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ORIGINAL RESEARCH

Newly Diagnosed Atrial Fibrillation After Transient Ischemic Attack Versus Minor Ischemic Stroke in the POINT Trial

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BACKGROUND: Atrial fibrillation/flutter (AF) after transient ischemic attack (TIA) has not been well studied. We compared the likelihood of new AF diagnosis after ischemic stroke versus TIA.

METHODS AND RESULTS: The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial enrolled adults within 12 hours of minor ischemic stroke or high-risk TIA. Our exposure was index event type (ischemic stroke versus TIA). The primary analysis used the original trial definition of TIA (resolution of symptoms/signs). In secondary analyses, TIA cases with infarction on neuroimaging were reclassified as strokes. Our primary outcome was a new AF diagnosis, ascertained from adverse event and treatment interruption/discontinuation reports. We calculated C-statistics for variables associated with newly diagnosed AF. We used Kaplan-Meier survival statistics and Cox models adjusted for demographics and vascular risk factors. Excluding 49 subjects with baseline AF, 2746 patients had index stroke and 2086 patients had index TIA. During the 90-day follow-up, 106 patients had newly diagnosed AF. Cumulative risks of AF were 2.7% (95% CI, 2.1%–3.4%) after stroke and 2.0% (95% CI, 1.5%–2.7%) after TIA (P=0.15). After reclassifying index events by neuroimaging, cumulative AF risk was higher after stroke (2.7%; 95% CI, 2.2%–3.4%) than TIA (1.8%; 95% CI, 1.3%–2.5%) (P=0.04). Index event type had negligible predictive utility (C-statistic, 0.54).

CONCLUSIONS: Among patients with cerebral ischemia, the distinction between TIA versus minor stroke did not stratify the risk of subsequent AF diagnosis, implying that patients with TIA should undergo similar heart-rhythm monitoring strategies as patients with ischemic stroke.

Key Words: arrhythmia ■ atrial fibrillation ■ atrial flutter ■ ischemic stroke ■ transient ischemic attack

Atrial fibrillation/flutter (AF) is a strong risk factor for ischemic stroke. Diagnosis of AF in a patient who has already experienced a stroke or transient ischemic attack (TIA) usually changes antithrombotic management from antiplatelet therapy to anticoagulant therapy[1,2] because numerous randomized clinical trials have shown that anticoagulation is superior to antiplatelet therapy for stroke prevention in patients with clinically apparent AF.[3]

Prior studies have shown that a new diagnosis of AF is established in almost one quarter of patients with a recent ischemic stroke or TIA.[4] However, most patients in these studies had experienced a stroke as opposed to a TIA, and rates of AF detection after TIA have not been well studied. In addition, although newly diagnosed AF has been associated with stroke recurrence in patients with an index stroke,[5,6] it is unknown whether this holds true after TIA. Addressing these knowledge gaps is important because optimal strategies for monitoring patients with stroke/TIA for AF remain unsettled.[7,8] We therefore compared rates of new AF diagnosis in patients with TIA versus ischemic stroke in the POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial.

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For Sources of Funding and Disclosures, see page 6.

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CLINICAL PERSPECTIVE

What Is New?

- This study provides novel findings suggesting that the likelihood of detecting atrial fibrillation/flutter is broadly similar after a transient ischemic attack versus an ischemic stroke, and distinguishing between these 2 types of cerebral ischemia does not help predict who will go on to receive a diagnosis of atrial fibrillation/flutter.

What Are the Clinical Implications?

- Our findings imply that decisions about heart-rhythm monitoring for detecting atrial fibrillation/flutter as a cause of cerebral ischemia should apply similarly to both patients with ischemic stroke and patients with transient ischemic attack.

Nonstandard Abbreviations and Acronyms

CRYSTAL-AF	Cryptogenic Stroke and Underlying AF
EMBRACE	30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event
POINT	Platelet-Oriented Inhibition in New TIA or Minor Ischemic Stroke

METHODS

Design

The POINT trial was a randomized clinical trial that compared clopidogrel versus placebo for the prevention of major ischemic events after minor ischemic stroke or high-risk TIA; all patients received aspirin therapy.[9] From 2010 through 2017, 4881 patients were enrolled at 269 sites in 10 countries and followed up for 90 days. The trial was approved by the ethics committee at each participating site, and all patients provided written consent. The trial was funded by the National Institute of Neurological Disorders and Stroke. The Weill Cornell Medicine institutional review board approved this analysis of POINT trial data. The deidentified data used for this analysis are available by request to National Institute of Neurological Disorders and Stroke, and the analytical code is available on reasonable request to the corresponding author.

