Beneficio della duplice terapia con Ticagrelor e Aspirina dopo ictus ischemico non severo o attacco ischemico transitorio di natura aterosclerotica

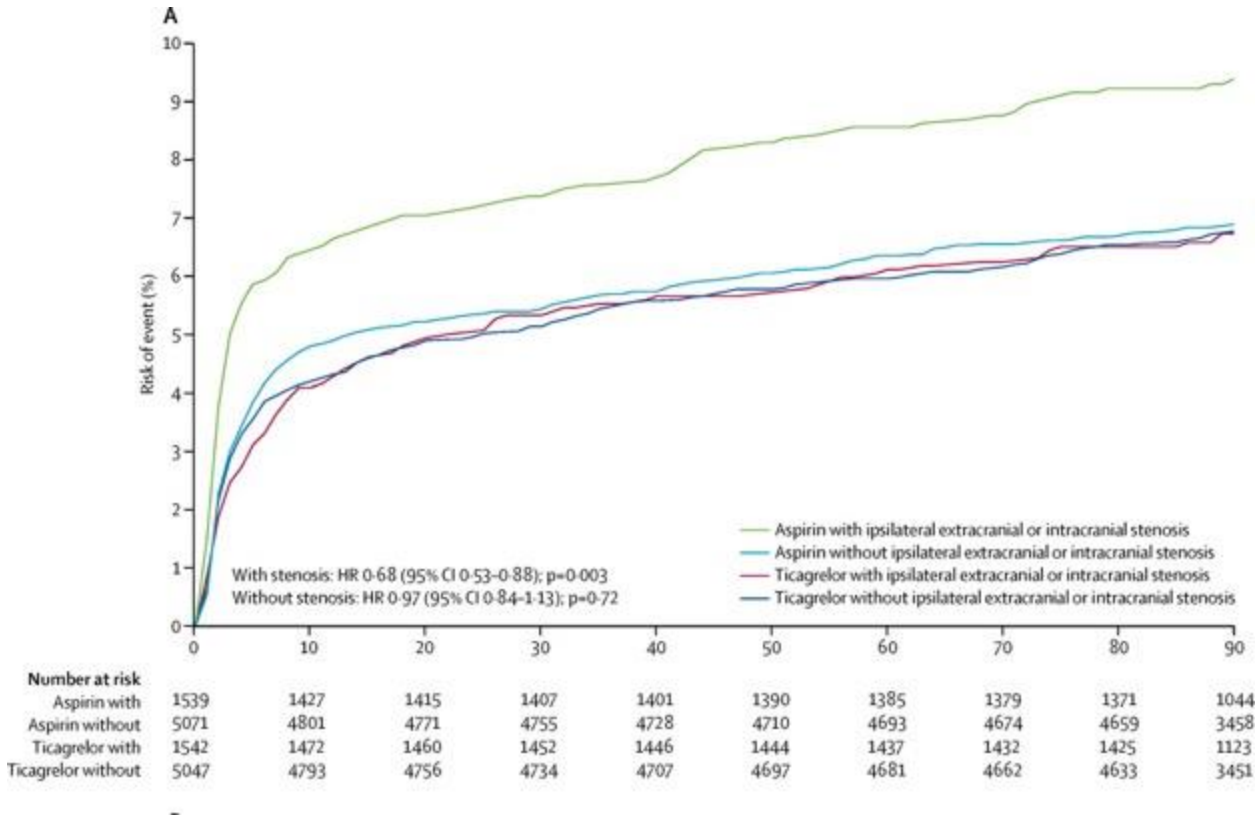
Sottoanalisi del THALES trial

Background

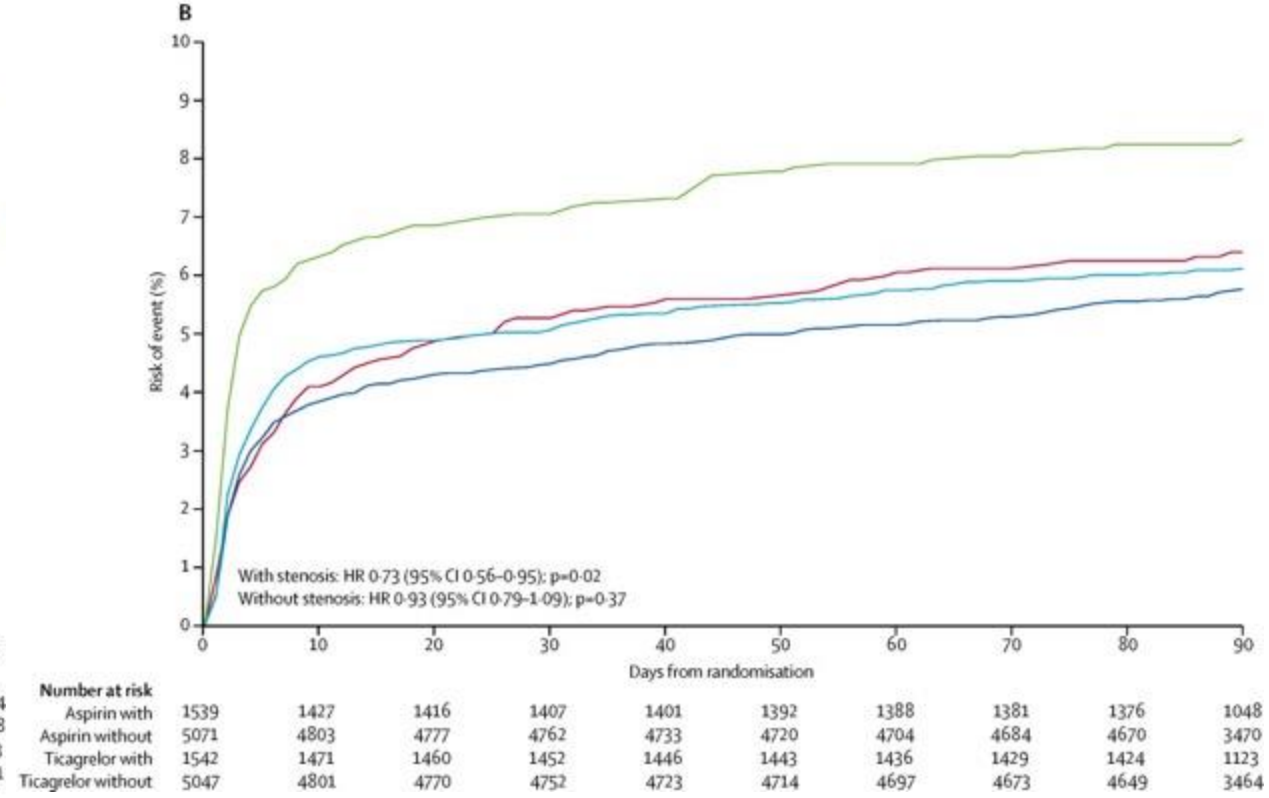
- Among patients with ischemic stroke, 40% present with ipsilateral stenosis of the cervicocranial vasculature and have the highest risk of recurrence among ischemic stroke etiologic subtypes.

