Predictors of Recurrent Ischaemic Stroke in Patients With Non-Cardioembolic Ischaemic Stroke: Insights from the OCEANIC-STROKE Randomised Trial of Asundexian for Secondary Stroke Prevention

Ashkan Shoamanesh[1], José Ferro[2], Hanne Christensen[3], Serefnur Ozturk[4], Ronen R. Leker[5], Peter Turcani[6], Eva Muehlhofer[7], Karleen Schulze[8], Mukul Sharma[1] on behalf of the OCEANIC-STROKE Investigators

[1]McMaster University, Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada; [2]CHLN-Hospital Santa Maria, Lisbon, Portugal; [3]Bispebjerg og Frederiksberg Hospital, Copenhagen, Denmark; [4]Selcuk University Faculty of Medicine, Department of Neurology, Neurointensive Care, Stroke Center, Konya, Turkey; [5]Department of Neurology, Stroke Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [6]1st Department of Neurology, Comenius University in Bratislava, Bratislava, Slovakia; [7]Bayer AG, Wuppertal, Germany; [8]McMaster University, Population Health Research Institute, Hamilton, Ontario, Canada

McMaster University

Population Health Research Institute
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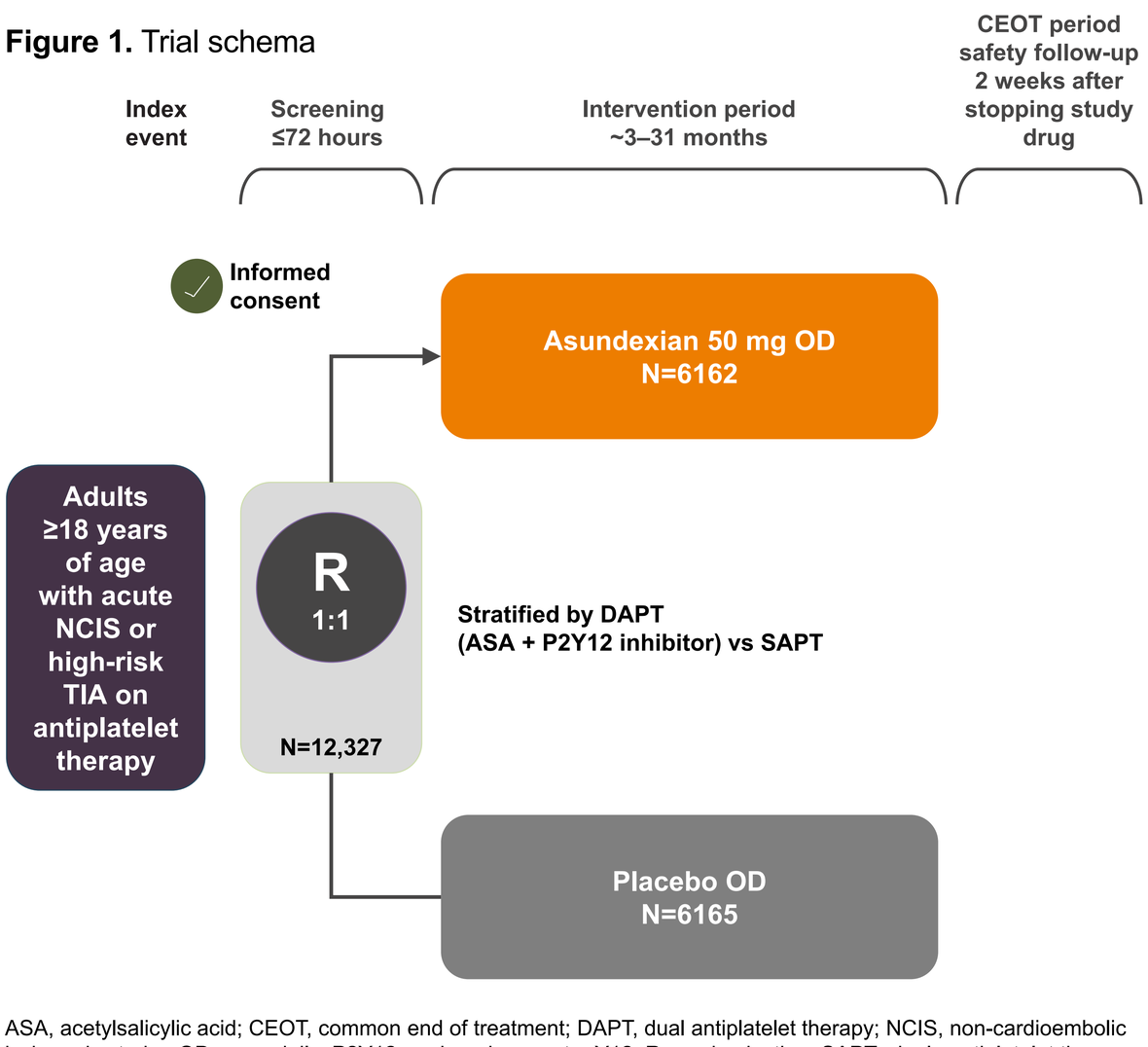
Background and Aims