Patient Population

The POINT trial randomized patients aged ≥18 years within 12 hours after the onset of a minor ischemic stroke (National Institutes of Health Stroke Scale score,[10] 0–3) or high-risk TIA (ABCD^2 score,[11] ≥4). Patients who were candidates for thrombolysis, thrombectomy, or carotid endarterectomy were excluded, as were patients requiring anticoagulant therapy. Brain imaging was required before randomization to rule out intracranial hemorrhage or a nonvascular cause of the patient's symptoms. For this analysis, we excluded patients who had known AF at baseline but were randomized because long-term anticoagulant therapy was not planned.

Measurements

Newly diagnosed AF after randomization was ascertained on the basis of adverse event reports and indications for study drug interruption (ie, patients who were switched to anticoagulant therapy after detection of incident atrial fibrillation). All serious adverse events occurring until the end of study participation were recorded by site principal investigators or study coordinators on an online case report form within 24 hours of discovery of the event. We performed a free-text search of adverse event report forms and treatment interruption/discontinuation report forms for the following terms: *AF*, *FIB*, *Fib*, *fib*, *FLUTTER*, *Flutter*, or *flutter*. All potential AF cases identified by these broad search terms were then manually reviewed to confirm that the site investigator was describing AF. AF was also ascertained from reports of baseline ECGs; in our primary analysis, AF cases documented on the day of randomization were considered preexisting and were excluded, but in a sensitivity analysis, we included these AF cases in our outcome.

Postrandomization ischemic stroke was adjudicated by an end point adjudication committee blinded to treatment assignment, and was defined as follows: (1) the rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a nonischemic cause or (2) the rapid worsening of an existing focal neurological deficit judged to be attributable to a new infarction.

The index qualifying event was classified as either a minor ischemic stroke or a high-risk TIA. In the POINT trial, the index event was classified as a TIA if neurological symptoms and signs had completely resolved by the time of randomization, and as an ischemic stroke if symptoms and signs had not resolved. For our study, we performed a secondary analysis in which patients with TIA with visible brain infarction (as reported by site investigators) were reclassified into the category of ischemic stroke, in line with updated definitions of stroke and TIA that were introduced after the start of

the POINT trial.[12] Visible brain infarction was classified as present or absent by site investigators after review of baseline computed tomography or magnetic resonance imaging obtained during routine clinical care. Study treatment assignment was classified as clopidogrel or placebo. Study region was classified as in the United States versus outside the United States. Other variables used in our analysis were age, sex, race, ethnicity, hypertension, diabetes mellitus, coronary artery disease, heart failure, valvular heart disease, and tobacco use.

Statistical Analysis

First, we examined the association between the qualifying event type (minor ischemic stroke versus high-risk TIA) and newly diagnosed AF after randomization. We used nonparametric receiver operating curve analyses and C-statistics to examine discrimination for newly diagnosed AF. Kaplan-Meier statistics and the log-rank test were used to compare the cumulative risk of AF after ischemic stroke versus TIA. Participants were censored at the time of recurrent ischemic stroke because such an event may have prompted more intensive measures to ascertain AF. For the same reason, cases of AF diagnosed on the same day as a recurrent ischemic stroke were not included in the outcome variable; in a sensitivity analysis, we did include AF cases diagnosed on the same day as a recurrent ischemic stroke. Cox proportional hazards models were used to examine the association between ischemic stroke (in comparison to TIA) and AF after adjustment for age, sex, race, ethnicity, study treatment assignment (clopidogrel or placebo), region (United States versus outside the United States), hypertension, diabetes mellitus, coronary artery disease, heart failure, valvular heart disease, and tobacco use. Second, we used a similar model with the same covariates to examine the association between newly diagnosed AF after randomization and postrandomization ischemic stroke. In this analysis, newly diagnosed AF was treated as a time-varying covariate. Cases of AF diagnosed on the same day as a recurrent ischemic stroke were not included in the exposure variable to reduce ascertainment bias. This was a post hoc analysis, there was no adjustment for multiple hypothesis testing, and $P<0.05$ was considered significant.

