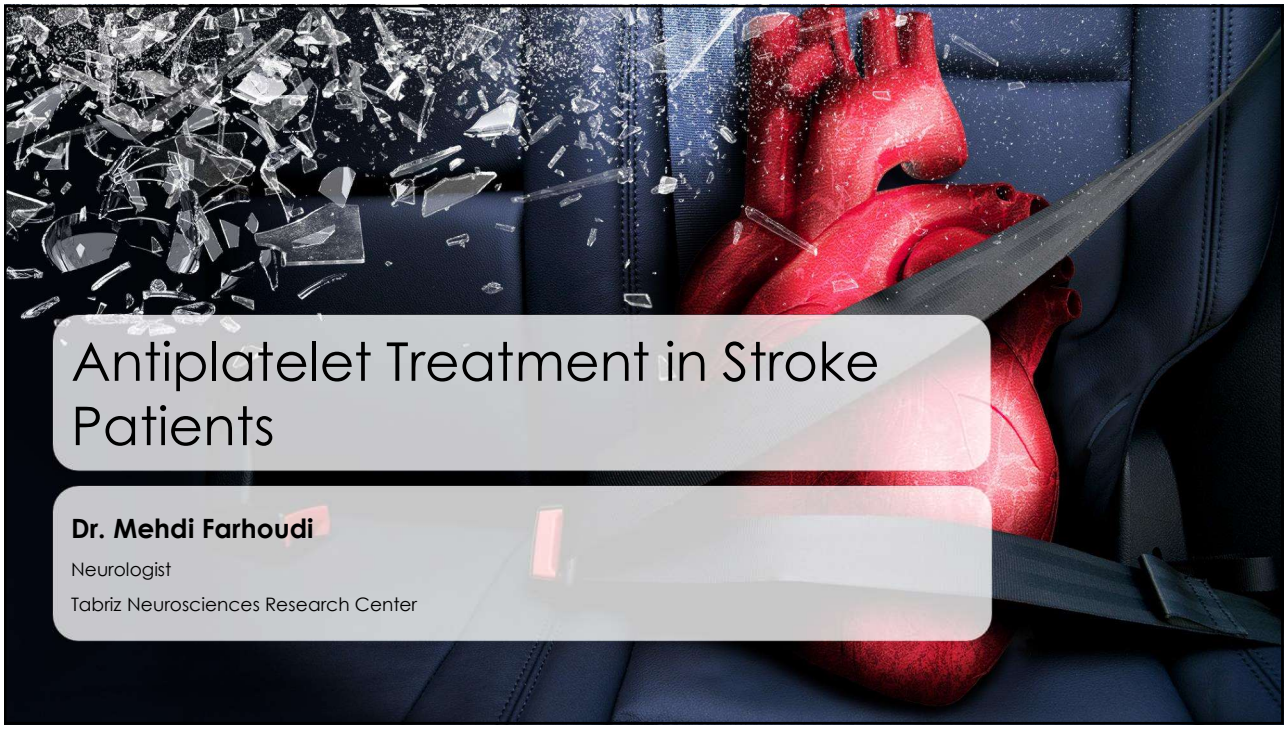

Antiplatelet Treatment in Stroke Patients

Dr. Mehdi Farhoudi
Neurologist
Tabriz Neurosciences Research Center

Burden of Stroke & TIA

Stroke is the leading cause of death worldwide

Ischemic stroke is responsible for about 80% of all strokes

In 2016, over 9.5 million new cases of ischemic stroke occurred worldwide

~50% of strokes preceded by a TIA take place in the first 48 hours after the TIA

Eur Heart J. 2018;39(7):508-579.
Aguilar, M.I. (2015). Acute ischemic stroke and transient ischemic attack

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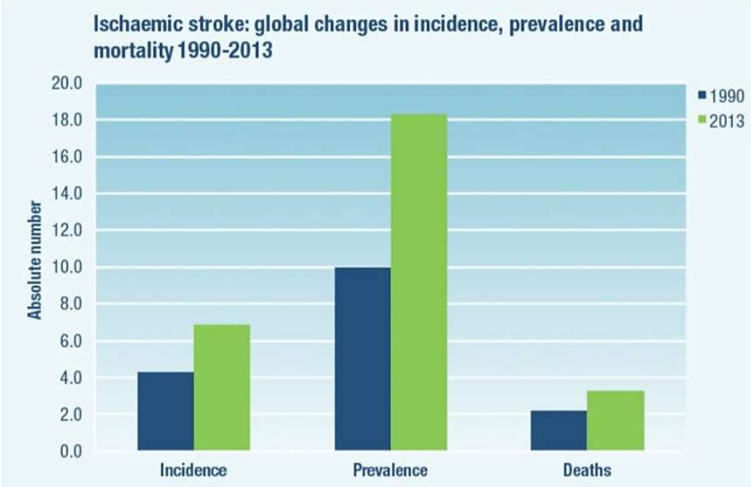
Global Incidence and Mortality of Ischemic Stroke