SOCRATES TRIAL

Stroke, myocardial infarction, or death

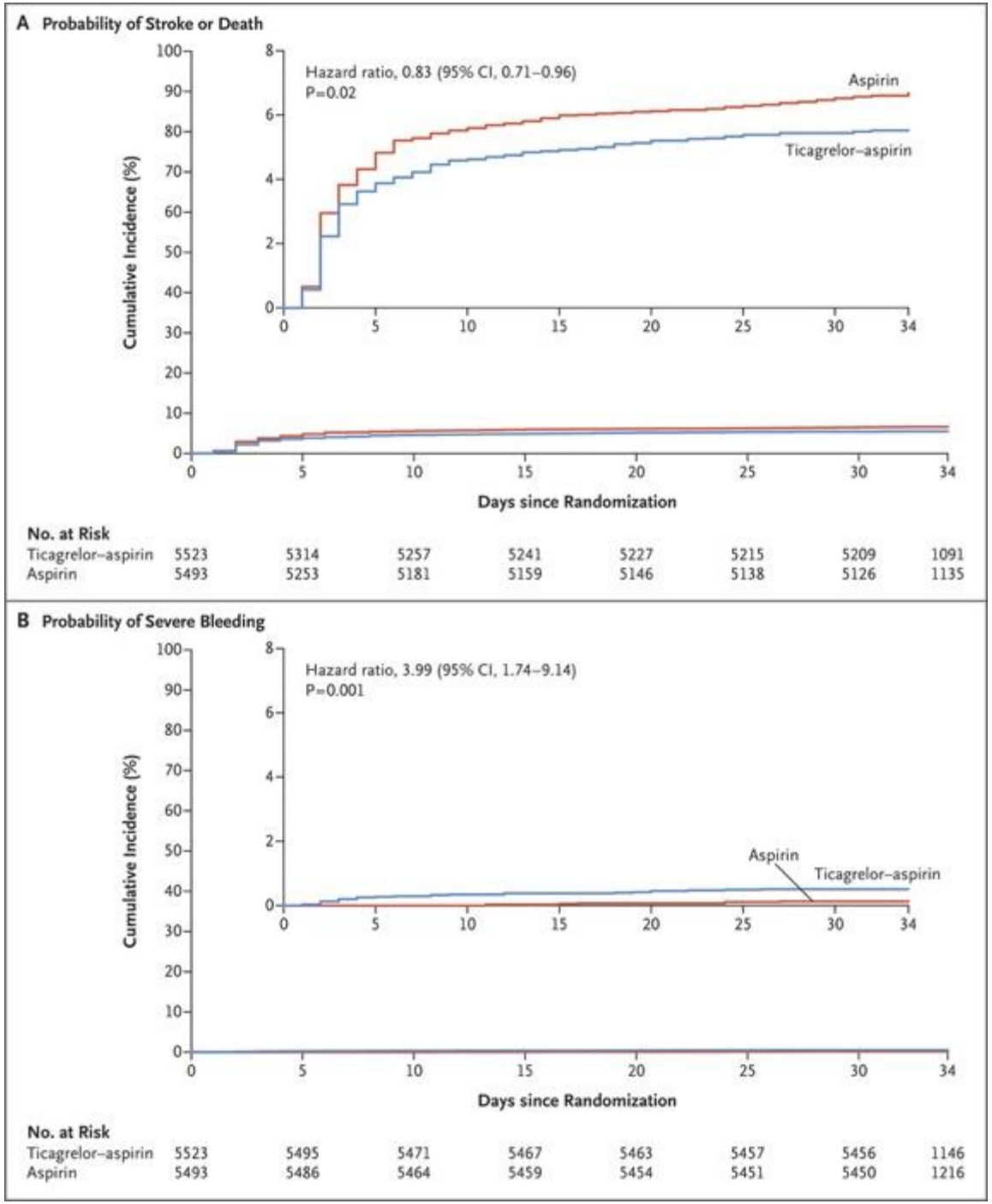


Ischaemic stroke



Lancet Neurol 2017; 16: 301–10

THALES TRIAL



N Engl J Med 2020; 383:207-217

CLINICAL AND POPULATION SCIENCES

Ticagrelor Added to Aspirin in Acute Nonsevere Ischemic Stroke or Transient Ischemic Attack of Atherosclerotic Origin

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Stroke. 2020;51:3504–3513.

Methods

- In the double-blind THALES (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death) trial, patients with a noncardioembolic, nonsevere ischemic stroke, or high-risk transient ischemic attack were randomized to ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2–30) or placebo added to aspirin (300–325 mg on day 1 followed by 75–100 mg daily for days 2–30) within 24 hours of symptom onset.

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Aim of the study

- The present paper aimed to evaluate the efficacy and safety of ticagrelor added to aspirin in the first 30 days following a TIA or minor ischemic stroke in patients with or without ipsilateral, potentially causal, ≥30% atherosclerotic stenosis of cervicocranial vasculature (prespecified analysis).
- The primary end point was time to the occurrence of stroke or death within 30 days.