RESULTS

Of the 4881 POINT trial subjects, we excluded 49 who had known AF at baseline and were randomized because the treating clinicians were not planning on long-term anticoagulant therapy. Among the 4832 remaining patients included in this analysis, the 2746 whose qualifying event was an ischemic stroke were slightly younger (mean age, 63 versus 66 years), more likely to be men, less likely to have coronary artery disease, and more likely to have been enrolled at a non-US site (Table 1). During the 90-day postrandomization follow-up period, 106 patients were newly diagnosed with AF, of whom 39 had been enrolled after an index TIA and 67 after an index ischemic stroke. The 106 patients with newly diagnosed AF were significantly older (mean age, 72 versus 64 years) and more likely to have been enrolled at a non-US site (Table 2).

The cumulative risk of newly diagnosed AF did not differ significantly by index event type ($P=0.15$), with 2.7% (95% CI, 2.1%–3.4%) of patients with ischemic stroke and 2.0% (95% CI, 1.5%–2.7%) of patients with TIA receiving a new diagnosis of AF by 90 days after randomization (Figure). After adjustment for covariates, there was a nonsignificant association between ischemic stroke as the qualifying event and postrandomization AF (hazard ratio [HR], 1.48; 95% CI, 0.99–2.20) (Table 3).

After reclassifying the index event type based on the presence of visible brain infarction on baseline imaging, there were 3042 patients with ischemic stroke and 1790 patients with TIA. In this analysis using updated definitions of TIA and ischemic stroke, the 90-day cumulative risk of newly diagnosed AF was significantly higher after ischemic stroke (2.7%; 95% CI,

Table 1. Baseline Characteristics of Patients in the POINT Trial, Stratified by Index Event

Characteristic*	Ischemic Stroke (N=2746)	Transient Ischemic Attack (N=2086)	*P* Value
Age, mean (SD), y	63 (13)	66 (13)	<0.001
Women	1181 (43.0)	986 (47.3)	0.003
Race			0.21
White	1977 (72.0)	1545 (74.1)	
Black	551 (20.1)	403 (19.3)	
Other†	128 (4.7)	87 (4.2)	
Unknown/Not Reported	90 (3.3)	51 (2.4)	
Hispanic ethnicity	228 (8.3)	156 (7.5)	0.57
Hypertension	1863 (67.8)	1469 (70.4)	0.06
Diabetes mellitus	730 (26.6)	594 (28.5)	0.14
Coronary artery disease	246 (9.0)	235 (11.3)	0.008
Heart failure	70 (2.6)	47 (2.3)	0.51
Valvular heart disease	41 (1.5)	35 (1.7)	0.61
Tobacco use	732 (26.7)	583 (28.0)	0.32
Enrolled at US site	2363 (86.1)	1872 (89.7)	<0.001
Study assignment to clopidogrel	1358 (49.5)	1043 (50.0)	0.71

POINT indicates Platelet-Oriented Inhibition in New TIA (Transient Ischemic Attack) or Minor Ischemic Stroke.

*Data are presented as number (percentage) unless otherwise specified.

†Includes Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, more than 1 race, and other.

Table 2. Baseline Characteristics of Patients in the POINT Trial, Stratified by Newly Diagnosed AF After Randomization

Characteristic*	New AF Diagnosis (N=106)	No AF Diagnosis (N=4726)	*P* Value
Age, mean (SD), y	72 (12)	64 (13)	<0.001
Women	46 (43.4)	2121 (44.9)	0.76
Race			0.26
White	85 (80.2)	3437 (72.7)	
Black	14 (13.2)	940 (19.9)	
Other†	3 (2.8)	212 (4.5)	
Unknown/Not Reported	4 (3.8)	137 (2.9)	
Hispanic ethnicity	10 (9.4)	374 (7.9)	0.56
Hypertension	75 (70.8)	3257 (68.9)	0.69
Diabetes mellitus	29 (27.4)	1295 (27.4)	0.99
Coronary artery disease	15 (14.2)	466 (9.9)	0.15
Heart failure	5 (4.7)	112 (2.4)	0.12
Valvular heart disease	4 (3.8)	72 (1.5)	0.07
Tobacco use	32 (30.2)	1283 (27.2)	0.49
Enrolled at US site	85 (80.2)	4150 (87.8)	0.02
Study assignment to clopidogrel	58 (54.7)	2343 (49.6)	0.30

