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)

BACKGROUND: Patients with minor acute ischemic stroke or transient ischemic attack are at high risk for subsequent stroke, and more potent antiplatelet therapy in the acute setting is needed. However, the potential benefit of more intense antiplatelet therapy must be assessed in relation to the risk for major bleeding. The SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was the first trial with ticagrelor in patients with acute ischemic stroke or transient ischemic attack in which the efficacy and safety of ticagrelor were compared with those of aspirin. The main safety objective was assessment of PLATO (Platelet Inhibition and Patient Outcomes)–defined major bleeds on treatment, with special focus on intracranial hemorrhage (ICrH).

METHODS: An independent adjudication committee blinded to study treatment classified bleeds according to the PLATO, TIMI (Thrombolysis in Myocardial Infarction), and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) definitions. The definitions of ICrH and major bleeding excluded cerebral microbleeds and asymptomatic hemorrhagic transformations of cerebral infarctions so that the definitions better discriminated important events in the acute stroke population.

RESULTS: A total of 13 130 of 13 199 randomized patients received at least 1 dose of study drug and were included in the safety analysis set. PLATO major bleeds occurred in 31 patients (0.5%) on ticagrelor and 38 patients (0.6%) on aspirin (hazard ratio, 0.83; 95% confidence interval, 0.52–1.34). The most common locations of major bleeds were intracranial and gastrointestinal. ICrH was reported in 12 patients (0.2%) on ticagrelor and 18 patients (0.3%) on aspirin. Thirteen of all 30 ICrHs (4 on ticagrelor and 9 on aspirin) were hemorrhagic strokes, and 4 (2 in each group) were symptomatic hemorrhagic transformations of brain infarctions. The ICrHs were spontaneous in 6 and 13, traumatic in 3 and 3, and procedural in 3 and 2 patients on ticagrelor and aspirin, respectively. In total, 9 fatal bleeds occurred on ticagrelor and 4 on aspirin. The composite of ICrH or fatal bleeding included 15 patients on ticagrelor and 18 on aspirin. Independently of bleeding classification, PLATO, TIMI, or GUSTO, the relative difference between treatments for major/severe bleeds was similar. Nonmajor bleeds were more common on ticagrelor.

CONCLUSIONS: Antiplatelet therapy with ticagrelor in patients with acute ischemic stroke or transient ischemic attack showed a bleeding profile similar to that of aspirin for major bleeds. There were few ICrHs.

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Clinical Perspective

What Is New?

- The SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; n=13 199) was the first outcome study with ticagrelor in patients with acute ischemic stroke (National Institutes of Health Stroke Scale score ≤5) or transient ischemic attack.
- Monotherapy with ticagrelor 90 mg twice daily for 90 days was compared with aspirin 100 mg daily.
- Ticagrelor was not superior to aspirin in reducing the primary composite end point of stroke, myocardial infarction, or death (hazard ratio, 0.89; 95% confidence interval, 0.78–1.01; *P*=0.07).
- The risk for major bleeding was similar with ticagrelor and aspirin.
- The number of intracranial hemorrhages was low.
- There was a numeric increase of minor bleeds with ticagrelor.

What Are the Clinical Implications?

- The SOCRATES trial contributes important data on the bleeding profile of ticagrelor in patients with acute cerebral ischemia, a patient population that has not been included in any other ticagrelor outcome study.
- Reassuringly, there was no increased risk in major bleeds with ticagrelor compared with aspirin, including intracranial bleeds.
- There were a numeric reduction in the primary efficacy end point and a numeric increase in minor bleeds, which may reflect a more pronounced antiplatelet effect of ticagrelor.
- The role of ticagrelor in the treatment of patients with acute cerebral ischemia is yet to be determined by additional clinical studies.

Ticagrelor is a potent antiplatelet drug. It is a reversibly binding and direct-acting oral antagonist of the $P2Y_{12}$ receptor on platelets,[1,2] and it does not require metabolic activation. Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1.[3]

Two large outcome studies in patients with coronary artery disease have demonstrated that ticagrelor, in combination with aspirin, is effective in preventing cardiovascular events.[4–6] The SOCRATES study (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes)[7,8] was the first trial with ticagrelor in patients with acute cerebral ischemia. The SOCRATES trial (ClinicalTrials.gov. Unique identifier: NCT01994720) was a randomized, double-blind study with antiplatelet monotherapy of ticagrelor compared with aspirin in patients with acute ischemic stroke (AIS; National Institutes of Health Stroke Scale ≤5) or high-risk transient ischemic attack (TIA) of noncardioembolic origin randomized within 24 hours of symptom onset. It showed a nonsignificant 11% relative risk reduction in the composite of stroke (ischemic or hemorrhagic), myocardial infarction, or death. Its predefined first secondary outcome, ischemic stroke, occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.76–1.00).

