EFFETTO DELLA DUPLICE TERAPIA ANTIAGGREGANTE CON TICAGRELOR O CLOPIDOGREL SULLA REATTIVITÀ PIASTRINICA IN PAZIENTI CON MINOR STROKE O ATTACCO ISCHEMICO TRANSITORIO

RISULTATI DEL PRINCE TRIAL

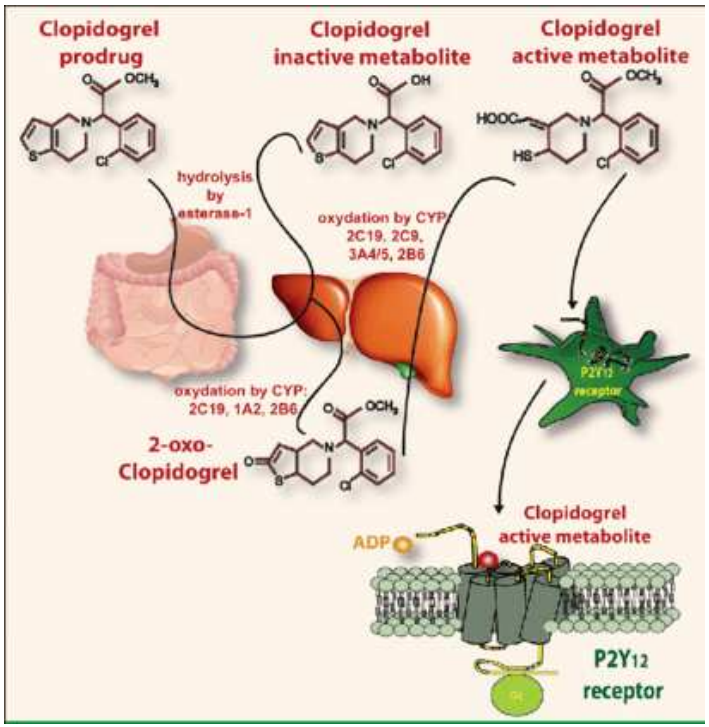
BACKGROUND

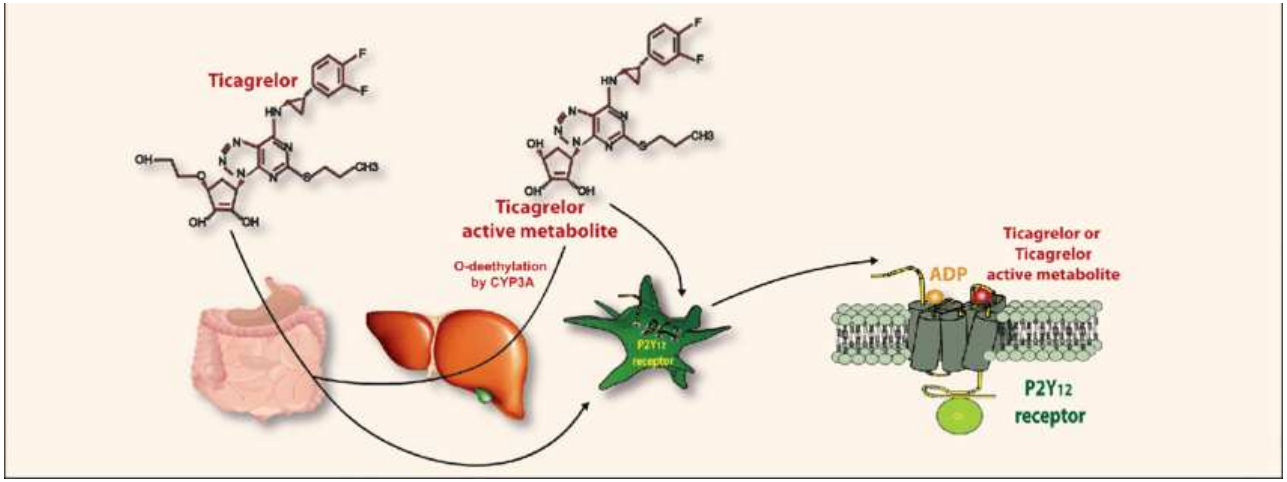
- Studies have shown that patients who are carriers of the cytochrome P450 (CYP) 2C19*2 and *3 loss-of-function alleles do not benefit from dual antiplatelet therapy (aspirin combined with clopidogrel), compared with aspirin alone

