Cerebral microbleeds and asundexian in non-cardioembolic ischemic stroke: Secondary analyses of the PACIFIC-STROKE randomized trial

Pargol Balali[1], Robert G Hart[2], Eric E Smith[3], Feryal Saad[4], Pablo Colorado[5], Robin Lemmens[6,7], Gian Marco De Marchis[8,9], Valeria Caso[10], Lizhen Xu[11], Laura Heenan[11], Stuart J Connolly[11], Hardi Mundl[12] and Ashkan Shoamanesh[2]; on behalf of the PACIFIC-STROKE Investigators

Abstract

Background and aims: Cerebral microbleeds are magnetic imaging resonance (MRI) markers of hemorrhage-prone cerebral small vessel disease that predict future risk of ischemic stroke and intracranial hemorrhage (ICrH). There exist concerns about the net benefit of antithrombotic therapy in patients with microbleeds. We aimed to investigate the effects of an oral factor-XIa inhibitor (asundexian), that is hypothesized to inhibit thrombosis without compromising hemostasis, on the development of new microbleeds over time and interactions between microbleeds and asundexian treatment on clinical outcomes. We additionally assessed associations between baseline microbleeds and the risks of clinical and neuroimaging outcomes in patients with non-cardioembolic ischemic stroke.

Methods: This is a secondary analysis of the PACIFIC-STROKE, international, multi-center Phase 2b double-blind, randomized clinical trial. PACIFIC-STROKE enrolled patients aged ⩾ 45 years with mild-to-moderate non-cardioembolic ischemic stroke who presented within 48 h of symptom onset for whom antiplatelet therapy was intended. Microbleeds were centrally adjudicated, and participants with an interpretable T2*-weighted sequence at their baseline MRI were included in this analysis. Patients were randomized to asundexian (10/20/50 mg daily) versus placebo plus standard antiplatelet treatment. Regression models were used to estimate the effects of (1) all pooled asundexian doses and (2) asundexian 50 mg daily on new microbleed formation on 26-week MRIs. Cox proportional hazards or regression models were additionally used to estimate interactions between treatment assignment and microbleeds for ischemic stroke/ transient ischemic attack (TIA) (primary outcome), and ICrH, all-cause mortality, hemorrhagic transformation (HT), and new microbleeds (secondary outcomes).

[1]Department of Neuroscience and Population Health Research Institute, McMaster University, Hamilton, ON, Canada
[2]Division of Neurology, Department of Medicine, McMaster University and Population Health Research Institute, Hamilton, ON, Canada
[3]Departments of Clinical Neurosciences, Radiology and Community Health Sciences and Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
[4]Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada
[5]Pharmaceuticals, Bayer US, Whippany, NJ, USA
[6]Divison of Experimental Neurology, Department of Neurosciences, KU Leuven (University of Leuven), Leuven, Belgium
[7]Department of Neurology, University Hospitals Leuven, Leuven, Belgium
[8]Department of Neurology and Stroke Center, Kantonsspital St. Gallen, St. Gallen, Switzerland
[9]Department of Clinical Research, University of Basel, Basel, Switzerland
[10]Stroke Unit, Santa Maria Della Misericordia Hospital, University of Perugia, Perugia, Italy
[11]Department of Statistics, Population Health Research Institute, Hamilton, ON, Canada
[12]TA Thrombosis, Bayer AG, Wuppertal, Germany

Corresponding author:
Ashkan Shoamanesh, Division of Neurology, Department of Medicine, McMaster University and Population Health Research Institute, Barton Street East, Hamilton, ON L9G 1J8, Canada.
Email: ashkan.shoamanesh@phri.ca
Twitter: @Ash_Shoamanesh

Results: Of 1746 participants (mean age, 67.0 ± 10.0; 34% female) with baseline MRIs, 604 (35%) had microbleeds. During a median follow-up of 10.6 months, 7.0% (n = 122) had ischemic stroke/TIA, 0.5% (n = 8) ICrH, and 2.1% (n = 37) died. New microbleeds developed in 10.3% (n = 155) of participants with adequate follow-up MRIs and HT in 31.4% (n = 345). In the total sample of patients with adequate baseline and 26-week follow-up MRIs (n = 1507), new microbleeds occurred in 10.2% of patients assigned to any asundexian dose and 10.5% of patients assigned to placebo (OR, 0.96; 95% CI, 0.66–1.41). There were no interactions between microbleeds and treatment assignment for any of the outcomes (p for interaction > 0.05). The rates of new microbleeds, HT, and ICrH were numerically less in patients with microbleeds assigned to asundexian relative to placebo. The presence of microbleeds was associated with a higher risk of HT (aOR, 1.6; 95% CI, 1.2–2.1) and new microbleeds (aOR, 4.4; 95% CI, 3.0–6.3).

Conclusion: Factor XIa inhibition with asundexian appears safe in patients with non-cardioembolic ischemic stroke and hemorrhage-prone cerebral small vessel disease marked by microbleeds on MRI. These preliminary findings will be confirmed in the ongoing OCEANIC-STROKE randomized trial.

Trial Registration: ClinicalTrials.gov Identifier: NCT04304508.

