.97–1.78), $p = 0.076$). The effect of clopidogrel on ischemic stroke did not differ between non-smokers (HR, 0.74 (95% CI, 0.56–0.98), $p = 0.03$) and smokers (HR, 0.63 (95% CI, 0.37–1.05), $p = 0.078$), p for interaction = 0.572. Similarly, the effect of clopidogrel on major hemorrhage did not differ between non-smokers (hazard ratio, 1.67 (95% CI, 0.40–7.00), $p = 0.481$) and smokers (HR, 2.59 (95% CI, 1.08–6.21), $p = 0.032$), p for interaction = 0.613.

Conclusions: In this post-hoc analysis of the POINT trial we found that the effect of clopidogrel on reducing subsequent ischemic stroke as well as risk of major hemorrhage did not depend on smoking status, indicating that smokers benefit to a similar degree from DAPT as non-smokers.

Keywords
Smoking, tobacco, cigarettes, stroke, clopidogrel

[1]Department of Primary Care, McDonald Army Health Center, Fort Eustis, VA, USA
[2]Department of Family Medicine and Population Health, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
[3]Department of Neurology, Clinical Neurosciences Center, University of Utah, Salt Lake City, UT, USA
[4]Department of Neurology, Duke University School of Medicine, Durham, NC, USA
[5]Department of Neurology, University of Massachusetts Medical School, Worcester, MA, USA
[6]Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA
[7]Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI, USA
[8]Department of Neurology, University of California, San Francisco, Sandler Neurosciences Center, San Francisco, CA, USA
[9]Dell Medical School, University of Texas at Austin, Austin, TX, USA

Corresponding author:
Adam Edward Lang, Department of Primary Care, McDonald Army Health Center, 576 Jefferson Avenue, Fort Eustis, VA 23604-5548, USA.
Email: a.edward.lang@gmail.com

Background

Tobacco smoking is a well-established major risk factor for stroke.[1] While smoking is directly attributable to a quarter of strokes,[2] previous data suggested a more pronounced benefit from clopidogrel in smokers versus non-smokers for secondary stroke prevention. It has been hypothesized that smoking may increase the active metabolite of clopidogrel, which could reduce the risk of stroke but also increase the risk of hemorrhage.[3] Post hoc analyses of several large phase 3 trials suggested that, at 3-month follow-up, smokers on clopidogrel have a lower risk of subsequent stroke without increased hemorrhage risk compared to non-smokers.[3,4]

The aims of this study were to determine the effect of smoking status on the risk of subsequent ischemic stroke and major hemorrhage in patients with minor ischemic stroke or TIA. Specifically, we hypothesized that smoking improves the effect of clopidogrel-based dual antiplatelet therapy (DAPT) on subsequent stroke risk reduction and does not increase the risk of major hemorrhage. To test our hypothesis, we performed a post-hoc analysis of the Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, which compared clopidogrel plus aspirin (DAPT) to aspirin monotherapy for prevention of recurrent ischemic stroke, myocardial infarction, or vascular death within 3 months of a high-risk TIA or minor ischemic stroke. The detailed methodology of POINT has been previously described.[5] Because it has been questioned whether there are differences in the metabolism of clopidogrel among different ages, genders, races, and disease states[6–9] we also conducted several subgroup analyses to determine whether the effect of smoking on clopidogrel was more pronounced in these populations.

Methods

This is a post-hoc analysis of the POINT trial. Patients were excluded if smoking status was not reported. This analysis was deemed exempt from full review by the Rhode Island Hospital institutional review board given the use of previously published deidentified data.

Population

The POINT randomized controlled trial enrolled patients from 269 sites spanning four continents over 7 years, with 82.8% of the 4881 enrolled patients being from the United States. Patients were 18 years of age or older and experienced an acute ischemic stroke with a score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) or high-risk TIA within the 12 h prior to randomization to one of two groups, either clopidogrel plus aspirin or placebo plus aspirin.

Endpoint

The efficacy and safety outcomes assessed were subsequent ischemic stroke and major hemorrhage, respectively. These outcomes were also evaluated in subgroups related to age (<60 vs ≥60 years), gender (male vs female), race (Black vs White), and type 2 diabetes mellitus (absent vs present).

Exposure

We defined "current smoking" as the use of combustible tobacco products at the time of TIA or ischemic stroke. Non-smokers included both former smokers and never smokers.