Major bleeding events, especially fatal and intracranial bleeds, are the most worrisome side effect in patients taking antithrombotic drugs. Even moderate doses of aspirin are associated with a risk of hemorrhagic events, including gastrointestinal bleeding.[9] Furthermore, accumulating data indicate a heightened risk of intracranial hemorrhage (ICrH) among patients with a history of stroke who are treated with potent antiplatelet therapy.[10,11] The primary safety objective in SOCRATES was assessment of PLATO (Platelet Inhibition and Patient Outcomes)–defined major bleeds,[7,8] with special emphasis on ICrH. The aims of this article are to describe the bleeding profile of monotherapy with ticagrelor versus aspirin in this population of patients with AIS and TIA; to characterize major bleeding using the PLATO, TIMI (Thrombolysis in Myocardial Infarction), and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) bleeding definitions[4,12,13]; and to identify factors associated with major bleeding.

METHODS

Patients participating in the SOCRATES study were randomized to blinded study treatment with aspirin as a loading dose of 300 mg followed by a maintenance dose of 100 mg daily or to ticagrelor as a loading dose of 180 mg followed by 90 mg twice daily for 90 days.

All bleed events not considered as PLATO minimal by the investigator were adjudicated by the independent Clinical Event Adjudication Committee, blinded to study treatment, and classified according to PLATO, TIMI, and GUSTO definitions and whether bleeds were spontaneous, traumatic, or procedural.[4,12,13] Procedure-related bleeds were defined as bleeding events directly provoked by a medical or dental procedure of any kind.

PLATO bleeding definitions have not been used in TIA and stroke studies but were selected to be consistent with the previous major ticagrelor trials. PLATO, TIMI, and GUSTO definitions were developed primarily for an acute coronary syndrome setting. In the SOCRATES study, they were adapted to the AIS/TIA population. For PLATO and GUSTO definitions, asymptomatic hemorrhagic transformations of brain infarctions and microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging were excluded from fulfilling ICrH criteria. This has been the common convention in recent large stroke trials.[14–18] The TIMI definition, which already excluded cerebral microhemorrhages, was updated

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to exclude asymptomatic hemorrhagic transformations. For PLATO, TIMI, and GUSTO bleeding definitions, see Table 1.

The bleeding events were assessed in patients on study treatment, which also included 7 days after intake of last dose of study drug to take into account the duration of the pharmacodynamic effect of aspirin.

The SOCRATES study design was approved by Institutional Review boards/relevant ethics committee at each participating site. Patients provided written informed consent before any study-specific procedures were performed.

Statistical Analyses

The safety analysis set consisted of all patients who received at least 1 dose of study drug (ticagrelor or aspirin). Patients were accounted for in treatment groups by actual treatment received. One patient randomized to ticagrelor inadvertently received aspirin instead and was thus included in the aspirin group for the safety analyses.

A brief description of baseline characteristics is presented for the safety population in the Results section. Categorical variables are described as counts and percentages. The time from randomization to the first bleed was compared with the use of the Cox proportional hazards model, with a factor for treatment group. *P* values and CIs for the HRs are based on the Wald statistics. *P* values and HRs were calculated for end points with ≥15 events in total for both treatments. Tables include HRs with CIs, *P* values, numbers and percentages of patients with events, and Kaplan-Meier estimates.

Study Funding

The study was sponsored by AstraZeneca. The Executive Committee was responsible for the overall design, ensuring

Table 1. Complete PLATO, TIMI, and GUSTO Definitions With Footnotes on What Was Analyzed in SOCRATES

PLATO, TMI, and GUSTO Bleeding Classifications		
PLATO[4]	**TIMI[12]**	**GUSTO[13]**
Major bleed, fatal/life-threatening Any of the following: Fatal Intracranial* Intrapericardial bleed with cardiac tamponade Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery Clinically overt or apparent bleeding associated with a decrease in Hb of >50 g/L Transfusion of ≥4 U (whole blood or PRBCs) for bleeding	Major bleed Any of the following: Fatal (a bleeding event that directly led to death within 7 d) Intracranial* Clinically overt signs of hemorrhage associated with a decrease in Hb of ≥50 g/L	Severe Any of the following: Fatal Intracranial* Bleeding that caused hemodynamic compromise requiring intervention (eg, systolic blood pressure <90 mm Hg that required blood or fluid replacement, vasopressor/inotropic support, or surgical intervention)
Major bleed, other Any of the following: Significantly disabling (eg, intraocular with permanent vision loss) Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/L to 50 g/L Transfusion of 2–3 U (whole blood or PRBCs) for bleeding	Minor bleed Clinically overt signs of hemorrhage (including imaging) associated with a decrease in Hb of 30–<50 g/L	Moderate bleed Bleeding requiring transfusion of whole blood or PRBCs without hemodynamic compromise (as defined above)
Minor bleed Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)	Medical attention for the bleed† Any overt sign of hemorrhage that meets 1 of the following criteria and that does not meet criteria for a major or minor bleeding event, as defined above: Requiring intervention: defined as medical practitioner guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently discontinuing or changing the dose of a medication or study drug Leading to hospitalization: defined as leading to or prolonging hospitalization Prompting evaluation: defined as unscheduled contact with a healthcare professional and diagnostic testing (laboratory or imaging)	Mild bleed† Bleeding without blood transfusion or hemodynamic compromise
Minimal bleed (collected but not adjudicated) All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment.	Minimal bleed† Any overt bleeding event that does not meet the criteria above	