AF indicates atrial fibrillation/flutter; and POINT, Platelet-Oriented Inhibition in New TIA (Transient Ischemic Attack) or Minor Ischemic Stroke.

*Data are presented as number (percentage) unless otherwise specified.

†Includes Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, more than 1 race, and other.

2.2%–3.4%) than after TIA (1.8%; 95% CI, 1.3%–2.5%) (*P*=0.04). After adjustment for covariates, there was a significant association between the updated definition of ischemic stroke as the qualifying event and postrandomization AF (HR, 1.73; 95% CI, 1.13–2.65) (Table 3).

In our multivariable model, there was a strong association between age and postrandomization AF (HR per 1-year increase, 1.05; 95% CI, 1.04–1.07). The predictive utility of age (C-statistic, 0.68; 95% CI, 0.63–0.73) was significantly greater than that of the index event type (ie, ischemic stroke versus TIA), even using the new definitions incorporating neuroimaging (C-statistic, 0.54; 95% CI, 0.50–0.59) (Table 4).

Of the 106 patients diagnosed with AF, 99 (93%) were instructed to stop study drug and start anticoagulant therapy. During the 90-day postrandomization follow-up period, 264 patients had an ischemic stroke, 3 of whom had a preceding postrandomization diagnosis of AF. The cumulative risk of ischemic stroke did not differ significantly by new AF status (*P*=0.77), with 12.9% (95% CI, 4.2%–36.3%) of patients with newly diagnosed AF and 5.7% (95% CI, 5.1%–6.4%) of patients without AF experiencing an ischemic stroke by 90 days after randomization. After adjustment for covariates, there was no association between newly diagnosed AF and postrandomization ischemic stroke (HR, 1.2; 95% CI, 0.4–3.6).

In a sensitivity analysis that included AF cases diagnosed on the same day as a recurrent ischemic stroke, there was only 1 additional AF case and the results were similar to the analyses reported above. In a sensitivity analysis that included AF cases documented by ECG on the day of randomization, there were 9 additional AF cases and the results were similar to the analyses reported above.

DISCUSSION

Among participants in a large, multicenter, randomized clinical trial, there was no significant difference in rates of newly diagnosed AF after TIA versus after ischemic stroke when these events were classified using traditional definitions. When using updated definitions of TIA and stroke that incorporated neuroimaging findings,[12] newly diagnosed AF was more common after stroke, but absolute differences in cumulative risk were small and the distinction between stroke and TIA had negligible predictive utility. More than 90% of patients discovered to have AF were prescribed anticoagulant therapy, and in this management context, a new diagnosis of AF after the index stroke or TIA was not associated with the risk of subsequent ischemic stroke.

Although numerous studies have examined the yield of various heart-rhythm monitoring strategies to detect AF after stroke, slightly fewer than half of such studies have included patients with both TIA and ischemic stroke.[4] Few have reported results stratified by TIA versus stroke, in many cases because the sample sizes were too small to allow subgroup analyses. The few studies to have reported AF detection rates separately in patients with stroke versus patients with TIA did not adjust for potential confounders.[13–16] Of the available randomized clinical trials comparing heart-rhythm monitoring strategies after stroke or TIA, most did not report subgroup analyses stratified by stroke versus TIA.[1,17,18] The CRYSTAL-AF (Cryptogenic Stroke and Underlying AF) trial found no evidence of an interaction between index event type and the yield of prolonged monitoring, although it did not compare rates between the index TIA versus index stroke groups. Therefore, it has been difficult to draw meaningful conclusions about the relative utility of heart-rhythm monitoring in these 2 populations. In this context, our study provides novel findings suggesting that the likelihood of AF detection is broadly similar after an index TIA versus an index ischemic stroke, and that distinguishing between index TIA versus index stroke does not help predict who will go on to receive an AF diagnosis.

