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)

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Risk for Major Bleeding in Patients Receiving Ticagrelor Compared with Aspirin After TIA or Acute Ischemic Stroke in the SOCRATES Study

Running Title: *Easton et al.;Ticagrelor Bleeding Profile in Stroke Patients*

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Abstract

***Background*—**Patients with minor acute ischemic stroke (AIS) or transient ischemic attack (TIA) 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 was the first trial with ticagrelor in patients with AIS or TIA, in which the efficacy and safety of ticagrelor were compared with aspirin. The main safety objective was assessment of PLATO-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 and GUSTO definitions. The definitions of ICrH and major bleeding excluded cerebral micro-bleeds 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 one 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 (HR 0.83, 95% CI 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 (four on ticagrelor and nine on aspirin) were hemorrhagic strokes and four (two in each group) were symptomatic hemorrhagic transformations of brain infarctions. The ICrHs were spontaneous in six and 13, traumatic in three and three, and procedural in three and two patients on ticagrelor and aspirin, respectively. In total, nine fatal bleeds occurred on ticagrelor and four on aspirin. The composite of ICrH or fatal bleeding included 15 patients on ticagrelor and 18 on aspirin. Independent of bleeding classification, PLATO, TIMI or GUSTO, the relative difference between treatments for major/severe bleedings was similar. Non-major bleeds were more common on ticagrelor.

***Conclusions*—**Antiplatelet therapy with ticagrelor in patients with AIS or TIA showed a similar bleeding profile as aspirin for major bleeds. There were few ICrHs.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov Unique Identifier: NCT01994720.

Key Words: safety; stroke; bleeding; aspirin; ticagrelor

Clinical Perspective

What is new?

- The SOCRATES trial (n=13,199) was the first outcome study with ticagrelor in patients with acute ischemic stroke (NIHSS ≤5) or TIA.
- Ninety days of monotherapy with ticagrelor 90 mg twice daily 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 numerical increase of minor bleedings 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 bleedings with ticagrelor compared with aspirin, including intracranial bleeds.
- There was a numerical reduction in the primary efficacy end point and a numerical increase in minor bleedings, which may reflect a more pronounced anti-platelet 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 P2Y12 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 (ENT-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.[4,5,6] The SOCRATES (Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes) study[7,8] was the first trial with ticagrelor in patients with acute cerebral ischemia. The SOCRATES trial (NCT01994720) was a randomized, double-blind study with antiplatelet monotherapy of ticagrelor compared with aspirin in patients with acute ischemic stroke (AIS) (National Institute of Health Stroke Scale [NIHSS] score ≤5) or high-risk transient ischemic attack (TIA) of non-cardioembolic origin randomized within 24 hours of symptom onset. It showed a non-significant 11% relative risk reduction in the composite of stroke (ischemic or hemorrhagic), MI 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 (HR, 0.87; 95% 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, there are accumulating data indicating a heightened risk of 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-defined major bleeds,[7,8] with special emphasis on ICrH. The aims of this paper 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 based on 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 and Definitions

Patients participating in the SOCRATES study were randomized to blinded study treatment with aspirin as 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 (CEC), 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 primarily developed for an acute coronary syndrome setting. In the SOCRATES study these were adapted to the AIS/TIA population. For PLATO and GUSTO definitions, asymptomatic hemorrhagic transformations of brain infarctions and micro-hemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging (MRI) 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 micro-hemorrhages, was updated 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 one 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*-value and confidence intervals for the hazard ratio (HR) are based on the Wald statistics. *P*-values and HRs were calculated for end points with more than or equal to 15 events in total for both treatments. Tables include HRs with confidence intervals, *P*-values, number and percentage 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 the integrity of the data, analysis of the results, and the decision to submit for publication. The corresponding author had full access to all the data.

Results

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

Baseline characteristics for the safety population were balanced across the two 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 (**Supplementary Table 1**).

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, Figure 1**). No patient had more than one PLATO major bleed.