- Ticagrelor combined with aspirin has been shown to be more efficacious than clopidogrel combined with aspirin for acute coronary syndromes, regardless of CYP2C19 genotypes

- However, the safety and efficacy of ticagrelor/aspirin versus clopidogrel/aspirin has not been evaluated in patients with minor stroke or transient ischaemic attack

DRUG METABOLISM





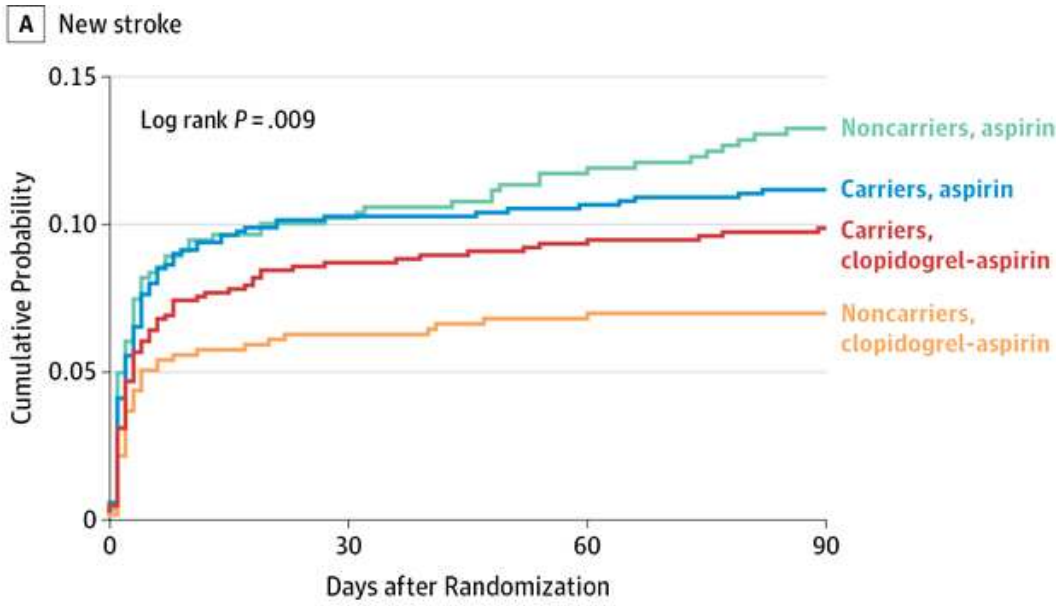
CHANCE GENETIC SUBSTUDY

2933 pts with acute minor ischemic stroke or TIA were randomized to

- clopidogrel + aspirin
- aspirin alone

CYP2C19 major alleles (**2*, **3*, **17*) were genotyped

The use of clopidogrel + aspirin reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the *CYP2C19* loss-of-function alleles



No. at risk				
Carriers, clopidogrel-aspirin	853	778	772	657
Carriers, aspirin	871	781	778	645
Noncarriers, clopidogrel-aspirin	608	567	563	471
Noncarriers, aspirin	597	535	526	445

JAMA. 2016;316(1):70-78.

High on treatment platelet reactivity to aspirin and clopidogrel in ischemic stroke: A systematic review and meta-analysis

Aidonio Fiolaki [a,b], Aristeidis H Katsanos [a,*], Athanassios P Kyritsis [a,c], Styliani Papadaki [b], Maria Kosmidou [d], Iraklis C Moschonas [b], Alexandros D. Tselepis [b], Sotirios Giannopoulos [a,c]