Baseline characteristics

Baseline	Patients with ipsilateral stenosis (N=2351)		Patients without ipsilateral stenosis (N=8665)	
	Ticagrelor (N=1136)	Placebo (N=1215)	Ticagrelor (N=4387)	Placebo (N=4278)
Age, y (SD)	67.1 (10.7)	67.6 (10.5)	64.7 (11.0)	64.4 (11.2)
Female sex, n (%)	369 (32.5)	388 (31.9)	1739 (39.6)	1783 (41.7)
Race, n (%)				
White patients	651 (57.3)	665 (54.7)	2322 (52.9)	2283 (53.4)
Black patients	4 (0.4)	6 (0.5)	17 (0.4)	26 (0.6)
Asian patients	468 (41.2)	531 (43.7)	1885 (43.0)	1808 (42.3)
Other	13 (1.1)	13 (1.1)	163 (3.7)	161 (3.8)
Region, n (%)				
Asia or Australia	470 (41.4)	533 (43.9)	1903 (43.4)	1823 (42.6)
Europe	615 (54.1)	635 (52.3)	2199 (50.1)	2168 (50.7)
North America	2 (0.2)	1 (0.1)	10 (0.2)	10 (0.2)
Central or South America	49 (4.3)	46 (3.8)	275 (6.3)	277 (6.5)
Median blood pressure (IQR), mm Hg				
Systolic	150 (138–165)	150 (136–163)	150 (134–162)	149 (134–163)
Diastolic	84 (78–90.5)	83 (77–90)	84 (79–92)	84 (79–92)
Median body mass index (IQR)	26.1 (23.5–29.0)	25.8 (23.1–28.7)	25.8 (23.2–29.1)	25.7 (23.2–29.0)

Stroke. 2020;51:3504–3513.

Baseline	Patients with ipsilateral stenosis (N=2351)		Patients without ipsilateral stenosis (N=8665)	
	Ticagrelor (N=1136)	Placebo (N=1215)	Ticagrelor (N=4387)	Placebo (N=4278)
Medical history, n (%)				
Hypertension	932 (82.0)	990 (81.5)	3366 (76.7)	3232 (77.5)
Dyslipidemia	463 (40.8)	468 (38.5)	1635 (37.3)	1581 (37.0)
Current smoker	356 (31.3)	347 (28.6)	1148 (26.2)	1081 (25.3)
Diabetes	356 (31.3)	367 (30.2)	1233 (28.1)	1190 (27.8)
Previous ischemic stroke	211 (18.6)	238 (19.6)	690 (15.7)	676 (15.8)
Previous TIA	66 (5.8)	65 (5.3)	209 (4.8)	175 (4.1)
Previous ischemic heart disease	173 (15.2)	164 (13.5)	359 (8.2)	369 (8.6)
Congestive heart failure	64 (5.6)	64 (5.3)	143 (3.3)	140 (3.3)
Taking aspirin prior to index event, n (%)	162 (14.3)	162 (13.3)	592 (13.5)	517 (12.1)
Taking clopidogrel prior to index event, n (%)	22 (1.9)	27 (2.2)	53 (1.2)	48 (1.1)
Taking proton-pump inhibitor	81 (7.1)	90 (7.4)	322 (7.3)	316 (7.4)
Time to randomization after onset of symptoms, n (%)				
<12 h	356 (31.3)	375 (30.9)	1456 (33.2)	1401 (32.7)
≥12 h	780 (68.7)	840 (69.1)	2931 (66.8)	2877 (67.3)
Qualifying event, n (%)				
TIA	158 (13.9)	175 (14.4)	333 (7.6)	365 (8.5)
Ischemic stroke	978 (86.1)	1040 (85.6)	4054 (92.4)	3913 (91.5)
Baseline ABCD2 score among patients with TIA as qualifying event, n (%)				
≤5	55 (4.8)	66 (5.4)	5 (0.1)	5 (0.1)
6 or 7	103 (9.1)	109 (9.0)	328 (7.5)	360 (8.4)
Baseline NIHSS score among patients with ischemic stroke as qualifying event, n (%)				
≤3	633 (55.7)	671 (55.2)	2726 (62.1)	2641 (61.7)
>3	345 (30.4)	369 (30.4)	1328 (30.3)	1272 (29.7)

