SOCRATES

Acute Stroke Or transient isChaemic attack tReated with Aspirin or Ticagrelor and patient outcomES

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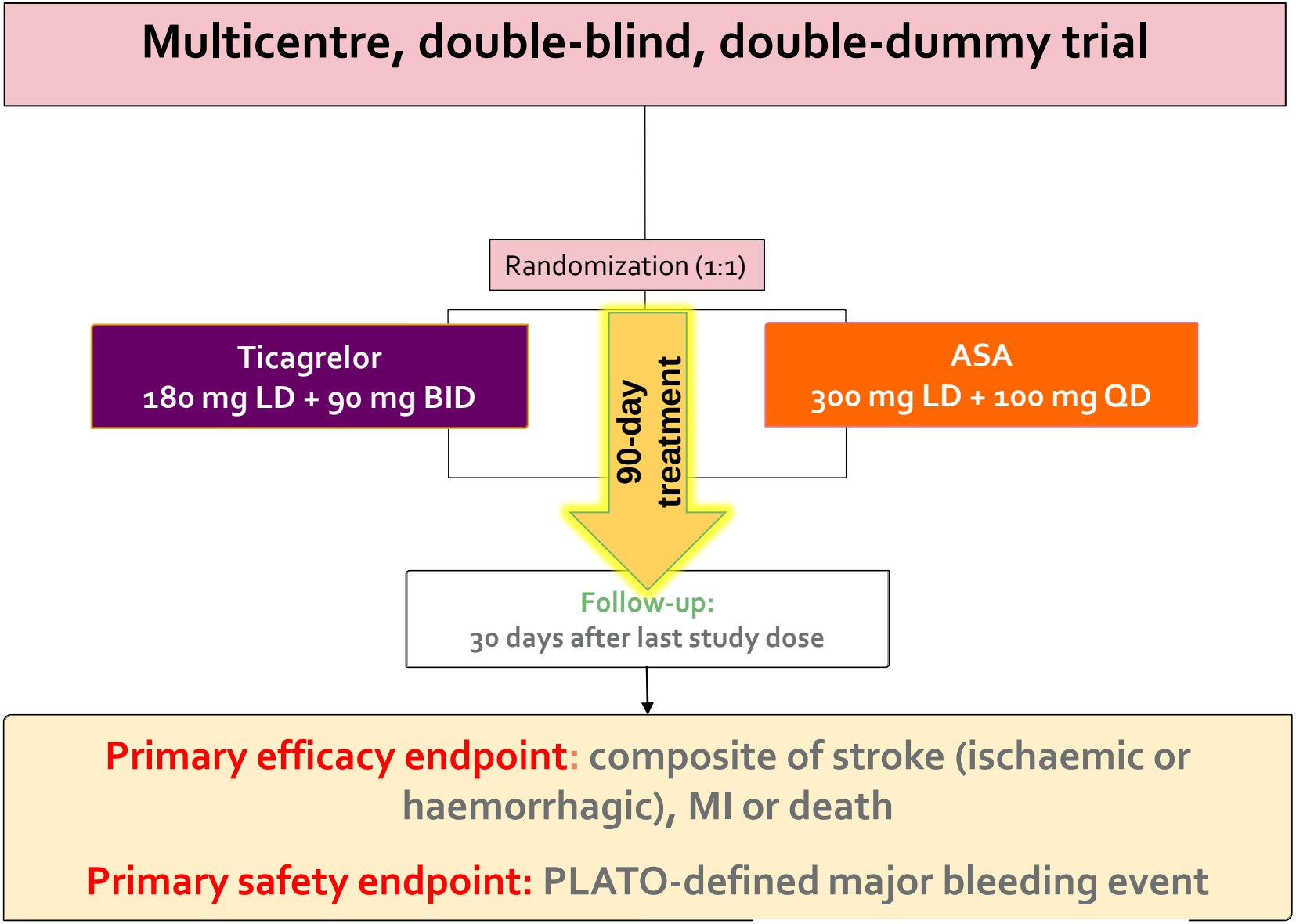
ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Gregory W. Albers, M.D., Hans Denison, M.D., Ph.D., J. Donald Easton, M.D., Scott R. Evans, Ph.D., Peter Held, M.D., Ph.D., Jenny Jonasson, Ph.D., Kazuo Minematsu, M.D., Ph.D., Carlos A. Molina, M.D., Yongjun Wang, M.D., and K.S. Lawrence Wong, M.D., for the SOCRATES Steering Committee and Investigators*

SOCRATES: Study design



Johnston SC *et al. Int J Stroke* 2015;10:1304–1308; Johnston SC *et al. N Engl J Med* 2(

