

Efficacy and Safety of Ticagrelor in Relation to Aspirin Use Within the Week Before Randomization in the SOCRATES Trial

K.S. Lawrence Wong, MD; Pierre Amarenco, MD; Gregory W. Albers, MD; Hans Denison, MD, PhD; J. Donald Easton, MD; Scott R. Evans, PhD; Peter Held, MD, PhD; Anders Himmelmann, MD, PhD; Scott E. Kasner, MD; Mikael Knutsson, PhD; Per Ladenvall, MD, PhD; Kazuo Minematsu, MD, PhD; Carlos A. Molina, MD; Yongjun Wang, MD; S. Claiborne Johnston, MD, PhD; for the SOCRATES Steering Committee and Investigators

Background and Purpose—SOCRATES (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes), comparing ticagrelor with aspirin in patients with acute cerebral ischemia, found a nonsignificant 11% relative risk reduction for stroke, myocardial infarction, or death ($P=0.07$). Aspirin intake before randomization could enhance the effect of ticagrelor by conferring dual antiplatelet effect during a high-risk period for subsequent stroke. Therefore, we explored the efficacy and safety of ticagrelor versus aspirin in the patients who received any aspirin the week before randomization.

Methods—A prespecified subgroup analysis in SOCRATES ($n=13\,199$), randomizing patients with acute ischemic stroke (National Institutes of Health Stroke Scale score of ≤ 5) or transient ischemic attack (ABCD² score of ≥ 4) to 90-day treatment with ticagrelor or aspirin. Patients in the prior-aspirin group had received any aspirin within the week before randomization. Primary end point was time to stroke, myocardial infarction, or death. Safety end point was PLATO (Study of Platelet Inhibition and Patient Outcomes) major bleeding.

Results—The 4232 patients in the prior-aspirin group were older, had more vascular risk factors, and vascular disease than the other patients. In the prior-aspirin group, the primary end point occurred in 138/2130 (6.5%) of patients on ticagrelor and in 177/2102 (8.3%) on aspirin (hazard ratio, 0.76; 95% confidence interval, 0.61–0.95; $P=0.02$); in patients with no prior-aspirin usage an event occurred in 304/4459 (6.9%) and 320/4508 (7.1%) on ticagrelor and aspirin, respectively (hazard ratio, 0.96; 95% confidence interval, 0.82–1.12; $P=0.59$). The treatment-by-prior-aspirin interaction was not statistically significant ($P=0.10$). In the prior-aspirin group, major bleeding occurred in 0.7% and 0.4% of patients on ticagrelor and aspirin, respectively (hazard ratio, 1.58; 95% confidence interval, 0.68–3.65; $P=0.28$).

Conclusions—In this secondary analysis from SOCRATES, fewer primary end points occurred on ticagrelor treatment than on aspirin in patients receiving aspirin before randomization, but there was no significant treatment-by-prior-aspirin interaction. A new study will investigate the benefit-risk of combining ticagrelor and aspirin in patients with acute cerebral ischemia (URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT03354429).

Clinical Trial Registration—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01994720.

(*Stroke*. 2018;49:1678-1685. DOI: 10.1161/STROKEAHA.118.020553.)

Key Words: aspirin ■ platelet aggregation inhibitors ■ stroke ■ ticagrelor ■ transient ischemic attack

Recent clinical trial and registry data show that patients with acute cerebral ischemic events are at high and immediate risk of experiencing potentially more severe and

disabling recurrent ischemic events, especially strokes.¹⁻³ Aspirin reduces the risk of subsequent stroke and death after acute cerebral ischemia^{4,5} and is recommended for secondary

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received January 2, 2018; final revision received April 24, 2018; accepted May 14, 2018.

From the Department of Medicine and Therapeutics, Chinese University of Hong Kong, Shatin (K.S.L.W.); Department of Neurology and Stroke Centre, Bichat Hospital, Paris Diderot University, France (P.A.); Stanford Stroke Center, Stanford University, CA (G.W.A.); Global Medicines Development, AstraZeneca, Gothenburg, Sweden (H.D., P.H., A.H., M.K., P.L.); Department of Neurology, University of California, San Francisco (J.D.E.); Department of Biostatistics, Harvard University, Boston, MA (S.R.E.); Department of Neurology, University of Pennsylvania, Philadelphia (S.E.K.); Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan (K.M.); Stroke Unit, Hospital Vall d'Hebron, Barcelona, Spain (C.A.M.); Department of Neurology, Beijing Tiantan Hospital, China (Y.W.); and Dean's Office, Dell Medical School, University of Texas at Austin (S.C.J.).

Current address for Dr Evans: Biostatistics Center, George Washington University, Washington DC, MD.

Guest Editor for this article was Markku Kaste, MD, PhD.

Presented in part at the International Stroke Conference, Houston, TX, February 22–24, 2017.