In both treatment groups the most common locations for PLATO major bleeds were intracranial and gastrointestinal. 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 nine (0.1%) on aspirin.

Bleeds were also classified based on provocation. Spontaneous PLATO major bleeds occurred in 22 patients on ticagrelor versus 31 patients on aspirin, procedural bleeds in five patients versus three 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 three procedural major bleeds developed after cerebral aneurysm clipping, after cerebral thrombectomy, and after thoracic surgery for aortic aneurysm, respectively.

Details on ICrHs by category and by provocation for each treatment group are presented in **Table 4**. Thirteen (four on ticagrelor vs nine on aspirin) were hemorrhagic strokes and four (two vs two) were symptomatic hemorrhagic transformations of the index or new ischemic stroke event. There were six other ICrHs (traumatic or procedure-related) on ticagrelor and seven on aspirin.

Asymptomatic hemorrhagic transformations of ischemic stroke were not considered as ICrHs (see section on Methods and Definitions). The number of events adjudicated to asymptomatic hemorrhagic transformations of the index or new ischemic stroke event was similar in both treatment groups (**Supplementary Table 2**).

Nine fatal bleeds occurred on ticagrelor and four on aspirin. For ticagrelor, six of the fatal bleeds were intracranial, two were aortic, and one 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 bleedings 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 (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%) 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 AEs. 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).

Due to 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 based on 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 non-major 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 of the 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, to study 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, e.g. in patients with recent ischemic stroke/TIA (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke [MATCH] trial),[10] in acute coronary syndromes (TRial to assess Improvement in Therapeutic Outcomes by optimising platelet InhibitioN with prasugrel [TRITON] TIMI 38)[11] and a broader atherosclerotic population (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events [TRA 2P] TIMI 50).[19]

In contrast, in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study[18] investigating patients with AIS (NIHSS ≤3) or high-risk TIA, there was no increase of major bleeds on treatment with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) versus placebo plus aspirin (75 mg per day 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 NIHSS 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. Due to the small number of major bleeds, it was not possible to identify factors associated with major bleeding or 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. Independent of bleeding classification, PLATO, TIMI or GUSTO, the relative difference between treatments for major/severe bleedings 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, while asymptomatic hemorrhagic transformations were not. The rationale for this was that asymptomatic hemorrhagic transformations are a common accompaniment of ischemic infarctions even in the absence of antiplatelet treatment. Furthermore, because there was no predefined schedule for re-imaging, 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 due to bleeding events in the ticagrelor group compared with aspirin, although the total number was low. The most common bleeding drug discontinuations due to adverse events were epistaxis, bruising, and spontaneous hematoma, which, in spite of being non-major, are nuisance bleeds that are important to the patients and may result in reduced compliance with antiplatelet treatment.

The SOCRATES study did not result in a significant outcome on efficacy. The low rate of major bleedings 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 acute ischemic stroke in the SOCRATES study, and there were few ICrHs. This was true irrespective of bleeding classification for major bleeding. PLATO non-major 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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References

1. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006;27:1038–10347.
2. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P, Cannon CP. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:1852–1856.
3. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. *J Cardiovasc Pharmacol Ther*. 2014;19:209–219. doi: 10.1177/1074248413511693.
4. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, Becker R, Wallentin L. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009;157:599–605. doi: 10.1016/j.ahj.2009.01.003.
5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327.
6. Bonaca MP, Goto S, Bhatt DL, Steg PG, Storey RF, Cohen M, Goodrich E, Mauri L, Ophuis TO, Ruda M, Špinar J, Seung KB, Hu D, Dalby AJ, Jensen E, Held P, Morrow DA, Braunwald E, Sabatine MS.. 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;134:861–71. doi: 10.1161/CIRCULATIONAHA.116.024637
7. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P,

Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; 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.
8. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Held P, Jonasson J, Minematsu K, Molina CA, Wong LK. 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.
9. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, Topol EJ. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol*. 2005;95:1218–1222.
10. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–337.
11. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
12. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449.
13. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.
14. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): study design and baseline data. *Cerebrovasc Dis*. 2004;17:253–261.
15. 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.
16. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *The Lancet Neurology*. 2007;6:961–969.
17. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251. doi: 10.1056/NEJMoa0805002.
18. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC; 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.
19. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA,

Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA; TRA 2P–TIMI 50 Steering Committee and Investigators.. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012;366:1404–1413. doi: 10.1056/NEJMoa1200933.