GUSTO indicates Global Use of Strategies to Open Occluded Coronary Arteries; Hb, hemoglobin; PLATO, Platelet Inhibition and Patient Outcomes; PRBC, packed red blood cell; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; and TIMI, Thrombolysis in Myocardial Infarction.

*Stroke study adaptation of bleeding classifications: For PLATO, TIMI, and GUSTO, intracranial bleed was defined as intracerebral hemorrhage excluding asymptomatic hemorrhagic transformations of brain infarctions and excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging.

†This item was not analyzed in the SOCRATES study.

Table 2. PLATO Major or Minor Bleeding Events (Safety Analysis Set)

Characteristic	Ticagrelor 90 mg Twice Daily (n=6549)		Aspirin 100 mg Once Daily (n=6581)			
	Patients With Events, n	KM%	Patients With Events, n	KM%	HR (95% CI)	*P* Value
PLATO major	31	0.5	38	0.6	0.83 (0.52–1.34)	0.45
Major, fatal/life-threatening	22	0.4	27	0.4	0.83 (0.47–1.46)	0.52
Fatal bleeding	9		4			
Intracranial bleeding	12	0.2	18	0.3	0.68 (0.33–1.41)	0.30
Fatal/intracranial bleeding	15	0.2	18	0.3	0.85 (0.43–1.68)	0.64
Major, other	9	0.1	11	0.2	0.84 (0.35–2.03)	0.70
PLATO major or minor	106	1.7	82	1.3	1.32 (0.99–1.76)	0.06

CI indicates confidence interval; HR, hazard ratio; KM%, Kaplan-Meier percentage at 90 days; and PLATO, Platelet Inhibition and Patient Outcomes.

PLATO minimal bleeds (nonadjudicated) were reported in 521 patients (8.0%) in the ticagrelor group and 239 patients (3.6%) in the aspirin group.

the integrity of the data, analysis of the results, and decision to submit for publication. The corresponding authors had full access to all the data.

RESULTS

In total, 13 130 (of 13 199 randomized) patients received at least 1 dose of study drug in the SOCRATES study.

Baseline characteristics for the safety population were balanced across the 2 treatment groups. The mean age was 65.9 years; 41.5% were women; 12.1% had a history of stroke before the index stroke/TIA; 73.7% had a history of hypertension; and 24.3% had a history of diabetes mellitus (Table I in the online-only Data Supplement).

PLATO major bleeds occurred in 31 patients (0.5%) on treatment with ticagrelor and in 38 patients (0.6%) on aspirin (HR, 0.83; 95% CI, 0.52–1.34; Table 2 and Figure 1). No patient had >1 PLATO major bleed.

In both treatment groups, the most common locations for PLATO major bleeds were intracranial and gas-