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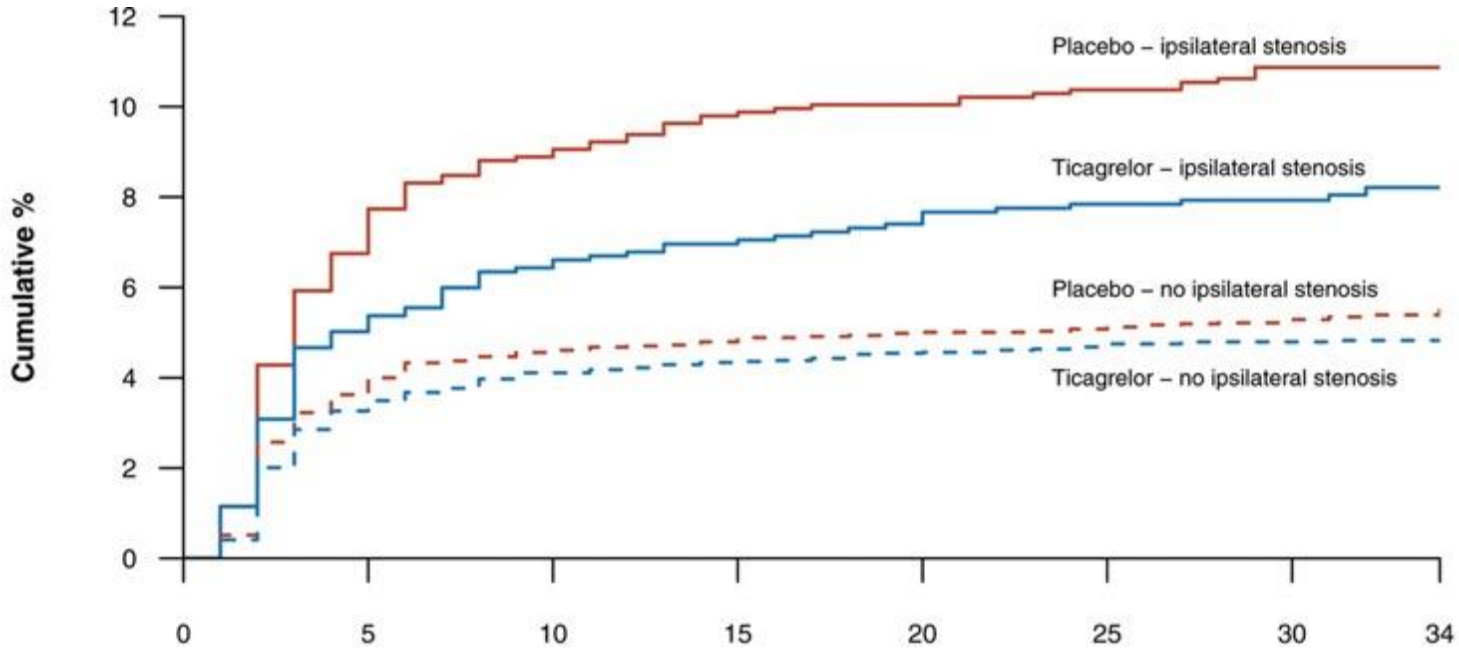
Kaplan-Meier event curves for the primary efficacy end point of stroke or death in patients with ipsilateral atherosclerotic stenosis of cervicocranial vasculature



No. at Risk								
T: ips	1136	1076	1060	1054	1049	1044	1043	211
P: ips	1215	1133	1105	1093	1089	1085	1079	247
T: no ips	4387	4238	4197	4187	4178	4171	4166	880
P: no ips	4278	4120	4076	4066	4057	4053	4047	888