Introduction

Cerebral microbleeds are radiological markers of hemorrhage-prone cerebral small vessel disease detected on blood-sensitive magnetic resonance imaging (MRI) sequences. Microbleeds are present in about one-third of patients with ischemic stroke and indicate prior microhemorrhage.[1,2] Microbleeds have been associated with a 1.2-fold increased risk of recurrent ischemic stroke and a 2.5-fold increased risk of intracerebral hemorrhage (ICH).[3] These associations have raised concerns about the net benefit of antithrombotic treatment in ischemic stroke patients with microbleeds and led some to advocate avoidance of anticoagulation in these patients. However, subgroup analyses of randomized trials conducted to date have not demonstrated deleterious treatment interactions between microbleeds and antithrombotic treatment for clinical outcomes.[4–7]

Factor XI/XIa inhibitors are new anticoagulants that are hypothesized to inhibit pathologic thrombus formation without compromising hemostasis. In the PACIFIC-STROKE randomized trial, Factor XIa inhibition with asundexian was suggested to reduce ischemic stroke/transient ischemic attack (TIA) in patients with acute non-cardioembolic ischemic stroke without significantly increasing bleeding when compared with placebo on top of background standard antiplatelet treatment.[8] We performed secondary analyses of the PACIFIC-STROKE trial with the primary aims of estimating the effect of asundexian relative to placebo on the development of new microbleeds during study participation and to investigate potential interactions between treatment assignment and microbleeds for the outcomes of ischemic stroke/TIA, intracranial hemorrhage (ICrH), mortality, hemorrhagic transformation (HT) of the

qualifying infarct, and new microbleeds on follow-up MRI. In addition, we aimed to characterize the determinants of microbleeds in PACIFIC-STROKE participants and the association between microbleeds and the risks of the aforementioned outcomes. We hypothesized that asundexian treatment would not increase the risk of new microbleeds on follow-up MRI and that there would be no significant interactions between baseline microbleeds and treatment assignment for the outcomes of interest.

Methods

Study design

The design and main results of the PACIFIC-STROKE trial have been reported elsewhere.[8] The protocol was approved by the relevant health authorities and the institutional review boards at each participating site, and written informed consent was obtained from participants or their legally authorized representative. The trial is registered at clinicaltrials.gov (NCT04304508). Further details are found in the supplemental material.

Study participants

Individuals aged ≥ 45 years with mild-to-moderate (National Institutes of Health Stroke Scale (NIHSS) = 0–15) non-cardioembolic ischemic stroke who presented within 48 h of symptom onset and were intended for antiplatelet therapy were eligible. The main exclusion criteria were prior ischemic stroke within 30 days of index event, history of atrial fibrillation, active bleeding or history of major bleeding, uncontrolled hypertension, estimated glomerular filtration rate of < 30 mL/min/1.73 m², significant

liver disease, or contraindication to MRI. To be included in the present secondary analyses, participants were additionally required to have an interpretable T2*-sequence allowing for microbleed detection available on their baseline MRI. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[9]

Intervention

Eligible participants were randomly assigned in a 1:1:1:1 ratio to receive one of three asundexian dosages (10, 20, and 50 mg once daily) or placebo, in addition to usual background antiplatelet therapy. Participants were followed for 6–12 months.

Data collection

Demographic information, vascular risk factors, and neuroimaging findings were prospectively recorded at the time of study enrollment.[8] Race/ethnicity was self-reported. Both patients and investigators were masked to the treatment assignment during the study period.

All participants were required to undergo at least two MRIs that met study requirements. In addition to the baseline MRI (obtained following the index stroke either prior to randomization or within 72 h after randomization), participants underwent a final study MRI at 26 weeks or as soon as possible after early termination of assigned study treatment. The initial 829 participants additionally underwent MRI at 13 weeks according to a pre-planned interim safety review. Requisite MRI acquisition parameters are described in the supplementary methods.

MRI data were transmitted to the central MRI Core Laboratory at the University of Calgary for independent interpretation by two radiologists blinded to participant data and treatment assignment, with differences resolved by consensus. Incident infarcts, white matter hyperintensities, and microbleeds were defined according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE).[10] HT was reported on baseline MRIs obtained after the first dose of study drug.

Microbleeds were categorized as present or absent, and if present, strictly lobar (with or without cerebellar microbleeds), strictly deep (deep/brainstem, cerebellar microbleeds, or both), or mixed (concurrent lobar and deep/brainstem microbleeds). In addition, their severity was categorized as absent (0 microbleeds), mild (1–2 microbleeds), moderate (3–10), or severe (>10 microbleeds).[4,6] New microbleeds were identified by direct comparison of the baseline MRI with the follow-up study MRI. The inter-rater reliability for microbleed presence on an independent test set was 0.94 (95% confidence interval (CI) 0.81–0.99), indicating excellent agreement.

Outcomes

New microbleeds were defined as any newly detected microbleeds on follow-up MRI. The primary efficacy outcome for treatment interactions was the composite of symptomatic ischemic stroke and TIA. Secondary outcomes included ICrH, all-cause mortality, HT of the qualifying infarct, and new microbleeds. TIA was defined as acute focal neurologic deficit related to brain or retinal ischemia, which lasted < 24 h without any neuroimaging manifestation of infarcts.[8] ICrH was specified as any bleeding inside the skull except for HT of the qualifying infarct.[8,11]

Statistical analysis

We compared patient characteristics using t-test or Wilcoxon rank-sum test for continuous variables and Fisher's exact or chi-square test for categorical variables as appropriate. Baseline characteristics associated with microbleed presence ($p < 0.05$) in univariable analyses were entered into a stepwise multivariable logistic regression model to identify variables that are independently associated with baseline microbleeds. An additional multivariable logistic regression model included imaging acquisition parameters, consisting of the type of T2*-weighted available for microbleed detection, magnet strength, slice thickness, and gap width was performed.

Multivariable Cox proportional hazards or logistic regression models, adjusting *a priori* for age, Asian ethnicity, hypertension, qualifying stroke subtype, and treatment assignment were used to estimate the contribution of microbleeds to risk of outcomes. In a sensitivity analysis, we repeated these analyses with additional adjustment for baseline characteristics that were determined to be independently associated with microbleeds.