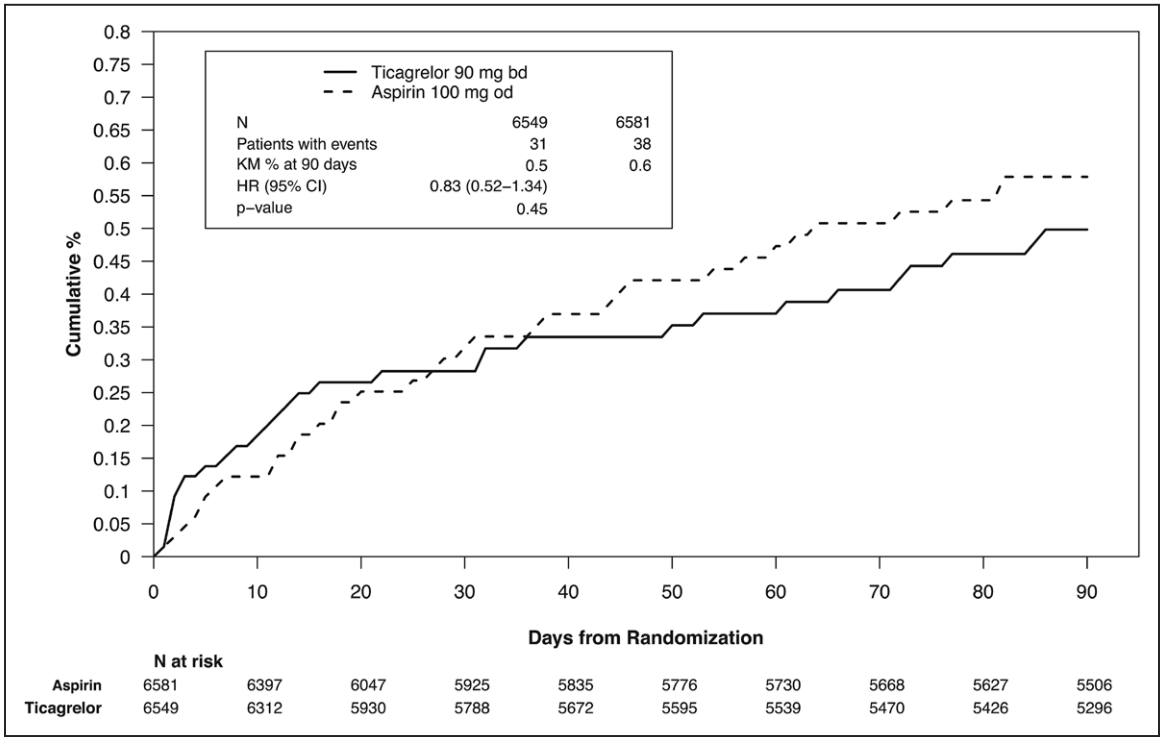

Figure 1. Kaplan-Meier plot of cumulative percentage of patients with PLATO (Platelet Inhibition and Patient Outcomes) major bleeding, on treatment (safety analysis set).[7]

bd Indicates twice daily; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; and OD, once daily. Reproduced from Johnston et al.[7] with permission from the publisher.

Table 3. PLATO Major Bleeding Events by Provocation (Safety Analysis Set)

Characteristic	Ticagrelor 90 mg Twice Daily (n=6549)		Aspirin 100 mg Once Daily (n=6581)			
	Patients With Events, n	KM%	Patients With Events, n	KM%	HR (95% CI)	*P* Value
PLATO major	31	0.5	38	0.6	0.83 (0.52–1.34)	0.45
Spontaneous	22	0.4	31	0.5	0.73 (0.42–1.25)	0.25
Procedural	5		3			
Traumatic	4		4			

CI indicates confidence interval; HR, hazard ratio; KM%, Kaplan-Meier percentage at 90 days; and PLATO, Platelet Inhibition and Patient Outcomes.

trointestinal. Intracranial bleeding was reported in 12 patients (0.2%) on treatment with ticagrelor and in 18 patients (0.3%) on aspirin. There were 10 (0.2%) gastrointestinal bleeds on ticagrelor and 9 (0.1%) on aspirin.

Bleeds were also classified on the basis of provocation. Spontaneous PLATO major bleeds occurred in 22 patients on ticagrelor versus 31 patients on aspirin, procedural bleeds in 5 patients versus 3 patients, and traumatic bleeds in 4 patients in each treatment group (Table 3). Procedural PLATO major bleeds (n=5) on ticagrelor developed in association with thrombolytic treatment of ischemic stroke (n=2), after decompressive craniotomy, after a cerebral thrombectomy procedure with angioplasty and stenting of the right internal carotid artery, and in association with percutaneous coronary intervention (pericardial bleed). On aspirin, the 3 procedural major bleeds developed after cerebral aneurysm clipping, after cerebral thrombectomy, and after thoracic surgery for aortic aneurysm.

Details on ICrHs by category and by provocation for each treatment group are presented in Table 4. Thirteen (4 on ticagrelor versus 9 on aspirin) were hemorrhagic strokes, and 4 (2 versus 2) were symptomatic hemorrhagic transformations of the index or new ischemic stroke event. There were 6 other ICrHs (traumatic or procedure-related) on ticagrelor and 7 on aspirin.

Asymptomatic hemorrhagic transformations of ischemic stroke were not considered ICrHs (see Methods). The numbers of events adjudicated to asymptomatic hemorrhagic transformations of the index or new ischemic stroke event were similar in both treatment groups (Table II in the online-only Data Supplement).

Nine fatal bleeds occurred in patients on ticagrelor and 4 in patients on aspirin. For ticagrelor, 6 of the fatal bleeds were intracranial, 2 were aortic, and 1 was gastrointestinal. All fatal bleeds on aspirin were intracranial.

There were 75 patients (1.1%) with 79 PLATO minor bleeds on ticagrelor and 45 patients (0.7%) with 49 events on aspirin. PLATO minimal bleeds were reported by investigators in 521 patients (8.0%) on ticagrelor and 239 patients (3.6%) on aspirin.