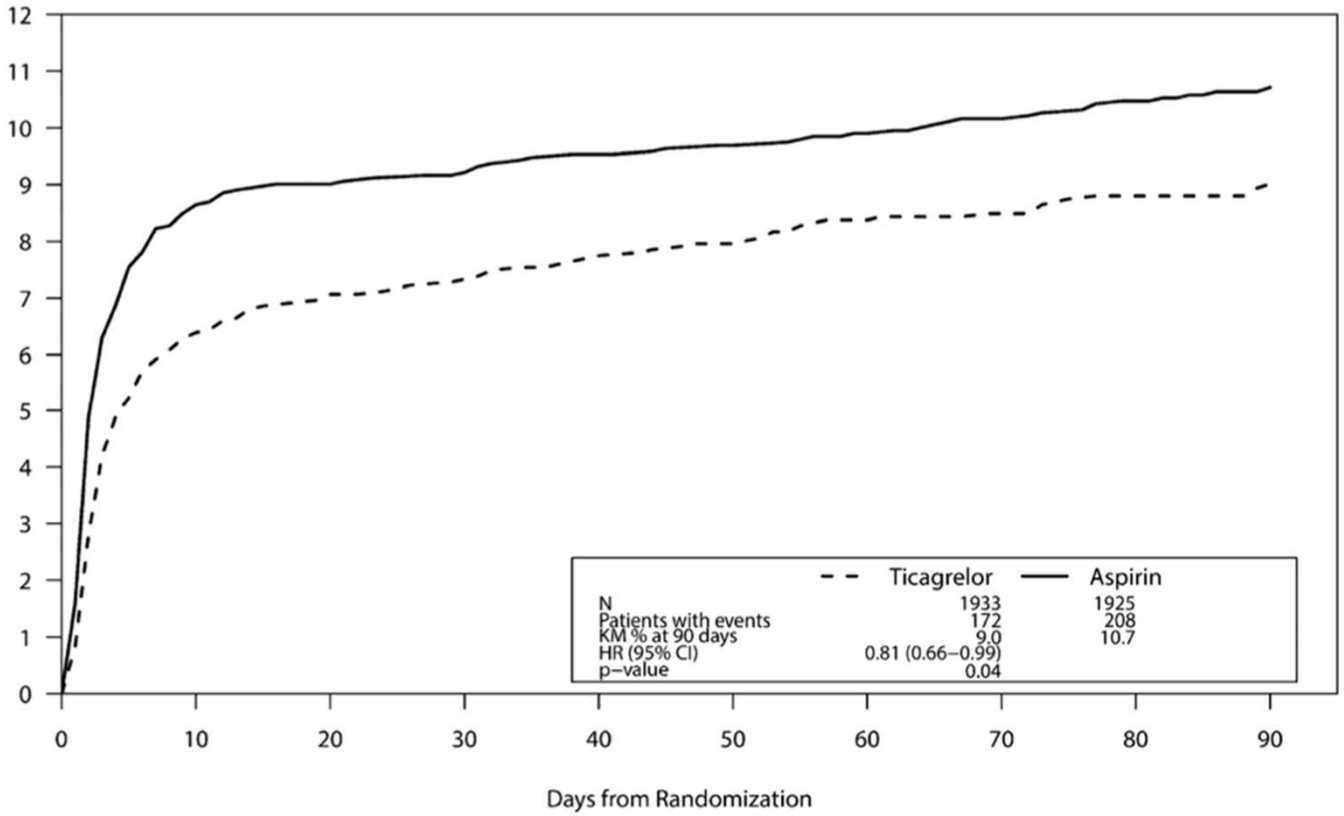
Overall, subgroup and sensitivity analyses on the risk of cerebrovascular ischemia in non-responders (patients with high on treatment platelet reactivity) compared to responders reported in included studies.

Analysis	Number of studies	RR (95%CI)	I^2, p for Cochran Q	95% estimated PI	p-Value
Overall analysis	18	1.81 (1.30, 2.52)	60.2%, p = 0.001	0.58, 5.66	p < 0.001
Sensitivity analysis[a]	16	1.61 (1.24, 2.09)	34.7%, p = 0.084	0.80, 3.22	p < 0.001
Subgroup analysis[b]					p = 0.610[c]
ASA	15	1.78 (1.21, 2.62)	66.2%, p < 0.001	0.48, 6.56	p = 0.007
Clopidogrel	3	2.12 (1.24, 3.62)	0%, p = 0.492	0.07, 67.77	p = 0.006

J Neurol Sci 2017;376:112-6.

SOCRATES TRIAL

Probability of survival free of the primary composite end point (stroke, myocardial infarction, or death)



Stroke. 2017;48:167-173.

Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial

Yilong Wang,[1,2,3,4] Weiqi Chen,[1,2,3,4] Yi Lin,[5] Xia Meng,[1,2,3,4] Guohua Chen,[6] Zhimin Wang,[7] Jialing Wu,[8] Dali Wang,[9] Jianhua Li,[10] Yibin Cao,[11] Yuming Xu,[12] Guohua Zhang,[13] Xiaobo Li,[14] Yuesong Pan,[1,2,3,4] Hao Li,[1,2,3,4] Xingquan Zhao,[1,2,3,4] Liping Liu,[1,2,3,4] Jinxi Lin,[1,2,3,4] Kehui Dong,[1,2,3,4] Jing Jing,[1,2,3,4] S Claiborne Johnston,[15] David Wang,[16] Yongjun Wang[1,2,3,4]

BMJ 2019;365:l2211

METHODS

- DESIGN: Open label, blinded endpoint, randomised controlled phase II trial.
- SETTING: Prospective studies conducted at 26 centres in China, August 2015 to March 2017
- PARTICIPANTS: 675 patients with acute minor stroke or transient ischaemic attack.
- INTERVENTION
  - Ticagrelor (180 mg loading dose, 90 mg twice daily thereafter)
  - Clopidogrel (300 mg loading dose, 75 mg daily thereafter)

} on a background of aspirin (100 mg daily for the first 21 days) within 24 hours of symptom onset.