Regression models were used to estimate the effects of (1) all pooled asundexian doses and (2) asundexian 50 mg daily on new microbleeds on follow-up MRIs at 26 weeks. Cox proportional hazards or logistic regression models were used to assess interactions between treatment assignment and microbleeds for the outcomes of interest. All the analyses followed the intention-to-treat paradigm.

The p-values were two-sided. Statistical significance was accepted at the 0.05 level. Statistical analyses were performed using SAS software (release 9.4).

Results

Overall, 1746 of 1808 (97%) PACIFIC-STROKE participants who were enrolled between June 15, 2020 and July 22, 2021 had an interpretable T2*-weighted sequence as part of their baseline MRI and were eligible for these analyses (Figure 1). The mean (SD) age was 67.0 (10.0) years and 34% were female. Clinical characteristics between

Figure 1. CONSORT flow diagram.
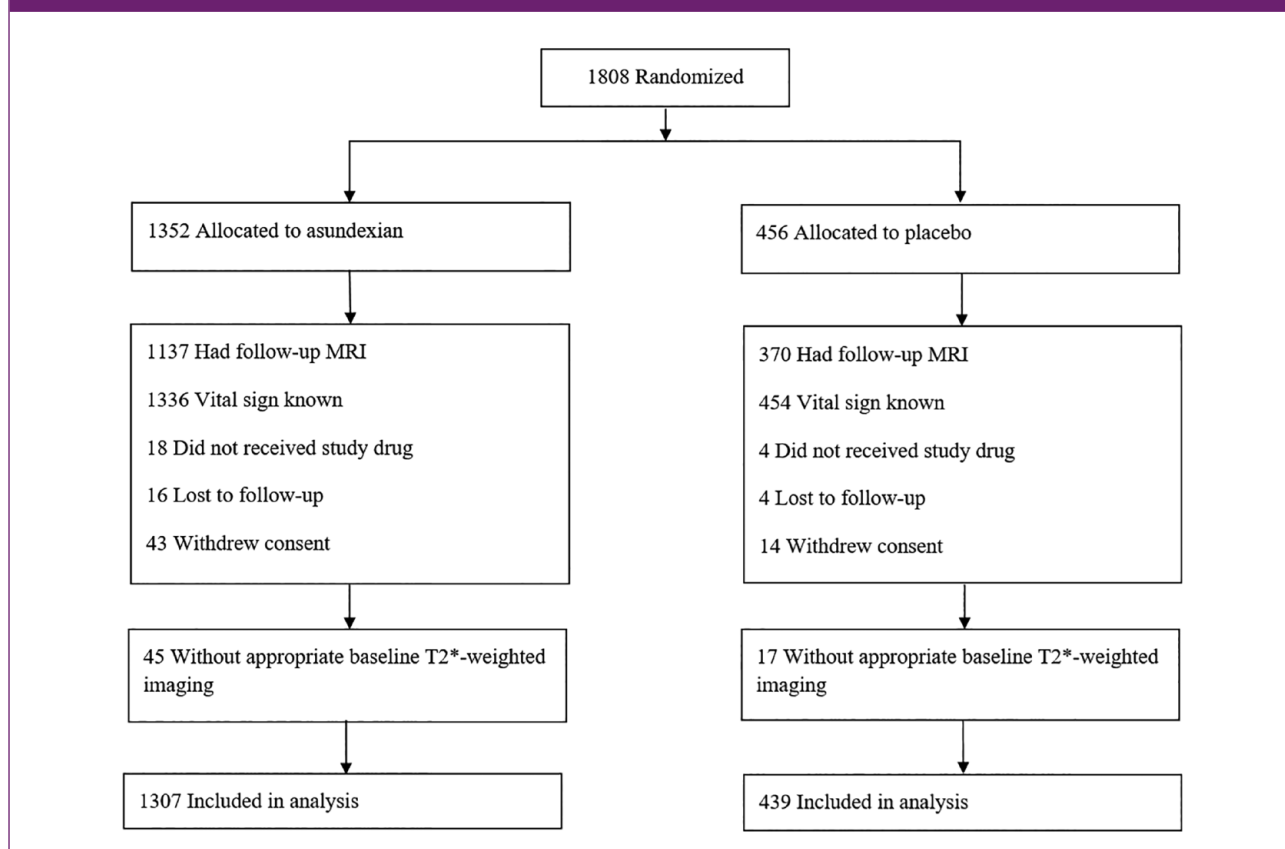
included and excluded participants were similar. However, included participants were less likely to be White, enrolled from North America, and have an ultimate diagnosis of cardioembolic stroke subtype (Supplemental Table S1).

Prevalent microbleeds were detected in 604 participants on baseline MRI (35%). Microbleed severity was mild in 387 (64%), moderate in 156 (26%), and severe in 61 (10%) of the participants with microbleeds. The location of microbleeds was strictly deep in 122 (20%), strictly lobar in 321 (53%), and mixed in 161 (27%).

Patients with microbleeds were older, more likely to be Asian, have a history of hypertension, heart failure, previous stroke/TIA, small vessel occlusion stroke subtype as their qualifying event, chronic macrohemorrhages, and more severe white matter disease on their MRI. In addition, they had higher presenting blood pressures and lower glomerular filtration rates (Supplemental Table S2). The MRI parameter associated with microbleed detection was reduced slice thickness, albeit a trend additionally existed for greater detection of microbleeds with susceptibility-weighted imaging/susceptibility-weighted angiography relative to gradient-recalled echo. Asian race (adjusted odds ratio (aOR), 1.65; 95% CI, 1.23–2.22), heart failure (aOR, 1.65; 95% CI, 1.05–2.59), previous stroke/TIA (aOR, 1.35; 95% CI, 1.01–1.80), and more severe white

matter hyperintensities on MRI (aOR per one-unit increase on the Fazekas scale, 1.55; 95% CI, 1.43–1.68) were independently associated with microbleeds in multivariable regression model (Table 1). After additional adjustment for imaging acquisition parameters, these associations were largely unchanged (Supplemental Table S3).