More patients had bleeding adverse events leading to permanent and premature discontinuation of study drug (adverse events leading to permanent and premature discontinuation of study drug [DAEs]) in the ticagrelor group than in the aspirin group: 82 (1.3%) and 37 (0.6%), respectively, corresponding to an HR of 2.26 (95% CI, 1.53–3.34; Figure 2). The most common bleeding DAEs were epistaxis, bruising, and spontaneous hematoma (>0.1% of patients in both treatment groups).

In the ticagrelor treatment group, the majority of bleeding DAEs were classified as PLATO minimal; 10 (0.2%) for PLATO major, 20 (0.3%) for PLATO minor, and 52 (0.8%)

Table 4. Intracranial Hemorrhages Fulfilling the Criteria for PLATO Major Bleeding, on Treatment (Safety Analysis Set)

Characteristic	Total Events, n		First Event, n (%)	
	Ticagrelor 90 mg Twice Daily	Aspirin 100 mg Once Daily	Ticagrelor 90 mg Twice Daily (n=6549)	ASA 100 mg Once Daily (n=6581)
ICrHs fulfilling the criteria for PLATO major bleeding*	12	18	12 (0.2)	18 (0.3)
Hemorrhagic stroke	4	9	4 (0.1)	9 (0.1)
Ischemic stroke with symptomatic hemorrhagic transformation	1	1	1 (0.0)	1 (0.0)
Symptomatic hemorrhagic transformation of index event	1	1	1 (0.0)	1 (0.0)
Other ICrH	6	7	6 (0.1)	7 (0.1)
By provocation				
Spontaneous ICrH	6	13	6 (0.1)	13 (0.2)
Traumatic ICrH	3	3	3 (0.0)	3 (0.0)
Procedural ICrH	3	2	3 (0.0)	2 (0.0)

This table includes events reported as both adverse events and end points. Patients may be counted in >1 bleeding event category.

This table includes events with an onset date on or after the date of first dose and up to and including 7 days after the date of last dose of study medication. ICrH indicates intracranial hemorrhage; and PLATO, Platelet Inhibition and Patient Outcomes.

*PLATO bleeding definitions have been adapted to the acute stroke population by excluding asymptomatic hemorrhagic transformations of brain infarctions and microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging.

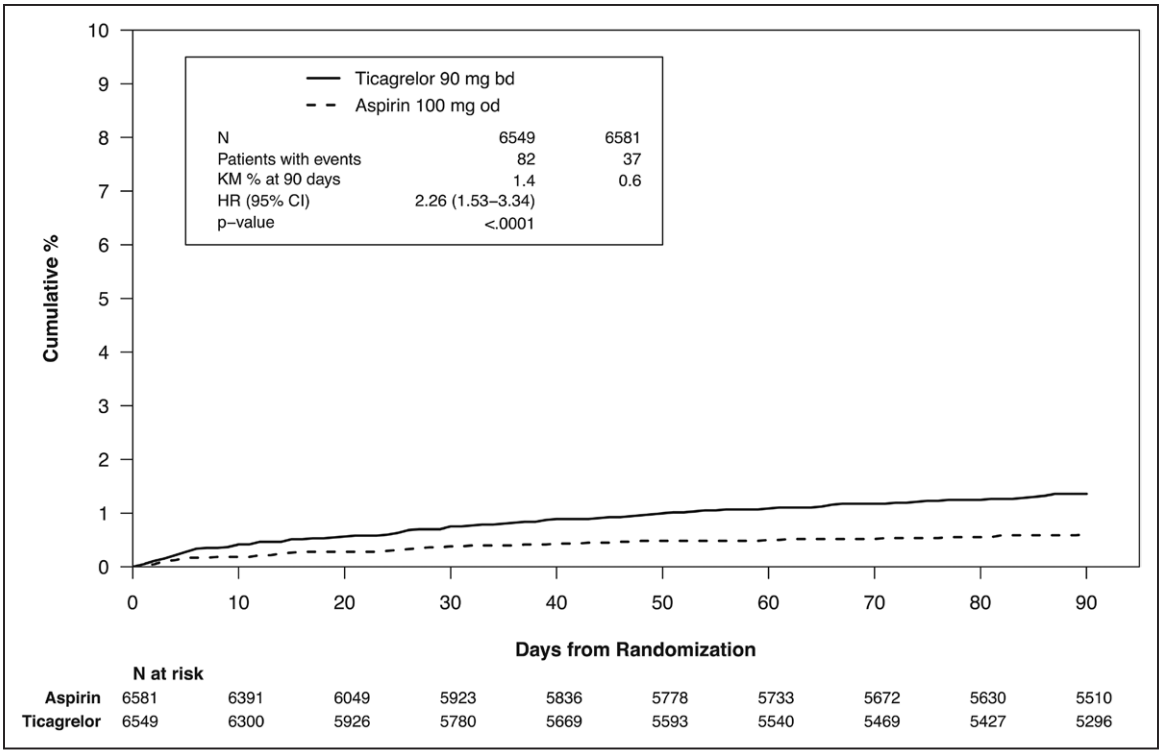

Figure 2. Kaplan-Meier plot of cumulative percentage of patients who prematurely discontinued study drug because of bleeding adverse event (safety analysis set).
bd Indicates twice daily; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; and OD, once daily.