Feign V, et al. neuroepidemiology 2015;45:161-176

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Stroke as a Devastating & Debilitating Disease

15 million
people worldwide suffer a stroke

5 million
People die of stroke

5 million
People left permanently disabled

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Aguilar, M.I. (2015). Acute ischemic stroke and transient ischemic attack

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NIHSS Stroke Scale

Level of consciousness	Facial paresis
LOC questions	Motor arm
LOC commands	Motor leg
Best gaze	Limb ataxia
Visual fields	Sensory
Best language	Dysarthria
Extinction and inattention	

NIHSS SCORE	STROKE SEVERITY	IMPACTED BRAIN DENSITY
0	No Stroke	
0 – 4	Minor Stroke	
5 – 15	Moderate Stroke	
16– 20	Moderate to Severe Stroke	
21 - 42	Severe Stroke	

National Institutes of Health Stroke Scale
J Neurosci Nurs. 2006;38(4 Suppl):309-15.

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ABCD2 Risk Stratification Score

Table-1: ABCD2 Scoring Criteria.

A	Age	≥60 years	1 point
B	Blood pressure	≥140/90 mm Hg	1 point
C	Clinical features	Unilateral weakness	2 points
Speech impairment without weakness			1 point
D	Duration	≥60 minutes	2 points
		10-59 minutes	1 point
D	Diabetes	Presence of diabetes mellitus	1 point

ABCD² score	2-day risk (%)	7-day risk (%)	90-day risk (%)
0–3 (low risk)	1.0	1.2	3.1
4–5 (moderate risk)	4.2	5.9	9.8
6–7 (high risk)	8.1	11.7	17.8

Aguilar, M.I. (2015). Acute ischemic stroke and transient ischemic attack

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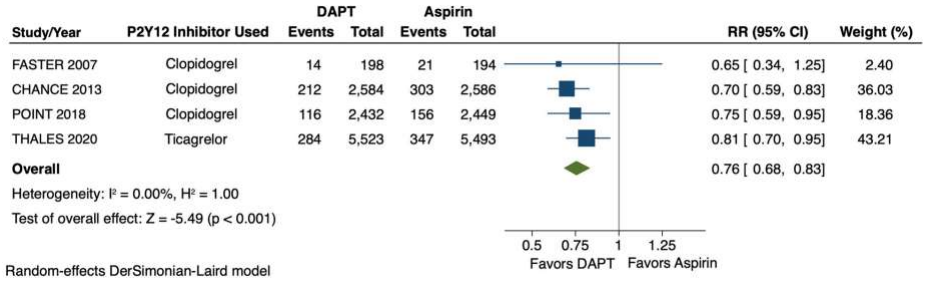
DAPT Versus Aspirin in Patients With Stroke or TIA

Meta-Analysis of Randomized Controlled Trials

4 trials with a total of 21459 patients

- **Recurrent ischemic or hemorrhagic stroke:**



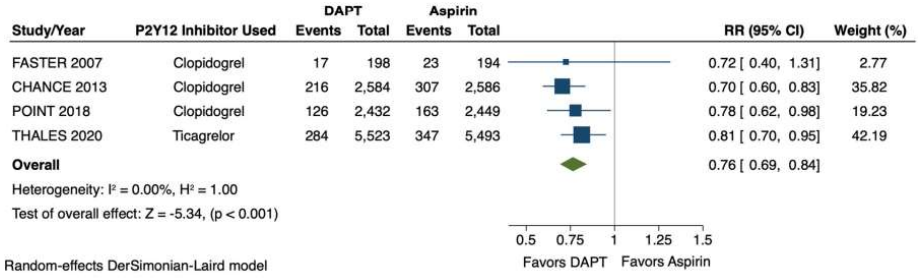
Stroke. 2021;52:e217–e223.

DAPT Versus Aspirin in Patients With Stroke or TIA

Meta-Analysis of Randomized Controlled Trials

4 trials with a total of 21459 patients

- **Major adverse cardiovascular events:**



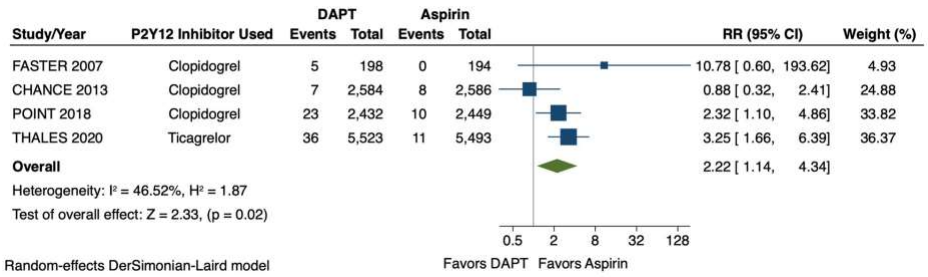
Stroke. 2021;52:e217–e223.