Correspondence to S. Claiborne Johnston, MD, PhD, The Dean's Office, Dell Medical School, University of Texas at Austin, 1401 Red River, Austin, TX 78712. E-mail clay.johnston@utexas.edu

© 2018 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.118.020553

prevention.⁶ In the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events), dual antiplatelet therapy with clopidogrel (P2Y₁₂ receptor antagonist) and aspirin significantly reduced the risk for stroke versus aspirin alone in a Chinese population with acute minor stroke or transient ischemic attack (TIA).¹ However, a large unmet medical need persists for novel, effective treatment options to improve outcomes among patients with acute minor ischemic stroke and TIA, particularly given the variability in clopidogrel response.⁷

The SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) investigated whether ticagrelor, a reversibly binding, direct-acting, oral P2Y₁₂ receptor antagonist and inhibitor of ENT1 (type 1 equilibrative nucleoside transporter),^{8,9} was superior to aspirin for prevention of the composite of stroke, myocardial infarction, and death, when initiated within 24 hours after symptom onset in patients with acute cerebral ischemia.¹⁰ A nonsignificant 11% relative risk reduction of the primary end point was found in SOCRATES.³

Addition of ticagrelor for patients who received aspirin before randomization in SOCRATES may confer the effect of dual antiplatelet therapy since aspirin's antiplatelet effect persists during the first week when the risk of new stroke events is highest. This prespecified analysis of SOCRATES explored ticagrelor safety and efficacy in patients receiving aspirin before randomization.

Methods

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy available at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

SOCRATES design and primary results have been presented previously.^{3,10} The trial was approved by the relevant Institutional Review Board/Ethics Committee at each site. Patients provided written informed consent before any study-specific procedures were performed.

Patients (n=13 199) with a noncardioembolic, nonsevere ischemic stroke (National Institutes of Health Stroke Scale score of ≤ 5) or high-risk TIA (ABCD² score of ≥ 4 or symptomatic ipsilateral stenosis of an extra or intracranial artery) were randomized (interactive web-based randomization system) within 24 hours of symptom onset to double-blinded treatment with ticagrelor 180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 to 90 or aspirin 300 mg on day 1 followed by 100 mg daily for days 2 to 90.

Concomitant medication information, particularly aspirin use, was collected; including start and stop date for medications initiated or stopped during the month before randomization. The prior-aspirin subgroup were patients receiving any aspirin within 7 days before randomization. Atherosclerosis was assessed by atherosclerosis, small-vessel disease, cardiac pathology, other causes, dissection phenotyping (ASCOD) to assign stroke cause and grade; A0=no atherosclerotic disease; A1 (likely causal) $\geq 50\%$ ipsilateral stenosis of extracranial or intracranial arteries or a mobile thrombus in the aortic arch; A2 (causal relationship possible but uncertain) $< 50\%$ stenosis of extracranial or intracranial artery or an aortic arch plaque of > 4 mm in thickness without mobile thrombus; A3 (unlikely causal)=plaque without stenosis or a stenosis in an artery contralateral to the cerebral infarct or a concomitant coronary or peripheral arterial disease; A9=insufficient information to grade atherosclerosis (no assessment of either intracranial arteries or extracranial arteries).¹¹ The prior-aspirin group was also analyzed by aspirin dose (> 150 mg versus ≤ 150 mg), to explore any dose-related impact on efficacy of prior-aspirin use, and by start day of aspirin treatment as either (1) starting the day

before or the same day as randomization, representing patients receiving an acute treatment with aspirin after onset of symptoms but before randomization, for example, as part of prehospital emergency care or at the emergency ward, or (2) starting earlier than the day before randomization considered as a proxy for chronic treatment, that is, aspirin treatment was ongoing at the time of the index event, since the start date was out of the possible time window of 24 hours between the start of the index event and randomization.

The primary end point for SOCRATES was the time from randomization to first occurrence of any event from the composite of stroke (ischemic or hemorrhagic), myocardial infarction, or death at 90 days; each of these components was based on standard definitions.¹⁰ An exploratory analysis of the primary end point at 7 days was performed; at this time point, because of platelet lifespan and renewal, any effect of aspirin intake before randomization is expected to have disappeared and a sufficient number of events was expected to have occurred to make it possible to detect an early treatment effect. The secondary efficacy end point was ischemic stroke. The primary safety end point was PLATO (Study of Platelet Inhibition and Patient Outcomes) major bleeding. An independent Clinical Event adjudication Committee, blinded to study treatment, adjudicated all components of the efficacy end point and classified all bleeding events, not considered as minimal by the investigator, according to the PLATO bleeding definition.^{10,12}

Statistical Methods

The prior-aspirin subgroup analysis was prespecified and exploratory. Efficacy analyses were based on the intention-to-treat principle using adjudicated events and including all randomized patients. Safety analyses of bleeding events were performed for patients receiving at least one dose of randomized treatment. Time from randomization to the first occurrence of any event for a given end point was analyzed by the Cox proportional hazards model with treatment as the only factor. Interaction between treatment assignment and prior-aspirin indicator was evaluated by including terms for treatment, prior-aspirin indicator, and treatment-by-prior-aspirin indicator interaction in the Cox model. Interaction terms with a *P* value of < 0.05 were considered to be statistically significant. This conservative approach of assessing interaction in subgroup analyses (rather than using $P < 0.10$) was considered appropriate, given that the primary outcome of the SOCRATES trial was not statistically significant ($P = 0.07$).³

Baseline characteristics were compared for patients in the prior-aspirin subgroup and those with no prior-aspirin usage. Categorical variables were presented as percentages and continuous variables as median with interquartile range or mean with SD. χ^2 test and *t* test were performed for comparison of categorical variables and continuous variables, respectively. *P* values of < 0.05 were considered significant.