Statistical analysis

We used multivariable Cox-regression to determine the effect of smoking on the risk of efficacy and safety outcomes. We performed interaction analyses to determine whether the effect of clopidogrel on these outcomes differed with respect to smoking status. Finally, we conducted additional subgroup analyses to determine whether smoking status affected the outcomes of interest in subjects with clinical factors that can impact the absorption and/or metabolism of clopidogrel to its active thiol metabolite, including age, gender, race, and history of type 2 diabetes mellitus. Kaplan-Meier survival curves of subsequent ischemic stroke in smoker and non-smoker were plotted. Since former smoker can be a pathophysiologically different group from never smoker, sensitivity analyses subgroup Cox regression were performed in current smoker and never smoker groups, and additionally in former smoker and never smoker. Schoenfeld residual test were performed to test for proportionality and accelerated failure-time parametric survival models were used if the Cox regression failed proportionality. Statistical analyses were performed using STATA (version 17, StataCorp) and $p < 0.05$ was used for statistically significance.

Results

Main results

Of 4881 patients enrolled in POINT, baseline smoking status was reported on 4877 patients. Among these, 1004 were current smokers and 3873 were non-smokers. Of non-smokers, 1332 were former smokers and 2541 were never smokers. The mean age in years was 64.6 ± 13.2 and 45% (2193/4877) were women. Current smokers were younger, and current and former smokers were more likely to be men. Further baseline characteristics can be found in Table 1. During 90-day follow-up, 266 subjects had a subsequent ischemic stroke and 33 had a major hemorrhage.

Table 1. Baseline characteristics and outcome between smokers and non-smokers on clopidogrel.

Characteristic	Smoking status, participants, no (%)		
	Smoker	Non-smoker	
		Former smoker	Never smoker
Total	1004	1332	2541
Demographic			
Age, mean (SD), years	57.9 (11.0)	67.6 (12.0)	65.6 (13.6)
Glucose, mean (SD), mg/dL	127.0 (60.5)	129.7 (57.9)	132.3 (62.2)
Sex			
Male	636 (63.3)	857 (64.3)	1191 (46.9)
Female	368 (36.7)	475 (35.7)	1350 (53.1)
Congestive heart failure	25 (2.5)	43 (3.2)	57 (2.2)
Coronary artery disease	88 (8.8)	213 (16.0)	196 (7.7)
Hypertension	631 (62.8)	990 (74.3)	1749 (68.8)
Diabetes mellitus	222 (22.1)	400 (30.0)	715 (28.1)
Infarct on imaging	442 (44.0)	496 (37.2)	853 (33.6)
Treatment randomization	496 (49.4)	675 (50.7)	1259 (49.5)

In univariable analysis, smoking did not confer a higher risk of subsequent ischemic stroke ((60/1004 (6.0%) vs 206/3873 (5.3%), $p=0.435$)) nor was it associated with an increased risk of major hemorrhage ((8/1004 (0.8%) vs 25/3873 (0.6%), $p=0.665$)) when compared to non-smoking. When compared to never smoking, smoking did not confer a higher risk of subsequent ischemic stroke ((60/1004 (6.0%) vs 141/2541 (5.5%), $p=0.620$)) nor were they associated with an increased risk of major hemorrhage ((8/1004 (0.8%) vs 17/2541 (0.7%), $p=0.660$)). When compared to never smoking, former smoking did not confer a higher risk of subsequent ischemic stroke ((65/1332 (4.9%) vs 141/2541 (5.5%), $p=0.378$)) nor was it associated with an increased risk of major hemorrhage ((8/1332 (0.6%) vs 17/2541 (0.7%), $p=1.000$)).

Association between smoking and ischemic stroke

In unadjusted Cox regression analysis, smokers (compared to non-smokers) did not have a significantly higher risk of ischemic stroke (hazard ratio, 1.14 (95% CI, 0.85–1.51), $p=0.387$). When adjusting for potential confounders, smoking was associated with a non-significant trend toward an increased risk of recurrent ischemic stroke during follow-up (adjusted hazard ratio, 1.31 (95% CI, 0.97–1.78), $p=0.076$).

The effect of smoking status on efficacy and safety of DAPT

In unadjusted analysis, the effect of clopidogrel-based DAPT on ischemic stroke risk was not significantly different in non-smokers (hazard ratio, 0.74 (95% CI, 0.56–0.98),

$p=0.03$) compared to smokers (hazard ratio, 0.63 (95% CI, 0.37–1.05), $p=0.078$), p for interaction $=0.572$ (Table 2). This is also visually demonstrated in Kaplan-Meier survival curve (Figure 1). In sensitivity analysis, after excluding former smokers (hazard ratio, 0.78 (95% CI, 0.48–1.28), $p=0.331$), the effect of clopidogrel-based DAPT on ischemic stroke risk was not significantly different in never smokers (hazard ratio, 0.34 (95% CI, 0.11–1.04), $p=0.059$), p for interaction $=0.555$. In addition, the effect of clopidogrel on major hemorrhage was not significantly different in non-smokers (hazard ratio, 1.67 (95% CI, 0.40–7.00), $p=0.481$) compared to smokers (hazard ratio, 2.59 (95% CI, 1.08–6.21), $p=0.032$), p for interaction $=0.613$. In sensitivity analysis, after excluding former smokers (hazard ratio, 2.97 (95% CI, 0.60–14.69), $p=0.183$), the effect of clopidogrel on major hemorrhage was not significantly different in never smokers (hazard ratio, 2.45 (95% CI, 0.86–6.95), $p=0.093$), p for interaction $=0.679$.