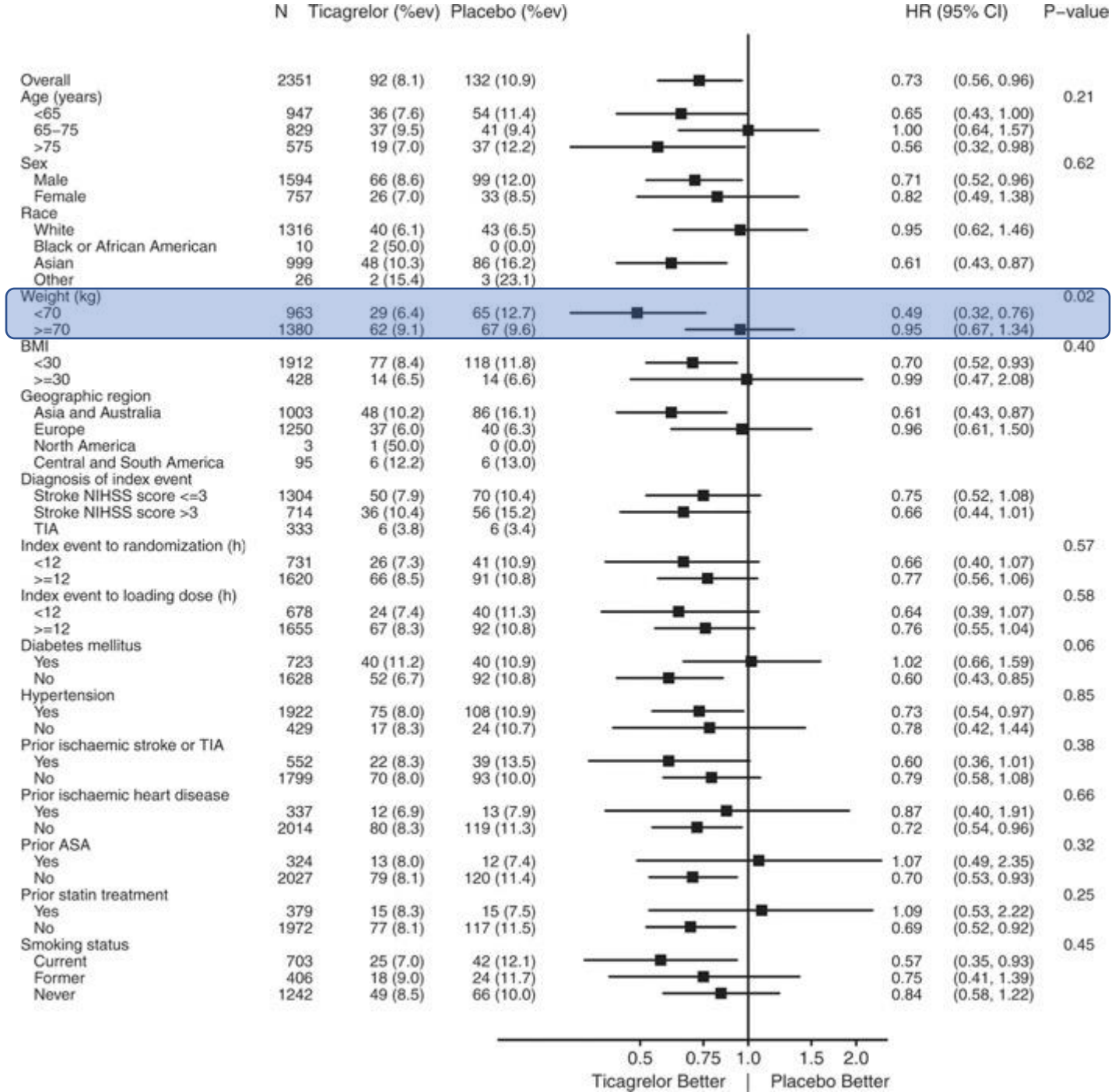
Stroke. 2020;51:3504–3513.