Results

Baseline characteristics were balanced among ticagrelor and aspirin groups.³ Criteria for prior-aspirin usage was met in 4232 patients (ticagrelor, 2130; aspirin, 2102), whereas 8967 patients (ticagrelor, 4459; aspirin, 4508) did not use aspirin in the 7 days before randomization (Table 1). There were multiple differences in baseline factors among prior- and no prior-aspirin subgroups, mainly driven by the chronic treatment prior-aspirin group (Table 1). There were some patients who had received clopidogrel before randomization (Table 1); a sensitivity analysis excluding these patients did not impact on the overall results of this study. The distribution of patients with ipsilateral atherosclerotic stenosis (A1–A2) was similar in the prior-aspirin and no prior-aspirin subgroups. However, patients with chronic treatment in the prior-aspirin subgroup had higher atherosclerotic burden overall (A1–A3) and higher presence of ipsilateral stenosis versus patients with acute treatment (Table 2).

Table 1. Baseline Characteristics of the Participants by Prior Aspirin

Characteristics	Prior Aspirin (n=4232)	Prior Aspirin Chronic Treatment (n=1731)	Prior Aspirin Acute Treatment (n=2501)	No Prior Aspirin (n=8967)	P Value (Prior Aspirin vs No Prior Aspirin)
Age, y, mean (SD)	67.1 (11.5)	70.4 (10.4)	64.8 (11.6)	65.3 (11.2)	<0.0001
Female sex, n (%)	1748 (41.3)	731 (42.2)	1017 (40.7)	3735 (41.7)	0.70
Race, n (%)					<0.0001
White	3008 (71.1)	1468 (84.8)	1540 (61.6)	5776 (64.4)	
Black	126 (3.0)	37 (2.1)	89 (3.6)	113 (1.3)	
Asian	1039 (24.6)	197 (11.4)	842 (33.7)	2867 (32.0)	
Other	59 (1.4)	29 (1.7)	30 (1.2)	211 (2.4)	
Region, n (%)					<0.0001
Asia and Australia	1059 (25.0)	199 (11.5)	860 (34.4)	2912 (32.5)	
Europe	2415 (57.1)	1197 (69.2)	1218 (48.7)	5126 (57.2)	
North America	613 (14.5)	241 (13.9)	372 (14.9)	441 (4.9)	
Central and South America	145 (3.4)	94 (5.4)	51 (2.0)	488 (5.4)	
Systolic BP, mm Hg, median (IQR)	150 (135–165)	150 (135–165)	150 (134–166)	150 (138–165)	0.09
Diastolic BP, mm Hg, median (IQR)	80 (74–90)	80 (73–90)	82 (74–91)	85 (80–93)	<0.0001
BMI, kg/m ² , median (IQR)	26.3 (23.9–29.7)	27.1 (24.2–30.5)	26.0 (23.6–29.1)	26.0 (23.4–29.1)	<0.0001
History of, n (%)					
Hypertension	3196 (75.5)	1523 (88.0)	1673 (66.9)	6534 (72.9)	<0.01
Diabetes mellitus	1170 (27.6)	616 (35.6)	554 (22.2)	2042 (22.8)	<0.0001
Dyslipidemia	2016 (47.6)	1061 (61.3)	955 (38.2)	3012 (33.6)	<0.0001
Ischemic stroke	639 (15.1)	469 (27.1)	170 (6.8)	954 (10.6)	<0.0001
TIA	394 (9.3)	244 (14.1)	150 (6.0)	462 (5.2)	<0.0001
Myocardial infarction	312 (7.4)	235 (13.6)	77 (3.1)	236 (2.6)	<0.0001
Coronary artery disease	510 (12.1)	375 (21.7)	135 (5.4)	634 (7.1)	0.0001
Congestive heart failure	136 (3.2)	105 (6.1)	31 (1.2)	346 (3.9)	0.06
Taking clopidogrel before randomization, n (%)	209 (4.9)	80 (4.6)	129 (5.2)	247 (2.8)	<0.0001
Time to randomization <12 h, n (%)	1108 (26.2)	647 (37.4)	461 (18.4)	3716 (41.4)	<0.0001
Ischemic stroke as a qualifying event, n (%)	2893 (68.4)	1154 (66.7)	1739 (69.5)	6774 (75.5)	<0.0001
Qualifying TIA baseline ABCD ² score of ≤5, n (%)*	967 (72.2)	398 (69.0)	569 (74.7)	1603 (73.1)	0.55
Qualifying ischemic stroke baseline NIHSS score of ≤3†	2092 (72.3)	800 (69.3)	1292 (74.3)	4425 (65.3)	<0.0001

BMI indicates body mass index; BP, blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*%Calculated based on total TIA patients.

†%Calculated on total stroke patients.

In the prior-aspirin group, a primary end point occurred in 138/2130 (Kaplan-Meier%, 6.5%) patients randomized to ticagrelor and in 177/2102 (Kaplan-Meier%, 8.3%) patients randomized to aspirin (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.61–0.95; $P=0.02$). For the no prior-aspirin group, 304/4459 (Kaplan-Meier%, 6.9%) of patients randomized to ticagrelor and 320/4508 (Kaplan-Meier%, 7.1%) of patients randomized to aspirin experienced a primary end point (HR, 0.96; 95% CI, 0.82–1.12; $P=0.59$; Table 3; Figure [A]). The treatment-by-prior-aspirin interaction did not reach statistical significance ($P=0.10$). The stroke component

was the major contributor to primary end point events. There was a consistent pattern for the effect in patients in the prior-aspirin group randomized to ticagrelor on deaths and myocardial infarctions (Table 3).