Studovaná populace

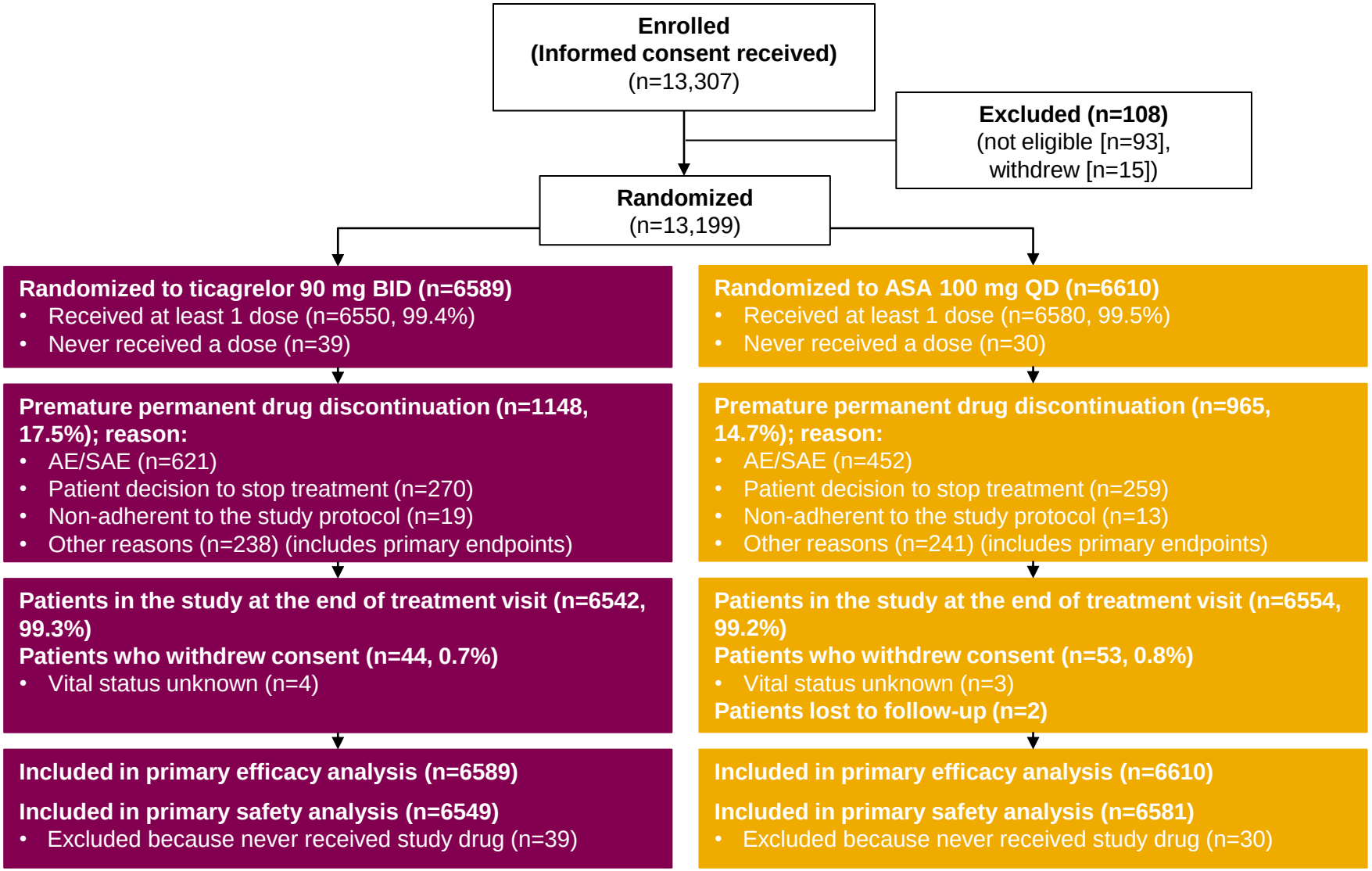
INCLUSION

- **Acute minor ischaemic stroke (NIHSS ≤5)**
- **high-risk TIA (ABCD² ≥4 or symptomatic intra- or extracranial arterial stenosis)**
- **Randomized within 24 hours of symptom onset**
- Able to provide informed consent, aged ≥40 years
- Head CT or MRI ruling out haemorrhage or other pathology, such as vascular malformation, tumour or abscess that could explain symptoms or contraindicate therapy