Outcomes

Outcome	Ipsilateral stenosis ≥30%	Ticagrelor (N=5523)		Placebo (N=5493)		Hazard ratio* (95% CI)	*P* value	*P* value for interaction
		No. of patients (%)	Event rate (KM estimate)	No. of patients (%)	Event rate (KM estimate)			
Primary efficacy end point								
Stroke or death	Yes	92 (8.1%)	7.9%	132 (10.9%)	10.9%	0.73 (0.56–0.96)	0.023	0.245
	No	211 (4.8%)	4.8%	230 (5.4%)	5.3%	0.89 (0.74–1.08)	0.230	
Stroke	Yes	87 (7.7%)	7.6%	127 (10.5%)	10.5%	0.72 (0.55–0.95)	0.020	0.277
	No	197 (4.5%)	4.5%	220 (5.1%)	5.1%	0.87 (0.72–1.05)	0.157	
Death	Yes	10 (0.9%)	0.8%	6 (0.5%)	0.5%	1.78 (0.65–4.91)	0.262	0.511
	No	26 (0.6%)	0.6%	21 (0.5%)	0.5%	1.21 (0.68–2.15)	0.517	
Secondary end point								
Ischemic stroke	Yes	87 (7.7%)	7.6%	127 (10.5%)	10.5%	0.72 (0.55–0.95)	0.020	0.373
	No	189 (4.3%)	4.3%	218 (5.1%)	5.0%	0.84 (0.69–1.02)	0.085	
Exploratory end point								
Disabling stroke or death (mRS score >1)	Yes	70 (6.2%)	6.1%	102 (8.5%)	8.5%	0.72 (0.53–0.98)	0.038	0.195
	No	151 (3.4%)	3.4%	158 (3.7%)	3.7%	0.93 (0.74–1.16)	0.526	
Safety end points								
GUSTO severe bleedings	Yes	4 (0.4%)		3 (0.2%)				
	No	24 (0.5%)	0.5%	4 (0.1%)	0.1%	5.87 (2.04–16.90)	0.001	
Intracranial hemorrhage or fatal bleedings	Yes	4 (0.4%)		3 (0.2%)				
	No	18 (0.4%)	0.4%	3 (0.1%)	0.1%	5.86 (1.73–19.90)	0.005	
Fatal bleedings	Yes	1 (0.1%)		1 (0.1%)				
	No	10 (0.2%)		1 (0.0%)				
Intracranial hemorrhage	Yes	4 (0.4%)		3 (0.2%)				
	No	16 (0.4%)	0.4%	3 (0.1%)	0.1%	5.21 (1.52–17.89)	0.009	
Hemorrhagic stroke	Yes	0 (0.0%)		0 (0.0%)				
	No	10 (0.2%)		2 (0.0%)				
GUSTO moderate or severe bleedings	Yes	6 (0.5%)		3 (0.2%)				
	No	30 (0.7%)	0.7%	8 (0.2%)	0.2%	3.67 (1.68–8.01)	0.001	
Premature permanent discontinuation of study drugs due to bleeding	Yes	43 (3.8%)	4.1%	11 (0.9%)	1.0%	4.21 (2.17–8.17)	<0.001	0.627
	No	109 (2.5%)	2.6%	21 (0.5%)	0.5%	5.15 (3.23–8.22)	<0.001	

Stroke. 2020;51:3504–3513.

Subgroup analysis in patients with ipsilateral stenosis



	N	Ticagrelor (%ev)	Placebo (%ev)	HR (95% CI)		P-value
Overall	2351	92 (8.1)	132 (10.9)	0.73	(0.56, 0.96)	
Age (years)						0.21
<65	947	36 (7.6)	54 (11.4)	0.65	(0.43, 1.00)	
65–75	829	37 (9.5)	41 (9.4)	1.00	(0.64, 1.57)	