The effect on the secondary efficacy end point, ischemic stroke, in patients with prior-aspirin usage randomized to ticagrelor (HR, 0.78; 95% CI, 0.62–0.99; $P=0.04$) was consistent with that on the primary end point (Table 3).

The primary end point censored at day 7 in the prior-aspirin subgroup showed that 80/2130 (3.8%) of patients treated with ticagrelor and 107/2102 (5.1%) treated with

Table 2. ASCOD Atherosclerosis Grade by Prior Aspirin

ASCOD Atherosclerosis Grade	No. of Patients, %			
	Prior Aspirin (n=4232)	Prior Aspirin Chronic Treatment (n=1731)	Prior Aspirin Acute Treatment (n=2501)	No Prior Aspirin (n=8967)
A0	1581 (37.4)	547 (31.6)	1034 (41.3)	3374 (37.6)
A1	384 (9.1)	152 (8.8)	232 (9.3)	736 (8.2)
A2	635 (15.0)	302 (17.4)	333 (13.3)	1326 (14.8)
A3	780 (18.4)	382 (22.1)	398 (15.9)	1116 (12.4)
A9	822 (19.4)	333 (19.2)	489 (19.6)	2372 (26.5)
Missing	30 (0.7)	15 (0.9)	15 (0.6)	43 (0.5)

A0, no atherosclerotic disease; A1 (likely causal), $\geq 50\%$ ipsilateral stenosis of extracranial or intracranial arteries or a mobile thrombus in the aortic arch; A2 (causal relationship possible but uncertain), $< 50\%$ stenosis of extracranial or intracranial artery or an aortic arch plaque of > 4 mm in thickness without mobile thrombus; A3 (unlikely causal), plaque without stenosis or a stenosis in an artery contralateral to the cerebral infarct or a concomitant coronary or peripheral arterial disease; A9, insufficient information to grade atherosclerosis (no assessment of either intracranial arteries or extracranial arteries).¹¹ ASCOD indicates Atherosclerosis, Small-Vessel Disease, Cardiac Pathology, Other Causes, Dissection.

aspirin experienced a primary end point (HR, 0.73; 95% CI, 0.55–0.98; $P=0.04$). In the no prior-aspirin group, a primary end point occurred within 7 days in 175/4459 (3.9%) in the ticagrelor group and 209/4508 (4.6%) in the aspirin group (HR, 0.84; 95% CI, 0.69–1.03; $P=0.10$; Figure [B]).

Table 3 shows the impact of timing and dose of prior aspirin on outcome. The HR for the primary end point for patients with prior-aspirin usage randomized to ticagrelor versus aspirin was similar in patients receiving an acute treatment (HR, 0.72; 95% CI, 0.54–0.97; $P=0.03$) and patients on chronic

Table 3. Efficacy Outcome by Prior-Aspirin Subgroup

Efficacy Outcome	Prior Aspirin*	Ticagrelor 90 mg bd (n=6589)			Aspirin 100 mg OD (n=6610)			HR (95% CI)	P Value	P Value Interaction‡
		n	Patients With Events, %	KM%†	n	Patients With Events, %	KM%†			
Composite of stroke/MI/death	Yes	2130	138 (6.5)	6.5	2102	177 (8.4)	8.3	0.76 (0.61–0.95)	0.02	0.10
	No	4459	304 (6.8)	6.9	4508	320 (7.1)	7.1	0.96 (0.82–1.12)	0.59	
Prior-aspirin therapy, by start day*	Chronic treatment§	890	58 (6.5)	6.6	841	66 (7.8)	7.4	0.82 (0.58–1.17)	0.27	0.58
	Acute treatment	1240	80 (6.5)	6.5	1261	111 (8.8)	8.8	0.72 (0.54–0.97)	0.03	
Prior-aspirin therapy, by dose*	Dose > 150 mg	792	51 (6.4)	6.5	796	64 (8.0)	8.0	0.80 (0.55–1.15)	0.23	0.74
	Dose ≤ 150 mg	1338	87 (6.5)	6.6	1306	113 (8.7)	8.4	0.74 (0.56–0.98)	0.03	
Stroke	Yes	2130	126 (5.9)	6.0	2102	154 (7.3)	7.2	0.80 (0.63–1.01)	0.06	0.41
	No	4459	264 (5.9)	6.0	4508	296 (6.6)	6.6	0.90 (0.76–1.06)	0.21	
MI	Yes	2130	8 (0.4)	0.4	2102	10 (0.5)	0.5	0.79 (0.31–1.99)	0.61	0.26
	No	4459	17 (0.4)	0.4	4508	11 (0.2)	0.3	1.57 (0.73–3.35)	0.25	
Death	Yes	2130	16 (0.8)	0.8	2102	25 (1.2)	1.2	0.63 (0.34–1.18)	0.15	0.02
	No	4459	52 (1.2)	1.2	4508	33 (0.7)	0.7	1.60 (1.03–2.47)	0.04	
Ischemic stroke	Yes	2130	123 (5.8)	5.8	2102	153 (7.3)	7.1	0.78 (0.62–0.99)	0.04	0.29
	No	4459	262 (5.9)	5.9	4508	288 (6.4)	6.4	0.92 (0.78–1.08)	0.31	

bd indicates twice daily; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; MI, myocardial infarction; and OD, once daily.