Outcomes and effect of treatment assignment

During a median follow-up of 10.6 months (interquartile range (IQR) = 8.1–12.4), 7% of the participants had recurrent ischemic stroke/TIA, 0.5% ICrH, and 2% died. In patients with adequate follow-up blood-sensitive MRIs sequences (n = 1507 (86.3%) median (IQR) baseline-to-follow-up MRI time = 25.9 (25.6–26.1) weeks), the rate of new microbleeds on follow-up MRI was 10.3% (Supplemental Figure S1). Among patients with baseline MRI after initiation of study drug within 72 h of randomization (n = 1100), any HT occurred in 31.4%.

Asundexian treatment was not associated with an increase in new microbleeds on follow-up MRI at 26 weeks. New microbleeds occurred in 10.2% (116/1137) of patients assigned to any asundexian dose strength (OR, 0.96; 95% CI, 0.66–1.41), 8.4% (31/368) of patients

Table 1. Multivariable model of patient characteristics and imaging findings independently associated with cerebral microbleeds.

	No. of patients	≥1 microbleed(s), N (%)	Unadjusted odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)[a]	p
Age	1746	604	1.02 (1.01–1.03)	<0.001	0.99 (0.98–1.00)	0.120
Race						
White	1445	467	Reference	NA	Reference	NA
Black	18	2	0.32 (0.08–1.25)	0.101	0.40 (0.10–1.65)	0.206
Asian	266	130	2.00 (1.54–2.61)	<0.001	1.65 (1.23–2.22)	<0.001
Other	3	0	0.30 (0.01–9.17)	0.490	0.42 (0.01–13.65)	0.625
Current tobacco use	471	145	0.79 (0.63–0.99)	0.042	0.78 (0.60–1.01)	0.060
Heart failure	100	46	1.66 (1.11–2.49)	0.014	1.65 (1.05–2.59)	0.029
Previous stroke/transient ischemic attack	274	121	1.62 (1.25–2.10)	<0.001	1.35 (1.01–1.80)	0.041
Qualifying stroke subtype						
Large artery atherosclerosis	310	105	Reference	NA	Reference	NA
Small vessel occlusion	786	315	1.31 (0.99–1.72)	0.057	1.36 (1.00–1.85)	0.052
Other	43	17	1.28 (0.66–2.46)	0.465	1.34 (0.65–2.77)	0.428
Cryptogenic	599	163	0.73 (0.54–0.98)	0.037	0.93 (0.66–1.30)	0.669
Cardioembolism	7	3	1.46 (0.32–6.66)	0.622	2.34 (0.51–10.78)	0.275
Total Fazekas score	1742	604	1.58 (1.47–1.70)	<0.001	1.55 (1.43–1.68)	<0.001
Chronic macrohemorrhage	28	19	4.09 (1.84–9.09)	<0.001	2.31 (0.92–5.78)	0.073

CI: confidence interval; NA: not applicable.
[a]Firth's logistic regression is used due to the quasi-complete separation feature in race data.

assigned to asundexian 50 mg daily (OR, 0.78; 95% CI, 0.48–1.28), and 10.5% (39/370) of patients assigned to placebo (reference).

The effect of asundexian treatment—analyzed as either (1) any asundexian dose strength or (2) 50 mg daily versus placebo—was not modified by microbleed presence, severity, or distribution for any of the clinical or MRI outcomes (Figures 2 and 3, and Supplemental Tables S4–S13). The rates of ICrH ((1) 1% with all pooled asundexian doses, (2) 2% with asundexian 50 mg daily vs 2% with placebo), HT of the qualifying infarct ((1) 37%, (2) 32% vs 38%), and new microbleeds ((1) 19%, (2) 19% vs 25%) were numerically less in patients with microbleeds assigned to asundexian treatment compared to those assigned to placebo.

Associations between baseline microbleeds and outcomes

The risk of ischemic stroke/TIA, ICrH, and all-cause mortality did not differ between patients with and without microbleeds (Table 2, and Figure 4) or between subgroups of microbleed location (Supplemental Figures S2–S4). However, patients with three or more microbleeds had an 8.5-fold excess risk of ICrH during follow-up (1.8% vs 0.3%; adjusted hazard ratio (aHR), 8.49; 95% CI, 1.70–42.40) (Table 2, and Supplemental Figure S4b). The absolute risk of ischemic stroke/TIA (10.1%) remained substantially higher than ICrH (1.8%) in patients with three or more microbleeds, and this held true for all microbleed severity and location subgroups. In the sensitivity analysis with additional adjustment for baseline characteristics that were determined to be associated with microbleeds in this cohort, the results remained unchanged except for the emergence of a statistically significant higher risk of ischemic stroke/TIA in patients with strictly deep/mixed microbleed versus no microbleeds (aHR, 1.64; 95% CI, 1.02–2.64) (Supplemental Table S14).