for PLATO minimal. In the aspirin treatment group, bleeding DAEs were distributed more evenly across the PLATO major (n=14, 0.2%), PLATO minor (n=10, 0.2%), and PLATO minimal (n=13, 0.2%) classifications.

End-point events were not reported as adverse events. Few end points were bleeding events. A sensitivity analysis including all bleeding end points as DAEs showed consistent results (87 [1.3%] and 48 [0.7%] in the ticagrelor and aspirin groups, respectively; HR 1.85; 95% CI, 1.30–2.63).

Because of the low number of PLATO major bleeds, it was not possible to make any conclusions on subgroups (Figure 3) or to identify risk factors for major bleeds.

The number of bleeds that were major/severe and minor/moderate according to the PLATO, TIMI, and GUSTO bleeding classifications by treatment with ticagrelor and aspirin is provided in Table 5. Although the number of patients differs on the basis of how inclusive the definition is (Table 1), the relative difference between treatments is similar for the major/severe bleeds.

DISCUSSION

The main results showed that the number of PLATO major bleeds, including ICrHs, was low and similar in both treatment groups. However, the number of patients with PLATO nonmajor bleeds was higher for ticagrelor than for aspirin.

Patients who experience minor AIS or TIA are at high risk for developing new ischemic stroke, even when treated with aspirin, the current standard of care. More effective antiplatelet therapy, despite a potential slight increase in bleeding risk, could significantly reduce the overall burden of TIA/ischemic stroke if initiated soon after symptom onset. Consequently, based on the potent antiplatelet effect of ticagrelor, SOCRATES was designed to test the efficacy and safety of monotherapy in patients with AIS or high-risk TIA. In addition, studying monotherapy was considered appropriate in light of the growing concern that patients with cerebral ischemic disease might be at especially high risk for ICrH on dual antiplatelet treatment, as suggested by results for patients with previous stroke in long-term antiplatelet studies for various indications, for example, in patients with recent ischemic stroke/TIA (MATCH trial [Management of Atherothrombosis with Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attack or Ischemic Stroke]),[10] in acute coronary syndromes (TRITON [Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel] TIMI 38),[11] and in a broader atherosclerotic population (TRA 2P [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events] TIMI 50).[19]

In contrast, in the CHANCE study (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebro-

