TICAGRELOR ADDED TO ASPIRIN IN ACUTE NON-SEVERE ISCHEMIC STROKE OR TIA OF ATHEROSCLEROTIC ORIGIN

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Disclosures

- I have received fees from
  - **AstraZeneca as an Executive Committee member of the SOCRATES&THALES trials**
  - Bayer as an Executive Committe member of the XANTUS registry, of Steering Committee of the ESUS trial
  - Pfizer as an Executive Committee member of the SPIRE trials program
  - Kowa as an Executive Committee member of the PROMINENT trial
  - BMS as a steering Committee member of the AXIOMATIC-SSP trial
  - Jansen as an advisory board member
  - GSK as an Endpoint Committee member of the SUMMIT trial
  - Fibrogen as a DSMB member of the ALPINE (Roxadustat) trials program
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Background

- Among patients with a transient ischemic attack (TIA) or minor ischemic strokes, those with ipsilateral atherosclerotic stenosis of cervicocranial vasculature have the highest risk of recurrent vascular events.[1]
- Ticagrelor is a potent, rapid acting P2Y12 inhibitor. Ticagrelor monotherapy was not superior to aspirin in SOCRATES trial (n=13,199) (NCT NCT01994720).[2]
- However, in 3081 patients in the SOCRATES trial with ipsilateral atherosclerotic stenosis ticagrelor was superior to aspirin (6.7% vs 9.4%, **HR 0.68 [0.53-0.88] P=0.003)** while in 10,118 patients with no ipsilateral stenosis (6.8% vs 6.9%) **HR** was **0.97 [0.84-1.13] $P_{interaction}$=0.017.**[3]
- In the THALES trial (n=11,016)(NCT03354429), ticagrelor added to aspirin was superior to aspirin alone in patients with TIA and minor stroke for the prevention of stroke or death (5.5% vs 6.6%, **HR 0.83 [0.71-0.96], P=0.015**).[4]
- Our aim was to evaluate the efficacy and safety of ticagrelor added to aspirin in patients with ipsilateral atherosclerotic stenosis

1. Amarenco P et al. One-year risk of stroke after transient ischemic attack or minor ischemic stroke. N Engl J Med 2016;374:1533-4
2. Johnston SC et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016;375: 35-43
3. Amarenco P et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack of atherosclerotic origin. Lancet Neurol. 2017;16:301-310
4. Johnston SC et al. Ticagrelor and Aspirin versus Aspirin in Acute Ischemic Stroke or TIA. N Engl J Med. 2020;383:207-217

THALES trial - Methods

- Investigators informed on severity and location of atherosclerosis of the cervicocranial vasculature, and classified their patients according to ASCOD Atherosclerosis phenotype criteria into a group with and a group without ipsilateral stenosis,[1]
- to perform this pre-specified, exploratory analysis.
- Outcomes were adjudicated by the investigators
- Analysis was by intention to treat.

1. Amarenco P et al. The A-S-C-O-D phenotyping of ischemic stroke. Cerebrovasc Dis. 2013;36:1-5

THALES Study Design

Study population:

Acute ischemic stroke (NIHSS ≤ 5)