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 more than 50 g/L Transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs) for bleeding **Major bleed – other** Any one of the following: Significantly disabling (e.g. 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 units (whole blood or PRBCs) for bleeding **Minor bleed** Requires medical intervention to stop or treat bleeding (e.g. epistaxis requiring visit to medical facility for packing) **Minimal bleed (collected but not adjudicated)** All others (e.g. bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment.	**TIMI major bleed** Any of the following: Fatal (a bleeding event that directly led to death within 7 days) Intracranial* Clinically overt signs of hemorrhage associated with a decrease in Hb of ≥50 g/L **Minor bleed** Clinically overt signs of hemorrhage (including imaging) associated with a decrease in Hb of 30–<50 g/L **Medical attention due to bleed**† Any overt sign of hemorrhage that meets one 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) **Minimal bleed**† Any overt bleeding event that does not meet the criteria above	**GUSTO severe** Any of the following: Fatal Intracranial* Bleeding that caused hemodynamic compromise requiring intervention (e.g. systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention) **Moderate bleed** Bleeding requiring transfusion of whole blood or PRBCs without hemodynamic compromise (as defined above) **Mild bleed**† Bleeding without blood transfusion or hemodynamic compromise

*Stroke study adaptation of bleeding classifications: For PLATO, TIMI and GUSTO, intracranial bleed was defined as ICH excluding asymptomatic hemorrhagic transformations of ischemic brain infarctions and excluding micro-hemorrhages <10 mm evident only on gradient-echo MRI. †This item not analyzed in the SOCRATES study.

Table 2. PLATO Major or Minor bleeding events (safety analysis set)

	Ticagrelor 90 mg bd (N=6549)		ASA 100 mg od (N=6581)			
Characteristic	**Patients with events**	**KM%**	**Patients with events**	**KM%**	**Hazard Ratio (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

KM%, Kaplan-Meier percentage at 90 days

PLATO Minimal bleeds (non-adjudicated) were reported in 521 patients (8.0%) in the ticagrelor group and 239 patients (3.6%) in the aspirin group.

Table 3. PLATO Major bleeding events by provocation (safety analysis set)

	Ticagrelor 90 mg bd (N=6549)		**ASA 100 mg od (N=6581)**			
Characteristic	**Patients with events (%)**	**KM%**	**Patients with events (%)**	**KM%**	**Hazard Ratio (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			

KM%, Kaplan-Meier percentage at 90 days

Table 4. Intracranial hemorrhages fulfilling the criteria for PLATO Major bleeding - on treatment (safety analysis set)

	Total Number of Events		First Event	
Characteristic	**Ticagrelor 90 mg bd**	**ASA 100 mg od**	**Ticagrelor 90 mg bd (N=6549)**	**ASA 100 mg od (N=6581)**
Intracranial hemorrhages fulfilling the criteria for PLATO Major bleeding[a]	12	18	12 (0.2%)	18 (0.3%)
Hemorrhagic stroke	4	9	4 (0.1%)	9 (0.1%)
Ischaemic 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 intracranial hemorrhage	6	7	6 (0.1%)	7 (0.1%)
By provocation				
Spontaneous intracranial hemorrhage	6	13	6 (0.1%)	13 (0.2%)
Traumatic intracranial hemorrhage	3	3	3 (0.0%)	3 (0.0%)
Procedural intracranial hemorrhage	3	2	3 (0.0%)	2 (0.0%)

[a]PLATO bleeding definitions have been adapted to the acute stroke population by excluding asymptomatic hemorrhagic transformations of ischemic brain infarctions and micro-hemorrhages <10 mm evident only on gradient-echo MRI.