- In the OCEANIC-STROKE trial, asundexian 50 mg once daily added to antiplatelet therapy reduced ischaemic stroke (IS) compared with placebo (cause-specific hazard ratio [HR] 0.74; 95% confidence interval [CI]: 0.65, 0.84) in patients with non-cardioembolic IS or high-risk transient ischaemic attack (TIA).[1] We examined baseline predictors of recurrent IS and whether these modified the treatment effect of asundexian.

Design

- We randomised 12,327 participants within 72 hours of acute non-cardioembolic IS or high-risk TIA to asundexian or placebo (**Figure 1**). The primary efficacy endpoint was time to first IS. Multivariable logistic regression identified baseline predictors of recurrent IS in patients with qualifying IS at study entry. Potential interactions between these variables and the treatment effect of asundexian for the primary efficacy endpoint were explored using the intention-to-treat principle.

Figure 1. Trial schema



ASA, acetylsalicylic acid; CEOT, common end of treatment; DAPT, dual antiplatelet therapy; NCIS, non-cardioembolic ischaemic stroke; OD, once daily; P2Y12, purinergic receptor Y12; R, randomisation; SAPT, single antiplatelet therapy; TIA, transient ischaemic attack.

Results

- Among 11,677 participants with index stroke, 843 IS occurred over a median follow-up of 1.6 years; the annualised rate of IS was 7.2%.
- In multivariable analysis, assignment to asundexian was associated with lower risk of recurrent IS (HR 0.73; 95% CI: 0.64, 0.84). Older age (per year; HR 1.01; 95% CI: 1.00, 1.02), Black race (HR 1.67; 95% CI: 1.14, 2.45) and Other race (HR 1.68; 95% CI: 1.22, 2.32) versus White race, history of diabetes (HR 1.39; 95% CI: 1.21, 1.60), previous stroke or TIA (HR 2.05; 95% CI: 1.77, 2.36), index IS attributed to large-artery atherosclerosis (HR 1.41; 95% CI: 1.23, 1.62), and medical history of atherosclerosis (HR 1.26; 95% CI: 1.09, 1.46) were associated with higher risk of recurrent IS (**Table 1**).
- No heterogeneity in the treatment effect of asundexian was observed across these variables for the primary efficacy endpoint (**Figure 2**).

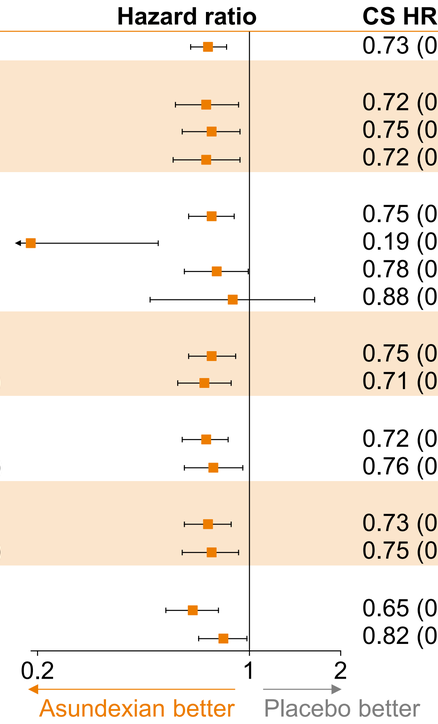
Table 1. Baseline predictors of recurrent ischaemic stroke