>75	575	19 (7.0)	37 (12.2)	0.56	(0.32, 0.98)	
Sex						0.62
Male	1594	66 (8.6)	99 (12.0)	0.71	(0.52, 0.96)	
Female	757	26 (7.0)	33 (8.5)	0.82	(0.49, 1.38)	
Race						
White	1316	40 (6.1)	43 (6.5)	0.95	(0.62, 1.46)	
Black or African American	10	2 (50.0)	0 (0.0)			
Asian	999	48 (10.3)	86 (16.2)	0.61	(0.43, 0.87)	
Other	26	2 (15.4)	3 (23.1)			
Weight (kg)						0.02
<70	963	29 (6.4)	65 (12.7)	0.49	(0.32, 0.76)	
>=70	1380	62 (9.1)	67 (9.6)	0.95	(0.67, 1.34)	
BMI						0.40
<30	1912	77 (8.4)	118 (11.8)	0.70	(0.52, 0.93)	
>=30	428	14 (6.5)	14 (6.6)	0.99	(0.47, 2.08)	
Geographic region						
Asia and Australia	1003	48 (10.2)	86 (16.1)	0.61	(0.43, 0.87)	
Europe	1250	37 (6.0)	40 (6.3)	0.96	(0.61, 1.50)	
North America	3	1 (50.0)	0 (0.0)			
Central and South America	95	6 (12.2)	6 (13.0)			
Diagnosis of index event						
Stroke NIHSS score <=3	1304	50 (7.9)	70 (10.4)	0.75	(0.52, 1.08)	
Stroke NIHSS score >3	714	36 (10.4)	56 (15.2)	0.66	(0.44, 1.01)	
TIA	333	6 (3.8)	6 (3.4)			
Index event to randomization (h)						0.57
<12	731	26 (7.3)	41 (10.9)	0.66	(0.40, 1.07)	
>=12	1620	66 (8.5)	91 (10.8)	0.77	(0.56, 1.06)	
Index event to loading dose (h)						0.58
<12	678	24 (7.4)	40 (11.3)	0.64	(0.39, 1.07)	
>=12	1655	67 (8.3)	92 (10.8)	0.76	(0.55, 1.04)	
Diabetes mellitus						0.06
Yes	723	40 (11.2)	40 (10.9)	1.02	(0.66, 1.59)	
No	1628	52 (6.7)	92 (10.8)	0.60	(0.43, 0.85)	
Hypertension						0.85
Yes	1922	75 (8.0)	108 (10.9)	0.73	(0.54, 0.97)	
No	429	17 (8.3)	24 (10.7)	0.78	(0.42, 1.44)	
Prior ischaemic stroke or TIA						0.38
Yes	552	22 (8.3)	39 (13.5)	0.60	(0.36, 1.01)	
No	1799	70 (8.0)	93 (10.0)	0.79	(0.58, 1.08)	
Prior ischaemic heart disease						0.66
Yes	337	12 (6.9)	13 (7.9)	0.87	(0.40, 1.91)	
No	2014	80 (8.3)	119 (11.3)	0.72	(0.54, 0.96)	
Prior ASA						0.32
Yes	324	13 (8.0)	12 (7.4)	1.07	(0.49, 2.35)	
No	2027	79 (8.1)	120 (11.4)	0.70	(0.53, 0.93)	
Prior statin treatment						0.25
Yes	379	15 (8.3)	15 (7.5)	1.09	(0.53, 2.22)	
No	1972	77 (8.1)	117 (11.5)	0.69	(0.52, 0.92)	
Smoking status						0.45
Current	703	25 (7.0)	42 (12.1)	0.57	(0.35, 0.93)	
Former	406	18 (9.0)	24 (11.7)	0.75	(0.41, 1.39)	
Never	1242	49 (8.5)	66 (10.0)	0.84	(0.58, 1.22)	