EXCLUSION

- Planned use of antithrombotic therapy in addition to study medication
- History of AF, ventricular aneurysm or suspicion of cardioembolic pathology for TIA or stroke
- **Planned carotid, cerebrovascular or coronary revascularization that requires halting study medication within 7 days of randomization**
- **IV or intra-arterial thrombolysis or mechanical thrombectomy in the 24 hours before randomization**
- History of previous symptomatic non-traumatic intracerebral bleeding at any time,* GI bleeding within past 6 months or major surgery within 30 days

SOCRATES: CONSORT diagram



 Johnston SC *et al*. *N Engl J Med* 2016;DOI:10.1056/NEJMoa1603060

SOCRATES: Baseline characteristics* (1)

Characteristic	Ticagrelor (n=6589)	ASA (n=6610)
Age (y) – mean (SD)	65.8 (11.23)	65.9 (11.37)
Females – no. (%)	2759 (41.9)	2724 (41.2)
Race* – no. (%)		
White	4374 (66.4)	4410 (66.7)
Black	119 (1.8)	120 (1.8)
Asian	1957 (29.7)	1949 (29.5)
Other	139 (2.1)	131 (2.0)
Ethnic background† – no. (%)		
Not Hispanic	6023 (91.4)	6050 (91.5)
Hispanic	566 (8.6)	558 (8.4)
Region – no. (%)		
Asia and Australia	1990 (30.2)	1981 (30.0)
Europe	3769 (57.2)	3772 (57.1)
North America	514 (7.8)	540 (8.2)
Central and South America	316 (4.8)	317 (4.8)

*The differences in baseline characteristics between treatment groups were not significant, except for the proportion of patients with a history of diabetes or hypertension (nominal $P<0.05$); †Self reported; SD, standard deviation

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SOCRATES: Baseline characteristics* (2)

Characteristic	Ticagrelor (n=6589)	ASA (n=6610)
Systolic blood pressure (mmHg) – median (IQR)	150 (137.0, 165.0)	150 (135.5, 165.0)
Diastolic blood pressure (mmHg) – median (IQR)	84 (78.0, 92.0)	84 (77.0, 91.0)
Body mass index (kg/m²) – median (IQR)	26.1 (23.5, 29.4)	26.0 (23.5, 29.3)
History of hypertension – no. (%)	4797 (72.8)	4933 (74.6)
History of dyslipidaemia – no. (%)	2531 (38.4)	2497 (37.8)
History of diabetes mellitus – no. (%)	1664 (25.3)	1548 (23.4)
Previous ischaemic stroke – no. (%)	765 (11.6)	828 (12.5)
Previous TIA – no. (%)	410 (6.2)	446 (6.7)
Previous myocardial infarction – no. (%)	280 (4.2)	268 (4.1)
History of coronary artery disease – no. (%)	573 (8.7)	571 (8.6)
History of congestive heart failure – no. (%)	234 (3.6)	248 (3.8)
Taking ASA before randomization – no. (%)	2130 (32.3)	2102 (31.8)
Taking clopidogrel before randomization – no. (%)	219 (3.3)	237 (3.6)
Time to randomization after symptom onset – no. (%)		
<12h	2400 (36.4)	2424 (36.7)
≥12h	4188 (63.6)	4186 (63.3)

*The differences in baseline characteristics between treatment groups were not significant, except for the proportion of patients with a history of diabetes or hypertension (nominal $P<0.05$); IQR, interquartile range

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SOCRATES: Baseline characteristics* (3)

Characteristic	Ticagrelor (n=6589)	ASA (n=6610)
Qualifying event – no. (%)		
TIA	**1790 (27.2)**	**1741 (26.3)**
Ischaemic stroke	**4798 (72.8)**	**4869 (73.7)**
Qualifying TIA baseline ABCD² score – no./total no (%)		
≤5	1313/1790 (73.4)	1257/1741 (72.2)
>5	471/1790 (26.3)	479/1741 (27.5)
Qualifying ischaemic stroke baseline NIHSS – no./total no. (%)		
NIHSS≤3	**3235/4798 (67.4)**	**3282/4869 (67.4)**
>3	1541/4798 (32.1)	1566/4869 (32.2)

*The differences in baseline characteristics between treatment groups were not significant, except for the proportion of patients with a history of diabetes or hypertension (nominal $P<0.05$)