This table includes both events reported as AEs and end points.

Patients may be counted in more than one 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 following the date of last dose of study medication.

Table 5. PLATO, TIMI and GUSTO bleeding events (safety analysis set)

	Ticagrelor 90 mg bd (N=6549)		ASA 100 mg od (N=6581)			
Characteristic	**Patients with events**	**KM%**	**Patients with events**	**KM%**	**Hazard Ratio (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

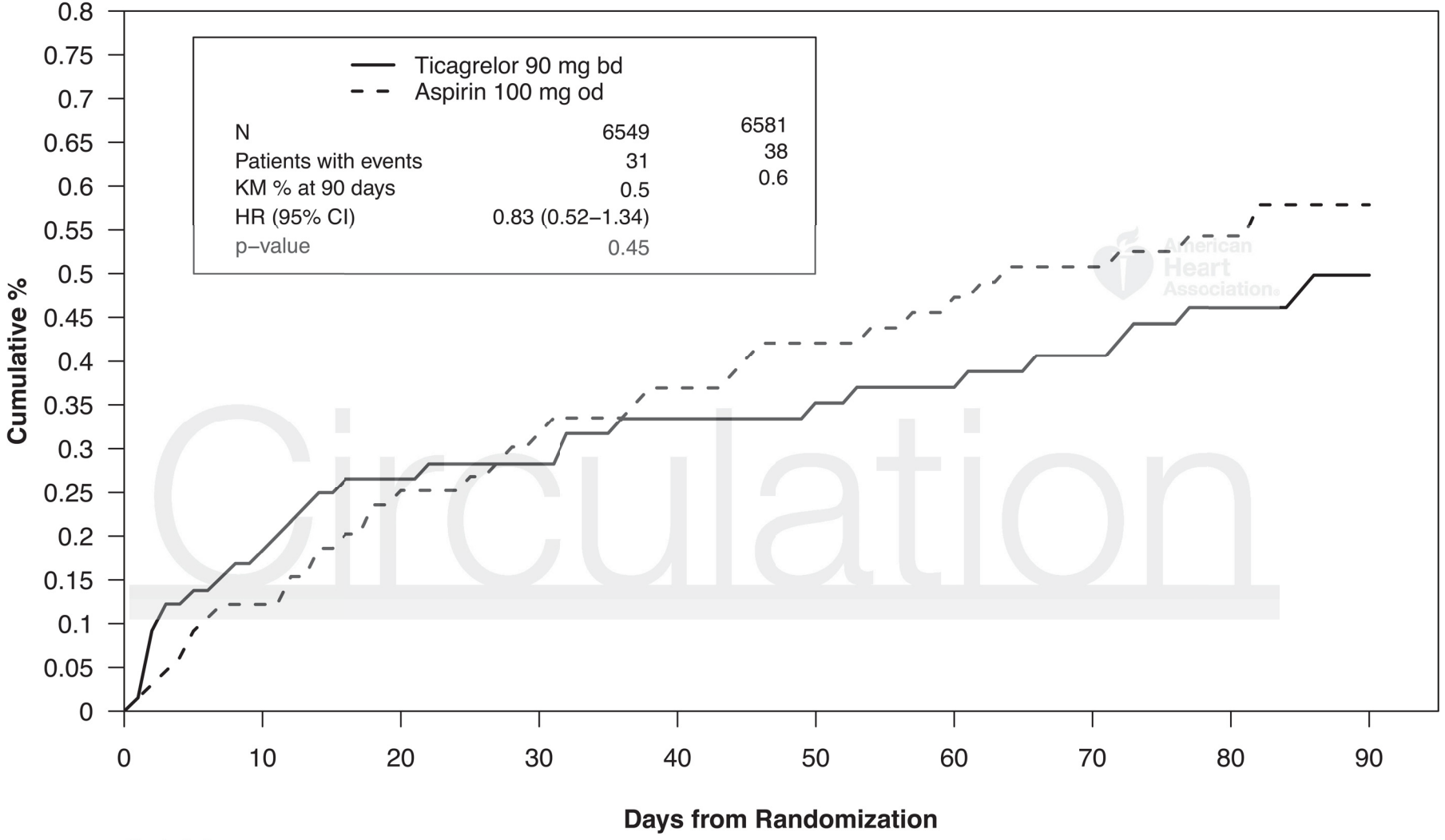
KM%, Kaplan-Meier percentage at 90 days

Figure Legends

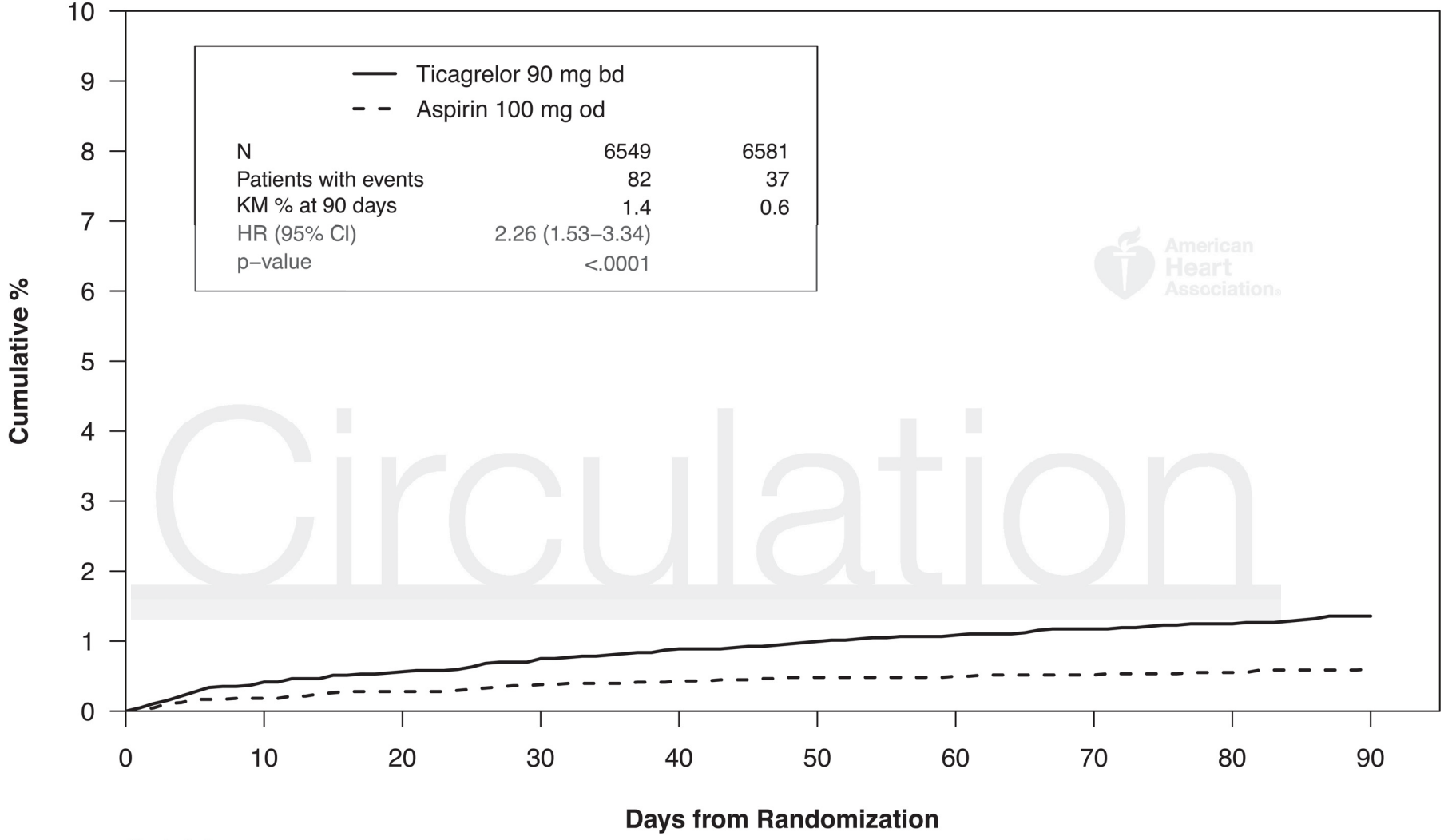
Figure 1. Kaplan-Meier plot of cumulative percentage of patients with PLATO major bleeding – on treatment (safety analysis set).[7] From Johnston et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med.* 2016;375:35–43. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. BD, twice daily; HR, hazard ratio; KM, Kaplan-Meier; OD, once daily