When controlling for age, sex, hypertension, and diabetes, the effect of smoking on ischemic stroke risk was not significantly different in participants on DAPT (adjusted hazard ratio, 1.13 (95% CI, 0.70–1.81), $p=0.628$) compared to those on aspirin (adjusted hazard ratio, 1.48 (95% CI, 1.00–2.18), $p=0.05$), p for interaction $=0.617$.

Discussion

We found that there was no difference in stroke outcomes at 90 days in smokers compared to non-smokers, as well as compared to the never smokers subgroup, on clopidogrel-based DAPT in this post-hoc analysis. These results do not align with the outcome of a meta-analysis showing that smokers had improved outcomes within 1 year of clopidogrel initiation, but not thereafter,[10] nor does it align with the "smoker's

Table 2. The effect of smoking on the efficacy of dual antiplatelet therapy for prevention of subsequent ischemic stroke in the full cohort and subgroups stratified by age, gender, race, and type 2 diabetes mellitus status.

	Smoker			Non-smoker		
	Number of patients	Hazard ratio (95% CI)	p-Value	Number of patients	Hazard ratio (95% CI)	p-Value
Total population	1004	0.63 (0.37, 1.05)	0.078	3873	0.74 (0.56, 0.98)	0.030
Subgroups						
Age, years						
<60	573	0.52 (0.26, 1.05)	0.067	1140	1.09 (0.63, 1.89)	0.756
≥60	431	0.81 (0.36, 1.80)	0.599	2733	0.65 (0.47, 0.90)	0.009
Gender						
Female	368	0.73 (0.31, 1.71)	0.466	1825	0.62 (0.41, 0.93)	0.020
Male	636	0.57 (0.30, 1.10)	0.096	2048	0.87 (0.60, 1.27)	0.469
Race						
Black	284	0.28 (0.10, 0.84)	0.023	681	0.73 (0.43, 1.24)	0.250
White	651	1.10 (0.57, 2.14)	0.78	2902	0.77 (0.55, 1.08)	0.128
T2DM status						
Has T2DM	222	0.86 (0.26, 2.83)	0.808	1115	0.78 (0.51, 1.19)	0.242
No T2DM	776	0.58 (0.33, 1.04)	0.077	2755	0.71 (0.49, 1.02)	0.064
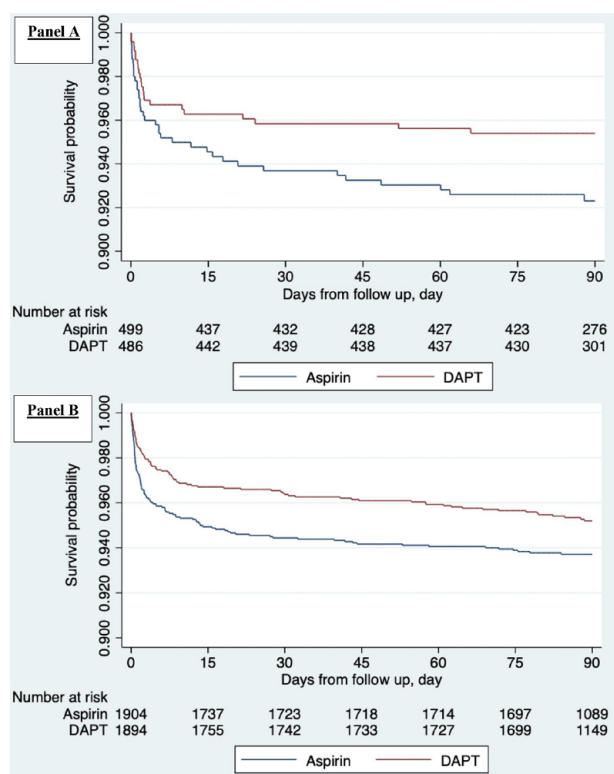
Figure 1. Kaplan-Meier survival curve of subsequent ischemic stroke for patients on Aspirin versus DAPT in smoker (Panel A) and non-smoker (Panel B).
DAPT: dual antiplatelet therapy.

paradox" premise (the idea that smoking may sometimes unexpectedly provide more favorable outcomes).[11] Moreover, we found no increased risk of stroke in smokers compared to non-smokers receiving clopidogrel. This may suggest that DAPT is effective regardless of smoking status.