*Patients in the prior-aspirin subgroup had received aspirin within 7 d before randomization.

†Kaplan-Meier %; the event rate at 90 d.

‡Interaction between treatment assignment and prior aspirin indicator was evaluated by including terms for treatment, prior-aspirin indicator, and treatment-by-prior-aspirin indicator interaction in the Cox model ($P < 0.05$ was considered statistically significant).

§Start of treatment occurring earlier than the day before randomization.

||Start of treatment occurring the day before or the same day as randomization.

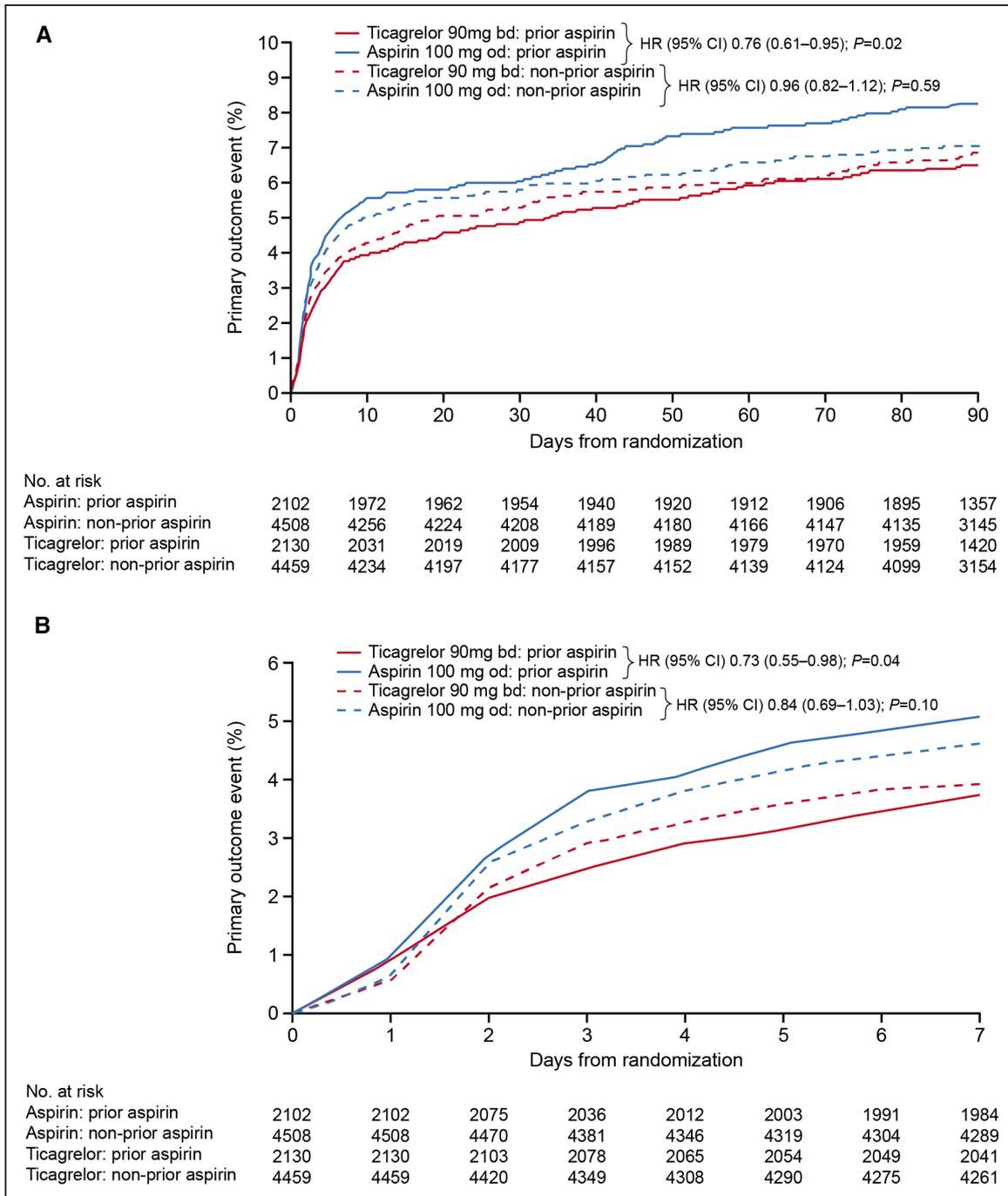


Figure. Kaplan-Meier curves for the primary end point (time to stroke, myocardial infarction, or death) in patients randomized to the aspirin or ticagrelor groups with or without taking aspirin before randomization: (A) full 90-d treatment period; (B) censored at 7 d. bd indicates twice daily; CI, confidence interval; HR, hazard ratio; and od, once daily.

treatment (HR, 0.82; 95% CI, 0.58–1.17; $P=0.27$); P value for interaction was 0.58.