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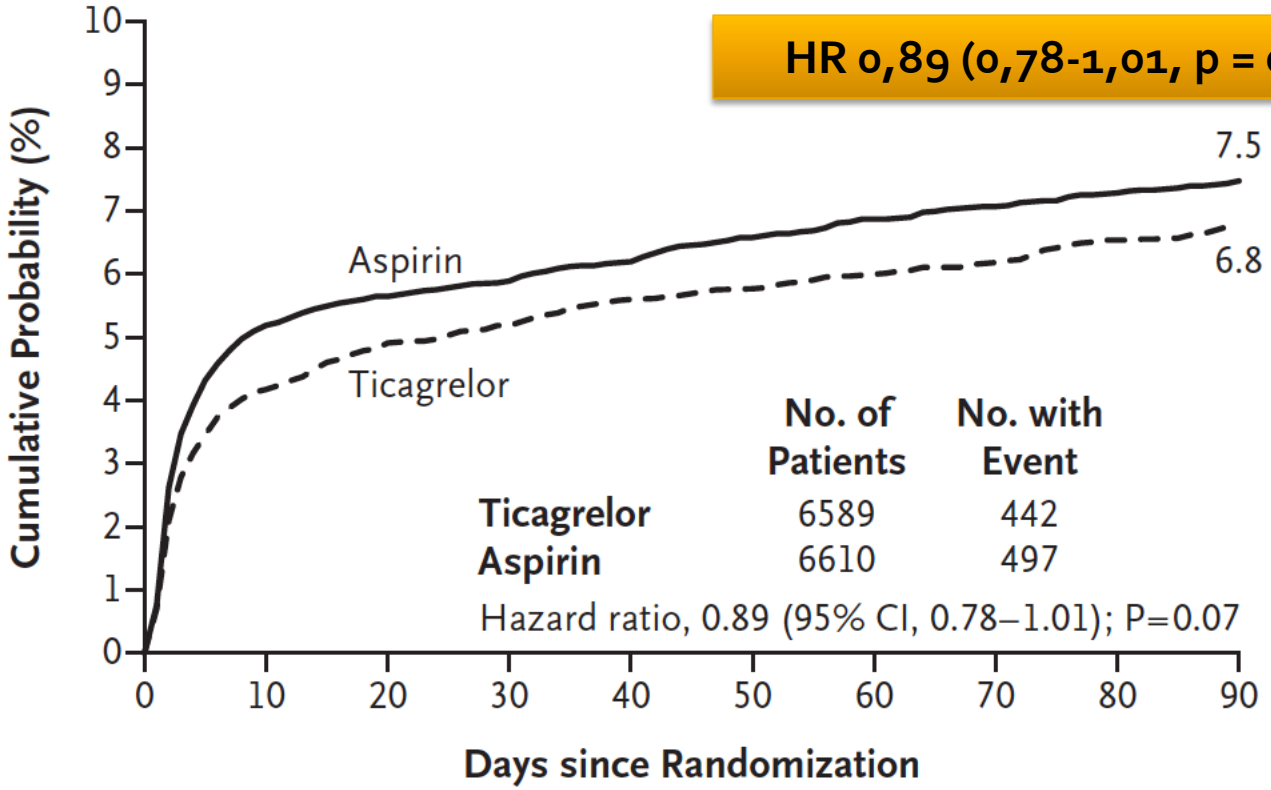
Primární endpoint (stroke, MI, death)