HT was more frequent in patients with microbleeds 37.2% (n = 149) versus those without 28% (n = 196; aOR, 1.57; 95% CI, 1.19–2.05) (Table 3). The strength of the

Figure 2. Response to treatment according to microbleed status for clinical outcomes. CMB: cerebral microbleed.
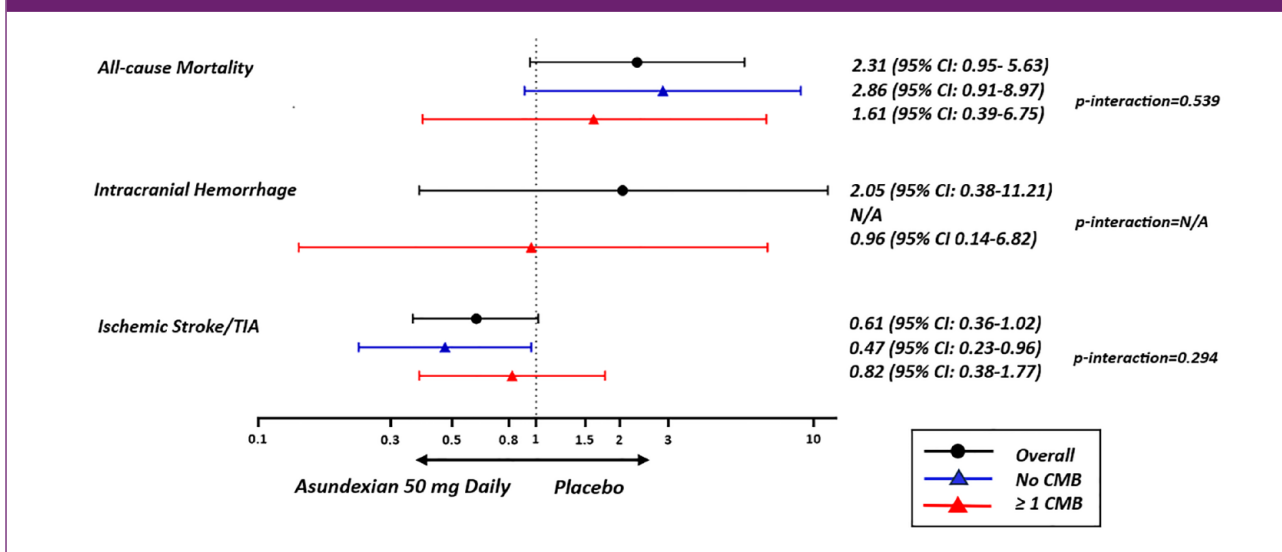
Figure 3. Response to treatment according to microbleed status for neuroimaging outcomes. CMB: cerebral microbleed.
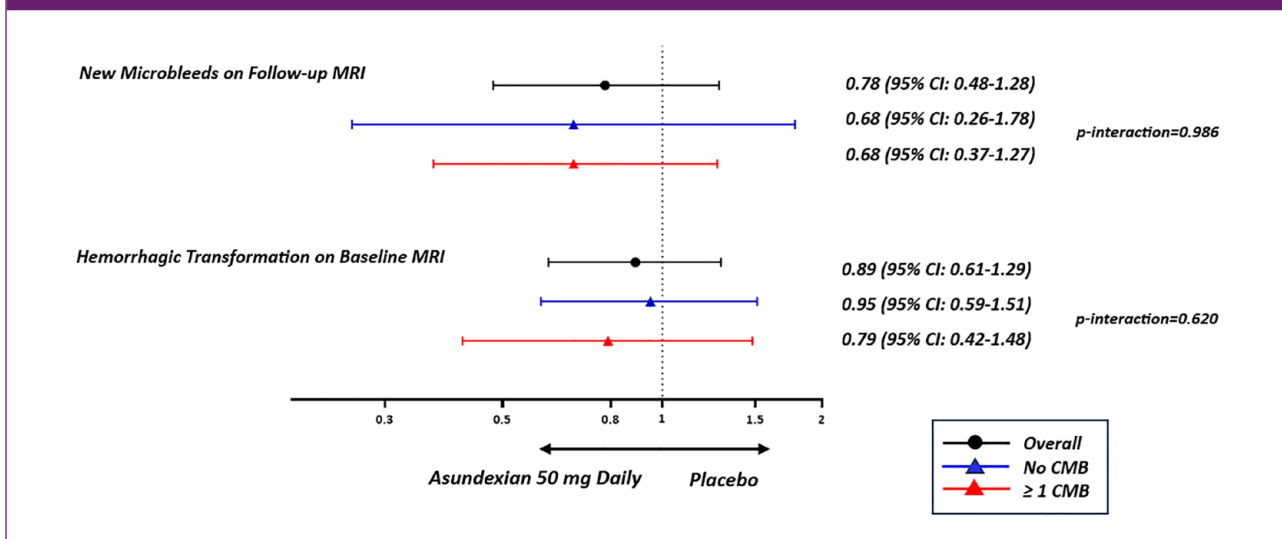
association between microbleeds and HT was similar irrespective of microbleed severity. However, a more robust association with HT was observed among patients with strictly lobar microbleeds (aOR, 1.67; 95% CI, 1.20–2.33) relative to patients with strictly deep/mixed patterns (aOR, 1.44; 95% CI, 1.01–2.06). Patients with at least one microbleed at baseline were at a fourfold increased risk of developing new microbleeds on their follow-up MRI (20% vs 5%; aOR, 4.37; 95% CI, 3.02–6.32) (Table 3). In total, 39% of patients with three or more microbleeds on baseline MRI developed new microbleeds on follow-up MRI (aOR, 11.06; 95% CI, 7.21–16.97 relative to patients without microbleeds). The rate of new microbleeds was 26% in patients with strictly deep/mixed microbleeds (aOR, 6.21;

95% CI, 4.08–9.48) and 15% in patients with strictly lobar microbleeds (aOR, 3.03; 95% CI, 1.93–4.75). These results were essentially unchanged in sensitivity analyses (Supplemental Table S15).