In the prior-aspirin group, major bleeding occurred in 0.7% of patients randomized to ticagrelor and in 0.4% randomized to aspirin (HR, 1.58; 95% CI, 0.68–3.65; $P=0.28$), with no increase of life-threatening bleedings, including intracranial bleedings (Table 4). The combination of major or minor bleedings in the prior-aspirin group was more common among patients randomized to ticagrelor versus aspirin (HR, 1.76; 95% CI, 1.09–2.85; $P=0.02$).

Discussion

In this prespecified exploratory analysis of SOCRATES, there was a trend toward a better treatment effect of ticagrelor over aspirin in patients who received aspirin in the 7 days before randomization, although the interaction for treatment by prior aspirin was not statistically significant when using the conservative threshold of $P<0.05$. Power to detect an interaction effect is generally less than that for the main effect. Failure to identify significant interaction does not imply homogeneity of effects and could be because of low power. In fact, the

Table 4. Safety Outcomes by Prior-Aspirin Subgroup

Safety Outcomes*	Prior Aspirin	Ticagrelor 90 mg bid (n=6549)			Aspirin 100 mg OD (n=6581)			HR (95% CI)	P Value	P Value Interaction‡
		n	Patients With Events, %	KM%†	n	Patients With Events (%)	KM%†			
Major Bleeding According to PLATO Bleeding Definition	Yes	2107	14 (0.7)	0.7	2083	9 (0.4)	0.4	1.58 (0.68–3.65)	0.28	0.07
	No	4442	17 (0.4)	0.4	4498	29 (0.6)	0.7	0.60 (0.33–1.09)	0.09	
Major, fatal/life-threatening	Yes	2107	7 (0.3)		2083	7 (0.3)				0.44
	No	4442	15 (0.3)	0.4	4498	20 (0.4)	0.5	0.77 (0.39–1.50)		
Fatal bleeding	Yes	2107	1 (0)		2083	1 (0)				
	No	4442	8 (0.2)		4498	3 (0.1)				
Intracranial hemorrhage	Yes	2107	4 (0.2)		2083	4 (0.2)				0.23
	No	4442	8 (0.2)	0.2	4498	14 (0.3)	0.3	0.58 (0.25–1.39)		
Major, other	Yes	2107	7 (0.3)		2083	2 (0.1)				
	No	4442	2 (0)		4498	9 (0.2)				
Major or minor	Yes	2107	45 (2.1)	2.3	2083	26 (1.2)	1.2	1.76 (1.09–2.85)	0.02	0.14
	No	4442	61 (1.4)	1.4	4498	56 (1.2)	1.3	1.12 (0.78–1.60)	0.55	

bid indicates twice daily; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; and OD, once daily.

*Safety analysis set.

†Kaplan-Meier %, the event rate at 90 d.

‡Kaplan-Meier %, hazard ratio, and 95% confidence intervals were not calculated if the total number of events was <15.

differences in the magnitude of subgroup-specific treatment effects (HR=0.76 in the prior-aspirin group versus HR=0.96 in no prior-aspirin group) suggests a degree of treatment effect heterogeneity. However, results from subgroup analyses must be interpreted with caution because these can increase both false-positive and false-negative errors. Therefore, the observation in this study should primarily be hypothesis-generating with necessary confirmation coming from a future study.

Interestingly, a recent publication based on reanalyses of clinical trial data with aspirin versus control in acute minor stroke and TIA demonstrated that aspirin substantially reduces the risk of early recurrent stroke and reduces disability after recurrent stroke.¹³ Thus, aspirin's preventive effect in the early period after acute cerebral ischemic events may be substantial, and a residual aspirin effect during the first week of treatment in SOCRATES may have provided additional benefit to ticagrelor, by conferring partial dual antiplatelet therapy.

An enhanced antiplatelet effect of clopidogrel with aspirin was seen in several studies. Studies investigating microembolization from atherosclerotic cerebral arteries in connection with acute cerebral ischemic events showed a reduction in events with dual antiplatelet therapy.^{14,15} Furthermore, the CHANCE trial of Chinese patients with minor ischemic stroke or TIA found a 32% relative risk reduction of a stroke at 90 days with a regimen including clopidogrel with aspirin versus one that included only aspirin.¹ The ongoing POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) is investigating whether the promising results of clopidogrel and aspirin versus aspirin in acute cerebral ischemic events demonstrated in CHANCE could be confirmed in a Western population.¹⁶

The higher vascular disease burden in the prior-aspirin group may reflect that aspirin was used more frequently for

prevention of atherothrombotic diseases in this subgroup. Potentially, patients with a higher vascular event risk in the prior-aspirin group, and with the index event occurring during aspirin treatment (breakthrough stroke), may have benefited more from intense antiplatelet therapy provided by ticagrelor.¹⁷ However, a large proportion of patients in the prior-aspirin group only received acute treatment before randomization, thus most likely after the start of the index event, and these patients benefited from ticagrelor at least as much as those with aspirin chronic treatment before randomization. Diminishing clinical effect of aspirin with long-term use has been hypothesized and could explain higher event rates in those previously taking aspirin who were randomized to aspirin and a trend toward better treatment effect of ticagrelor^{13,17}; however, this would not explain the similar effect seen in those who received only acute aspirin treatment before randomization. The observation that patients who received only acute treatment with aspirin after the index event had a favorable outcome may indicate the benefit of dual antiplatelet with ticagrelor and aspirin in the acute setting of cerebral ischemic events. Finally, atherosclerotic phenotyping could not confirm an increased prevalence of ipsilateral atherosclerotic stenosis in the prior-aspirin group; a higher prevalence of ipsilateral atherosclerotic stenosis could have rendered this subgroup more responsive to ticagrelor, as shown in a recent SOCRATES publication.¹⁸ Although atherosclerotic phenotype was more common in the chronic treatment than in the acute treatment prior-aspirin group, this difference did not translate into a differentiated treatment effect.