Our findings imply that decisions about heart-rhythm monitoring for detecting AF as a cause of

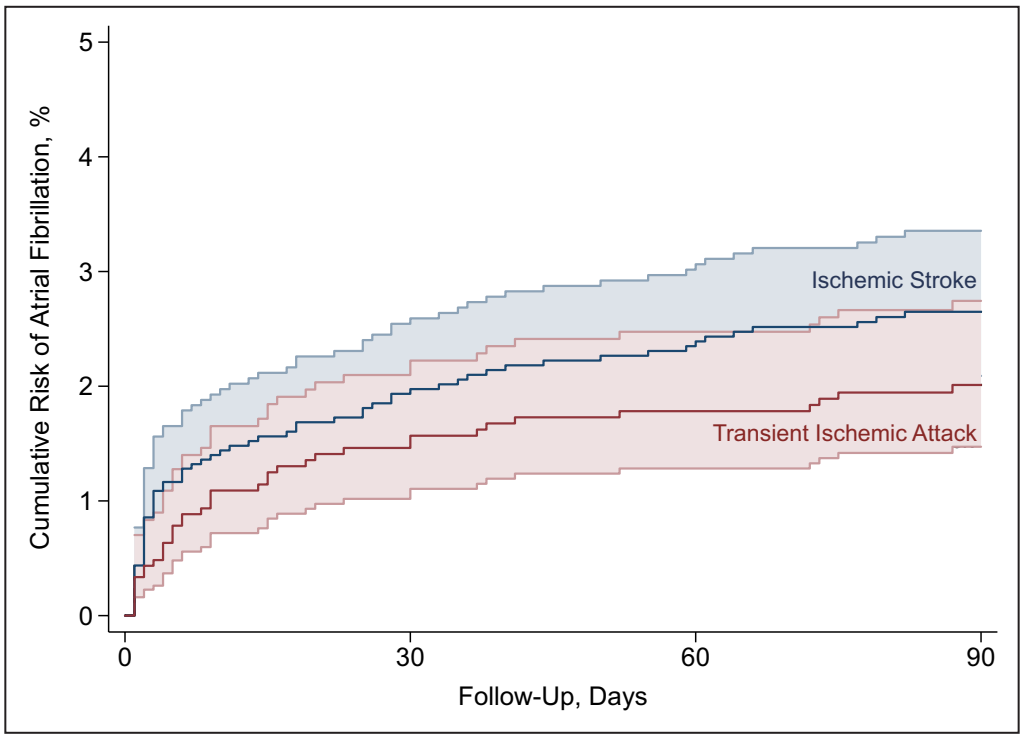

Figure. Cumulative rates of atrial fibrillation/flutter among patients enrolled in the POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial, stratified by index event.

cerebral ischemia should apply similarly to both patients with TIA and patients with ischemic stroke. Although patients with TIA have been excluded from most prior studies on heart-rhythm monitoring after a cerebrovascular event, our findings support current recommendations that empirically apply to both patients with stroke and patients with TIA.[7] We found no association between poststroke/TIA AF cases and subsequent ischemic stroke, but >90% of patients were started on anticoagulation, so our study cannot speak to the natural history of untreated AF in this population. The practice pattern on anticoagulation for AF in the POINT trial reinforces findings from the CRYSTAL-AF and EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trials, which also found that >90% of European and North American stroke specialists prescribed anticoagulation if AF was detected after a stroke or TIA.[1,2]

Our study has several limitations. First, the POINT trial protocol did not require continuous heart-rhythm monitoring, which has been shown to substantially increase the detection of AF compared with routine clinical follow-up. Furthermore, not all patients with AF are started on anticoagulation, and thus relying on drug interruption reports may have also underestimated true AF rates. These limitations may have affected our outcome by underestimating AF rates. Because we lacked data on the relative timing and intensity of monitoring in the stroke versus TIA groups, it may be possible that AF detection after TIA was lower because of less rigorous cardiac monitoring. Second, we analyzed a clinical trial population who is unlikely to be fully representative of the overall population of patients with stroke and TIA, especially because the POINT trial included only patients with stroke with minor deficits and patients with TIA with high-risk features and excluded those requiring carotid revascularization. As a comparison, the mean National Institutes of Health Stroke Scale scores among patients with minor ischemic stroke in the POINT trial were 2.0, versus mean National Institutes of Health Stroke Scale scores of 1.6 and 1.9 in the 2 treatment groups of the CRYSTAL-AF trial.