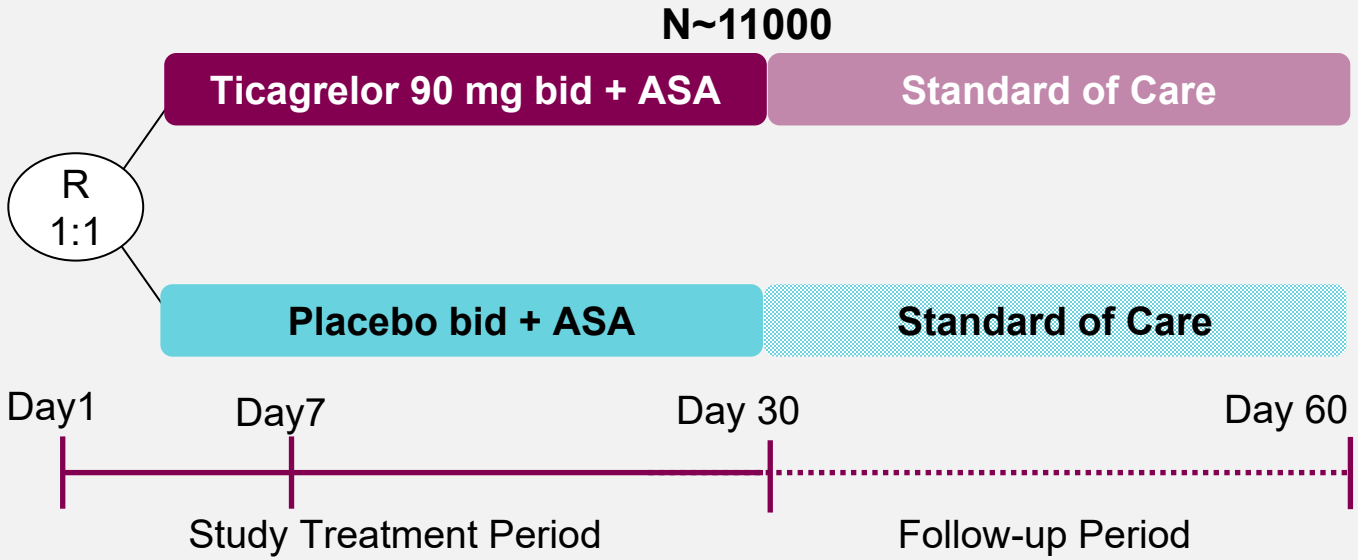
OR

High-risk transient ischemic attack (TIA) (ABCD² ≥ 6 or symptomatic arterial stenosis ≥ 50%)

- Randomized within 24 hours
- Patients ≥ 40 years

Key exclusion criteria:

- No cardioembolic origin
- No thrombolysis or thrombectomy
- No indication for antiplatelet other than ASA (aspirin) or for anticoagulation therapy
- No previous intracranial hemorrhage
- No planned carotid intervention within 3 days