A Primary End Point: Stroke, Myocardial Infarction, or Death

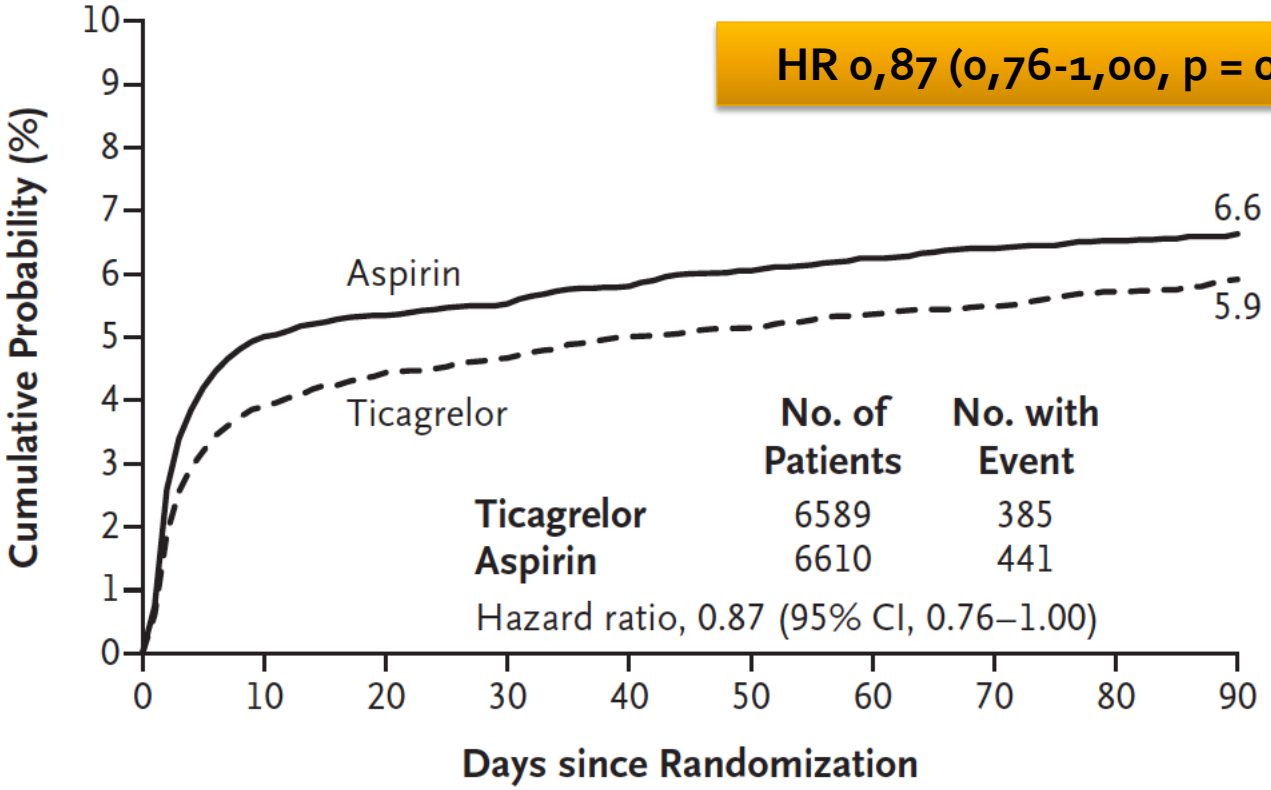


No. at Risk

Aspirin	6610	6228	6186	6162	6129	6100	6078	6053	6030	4502
Ticagrelor	6589	6265	6216	6186	6153	6141	6118	6094	6058	4574