Taking all these findings together, it is reasonable to assume that the initial dual antiplatelet effect from aspirin intake 7 days before randomization during the period with the highest risk for new stroke events was the major contributor to

the potential treatment effect of ticagrelor in the prior-aspirin group, observed in the 7-day analysis, as well as at 90 days.

In a secondary publication from the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54), addition of ticagrelor to aspirin for long-term secondary prevention in patients with coronary disease provided a significant relative risk reduction of stroke by 25%, but with more major bleeding (HR, 2.32; 95% CI, 1.68–3.21; $P < 0.001$).¹⁹ In CHANCE, major bleeding event rates were similar for aspirin alone and the combination of clopidogrel and aspirin.¹ In SOCRATES, the number of major bleeding events were few and similar for ticagrelor and aspirin.¹² Overall, major or minor bleeding tended to be more common on ticagrelor than aspirin in the prior-aspirin group, which may reflect a more pronounced antiplatelet effect, whereas severe, life-threatening bleeding rates were not.

Although this global data set is of reasonable size to justify subgroup analyses, the results from these analyses should be interpreted with caution for several reasons. The primary outcome in SOCRATES was not statistically significant. The prior-aspirin usage was not randomly assigned and there were differences in baseline factors among the subgroups; however, the key comparator of interest was randomized: treatment with ticagrelor or aspirin. In addition, the effect of aspirin intake before randomization would gradually disappear during the first treatment week, providing only a partial dual antiplatelet therapy in the ticagrelor prior-aspirin subgroup. Therefore, the findings about bleeding risk and efficacy of combining ticagrelor and aspirin versus aspirin alone in patients with acute stroke or TIA need to be confirmed in a randomized trial.

In conclusion, the results of the present analyses and the literature on dual antiplatelet therapy in patients with acute cerebral ischemic events support the hypothesis that the combination of ticagrelor and aspirin may be a more effective treatment than aspirin alone in preventing subsequent ischemic events in patients with acute minor ischemic stroke or TIA. This hypothesis will be addressed in the THALES trial (Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death; URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT03354429).

Acknowledgments

Editorial support (formatting tables and figures, coordinating reviews, and preparing the article for submission) was provided by Jackie Phillipson (Zoetic Science, an Ashfield company, part of UDG Healthcare plc, Macclesfield, United Kingdom); this assistance was funded by AstraZeneca.

Sources of Funding

The trial was funded by AstraZeneca.

Disclosures

Dr Wong reports honoraria as a member of a steering committee for Johnson & Johnson, AstraZeneca (modest), and Bayer (modest); honoraria for participation in clinical trials, contributions to advisory boards, or oral presentations from Bayer (modest), Sanofi-Aventis (modest), Bristol-Myers Squibb, Boehringer Ingelheim (modest), and Pfizer (modest). Dr Amarenco reports receipt of significant research grant

support from AstraZeneca, Sanofi, and Bristol-Myers Squibb (for <http://www.TIAregistry.org>), the French Government and Pfizer (for the TST trial [Treat Stroke to Target]), and Boston Scientific (for the WATCH-AF registry [Warfarin Aspirin Ten(X)-a Inhibitors LAA Closure in Cerebral Infarct and Hemorrhage and AF registry]). He has received modest consultant/advisory board fees from Amgen and Bristol-Myers Squibb. He has also received modest honoraria from Amgen (speaker activities), Pfizer (Studies of PCSK9 Inhibition and the Reduction of Vascular Events program Executive Committee), AstraZeneca (SOCRATES trial [Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes] Executive Committee), and Kowa (PROMINENT [Pemaifibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes study] Executive committee), and significant honoraria from Bayer (XANTUS [Xarelto® for Prevention of Stroke in Patients With Atrial Fibrillation study] Executive Committee), AstraZeneca (THALES [Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death trial] Executive Committee), and Fibrogen (ALPINE program trials Data and Safety Monitoring Board member). Dr Albers reports equity interest and consulting fees from iSchemaView (significant), and consultant fees from Janssen (modest). Drs Denison, Held, Himmelmann, Knutsson, and Ladenvall are employees of AstraZeneca (all significant). Dr Easton received research grant support from AstraZeneca (significant) for the SOCRATES trial (URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01994720) and receives research support (significant) from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke as a coprincipal investigator for the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; U01 NS062835-01A1); POINT received some free study drug and placebo from Sanofi (URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00991029). He also receives support (modest) from Boehringer Ingelheim as a consultant for the planning and conduct of the RE-SPECT ESUS trial (Dabigatran Etxilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source; URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02239120). Dr Evans is a statistical consultant to AstraZeneca (significant). Dr Kasner reports a grant from AstraZeneca during the conduct of this study; as well as grants from Bayer (significant), Bristol Myers Squibb, WL Gore (significant), and Acorda (all others modest); consulting fees from Merck, Boehringer Ingelheim, Abbvie, Medtronic, and Johnson & Johnson (modest), outside the submitted work. Dr Minematsu reports honoraria (all modest for seminar presentations) from Bayer Yakuhin, Otsuka Pharmaceutical, Boehringer Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma Cooperation, Japan Stryker, Kowa, Nihon Medi-Physics Co, BMS, Sumitomo Dainippon Pharma Co, Daiichi Sankyo, Asters Pharma, and immediate family members have received modest honoraria from Nippon Chemiphar. He has also received modest honoraria (for a supervising brochure) from Sawai Pharmaceuticals, and modest fees (advisory board) from CSL Behring and Medico's Hirata. Dr Molina serves in the Steering Committee (significant) of CLOTBUSTER trial (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator for Emergent Revascularization in Acute Ischemic Stroke; Cerevast); SOCRATES (AstraZeneca), IMPACT-24b (Implant Augmenting Cerebral Blood Flow Trial 24 Hours From Stroke Onset; Brainsgate), REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours trial; Fundació Ictus Malaltia Vascular). He has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from AstraZeneca (modest), Boehringer Ingelheim, Daiichi Sankyo, BMS, Covidien, Cerevast, Brainsgate. Dr Molina has no ownership interest and does not own stocks of any pharmaceutical or medical device company. Dr Wang reports research grant support from AstraZeneca (modest). Dr Johnston reports receiving research grants from the National Institutes of Neurological Disorders and Stroke and NIH. His institution has received research support from AstraZeneca. He has received research support from Biogen (consulting agreement and compensation agreement—both significant), and was a consultant to AstraZeneca as the Committee Chair (significant) for SOCRATES. He has also received travel and hotel expenses from AstraZeneca to attend meetings.