Ticagrelor dose: 180 mg loading dose day 1, followed by 90 mg BID day 2-30

Aspirin dose: 300-325 mg day 1, followed by 75-80 mg day 2-30

Endpoints

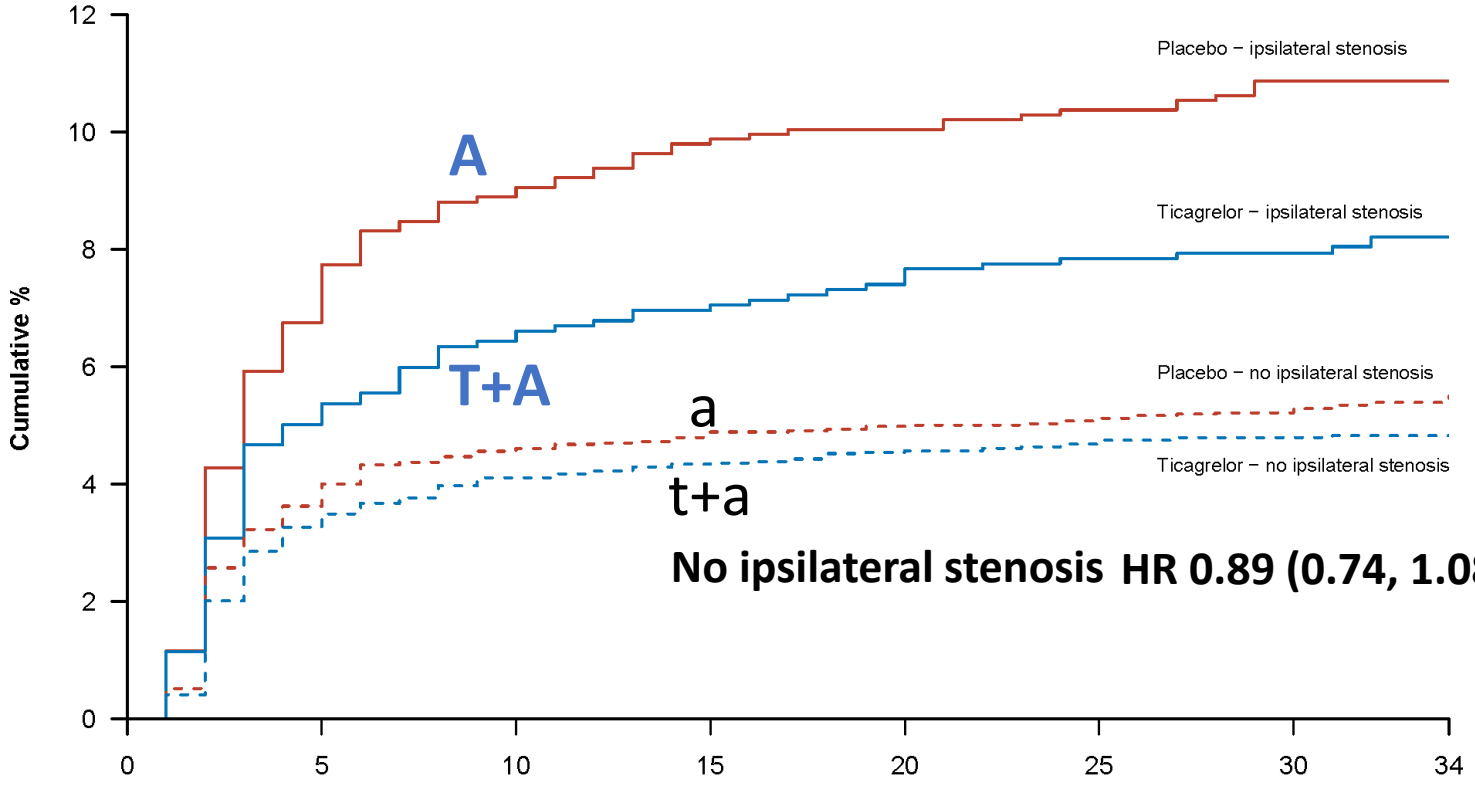
- Primary endpoint:
  - Time to the first occurrence of any event in the composite of stroke (ischemic or hemorrhagic) and death
- Secondary endpoints:
  - Time to the first occurrence of any ischemic stroke
- Safety endpoint:
  - Time to first severe bleeding event (GUSTO definition)
- Exploratory endpoint:
  - Disabling stroke (stroke event with mRS>1 at 30 days)

Baseline Characteristics	Patients with ipsilateral stenosis		Patients without ipsilateral stenosis	
	(N=2351)		(N=8665)	
	Ticagrelor+Aspirin	Aspirin	Ticagrelor+Aspirin	Aspirin
	(N=1136)	(N=1215)	(N=4387)	(N=4278)
Age – yr	67.1 (10.7)	67.6 (10.5)	64.7 (11.0)	64.4 (11.2)
Female sex – %	369 (32.5%)	388 (31.9%)	1739 (39.6%)	1783 (41.7%)
Race – %				
White	651 (57.3%)	665 (54.7%)	2322 (52.9%)	2283 (53.4%)
Black or African American	4 (0.4%)	6 (0.5%)	17 (0.4%)	26 (0.6%)
Asian	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%)
Qualifying event – no. (%)				
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%)
Time to randomization after onset of symptoms – no. (%)				
<12 hr	356 (31.3%)	375 (30.9%)	1456 (33.2%)	1401 (32.7%)
≥12 hr	780 (68.7%)	840 (69.1%)	2931 (66.8%)	2877 (67.3%)
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)

Baseline characteristics Medical history – %	Patients with ipsilateral stenosis		Patients without ipsilateral stenosis	
	(N=2351)		(N=8665)	
	Ticagrelor+Aspirin	Aspirin	Ticagrelor+Aspirin	Aspirin
	(N=1136)	(N=1215)	(N=4387)	(N=4278)
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 mellitus	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%)
Taking aspirin prior to index event – no. (%)	162 (14.3%)	162 (13.3%)	592 (13.5%)	517 (12.1%)