DAPT Versus Aspirin in Patients With Stroke or TIA

Meta-Analysis of Randomized Controlled Trials

4 trials with a total of 21459 patients

- **Major bleeding:**



Stroke. 2021;52:e217–e223.

DAPT Versus Aspirin in Patients With Stroke or TIA

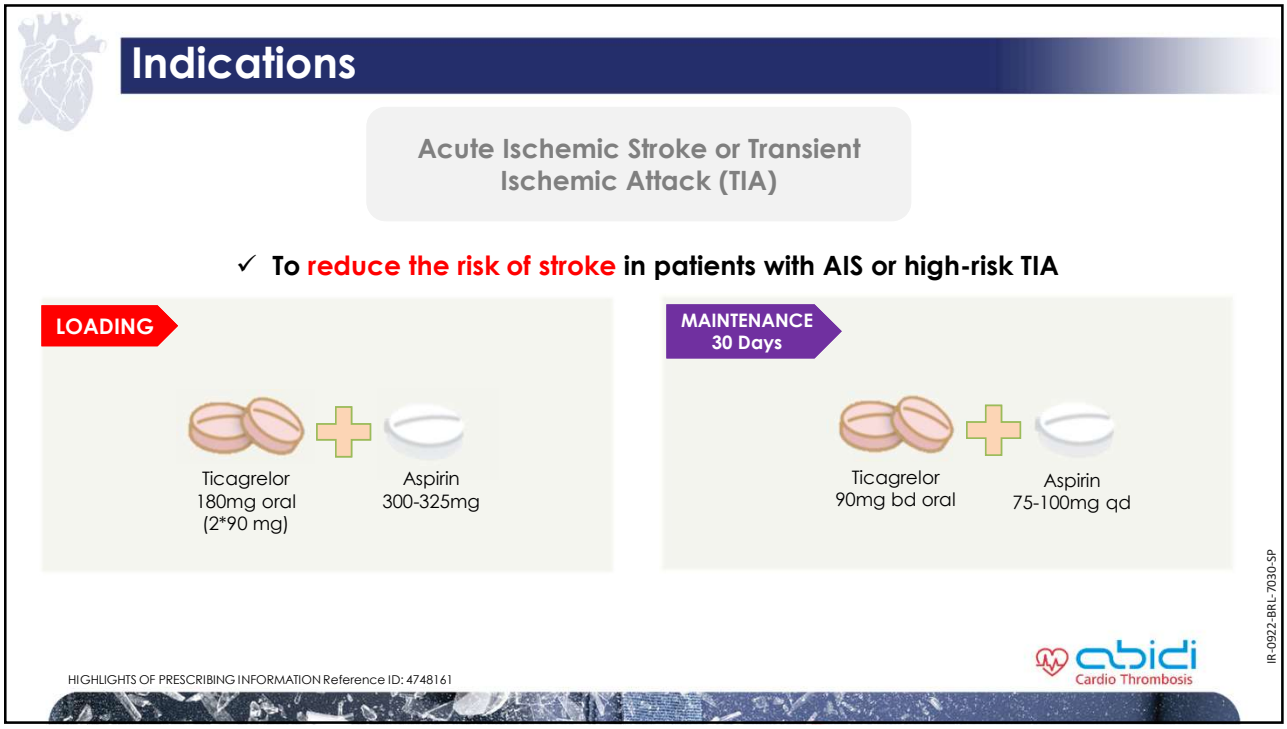
Meta-Analysis of Randomized Controlled Trials

4 trials with a total of 21459 patients

- DAPT with aspirin and ticagrelor or clopidogrel given within 24 hours of high-risk TIA or non-cardioembolic mild to moderate stroke effectively reduces the risk of recurrent stroke and MACE compared with aspirin monotherapy.
- DAPT is associated with a higher risk of bleeding events, but there is no difference in the risk of all-cause death.

Stroke. 2021;52:e217–e223.


Ticagrelor in AIS & TIA
Clinical Studies
IR-0922-BRL-7030-SP


Indications
Acute Ischemic Stroke or Transient Ischemic Attack (TIA)
✓ To reduce the risk of stroke in patients with AIS or high-risk TIA
LOADING
Ticagrelor 180mg oral (2*90 mg)
Aspirin 300-325mg
MAINTENANCE 30 Days
Ticagrelor 90mg bd oral
Aspirin 75-100mg qd
HIGHLIGHTS OF PRESCRIBING INFORMATION Reference ID: 4748161
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The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial

NEJM 2020

Randomized, placebo-controlled, double-blind

To investigate whether ticagrelor combined with aspirin are superior to aspirin alone in preventing stroke or death in patients with non-severe, non-cardioembolic ischemic stroke or high-risk transient ischemic attack.