References

- Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340.
- Amarenco P, Lavallée PC, Labreuche J, Albers GW, Bornstein NM, Canhão P, et al; TIARegistry.org Investigators. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374:1533–1542. doi: 10.1056/NEJMoa1412981.
- Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al; SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med*. 2016;375:35–43. doi: 10.1056/NEJMoa1603060.
- CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomized placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641–1649. doi: 10.1016/S0140-6736(97)04010-5.
- International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;349:1569–1581. doi: 10.1016/S0140-6736(97)04011-7.
- Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024.
- Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, et al; CHANCE Investigators. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA*. 2016;316:70–78. doi: 10.1001/jama.2016.8662.
- Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovasc Ther*. 2009;27:259–274. doi: 10.1111/j.1755-5922.2009.00096.x.
- Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014;63:2503–2509. doi: 10.1016/j.jacc.2014.03.031.
- Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Held P, et al. Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial: rationale and design. *Int J Stroke*. 2015;10:1304–1308. doi: 10.1111/ijs.12610.
- Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). *Cerebrovasc Dis*. 2013;36:1–5. doi: 10.1159/000352050.
- Easton JD, Aunes M, Albers GW, Amarenco P, Bokelund-Singh S, Denison H, et al; SOCRATES Steering Committee and Investigators. Risk for major bleeding in patients receiving ticagrelor compared with aspirin after transient ischemic attack or acute ischemic stroke in the SOCRATES study (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes). *Circulation*. 2017;136:907–916. doi: 10.1161/CIRCULATIONAHA.117.028566.
- Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet*. 2016;388:365–375. doi: 10.1016/S0140-6736(16)30468-8.
- Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial. *Circulation*. 2005;111:2233–2240. doi: 10.1161/01.CIR.0000163561.90680.1C.
- Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al; CLAIR Study Investigators. Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolisation in Patients With Acute Symptomatic Cerebral or Carotid Artery Stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9:489–497. doi: 10.1016/S1474-4422(10)70060-0.
- Johnston SC, Easton JD, Farrant M, Barsan W, Battenhouse H, Conwit R, et al. Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8:479–483. doi: 10.1111/ijs.12129.
- Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Antiplatelet regimen for patients with breakthrough strokes while on aspirin. A systematic review and meta-analysis. *Stroke*. 2017;48:2610–2613. doi: 10.1161/STROKEAHA.117.017895.
- Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, et al; SOCRATES Steering Committee and Investigators. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *Lancet Neurol*. 2017;16:301–310. doi: 10.1016/S1474-4422(17)30038-8.
- Bonaca MP, Goto S, Bhatt DL, Steg PG, Storey RF, Cohen M, et al; Prevention of stroke with ticagrelor in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54). *Circulation*. 2016;134:861–871. doi: 10.1161/CIRCULATIONAHA.116.024637.

Efficacy and Safety of Ticagrelor in Relation to Aspirin Use Within the Week Before Randomization in the SOCRATES Trial

K.S. Lawrence Wong, Pierre Amarenco, Gregory W. Albers, Hans Denison, J. Donald Easton, Scott R. Evans, Peter Held, Anders Himmelmann, Scott E. Kasner, Mikael Knutsson, Per Ladenvall, Kazuo Minematsu, Carlos A. Molina, Yongjun Wang and S. Claiborne Johnston for the SOCRATES Steering Committee and Investigators

Stroke. 2018;49:1678-1685; originally published online June 18, 2018;

doi: 10.1161/STROKEAHA.118.020553

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2018 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/49/7/1678>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>