THALES –Ipsilateral atherosclerotic stenosis Primary endpoint: Stroke and death

Ipsilateral stenosis HR 0.73 (0.56, 0.96) P=0.023



A 10.9%

T+A 7.9%

NNT=34

a 5.3%

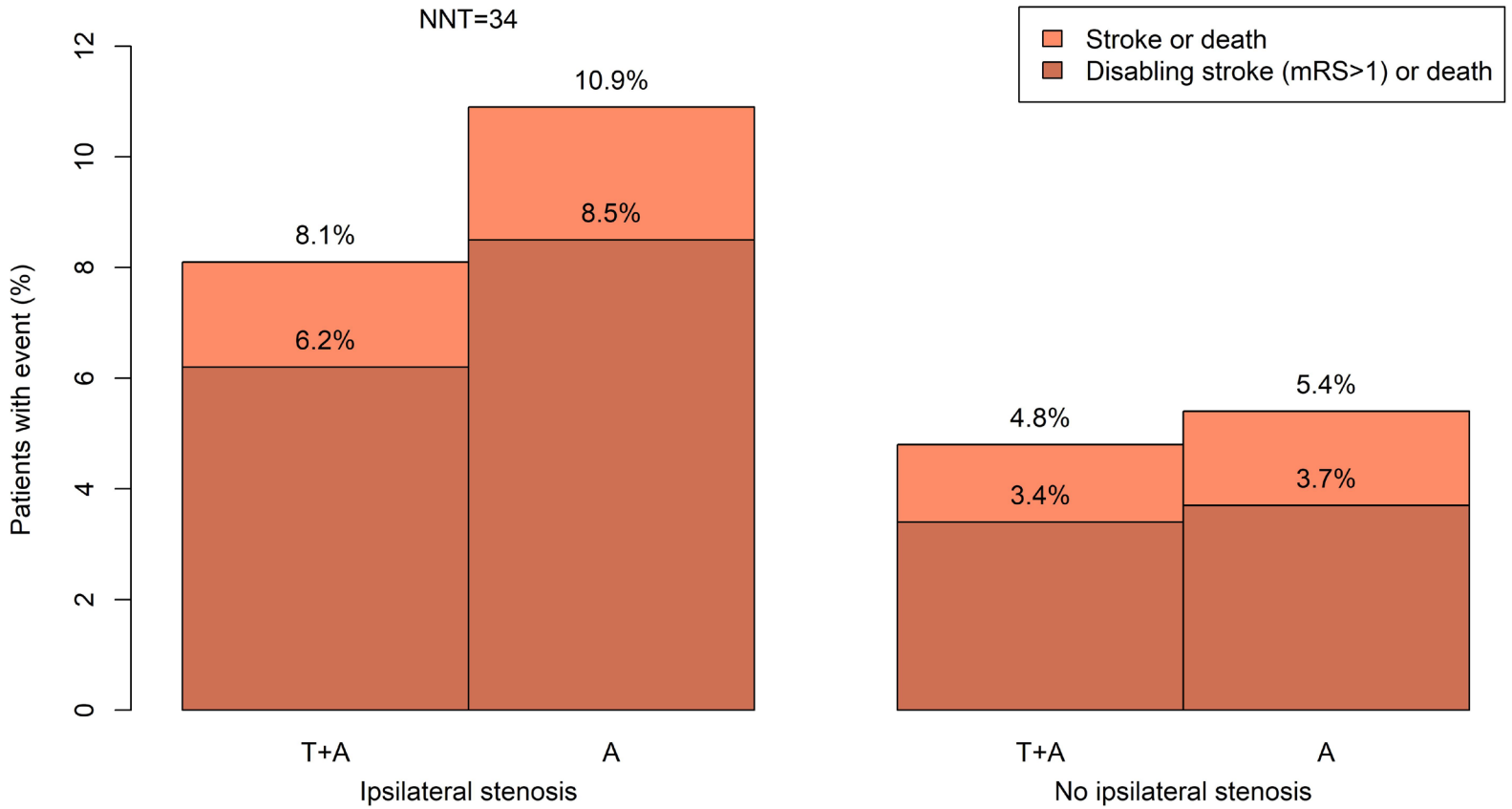
t+a 4.8%

No ipsilateral stenosis HR 0.89 (0.74, 1.08)