Discussion

In this well-characterized cohort of patients with non-cardioembolic ischemic stroke presenting within 48 h of symptom onset, microbleeds were prevalent and associated with Asian race, history of heart failure and stroke/TIA, and higher severity of white matter disease. Treatment with asundexian did not increase new microbleed formation on follow-up MRI and no interactions were observed between

Table 2. Risk of ischemic stroke/TIA, ICrH, and all-cause mortality stratified by baseline microbleed status.

	No. of patients	Ischemic stroke/TIA			Intracranial hemorrhage			All-cause mortality		
		Events, N (%)	HR, (95% CI)	aHR[a], (95% CI)	Events, N (%)	HR, (95% CI)	aHR[a], (95% CI)	Events, N (%)	HR, (95% CI)	aHR[a], (95% CI)
CMB presence										
None	1142	72 (6.3)	Reference	Reference	3 (0.3)	Reference	Reference	21 (1.8)	Reference	Reference
CMB	604	50 (8.3)	1.30 (0.91–1.87)	1.17 (0.81–1.69)	5 (0.8)	3.16 (0.75–13.21)	3.89 (0.86–17.52)	16 (2.6)	1.43 (0.75–2.75)	1.43 (0.74–2.78)
CMB burden										
No CMB	1142	72 (6.3)	Reference	Reference	3 (0.3)	Reference	Reference	21 (1.8)	Reference	Reference
1–2 CMBs	387	28 (7.2)	1.14 (0.74–1.77)	1.09 (0.70–1.69)	1 (0.3)	0.99 (0.10–9.50)	1.27 (0.13–12.72)	7 (1.8)	0.98 (0.42–2.30)	1.01 (0.42–2.38)
3 or more CMBs	217	22 (10.1)	1.59 (0.99–2.56)	1.30 (0.79–2.15)	4 (1.8)	6.99 (1.57–31.25)	8.49 (1.70–42.40)	9 (4.1)	2.25 (1.03–4.92)	2.17 (0.97–4.86)
CMB topography										
No CMB	1142	72 (6.3)	Reference	Reference	3 (0.3)	Reference	Reference	21 (1.8)	Reference	Reference
Strictly deep/ mixed CMBs	283	28 (9.9)	1.56 (1.01–2.42)	1.38 (0.88–2.17)	3 (1.1)	3.99 (0.81–19.76)	5.36 (0.92–31.24)	8 (2.8)	1.54 (0.68–3.47)	1.54 (0.66–3.57)
Strictly lobar CMBs	321	22 (6.9)	1.08 (0.67–1.74)	0.98 (0.60–1.59)	2 (0.6)	2.40 (0.40–14.39)	2.88 (0.45–18.25)	8 (2.5)	1.35 (0.60–3.04)	1.34 (0.59–3.04)

TIA: transient ischemic attack; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio; CMB: cerebral microbleed.
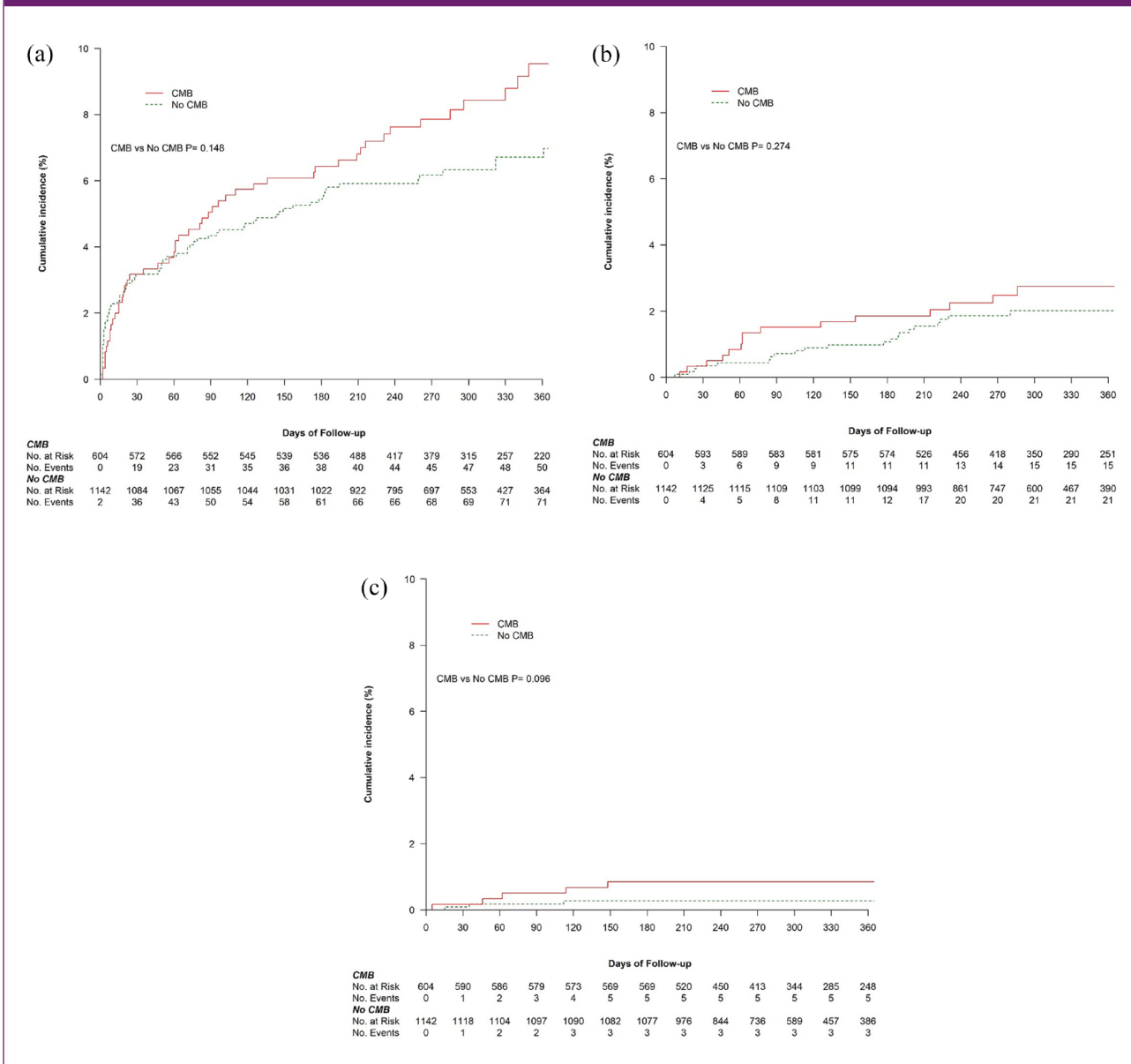[a]Adjusted for age, Asian ethnicity, hypertension, qualifying stroke subtype, and treatment assignment.