Figure 2. Kaplan-Meier plot of cumulative percentage of patients who prematurely discontinued study drug due to bleeding AE (safety analysis set). BD, twice daily; HR, hazard ratio; KM, Kaplan-Meier; OD, once daily

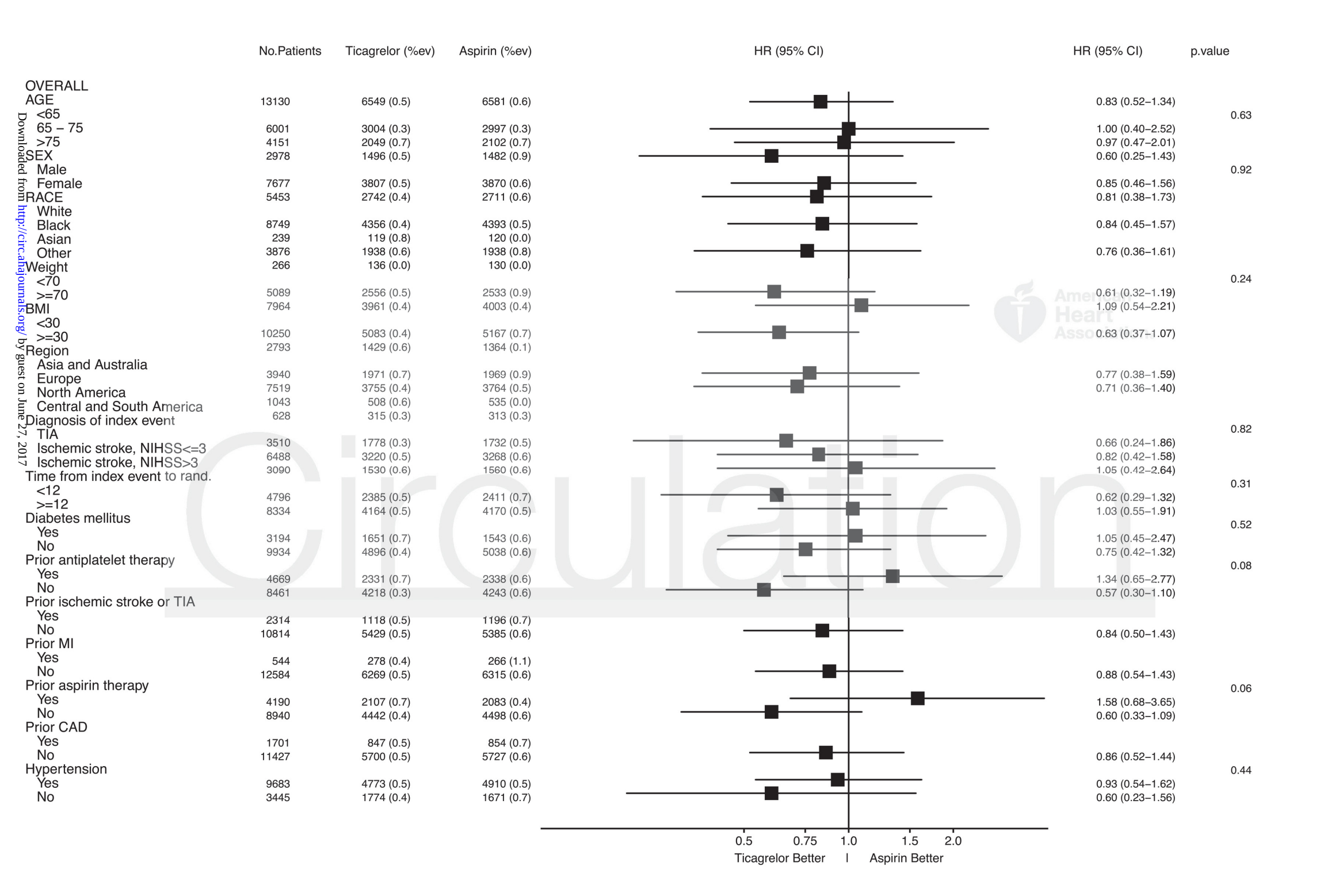
Figure 3. Forest plot of PLATO major bleeding events by subgroup – on treatment (safety analysis set). BMI, body mass index; CAD, coronary artery disease; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; MI, myocardial infarction; TIA, transient ischemic attack