Ischemic stroke

B Ischemic Stroke

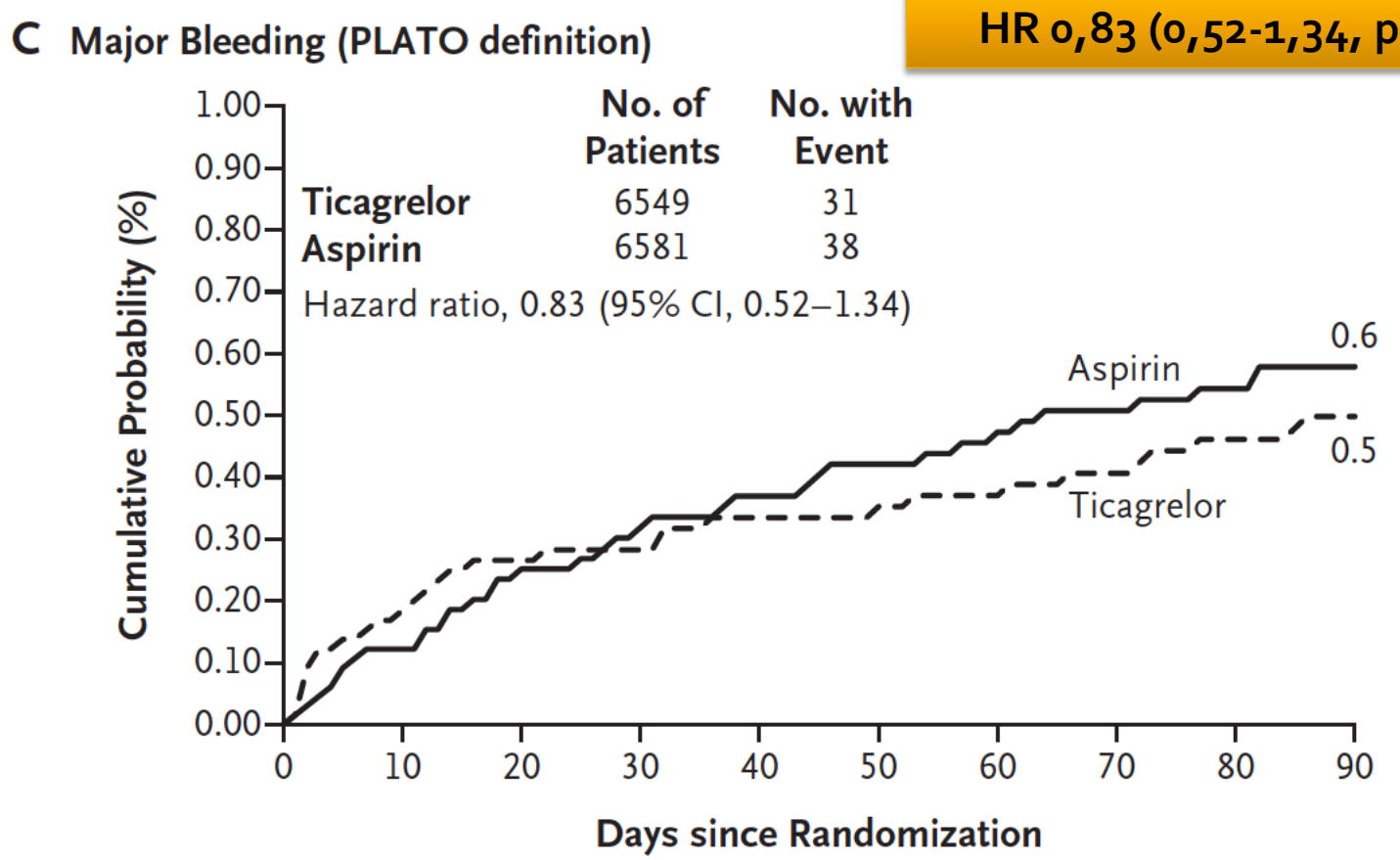


No. at Risk

Aspirin	6610	6230	6193	6169	6134	6112	6092	6065	6046	4518
Ticagrelor	6589	6272	6230	6204	6169	6157	6133	6102	6073	4587

Primary safety endpoint – PLATO defined Major bleeding

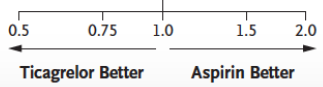
HR 0,83 (0,52-1,34, p = 0,45)



Primární a sekundární endpointy

Outcome	Ticagrelor (N=6589)		Aspirin (N=6610)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*event rate**	*no. of patients (%)*	*event rate**		
Primary end point						
Stroke, myocardial infarction, or death	442 (6.7)	6.8	497 (7.5)	7.5	0.89 (0.78–1.01)	0.07
Secondary end points†						
Ischemic stroke	385 (5.8)	5.9	441 (6.7)	6.6	0.87 (0.76–1.00)	0.046‡
Ischemic stroke, myocardial infarction, or cardiovascular death	423 (6.4)	6.5	475 (7.2)	7.2	0.89 (0.78–1.01)	0.07
All stroke	390 (5.9)	6.0	450 (6.8)	6.8	0.86 (0.75–0.99)	0.03‡
Disabling stroke§	277 (4.2)	4.2	307 (4.6)	4.7	0.90 (0.77–1.06)	0.21
Fatal stroke	18 (0.3)	0.3	17 (0.3)	0.3	1.06 (0.55–2.06)	0.86
Myocardial infarction	25 (0.4)	0.4	21 (0.3)	0.3	1.20 (0.67–2.14)	0.55
Death	68 (1.0)	1.0	58 (0.9)	0.9	1.18 (0.83–1.67)	0.36
Cardiovascular death	41 (0.6)	0.6	35 (0.5)	0.5	1.18 (0.75–1.85)	0.48
Net clinical outcome: stroke, myocardial infarction, death, or life-threatening bleeding	457 (6.9)	7.0	508 (7.7)	7.6	0.90 (0.79–1.02)	0.09