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

Outcome	Ticagrelor+Aspirin (N=5523)		Aspirin (N=5493)		Hazard Ratio (95% CI)	P value	P value for interaction
	no. of patients	event rate (KM)	no. of patients	event rate (KM)			
Primary endpoint (stroke, or death)							
Patients with ipsilateral extra- or intracranial stenosis ≥30%	92 (8.1%)	7.9%	132 (10.9%)	10.9%	0.73 (0.56, 0.96)	0.023	0.245
No ipsilateral stenosis	211 (4.8%)	4.8%	230 (5.4%)	5.3%	0.89 (0.74, 1.08)	0.230	
First secondary endpoint (ischemic stroke)							
Patients with ipsilateral extra- or intracranial stenosis	87 (7.7%)	7.6%	127 (10.5%)	10.5%	0.72 (0.55, 0.95)	0.020	0.373
No ipsilateral stenosis	189 (4.3%)	4.3%	218 (5.1%)	5.0%	0.84 (0.69, 1 .02)	0.085	
Other endpoints							
Stroke							
Patients with ipsilateral extra- or intracranial stenosis	87 (7.7%)	7.6%	127 (10.5%)	10.5%	0.72 (0.55, 0.95)	0.020	0.277
No ipsilateral stenosis	197 (4.5%)	4.5%	220 (5.1%)	5.1%	0.87 (0.72. 1.05)	0.157	
Disabling stroke or death							
Patients with ipsilateral extra- or intracranial stenosis	70 (6.2%)	6.1%	102 (8.5%)	8.5%	0.72 (0.53, 0.98)	0.038	0.195
No ipsilateral stenosis	151 (3.4%)	3.4%	158 (3.7%)	3.7%	0.93 (0.74, 1.16)	0.526	

THALES –Ipsilateral atherosclerotic stenosis Disabling Stroke at 30 days



Safety Outcome	Ticagrelor+Aspirin (N=5523)		Aspirin (N=5493)		Hazard Ratio (95% CI)	P value	P value for interaction
	no. of patients	event rate (KM)	no. of patients	event rate (KM)			
Death							
Patients with ipsilateral extra- or intracranial stenosis	10 (0.9%)	0.8%	6 (0.5%)	0.5%	1.78 (0.65, 4.91)	0.262	0.511
No ipsilateral stenosis	26 (0.6%)	0.6%	21 (0.5%)	0.5%	1.21 (0.60, 2.15)	0.517	
GUSTO severe bleeding							
Patients with ipsilateral extra- or intracranial stenosis	4 (0.4%)		3 (0.2%)				
No ipsilateral stenosis	24 (0.5%)	0.5%	4 (0.1%)	0.1%	5.87 (2.04, 16.90)	0.001	
Intracranial hemorrhage or fatal bleeding							
Patients with ipsilateral extra- or intracranial stenosis	4 (0.4%)		3 (0.2%)				
No ipsilateral stenosis	18 (0.4%)	0.4%	3 (0.1%)	0.1%	5.86 (1.73, 19.90)	0.005	

THALES –Ipsilateral atherosclerotic stenosis Conclusions

- In patients with ipsilateral atherosclerotic stenosis, 30-day absolute event rate of stroke or death was higher (10.9% on aspirin alone) and absolute risk reduction was greater on ticagrelor added to aspirin (3.0%) than in patients with no ipsilateral stenosis (5.3% and 0.5%, respectively)
- This is concordant with prior studies suggesting that atherosclerotic disease carries a greater risk than other stroke subtypes without stenosis among patients with TIA or minor ischemic stroke event on aspirin
- Given both the SOCRATES and THALES results, targeting patients with atherosclerotic stenosis for dual therapy with ticagrelor and aspirin could yield a clinically meaningful relative and absolute risk reduction of stroke and death as compared to aspirin alone with a number needed to treat of 34 and a number needed to harm of 951.

Stroke