N at risk										
Aspirin	6581	6397	6047	5925	5835	5776	5730	5668	5627	5506
Ticagrelor	6549	6312	5930	5788	5672	5595	5539	5470	5426	5296



N at risk										
Aspirin	6581	6391	6049	5923	5836	5778	5733	5672	5630	5510
Ticagrelor	6549	6300	5926	5780	5669	5593	5540	5469	5427	5296



Risk for Major Bleeding in Patients Receiving Ticagrelor Compared with Aspirin After TIA or Acute Ischemic Stroke in the SOCRATES Study

J. Donald Easton, Maria Aunes, Gregory W. Albers, Pierre Amarenco, Sara Bokelund Singh, Hans Denison, Scott R. Evans, Peter Held, Marianne Jahreskog, Jenny Jonasson, Kazuo Mimematsu, Carlos A. Molina, Yongjun Wang, K. S. Lawrence Wong and S. Claiborne Johnston
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SUPPLEMENTARY MATERIAL

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Easton JD, Aunes MD, Albers GW, et al. Risk for Major Bleeding in Patients Receiving Ticagrelor Compared with Aspirin after TIA or Acute Ischemic Stroke in the SOCRATES Study. Circulation, 2017.

Supplementary table 1: Baseline Characteristics (safety analysis set)

Characteristic	Ticagrelor (N=6549)	Aspirin (N=6581)
Age (years) – mean (SD)	65.8 (11.23)	65.9 (11.37)
Female sex – no. (%)	2742 (41.9%)	2711 (41.2%)
Previous ischemic stroke – no. (%)	763 (11.7%)	825 (12.5%)
History of hypertension – no. (%)	4773 (72.9%)	4910 (74.6%)
History of diabetes mellitus – no. (%)	1651 (25.2%)	1543 (23.4%)
Qualifying event		
Ischemic stroke – no. (%)	4771 (72.9%)	4849 (73.7%)
TIA – no. (%)	1778 (27.1%)	1732 (26.3%)
Qualifying ischemic stroke baseline NIHSS		
≤3 – no. (%)	3220 (49.2%)	3268 (49.7%)
>3 – no. (%)	1530 (23.4%)	1560 (23.7%)

NIHSS National Institute of Health Stroke Scale

Supplementary table 2: Patients with adjudicated asymptomatic hemorrhagic transformations of index and outcome ischemic stroke events – on treatment (safety analysis set)

Characteristic	Total number of events	
	Ticagrelor 90 mg bd (N=6549)	ASA 100 mg od (N=6581)
Asymptomatic hemorrhagic transformation of outcome ischemic stroke	8	8
Fatal	1	0
Non-fatal	7	8
Asymptomatic hemorrhagic transformation of index event	14	19

Since there was no predefined schedule for re-imaging, asymptomatic events were not systematically studied.
Fatal outcome due to the ischemic stroke.

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