11,016
Patients

Eligible patients were ≥ 40 years old and,

- Mild-to-moderate acute non-cardioembolic ischemic stroke (NIHSS ≤ 5)
- High-risk TIA (ABCD2 ≥ 6 or symptomatic ≥50% intracranial or extracranial arterial stenosis)

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N Engl J Med 2020; 383:207-217

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The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial

Exclusion criteria:

- intravenous or intraarterial thrombolysis or mechanical thrombectomy
- Any suspicion of cardioembolic origin (AF, ventricular aneurysm)
- History of ICH
- GI bleeding within the past 6 months
- Major surgery within 30 days

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N Engl J Med 2020; 383:207-217

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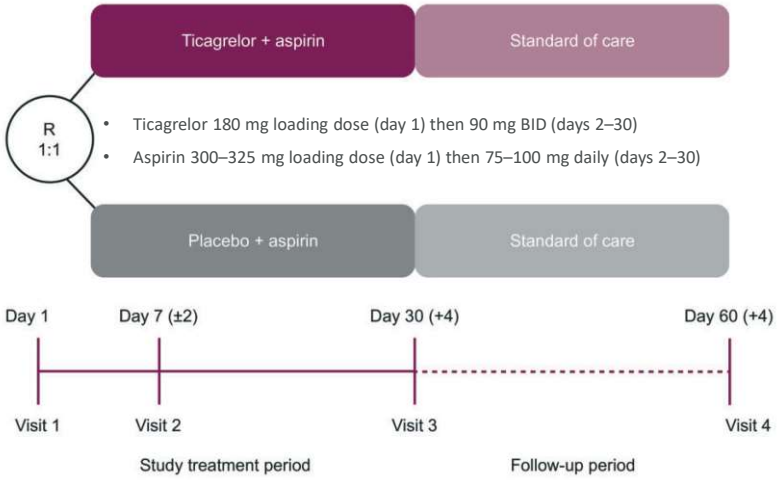
The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial

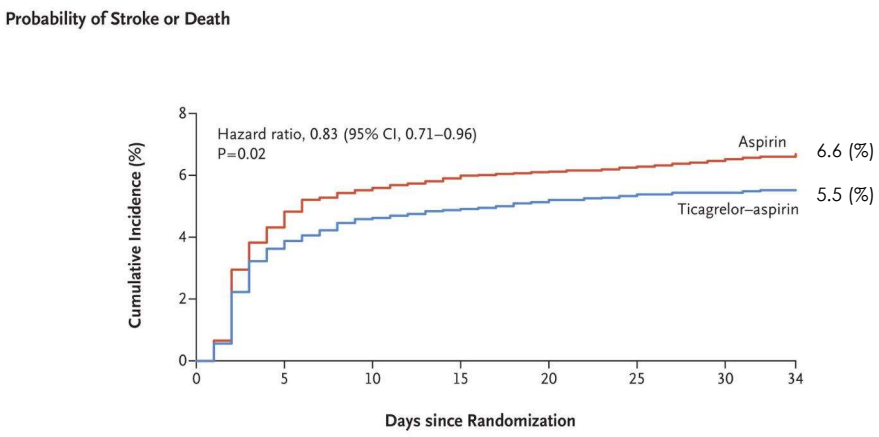


N Engl J Med 2020; 383:207-217

IR-0922-BRL-7030-SP

The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial



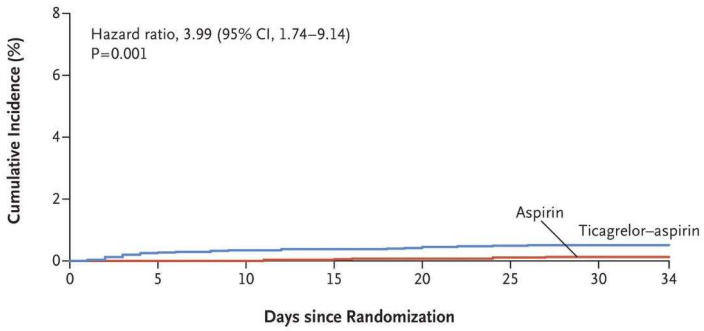
N Engl J Med 2020; 383:207-217

IR-0922-BRL-7030-SP

The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial

Probability of Severe Bleeding



N Engl J Med 2020; 383:207-217

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The Acute Stroke or TIA Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death

THALES Trial

CONCLUSIONS

Among patients with a mild-to-moderate acute non-cardioembolic ischemic stroke or TIA, the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups and severe bleeding was more frequent with ticagrelor.

N Engl J Med 2020; 383:207-217

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Ticagrelor Added to Aspirin in Acute Non-severe Ischemic Stroke or TIA of

Atherosclerotic Origin

Stroke 2020

Atherosclerotic Subgroup of the THALES trial

Among patients with a TIA or minor AIS, those with ipsilateral atherosclerotic stenosis of cervicocranial vasculature have the highest risk of recurrent vascular events.