Subgroup	No. of Patients	Ticagrelor	Aspirin	Hazard Ratio (95% CI)	P Value for Interaction
		total patients (% with event)			
Overall	13,199	6589 (6.7)	6610 (7.5)	0.89 (0.78–1.01)	
Age (yr)					0.06
<65	6,028	3021 (5.7)	3007 (7.0)	0.81 (0.66–0.99)	
65–75	4,176	2064 (7.0)	2112 (8.5)	0.81 (0.65–1.01)	
>75	2,995	1504 (8.4)	1491 (7.2)	1.16 (0.90–1.50)	
Sex					0.89
Male	7,716	3830 (7.0)	3886 (7.8)	0.89 (0.76–1.05)	
Female	5,483	2759 (6.3)	2724 (7.2)	0.88 (0.72–1.08)	
Race					0.21
White	8,784	4374 (5.6)	4410 (5.8)	0.96 (0.81–1.15)	
Black	239	119 (3.4)	120 (7.5)	NA	
Asian	3,906	1957 (9.6)	1949 (11.5)	0.82 (0.67–0.99)	
Other	270	139 (4.3)	131 (5.3)	NA	
Weight					0.76
<70 kg	5,119	2574 (7.8)	2545 (8.8)	0.87 (0.72–1.06)	
≥70 kg	7,997	3978 (6.1)	4019 (6.6)	0.91 (0.76–1.08)	
BMI					0.61
<30	10,304	5110 (7.2)	5194 (7.8)	0.91 (0.79–1.05)	
≥30	2,802	1437 (5.3)	1365 (6.3)	0.83 (0.61–1.14)	
Region					0.30
Asia and Australia	3,971	1990 (9.6)	1981 (11.5)	0.83 (0.68–1.00)	
Europe	7,541	3769 (5.3)	3772 (6.0)	0.87 (0.72–1.05)	
North America	1,054	514 (6.8)	540 (5.2)	1.34 (0.81–2.19)	
Central and South America	633	316 (5.4)	317 (4.7)	1.14 (0.57–2.29)	
Diagnosis of index event					0.38
TIA	3,531	1790 (4.9)	1741 (5.0)	0.98 (0.72–1.31)	
Ischemic stroke, NIHSS ≤3	6,517	3235 (6.2)	3282 (7.6)	0.81 (0.67–0.98)	
Ischemic stroke, NIHSS >3	3,107	1541 (9.8)	1566 (10.0)	0.97 (0.78–1.22)	
Time from index event to randomization					0.22
<12 hr	4,824	2400 (6.9)	2424 (8.5)	0.80 (0.65–0.98)	
≥12 hr	8,374	4188 (6.6)	4186 (7.0)	0.95 (0.80–1.12)	
Diabetes mellitus					0.99
Yes	3,212	1664 (8.4)	1548 (9.5)	0.88 (0.70–1.11)	
No	9,981	4919 (6.1)	5062 (6.9)	0.88 (0.76–1.03)	
Previous antiplatelet therapy					0.51
Yes	4,716	2358 (7.1)	2358 (8.4)	0.84 (0.68–1.03)	
No	8,483	4231 (6.5)	4252 (7.1)	0.92 (0.78–1.08)	
Previous ischemic stroke or TIA					0.33
Yes	2,321	1121 (6.7)	1200 (8.5)	0.78 (0.57–1.04)	
No	10,872	5462 (6.7)	5410 (7.3)	0.92 (0.80–1.06)	
Previous myocardial infarction					0.97
Yes	548	280 (6.4)	268 (7.1)	0.89 (0.46–1.69)	
No	12,645	6303 (6.7)	6342 (7.5)	0.89 (0.78–1.01)	
Previous aspirin therapy					0.10
Yes	4,232	2130 (6.5)	2102 (8.4)	0.76 (0.61–0.95)	
No	8,967	4459 (6.8)	4508 (7.1)	0.96 (0.82–1.12)	
Previous coronary artery disease					0.85
Yes	1,712	852 (6.2)	860 (7.2)	0.86 (0.59–1.24)	
No	11,481	5731 (6.8)	5750 (7.6)	0.89 (0.78–1.02)	
Hypertension					0.82
Yes	9,730	4797 (6.8)	4933 (7.7)	0.88 (0.76–1.02)	
No	3,463	1786 (6.4)	1677 (7.0)	0.91 (0.70–1.18)	