In summary, in a large sample of patients enrolled in a randomized clinical trial, there was no substantial difference in rates of AF detection after a high-risk TIA versus after a minor ischemic stroke. Consideration of whether the index event was a minor stroke or high-risk TIA did not serve as a good predictor of subsequent AF diagnosis, implying that patients with high-risk TIA should undergo similar heart-rhythm monitoring strategies as patients with minor ischemic stroke. Randomized clinical trials have found that continuous heart-rhythm monitoring of at least a few weeks' duration significantly increases the detection of AF after

Table 3. Associations Between Ischemic Stroke (Versus TIA) and Newly Diagnosed AF Among Patients in the POINT Trial

Model	Hazard Ratio (95% CI)*	*P* Value
Original definition of ischemic stroke and TIA†		
1. Unadjusted	1.33 (0.90–1.98)	0.155
2. Model 1 plus US (vs non-US) site and study treatment‡	1.30 (0.88–1.93)	0.192
3. Model 2 plus age, sex, race, and ethnicity	1.48 (0.99–2.20)	0.054
4. Model 3 plus vascular risk factors§	1.48 (0.99–2.20)	0.055
Revised definition of ischemic stroke and TIA‖		
1. Unadjusted	1.55 (1.01–2.36)	0.043
2. Model 1 plus US (vs non-US) site and study treatment	1.53 (1.00–2.34)	0.048
3. Model 2 plus age, sex, race, and ethnicity	1.73 (1.13–2.65)	0.011
4. Model 3 plus vascular risk factors	1.73 (1.13–2.65)	0.012

AF indicates atrial fibrillation/flutter; POINT, Platelet-Oriented Inhibition in New TIA or Minor Ischemic Stroke; and TIA, transient ischemic attack.

*Hazard ratios are for the comparison of Black race in reference to White race.

†The index event was classified as a TIA if the neurological symptoms and signs had completely resolved by the time of randomization, and as an ischemic stroke if symptoms and signs had not resolved.

‡Aspirin plus clopidogrel vs aspirin alone.

§Hypertension, diabetes mellitus, coronary artery disease, heart failure, valvular heart disease, and tobacco use.

‖Patients with TIA with visible brain infarction were reclassified into the category of ischemic stroke, based on updated definitions of stroke and TIA that were introduced after the start of the POINT trial.

cerebrovascular ischemia,[1,2] and current guidelines state that prolonged monitoring for approximately a month is reasonable.[7] In almost all cases, detection of AF in the POINT trial prompted a switch from antiplatelet to anticoagulant therapy, and in the context of such treatment strategies, patients with newly diagnosed AF did not appear to face a significantly higher risk of ischemic stroke. Our findings may help inform decisions about optimal heart-rhythm monitoring strategies and the treatment of any resultant findings, which at the moment remain challenging given numerous gaps in the evidence base.

Table 4. Discriminatory Ability of Variables Associated With Newly Diagnosed AF Among Patients in the POINT Trial

Variable	C-Statistic (95% CI)
Age	0.68 (0.63–0.73)
Ischemic stroke (vs TIA), original definition*	0.53 (0.49–0.58)
Ischemic stroke (vs TIA), revised definition†	0.54 (0.50–0.59)

AF indicates atrial fibrillation/flutter; POINT, Platelet-Oriented Inhibition in New TIA or Minor Ischemic Stroke; and TIA, transient ischemic attack.

*The index event was classified as a TIA if the neurological symptoms and signs had completely resolved by the time of randomization, and as an ischemic stroke if symptoms and signs had not resolved.

†Patients with TIA with visible brain infarction were reclassified into the category of ischemic stroke, based on updated definitions of stroke and TIA that were introduced after the start of the POINT trial.

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Disclosures

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