Of 11016 randomized patients, 2351 (21.3%) patients had an ipsilateral atherosclerotic stenosis

After 30 days, a primary end point occurred in patients with ipsilateral stenosis:

- 8.1% randomized to ticagrelor
- 10.9% randomized to placebo

Stroke. 2020;51:3504–3513

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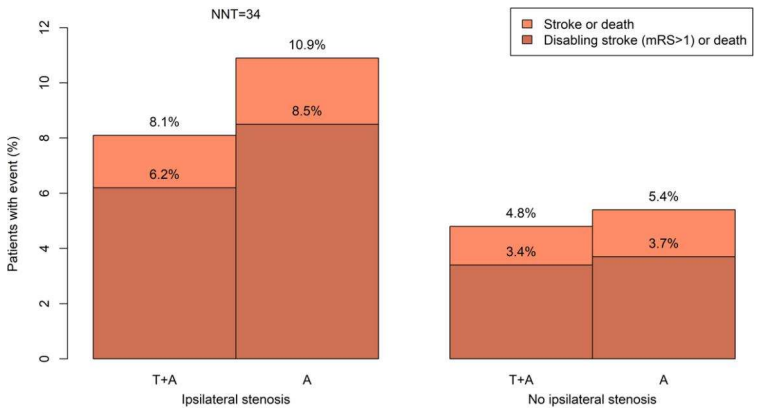
Ticagrelor Added to Aspirin in Acute Non-severe Ischemic Stroke or TIA of

Atherosclerotic Origin



Stroke. 2020;51:3504–3513

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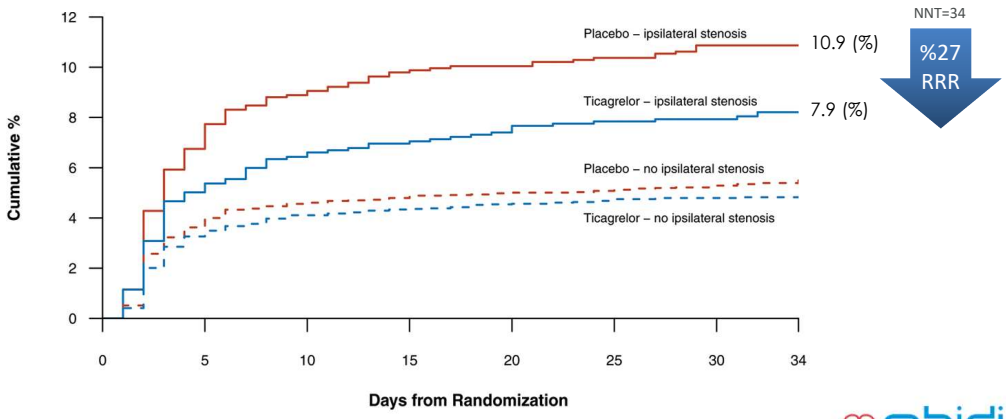
IR-0922-BRL-7030-SP

Ticagrelor Added to Aspirin in Acute Non-severe Ischemic Stroke or TIA of

Atherosclerotic Origin

Death or Stroke



Stroke. 2020;51:3504–3513

IR-0922-BRL-7030-SP

Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or TIA

PRINCE study

Phase II trial

open label, blinded endpoint, randomized controlled phase II trial

To test the hypothesis that ticagrelor plus aspirin is safe and superior to clopidogrel plus aspirin for reducing high platelet reactivity at 90 days and stroke recurrence in patients with minor stroke or TIA, particularly in carriers of the CYP2C19 loss-of-function allele and patients with large artery atherosclerosis.

In China
675 patients enrolled and treated with the study drug within 24 h of symptom onset

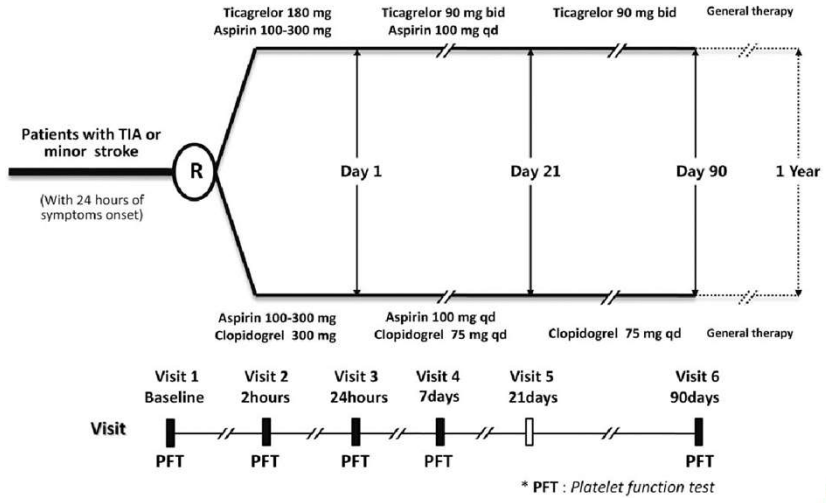
Eligible patients aged 40 - 80 years and,