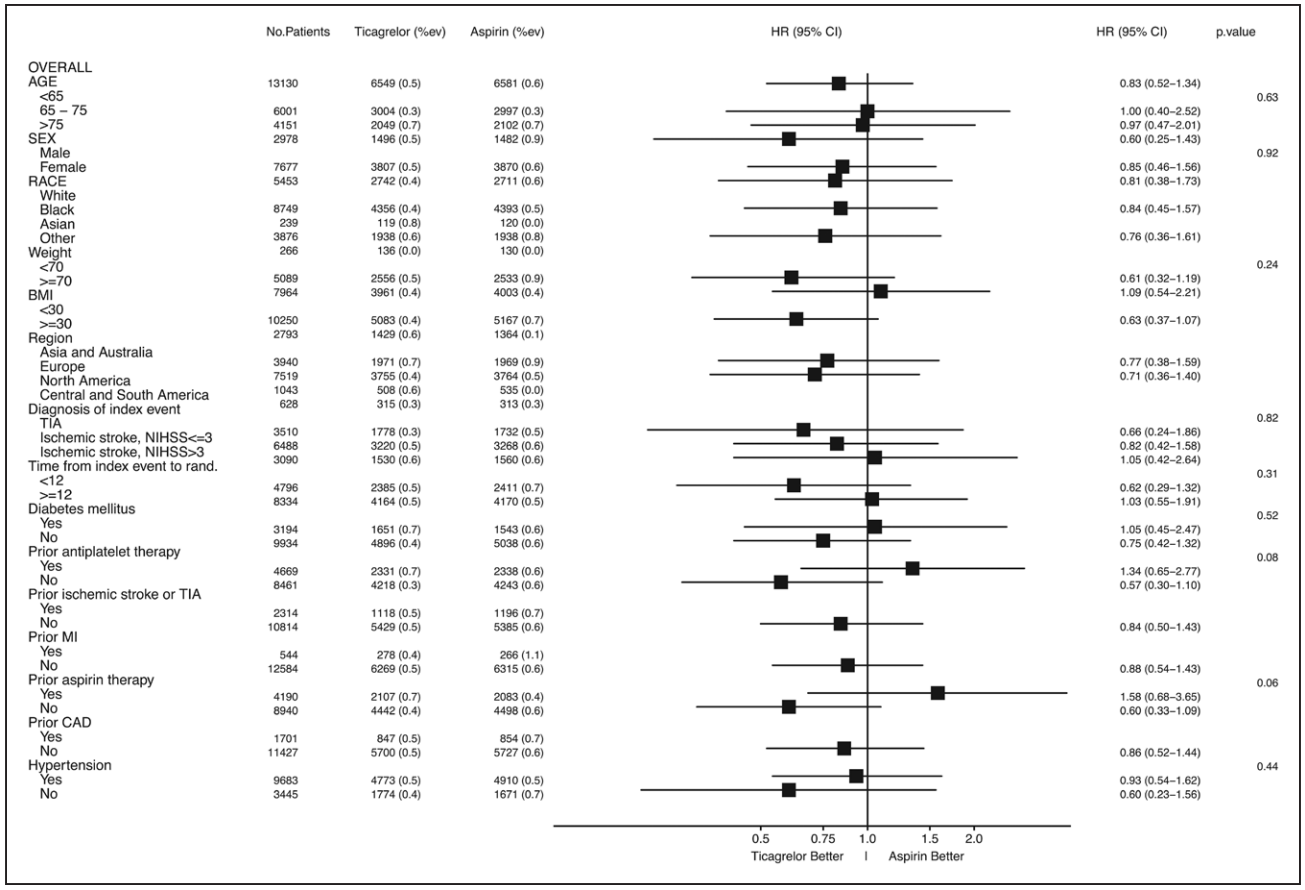

Figure 3. Forest plot of PLATO (Platelet Inhibition and Patient Outcomes) major bleeding events by subgroup, on treatment (safety analysis set).

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

vascular Events)[18] investigating patients with AIS (National Institutes of Health Stroke Scale score ≤3) or high-risk TIA, there was no increase in major bleeds on treatment with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg followed by 75 mg/d for 90 days plus aspirin at a dose of 75 mg/d for the first 21 days) versus placebo plus aspirin (75 mg/d for 90 days). The SOCRATES study had the same duration of study treatment and a similar population but allowed inclusion of patients with AIS with a slightly higher National Institutes of Health Stroke Scale score of ≤5.

In SOCRATES, the results showed that PLATO-defined major bleeds were uncommon and that there was no difference between the treatment groups. Fatal bleeds were few. Because of the small number of major bleeds, it was not possible to identify factors associated with major bleeding or to discern a specific bleeding profile. As expected in this population, the most common locations of major bleeds were intracranial and gastrointestinal, and they were equally distributed on ticagrelor and on aspirin. Independently of bleeding classification, PLATO, TIMI, or GUSTO, the relative difference between treatments for major/severe bleeds was similar. There was a stroke study adaptation of the definitions. Symptomatic hemorrhagic transformations of index stroke or new ischemic stroke events were classified as major bleeding events, whereas asymptomatic hemorrhagic transformations were not. The rationale for this was that asymptomatic hemorrhagic transformations are a common accompaniment of infarctions even in the absence of antiplatelet treatment. Furthermore, because there was no predefined schedule for reimaging, asymptomatic events were not systematically studied, whereas new neurological symptoms would trigger imaging.

PLATO-defined minor and minimal bleeds were more common on ticagrelor than on aspirin, which might reflect a more potent antiplatelet effect. This finding was also associated with a higher number of permanent and premature study drug discontinuations as a result of bleeding events in the ticagrelor group compared with aspirin, although the total number was low. The most common bleeding adverse events leading to drug discontinuation were epistaxis, bruising, and spontaneous hematoma, which, despite being nonmajor, are nuisance bleeds that are important to the patients and may result in reduced compliance with antiplatelet treatment.

Table 5. PLATO, TIMI, and GUSTO Bleeding Events (Safety Analysis Set)

Characteristic	Ticagrelor 90 mg Twice Daily (n=6549)		Aspirin 100 mg Once Daily (n=6581)			
	Patients With Events, n	KM%	Patients With Events, n	KM%	HR (95% CI)	*P* Value
PLATO major	31	0.5	38	0.6	0.83 (0.52–1.34)	0.45
PLATO major or minor	106	1.7	82	1.3	1.32 (0.99–1.76)	0.06
TIMI major	21	0.3	27	0.4	0.79 (0.45–1.40)	0.43
TIMI major or minor	27	0.4	32	0.5	0.86 (0.52 –1.44)	0.57
GUSTO severe	18	0.3	21	0.3	0.87 (0.47–1.64)	0.67
GUSTO severe or moderate	31	0.5	32	0.5	0.99 (0.60–1.62)	0.96

CI indicates confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HR, hazard ratio; KM%, Kaplan-Meier percentage at 90 days; PLATO, Platelet Inhibition and Patient Outcomes; and TIMI, Thrombolysis in Myocardial Infarction.