	Unadjusted univariable models		Adjusted multivariable model†	
Baseline predictive variables	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Asundexian (50 mg) vs placebo	0.73 (0.64, 0.84)	<0.001	0.73 (0.64, 0.84)	<0.001
DAPT vs SAPT	1.24 (1.08, 1.44)	0.003	1.12 (0.97, 1.30)	0.12
Age, per year	1.01 (1.01, 1.02)	<0.001	1.01 (1.00, 1.02)	0.006
Female (vs male) sex	0.86 (0.75, 1.00)	0.05		
Race (vs White)		<0.001		<0.001
Black	1.78 (1.22, 2.61)		1.67 (1.14, 2.45)	
Asian	1.19 (1.03, 1.39)		1.11 (0.95, 1.30)	
Other	1.72 (1.25, 2.38)		1.68 (1.22, 2.32)	
Medical history (reported vs not)				
Hypertension	1.33 (1.11, 1.59)	0.002	1.04 (0.86, 1.25)	0.67
Diabetes	1.58 (1.38, 1.81)	<0.001	1.39 (1.21, 1.60)	<0.001
Stroke or TIA	2.29 (1.99, 2.63)	<0.001	2.05 (1.77, 2.36)	<0.001
Atherosclerosis	1.53 (1.34, 1.76)	<0.001	1.26 (1.09, 1.46)	0.002
Any tobacco use vs none	1.13 (0.98, 1.29)	0.09		
Index stroke descriptors				
TOAST large-artery atherosclerosis (vs other)	1.50 (1.28, 1.75)	<0.001	1.41 (1.23, 1.62)	<0.001
NIHSS at randomisation (≤3 vs ≥4)	0.85 (0.73, 0.98)	0.02	0.91 (0.79, 1.06)	0.23
Intravenous thrombolysis and/or endovascular therapy for index event (vs no acute treatment)	0.84 (0.72, 0.99)	0.04	0.89 (0.76, 1.05)	0.17

Variable completeness: TOAST n=11,676; NIHSS at randomisation n=11,673.
†Variables identified as significant in univariable analyses (*P* <0.05) were included in the multivariable model using complete case analysis (n=11,672).
CI, confidence interval; DAPT, dual antiplatelet therapy; NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Figure 2. Exploratory subgroup analyses for the primary efficacy endpoint according to independent predictors of recurrent ischaemic stroke

Group	Asundexian 50 mg, n/N (%)	Placebo, n/N (%)	CS HR (95% CI)
Overall	358/5839 (6.1)	485/5838 (8.3)	0.73 (0.64, 0.84)
Age			
<65 years	119/2225 (5.3)	166/2226 (7.5)	0.72 (0.57, 0.92)
65–75 years	140/2186 (6.4)	183/2178 (8.4)	0.75 (0.60, 0.93)
>75 years	99/1428 (6.9)	136/1434 (9.5)	0.72 (0.56, 0.93)
Race			
White	218/3843 (5.7)	290/3834 (7.6)	0.75 (0.63, 0.89)
Black	5/133 (3.8)	23/129 (17.8)	0.19 (0.07, 0.50)
Asian	117/1677 (7.0)	150/1680 (8.9)	0.78 (0.61, 0.99)
Other	18/186 (9.7)	22/195 (11.3)	0.88 (0.47, 1.64)
Diabetes prior to randomisation			
No	204/3885 (5.3)	271/3890 (7.0)	0.75 (0.63, 0.90)
Yes	154/1954 (7.9)	214/1948 (11.0)	0.71 (0.58, 0.87)
History of stroke or TIA prior to index event			
No	222/4623 (4.8)	307/4602 (6.7)	0.72 (0.60, 0.85)
Yes	136/1216 (11.2)	178/1236 (14.4)	0.76 (0.61, 0.95)
Medical history of atherosclerosis			
No	208/3974 (5.2)	283/3964 (7.1)	0.73 (0.61, 0.87)
Yes	150/1865 (8.0)	202/1874 (10.8)	0.75 (0.60, 0.92)
Large-artery atherosclerosis stroke subtype			
No	155/3326 (4.7)	238/3354 (7.1)	0.65 (0.53, 0.79)
Yes	203/2512 (8.1)	247/2484 (9.9)	0.82 (0.68, 0.98)



CI, confidence interval; CS, cause specific; HR, hazard ratio; TIA, transient ischaemic attack.

Conclusion

- Baseline characteristics identify patients with acute non-cardioembolic IS at increased risk of IS recurrence. Asundexian, when added to standard antiplatelet therapy, reduced IS compared with placebo, with a consistent effect across multiple identified high-risk subgroups.

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Presenter contact details

Name: Dr. Ashkan Shoamanesh
Email: ashkan.shoamanesh@phri.ca

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