- Acute minor ischemic stroke
  - NIHSS ≤3
- Moderate to High-risk TIA
  - ABCD2 stroke risk score of ≥4
  - ≥50% symptomatic stenosis of cervical or intracranial vessels

BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

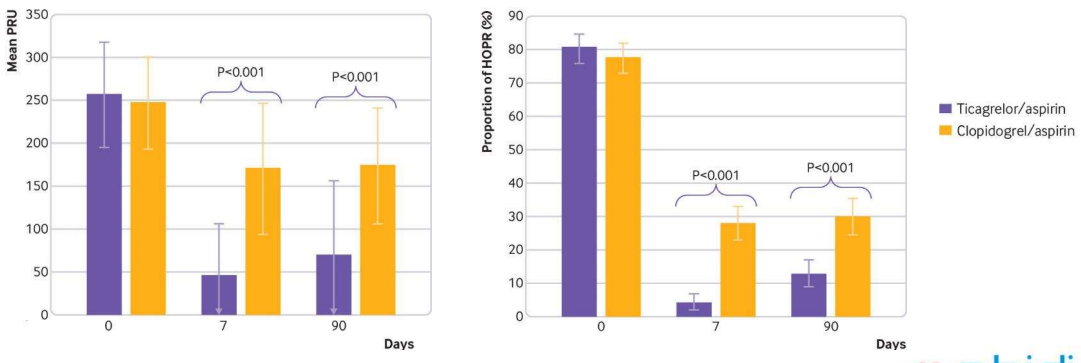


BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

Platelet reactivity in trial groups at baseline and follow-up, showing P2Y12 reaction units (PRU) and proportion of patients with high platelet reactivity (HOPR):



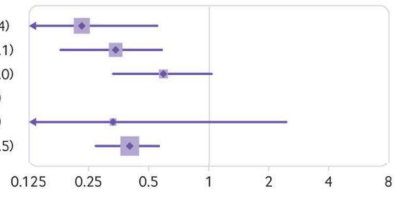
BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

Effect of ticagrelor/aspirin vs clopidogrel/aspirin on high platelet reactivity and clinical outcome at 90 days, stratified by metabolizer status:

Outcome Phenotype	Ticagrelor/aspirin No with event/total No (%)	Clopidogrel/aspirin No with event/total No (%)	Hazard ratio or risk ratio (95% CI)	Hazard ratio or risk ratio (95% CI)	P value	P for interaction
HOPR at 90 days						
Poor	4/38 (10.5)	14/33 (42.4)		0.23 (0.07 to 0.55)	0.004	
Intermediate	12/113 (10.6)	41/124 (33.1)		0.34 (0.18 to 0.58)	<0.001	
Extensive	16/117 (13.7)	25/119 (21.0)		0.59 (0.33 to 1.03)	0.07	0.42
Ultra	0/1 (0.0)	2/5 (40.0)		NA		
Unknown	1/6 (16.7)	2/4 (50.0)		0.33 (0.02 to 2.44)	0.29	
Total	33/275 (12.0)	84/285 (29.5)		0.40 (0.27 to 0.56)	<0.001	



HOPR = P2Y12 reaction units of more than 208, as measured the VerifyNow P2Y12 assay.

BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

Stroke recurrence at 90 days, by cause:

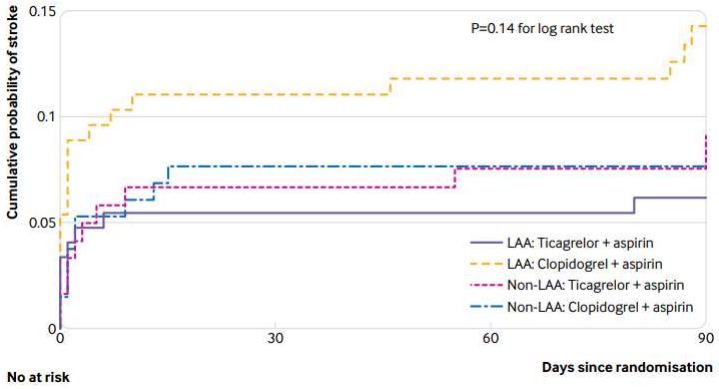
Cause of stroke*	Trial participants (No with event/total No (%))		Hazard ratio (95% CI)*	P	P for interaction
	Ticagrelor/aspirin (n=336)	Clopidogrel/aspirin (n=339)			
Large artery atherosclerosis	9/151 (6.0)	20/153 (13.1)	0.45 (0.20 to 0.98)	0.04	0.13
Non-large artery atherosclerosis	10/124 (8.1)	10/136 (7.4)	1.10 (0.46 to 2.63)	0.84	—

BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

Stroke recurrence at 90 days, by cause:



BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

Effect of ticagrelor/aspirin versus clopidogrel/aspirin on efficacy and safety outcomes in PRINCE trial:

Outcomes	Trial participants (No with event/total No (%))		Hazard ratio or risk ratio (95% CI)	P
	Ticagrelor/aspirin	Clopidogrel/aspirin		
Primary safety outcomes				
Major bleeding	5/336 (1.5)	4/339 (1.2)	1.27 (0.34 to 4.72)	0.72
Major, fatal, life threatening bleeding	4/336 (1.2)	3/339 (0.9)	1.35 (0.30 to 6.03)	0.69
Fatal bleeding	1/336 (0.3)	1/339 (0.3)	1.01 (0.06 to 16.13)	1.00
Intracranial hemorrhage	3/336 (0.9)	2/339 (0.6)	1.27 (0.34 to 4.72)	0.72
Major, other	1/336 (0.3)	1/339 (0.3)	1.01 (0.06 to 16.18)	0.99
Minor bleeding	11/336 (3.3)	8/339 (2.4)	1.40 (0.56 to 3.47)	0.47
Major or minor bleeding	16/336 (4.8)	12/339 (3.5)	1.36 (0.64 to 2.88)	0.42
Minimal bleeding	64/336 (19.0)	36/339 (10.6)	1.86 (1.24 to 2.80)	0.003
Any bleeding	75/336 (22.3)	48/339 (14.2)	1.65 (1.15 to 2.37)	0.007
Other safety outcomes				
Respiratory, thoracic, and mediastinal disorders	22/336 (6.5)	0/339 (0.0)	—	<0.001
Dyspnea	14/336 (4.2)	0/339 (0.0)	—	<0.001
Epistaxis	6/336 (1.8)	0/339 (0.0)	—	0.04

BMJ 2019;365:l2211

IR-0922-BRL-7030-SP

PRINCE study

- A total of stopped receiving the study drug before 90 days:
  - 20.5% patients in the ticagrelor/aspirin group
  - 13.9% in the clopidogrel/aspirin group
- The most common reasons were dyspnea and epistaxis.
- The rate of permanent discontinuation caused by dyspnea was:
  - 4.2% in the ticagrelor/aspirin group
  - 0.0% in the clopidogrel/aspirin group
- The rate of permanent discontinuation caused by epistaxis was:
  - 1.8% in the ticagrelor/aspirin group
  - 0.0% in the clopidogrel/aspirin group

BMJ 2019;365:l2211

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PRINCE study

CONCLUSION

- Patients with minor stroke or TIA who are treated with ticagrelor plus aspirin have a lower proportion of high platelet reactivity than those who are treated with clopidogrel plus aspirin,
- Particularly for those who are carriers of the CYP2C19 loss-of-function allele.

BMJ 2019;365:l2211

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Milestone Trials of DAPT in Minor Stroke & High-Risk TIA

	CHANCE & POINTS (Clopidogrel + ASA)	THALES (Ticagrelor + ASA)	PRINCE II (Clopidogrel vs Ticagrelor) + ASA	
Rate of stroke	6.54 %	5.14 %		
Rate of Ischemic stroke	6.30 %	5.00 %	۸٫۳ %	۵٫۴ %
Moderate-to-severe bleeding rates	0.60 %	0.65 %	۴٫۸ %	۳٫۵ %
Duration of DAPT therapy	21 & 90 days	30 days	90 days	

Results of the PRINCE & THALES trial:
In patients with acute ischemic stroke and high-risk TIA, ***ticagrelor + aspirin*** reduced the risk of the composite of stroke or death compared with clopidogrel and aspirin.

BMJ 2019;365:l2211
Stroke. 2020;51(11):3472-3474.

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Efficacy and safety of ticagrelor vs aspirin in acute stroke or TIA of *atherosclerotic origin* subgroup analysis of

SOCRATES

a randomized, double-blind, controlled trial

	Ticagrelor (n=6589)*		Aspirin (n=6610)†		Hazard ratio (95% CI)‡	p value	p value for interaction
	Number of patients	Event proportion (KM estimate)	Number of patients	Event proportion (KM estimate)			
Primary endpoint							
Stroke, myocardial infarction, or death	..	..	..	..	..	..	0·017
With ipsilateral extracranial or intracranial stenosis	103 (6·7%)	6·7%	147 (9·6%)	9·4%	0·68 (0·53–0·88)	0·003	..
Without ipsilateral extracranial or intracranial stenosis	339 (6·7%)	6·8%	350 (6·9%)	6·9%	0·97 (0·84–1·13)	0·72	..
Secondary endpoints							
Ischaemic stroke	..	..	..	..	..	..	0·12
With ipsilateral extracranial or intracranial stenosis	98 (6·4%)	6·4%	131 (8·5%)	8·3%	0·73 (0·56–0·95)	0·02	..
Without ipsilateral extracranial or intracranial stenosis	287 (5·7%)	5·8%	310 (6·1%)	6·1%	0·93 (0·79–1·09)	0·37	..
All strokes	..	..	..	..	..	..	0·12
With ipsilateral extracranial or intracranial stenosis	98 (6·4%)	6·4%	132 (8·6%)	8·4%	0·72 (0·56–0·94)	0·02	..
Without ipsilateral extracranial or intracranial stenosis	292 (5·8%)	5·9%	318 (6·3%)	6·3%	0·92 (0·79–1·08)	0·31	..