Furthermore, the effect of clopidogrel on major hemorrhage risk did not differ based on smoking status in our study. This is consistent with outcomes in previous studies finding no increased risk of hemorrhage based on smoking status.[4,12,13] Therefore, any pharmacokinetic effect smoking may have specifically on enhancing the antiplatelet effects of clopidogrel does not appear to meaningfully affect clinical outcomes.

There was trend toward an increased risk of stroke in smokers overall, regardless of treatment group, and there was no significant interaction between clopidogrel and smoking status on stroke risk. There was also a trend toward a higher risk of stroke in those on aspirin alone. Together with prior observations this indicates that aspirin may not provide sufficient antiplatelet effects in smokers.[14–17]

We hypothesized that the effect of clopidogrel would exhibit its benefits to a greater extent on smokers in groups that have exhibited a predisposition to clopidogrel non-response or poor outcomes (age over 60 years, women, Black race, and those with a history of type 2 diabetes mellitus). Our analysis showed that the effect of clopidogrel on ischemic stroke outcomes in these subgroups did not differ based on smoking status.

A post-hoc analysis of the CHANCE trial, which compared DAPT to aspirin alone for treatment after minor ischemic stroke or high-risk transient ischemic attack (TIA), found those smoking over five cigarettes daily on DAPT had significantly lower incidence of stroke within 90 days compared to never smokers on DAPT.[3] This analysis of CHANCE did not report patient characteristics, making it unclear if the reported difference caused by smoking might be influenced by another variable. Additionally, the POINT trial did not include data on the frequency of cigarette use. It is possible that there is a threshold that depends on frequency of smoking at which the interaction between

smoking and clopidogrel occurs. Therefore, given it is likely that the POINT trial included some participants who smoked under five cigarettes daily, the average frequency may have been lower than that of the CHANCE population, and below the hypothetical threshold, resulting in no difference in outcomes.

Limitations

It is difficult to determine the true impact of smoking status on the effectiveness of clopidogrel at preventing stroke in our study for several reasons: (1) Baseline smoking was the only timepoint collected in the POINT trial; (2) smoking status may have varied over time (e.g. patients quitting at various timepoints before and after stroke, relapses, as well as intra- and inter-patient variability regarding the amount of tobacco smoked); and the fact that (3) recurrent stroke risk reduces over time after smoking cessation.[18–21] In this analysis, we are not aware of how many people quit after the initial event, nor are we able to quantify the number of cigarettes per day that participants were smoking, both of which could affect the interaction with clopidogrel over time and, independently, the overall stroke risk.

The POINT trial protocol recommended standard secondary prevention practices but did not specify what smoking cessation counseling and treatment was to be provided. Outcomes were assessed up to 90 days after the index TIA or minor ischemic stroke and data were not collected on post-baseline smoking status.[5] It is reasonable to assume some participants quit smoking after their initial event, given that only one third of smokers continue smoking after cardiovascular events.[22] Of strokes that occur within 90 days of a TIA, up to half occur within the first 2 days.[23–29] After cessation in those previously smoking over 20 cigarettes daily, CYP1A2 activity levels decrease exponentially and reach a new steady-state at 7 days post-cessation.[30] Therefore, it is likely that, within the highest risk time period of recurrent stroke, smoking status at the time of event still has an impact on clopidogrel pharmacokinetics regardless of status immediately post-event. However, after 1 week, in baseline smokers who quit immediate post-event, baseline smoking status likely has negligible effects on clopidogrel pharmacokinetics.

While we did account for variables that could impact outcomes related to the interaction between smoking and clopidogrel, there are likely others that were not accounted that require further investigation.

Conclusion

Ischemic stroke and major hemorrhage outcomes at 3 months in clopidogrel-based DAPT users versus aspirin monotherapy were not dependent on smoking status in this post-hoc analysis of POINT trial participants. The efficacy

outcome of stroke did not differ based on age, gender, race, or type 2 diabetes status. There was a trend toward an increased risk of stroke in smokers, but this was likely largely driven by the aspirin monotherapy group. Future studies may be improved by considering information on longitudinal smoking behaviors, particularly use at various time points after the index event.

ORCID iDs

Adam Edward Lang https://orcid.org/0000-0002-4347-6514
Adam de Havenon https://orcid.org/0000-0001-8178-8597

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