Stroke. 2020;51:3504–3513.

Distribution of Ipsilateral Atherosclerotic Stenosis According to Geographical Regions

	Europe	Asia/Australia
	No. of patients (%)	No. of patients (%)
Ipsilateral stenosis ≥30%	1250	1003
Extracranial	1093 (87%)	550 (55%)
Intracranial	328 (26%)	703 (70%)
Ipsilateral stenosis ≥50%	739 (59%)	683 (68%)
Extracranial	593 (47%)	308 (31%)
Intracranial	252 (20%)	512 (51%)
Aortic arch atheroma ≥4 mm	43 (3%)	18 (2%)

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Limitations

- Subgroup analysis: not selected as a secondary analysis in the hierarchical testing, and thus it should be seen exploratory and hypothesis generating.
- Low proportion of patients (21.3%) with ipsilateral atherosclerotic stenosis ≥30% with or without aortic arch plaque of ≥4 mm, although in practice it is 40%, because some investigators may have treated their patients outside the trial with clopidogrel plus aspirin.
- Low proportion of patients who underwent a carotid artery revascularization, although the results in these patients suggest a large relative risk reduction in the primary end point and a 15% absolute risk difference without increase GUSTO severe bleedings.
- In 20% of patients the information on the presence of ipsilateral stenosis was not obtained as data was based on imaging performed as part of clinical practice.
- Permanent discontinuation of study drug was more common on ticagrelor than on placebo.

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Conclusions

- In this exploratory analysis comparing ticagrelor added to aspirin to aspirin alone, there was no interaction between treatment group and ipsilateral atherosclerosis stenosis subgroup but did identify a higher absolute risk and a greater absolute risk reduction of stroke or death at 30 days in the ipsilateral atherosclerosis stenosis group than in those without.
- Taken together with similar subgroup analysis of the SOCRATES trial showing significant interaction, ticagrelor added to aspirin yielded a clinically meaningful relative and absolute risk reduction of stroke and death as compared to aspirin alone with an NNT of 34 (95% CI, 19–171) and an NNH of 951 (95% CI, 182 to −296).
- These patients form a group to target with this therapy after a TIA or a minor ischemic stroke.

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