Lancet Neurol. 2017;16(4):301-310.

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IR-0922-BRL-7030-SP

Conclusion

- Ticagrelor inhibits platelet function more than clopidogrel especially in patients with *CYP2C19* loss of function allele.
- prevalence of the *CYP2C19* loss of function allele is high especially in Asian populations.
- If a patient had a thromboembolic event while on Clopidogrel, may be he has a loss of function mutation, consider Ticagrelor as an alternative.
- Ticagrelor seems to have better efficacy in patients with atherosclerotic origin.
- Considering new antiplatelet agents (such as Ticagrelor) could be alternatives specially for those carriers with CYP2C19 loss of function alleles.

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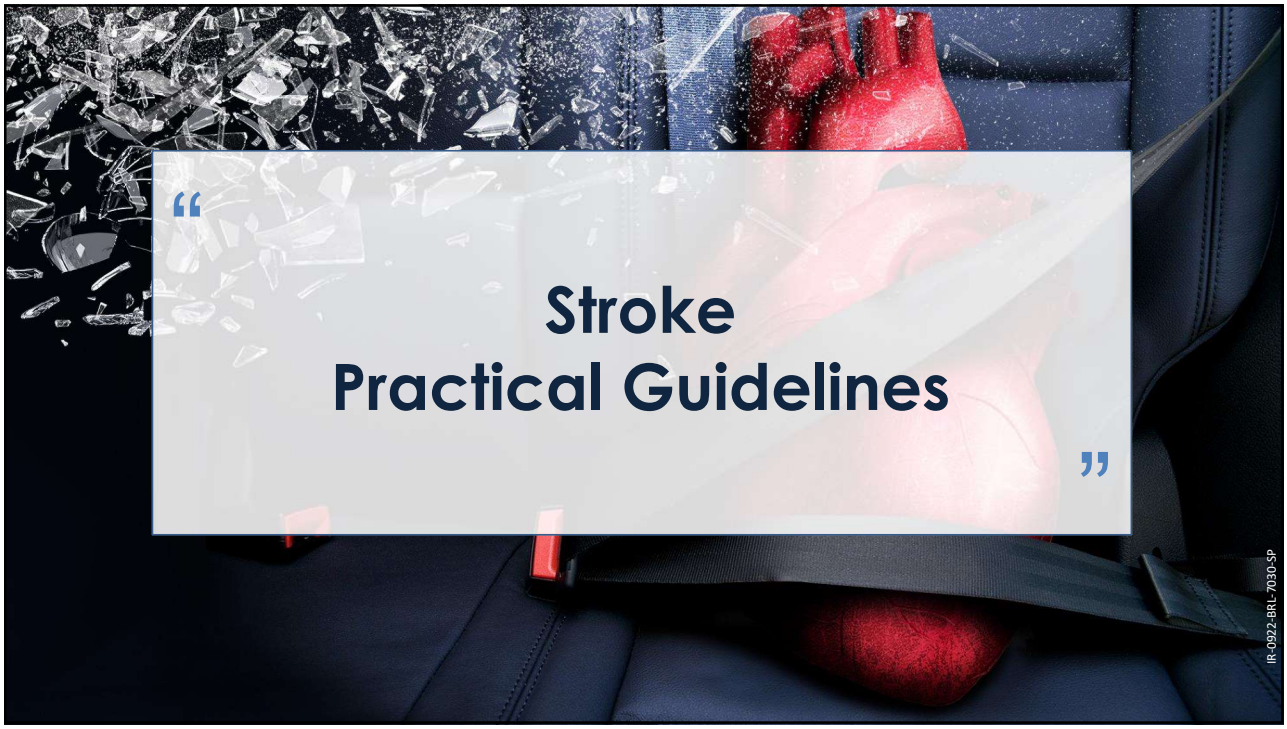

2019 AHA/ASA Guidelines

American Heart Association | American Stroke Association

Secondary Stroke Prevention	COR	LOE
For patients with non-cardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.	I	A
For early secondary prevention in patients with non-cardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics.	I	C-EO

IR-0922-BRL-7030-SP

Stroke. 2019;50(12):e344-e418.

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2021 AHA/ASA Guidelines

American Heart Association | American Stroke Association

Recommendations for Intracranial Large Artery Atherosclerosis	COR	LOE
In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk.	IIb	B-NR

Recommendations for Antithrombotic Medications	COR	LOE
For patients with recent (< 24 hours) minor to moderate stroke (NIHSS score ≤5), high-risk TIA (ABCD2 score ≥ 6), or symptomatic intracranial or extracranial ³30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH.	IIb	B-SR

IR-0922-BRL-7030-SP

Stroke. 2021;52:e364–e467

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