microbleeds and asundexian treatment (vs placebo) for the clinical and radiological outcomes of interest. Although our analyses may have lacked power to definitively exclude an interaction, reassuring the rates of ICrH, HT, and new microbleeds was numerically less with asundexian treatment versus placebo in patients with microbleeds. A higher numerical rate of recurrent ischemic stroke/TIA, all-cause mortality, and ICrH was observed in patients with microbleeds, but these were not statistically significant. However, patients with microbleeds had a 1.5-fold greater risk of developing any HT and a fourfold greater risk of new microbleeds on follow-up MRI. In addition, patients with deep/mixed microbleeds were at a 1.6-fold increased risk of recurrent ischemic stroke/TIA in our broadened adjusted model.

Factor XI/XIa inhibitors are hypothesized to prevent ischemic vascular events without increasing the risk of bleeding. Consistent with this hypothesis, we observed no increase in ICrH, HT, or new microbleeds with asundexian when used on top of background antiplatelet treatment in patients with hemorrhage-prone cerebral small vessel disease marked by microbleeds on MRI. Consistent with prior microbleed subgroup analyses of randomized trials of antithrombotic treatment, we did not observe any treatment interaction between microbleeds and asundexian treatment for the clinical and MRI outcomes of interest.[4,6,7]

Our observed 35% prevalence of microbleeds is consistent with prior studies of patients with ischemic stroke/TIA.[3,12] Contrary to prior studies, we did not find a significant association between microbleeds and recurrent ischemic stroke/TIA and all-cause mortality, although these clinical outcomes occurred more frequently in patients with microbleeds, and, in the case of ischemic stroke/TIA, with increasing microbleed number.[3,4,6] Of note, our sensitivity analysis demonstrated that the presence of strictly deep/mixed microbleeds was associated with 1.6 times higher risk of ischemic stroke/TIA. Our analysis may have thus lacked sufficient follow-up time and the power to detect more differences relative to larger observational cohorts with longer follow-up durations.[3] Patients with three or more microbleeds—indicating a moderate–severe burden of disease—participating in PACIFIC-STROKE were at an 8.5-fold increased risk of ICrH during study follow-up. Yet, in keeping with prior pooled analyses of ischemic stroke/TIA cohorts, patients with microbleeds had substantially higher absolute risks of ischemic stroke/TIA than ICrH, irrespective of microbleed severity or location.[1–3] These consistent findings challenge existing concerns surrounding the use of antithrombotic treatments in patients with ischemic stroke/TIA and microbleeds on MRI.

Figure 4. Kaplan–Meier curves for clinical outcomes stratified by cerebral microbleed status. (a) Ischemic stroke/TIA. (b) All-cause mortality. (c) ICrH. CMB: cerebral microbleed.

(a)

CMB													
No. at Risk	604	572	566	552	545	539	536	488	417	379	315	257	220
No. Events	0	19	23	31	35	36	38	40	44	45	47	48	50
No CMB													
No. at Risk	1142	1084	1067	1055	1044	1031	1022	922	795	697	553	427	364
No. Events	2	36	43	50	54	58	61	66	66	68	69	71	71

(b)

CMB													
No. at Risk	604	593	589	583	581	575	574	526	456	418	350	290	251
No. Events	0	3	6	9	9	11	11	11	13	14	15	15	15
No CMB													
No. at Risk	1142	1125	1115	1109	1103	1099	1094	993	861	747	600	467	390
No. Events	0	4	5	8	11	11	12	17	20	20	21	21	21

(c)

CMB												
No. at Risk	604	590	586	579	573	569	569	520	450	413	344	285	248
No. Events	0	1	2	3	4	5	5	5	5	5	5	5	5
No CMB												
No. at Risk	1142	1118	1104	1097	1090	1082	1077	976	844	736	589	457	386
No. Events	0	1	2	2	3	3	3	3	3	3	3	3	3