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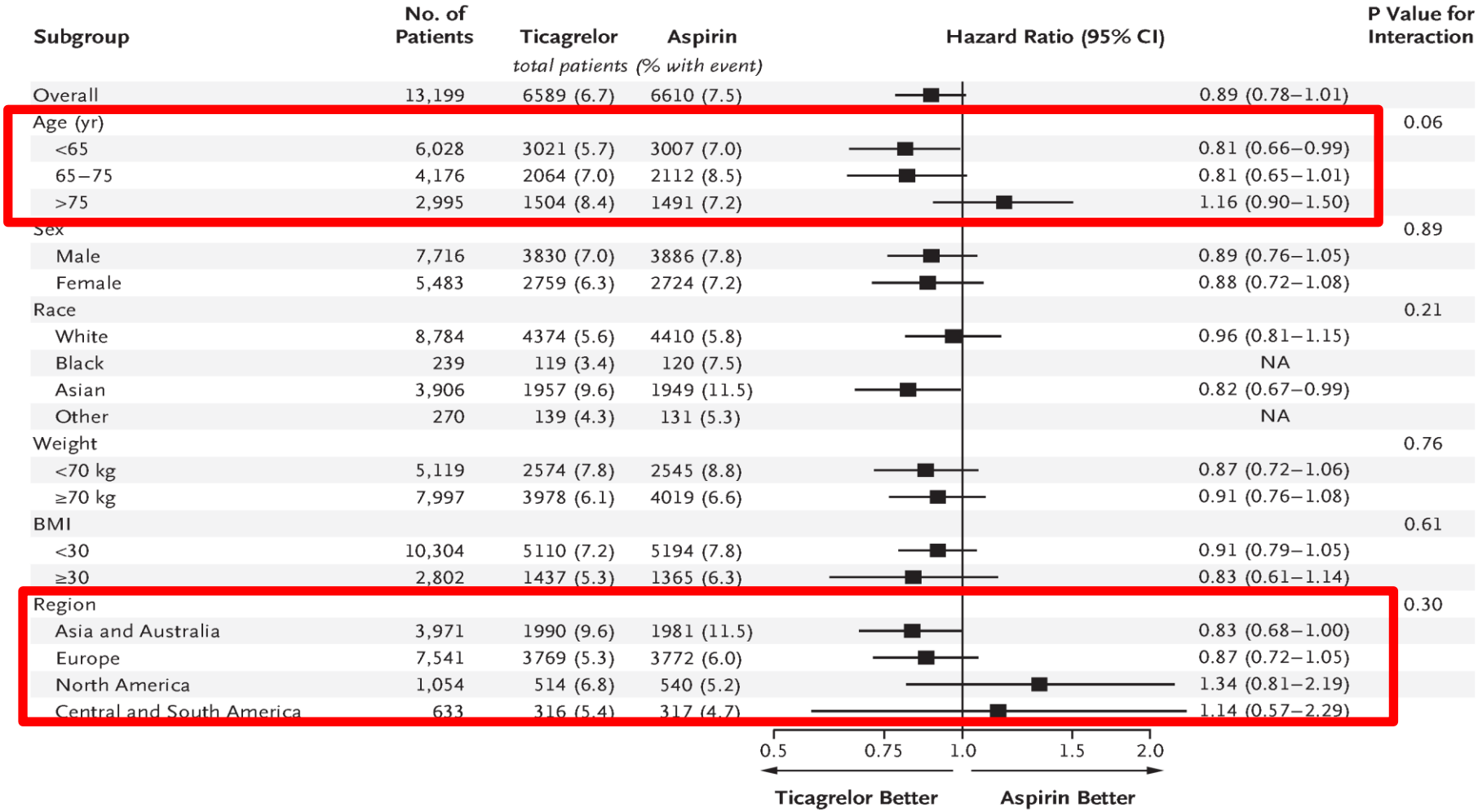
SOCRATES: Primary endpoint by subgroup (1)

There were no significant treatment–subgroup interactions



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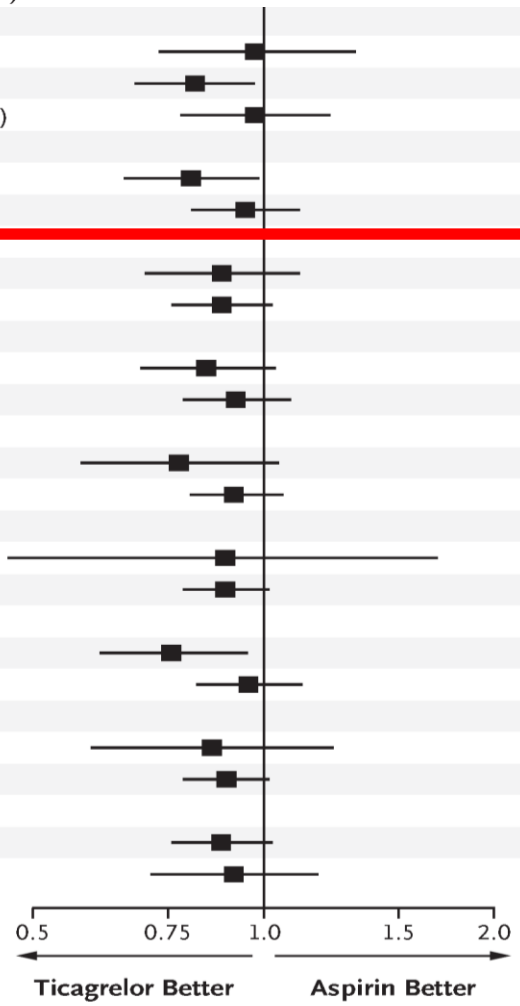

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Závěr

CONCLUSIONS

In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.)

Selektovaná populace

- Exkluze rekanalizační léčby
- Exkluze pacientů plánovaných k revaskularizaci velkých tepen – CEA, CAS