The SOCRATES study did not result in a significant outcome on efficacy. The low rate of major bleeds offers the possibility that dual treatment with ticagrelor plus aspirin may be more beneficial for patients with acute cerebral ischemic disease. Patients with acute TIA and minor cerebral ischemia are at high risk for evolving and recurring ischemic injury yet have no or small infarctions and therefore likely a lower risk of intracerebral hemorrhage.

Limitations

The present analysis presents some limitations. Although the trial was large, the number of major bleeds available to assess bleed risk factors was small. This is partly explained by the limited amount of acute brain injury in this population and the 3-month trial duration. However, the fact that there were few major bleeds is reassuring in a population with acute cerebral ischemia and high risk of evolving ischemic injury.

Conclusions

There was no increased risk for major bleeding in patients receiving ticagrelor compared with aspirin after TIA or AIS in the SOCRATES study, and there were few ICrHs. This was true regardless of bleeding classification for major bleeding. PLATO nonmajor bleeds and bleeds leading to discontinuation of treatment were more common on ticagrelor, but the total number of bleeding events leading to discontinuation of study drug was low.

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DISCLOSURES

Dr Easton received research grant support from AstraZeneca for the SOCRATES trial (ClinicalTrials.gov. Unique identifier: NCT01994720) and receives research support from the 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; 1U01S062835-01A1); POINT received some free study drug and placebo from Sanofi (ClinicalTrials.gov. Unique identifier: NCT00991029). He also receives support from Boehringer Ingelheim and Bristol-Myers Squibb as a consultant for the planning and conduct of the RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source; ClinicalTrials.gov. Unique identifier: NCT02239120) and PARFAIT (Safety and Efficacy Study of a Protease Activated Receptor-4 Antagonist Being Tested to Reduce the Chances of Having Additional Strokes or "Mini Strokes"; ClinicalTrials.gov. Unique identifier: NCT02671461) trials. Dr Aunes, M. Jahreskog, Dr Denison, Dr Held, Dr Jonasson, and S. Bokelund-Singh are employees of AstraZeneca. Dr Albers reports equity interest in iSchemaView and consultant fees from Lundbeck, Covidien, Johnson & Johnson, Biogen, and AstraZeneca. Dr Amarenco reports research grant support and lecture fees from Pfizer, Sanofi, Bristol-Myers-Squibb, Merck, AstraZeneca, and Boehringer-Ingelheim; consultancy fees from Pfizer, BMS, Merck, Boehringer-Ingelheim, AstraZeneca, Bayer, Daiichi-Sankyo, Lundbeck, Edwards, Boston Scientific, Kowa, GSK, and FibroGen; lecture fees from Bayer, Boston Scientific, and St. Jude Medical. and research grants from the French government. Dr Evans is a statistical consultant to AstraZeneca. Dr Minematsu reports honoraria from Otsuka Pharmaceutical, Boehringer-Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma Corporation, Japan Stryker, Kowa, Nihon Medi-Physics Co, BMS, Sawai Pharmaceutical Co, Sumitomo Dainippon Pharma Co Ltd, Medico's Hirata, Dai-ichi Sankyo, Asteras Pharma, Kyowa Hakko Kirin Pharma, Inc, Sanofi SA, MSD, Eisai Co, and Towa Pharmaceutical Co. Dr Molina serves on the Steering Committee of CLOTBUST-ER trial [Phase 3, Randomized, Placebo-Controlled, Double-Blinded Trial of the Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator (tPA) for Emergent Revascularization in Acute Ischemic Stroke; Cerevast],

SOCRATES (AstraZeneca), IMPACT-24b (Implant Augmenting Cerebral Blood Flow Trial 24 Hours From Stroke Onset; Brainsgate), and REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; Fundació Ictus Malaltia Vascular). He has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, BMS, Covidien, Cerevast, and Brainsgate. Dr Wang reports research grant support from AstraZeneca. Dr Wong reports honoraria as a member of a steering committee for Johnson & Johnson, AstraZeneca, and Bayer and honoraria for participation in clinical trials, contributions to advisory boards, or oral presentations from Bayer, Sanofi-Aventis, Bristol-Myers Squibb, Boehringer Ingelheim, and Pfizer. Dr Johnston was a consultant to AstraZeneca during the planning of the trial, and his institution received research support for its conduct.

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FOOTNOTES

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