Patients with acute ischemic stroke and microbleeds on MRI have previously been reported to have higher risk of HT both with and without revascularization treatments, particularly in patients with higher microbleed severity.[13–15] Similarly, we observed a 1.5-fold excess risk of any HT on MRI in patients with microbleeds. These observations suggest that the same underlying microangiopathic processes that increase vascular fragility and permeability leading to microbleed formation, also lead to an increased risk of HT of infarcted tissue. Our results suggest that patients with lobar microbleeds, indicative of underlying cerebral amyloid angiopathy, may be particularly at heightened risk of HT. Moreover, in line with previous observations, patients with baseline microbleeds were at greater risk of developing new microbleeds,[16,17] and the association increased with greater microbleed severity. The rate of new microbleeds on MRI overall was 10% and was as high as 39% in patients with three or more baseline microbleeds suggesting active underlying microangiopathic processes in the acute/subacute phase of ischemic stroke.[18,19]

Our study has several advantages. It is first to investigate the effect of Factor XI/XIa inhibition (vs placebo) on cerebral microbleed formation and clinical outcomes in patients with hemorrhage-prone cerebral small vessel disease marked by microbleeds. We report results from a large international prospective sample of well-characterized

Table 3. Risk of HT and new cerebral microbleeds on MRI stratified by baseline microbleed status.

Characteristic	Hemorrhagic transformation				New microbleeds			
	No. of patients	Events, N (%)	OR, (95% CI)	aOR[a,b], (95% CI)	No. of patients	Events, N (%)	OR, (95% CI)	aOR[a,c], (95% CI)
CMB presence								
None	699	196 (28.0)	Reference	Reference	982	48 (4.9)	Reference	Reference
CMB	401	149 (37.2)	1.52 (1.17–1.97)	1.57 (1.19–2.05)	525	107 (20.4)	4.98 (3.48–7.14)	4.37 (3.02–6.32)
CMB burden								
No CMB	699	196 (28.0)	Reference	Reference	982	48 (4.9)	Reference	Reference
1–2 CMBs	245	91 (37.1)	1.52 (1.12–2.06)	1.55 (1.13–2.13)	334	33 (9.9)	2.13 (1.34–3.39)	1.87 (1.16–3.00)
3 or more CMBs	156	58 (37.2)	1.52 (1.06–2.19)	1.58 (1.09–2.31)	191	74 (38.7)	12.31 (8.16–18.56)	11.06 (7.21–16.97)
CMB topography								
No CMB	699	196 (28.0)	Reference	Reference	982	48 (4.9)	Reference	Reference
Strictly deep/ mixed CMBs	189	68 (36.0)	1.44 (1.03–2.03)	1.44 (1.01–2.06)	246	65 (26.4)	6.99 (4.66–10.48)	6.21 (4.08–9.48)
Strictly lobar CMBs	212	81 (38.2)	1.59 (1.15–2.19)	1.67 (1.2–2.33)	279	42 (15.1)	3.45 (2.23–5.34)	3.03 (1.93–4.75)

HT: hemorrhagic transformation; MRI: magnetic resonance imaging; OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio; CMB: cerebral microbleed.
[a]Adjusted for age, Asian ethnicity, hypertension, qualifying stroke subtype, and treatment assignment.
[b]All HTs (hemorrhagic infarction 1 and 2 and parenchymal hematoma 1 and 2) on baseline MRIs which were done after the initial dose of the study drug (up to 72 h after randomization).
[c]New microbleeds were rated for patients who had an interpretable T2*.

non-cardioembolic ischemic stroke with a standardized MRI protocol. MRI rating was performed centrally by experienced radiologists blinded to patient data and treatment assignment, with excellent inter-rater reliability for microbleeds. Asundexian treatment assignment was randomized and concealed from both patients and health care providers.

Our study also has limitations. Our analyses may have been underpowered, particularly for the clinical outcomes of ICrH and mortality due to the small number of events and relatively short median follow-up time. Moreover, subgroup analyses of randomized trials can be prone to bias from inadequate randomization or multiple testing, leading to spurious findings. The trial eligibility criteria, potential for selection bias during recruitment, and the unavailability of adequate T2*-weighted sequences during follow-up MRI in all PACIFIC-STROKE participants could limit the generalizability of our findings. In this regard, prospective observational cohorts with standardized longitudinal assessments would be better suited to characterize the natural history of disease. Reassuringly, however, the

prevalence of microbleeds in our cohort and their associations with baseline demographics and outcomes were quite consistent with the existing literature. About 3% of the PACIFIC-STROKE trial participants were excluded from this post hoc analysis due to unavailability of adequate baseline T2*-weighted sequences, which might have biased our results. However, other than the overrepresentation of Asian ethnicity among the included cohort, the included patients had similar baseline characteristics as those excluded from these analyses. In view of the higher rate of microbleeds and risk of ICrH in Asian patients with ischemic stroke, our sample may have been more susceptible to hemorrhagic events.

Conclusion

Asundexian treatment appears to be safe when used on top of antiplatelet treatment in patients with non-cardioembolic ischemic stroke and hemorrhage-prone cerebral small vessel disease marked by microbleeds on MRI. These results will be confirmed in the ongoing OCEANIC-STROKE randomized trial.

Data availability

The de-identified, individual participant-level data can be made available to investigators for secondary analyses after review of a submitted proposal by the PACIFIC-Stroke steering committee. Requests should be addressed to the corresponding author (ashkan.shoamanesh@phri.ca) or the sponsor representative (hardi.mundl@bayer.com). Requesters will be required to complete a study questionnaire. All requests will be assessed by the Steering Committee to review and comment on any potential publication of data from the trial.

ORCID iDs

Eric E Smith https://orcid.org/0000-0003-3956-1668
Valeria Caso https://orcid.org/0000-0002-2020-8891
Hardi Mundl https://orcid.org/0000-0001-6218-3058
Ashkan Shoamanesh https://orcid.org/0000-0002-2802-1626

Supplemental material

Supplemental material for this article is available online.

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