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ENDPOINT

- **Primary outcome:** proportion of patients with high platelet reactivity at 90 days (P2Y12 reaction units>208)

- **Secondary outcomes**
  - high platelet reactivity at 90 days (7 days either way) in patients carrying genetic variants that would affect clopidogrel metabolism
  - any stroke (ischaemic or haemorrhagic) recurrence at 90 days (7 days either way), six months, and one year.

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Characteristic	Trial group	
	Ticagrelor/aspirin (n=336)	Clopidogrel/aspirin (n=339)
Age (years)		
Mean (standard deviation)	61.1 (8.5)	60.5 (9.0)
Median (interquartile range)	62.0 (55.0-67.0)	61.0 (54.0-67.0)
Female sex (No (%))	91 (27.1)	90 (26.5)
Systolic blood pressure (mm Hg)		
Mean (standard deviation)	152.3 (22.5)	154.9 (21.2)
Median (interquartile range)	150.0 (137.5-168.0)	154.0 (140.0-170.0)
Diastolic blood pressure (mm Hg)		
Mean (standard deviation)	87.7 (13.0)	89.4 (12.8)
Median (interquartile range)	87.5 (80.0-96.0)	88.0 (80.0-97.0)
Body mass index*		
Mean (standard deviation)	25.0 (3.8)	25.0 (3.8)
Median (interquartile range)	24.6 (22.6-27.0)	24.8 (22.7-27.3)
Pulse rate (beat/min; mean (SD))	75.1 (10.1)	76.3 (11.5)
Medical history (No (%))		
Hypertension	203 (60.4)	208 (61.4)
Dyslipidaemia	20 (6.0)	21 (6.2)
Diabetes mellitus	79 (23.5)	85 (25.1)
Ischaemic stroke	59 (17.6)	62 (18.3)
Transient ischaemic attack	8 (2.4)	10 (2.9)
Coronary artery disease	26 (7.7)	25 (7.4)
Known atrial fibrillation	0 (0.0)	4 (1.2)
Flutter valvular heart disease	1 (0.3)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)
Smoking status (No (%))		
Non-smoker	150 (44.6)	155 (45.7)
Current smoker	160 (47.6)	159 (46.9)
Ex-smoker	26 (7.7)	25 (7.4)

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Characteristic	Trial group	
	Ticagrelor/aspirin (n=336)	Clopidogrel/aspirin (n=339)
Drug use before randomisation (No (%))		
Proton pump inhibitor	2 (0.6)	3 (0.9)
Statin	36 (10.7)	30 (8.8)
Aspirin	77 (22.9)	69 (20.4)
Clopidogrel	5 (1.5)	10 (2.9)
Ticagrelor	0 (0.0)	0 (0.0)
Time to randomisation after onset of symptoms (h; mean (range))	14.0 (8.3-20.6)	13.8 (8.0-20.8)
Time to randomisation after onset of symptoms (No (%))		
<12 h	139 (41.4)	144 (42.5)
≥12 h	197 (58.6)	195 (57.5)
Qualifying event (No (%))		
Minor stroke	275 (81.8)	289 (85.3)
Transient ischaemic attack	61 (18.2)	50 (14.7)
Baseline $ABCD^2$ score among patients with transient ischaemic attack as the qualifying event (median (interquartile range))†	5.0 (4.0-5.0)	4.5 (4.0-5.0)
SSS-TOAST stroke subtype (No (%))‡		
Large artery atherosclerosis	151 (54.9)	153 (52.9)
Cardioaortic embolism	8 (2.9)	5 (1.7)
Small artery occlusion	104 (37.8)	109 (37.7)
Other causes	7 (2.5)	9 (3.1)
Undetermined causes	5 (1.8)	13 (4.5)
Unknown	2 (0.7)	7 (2.4)
Unclassified	3 (1.1)	6 (2.1)

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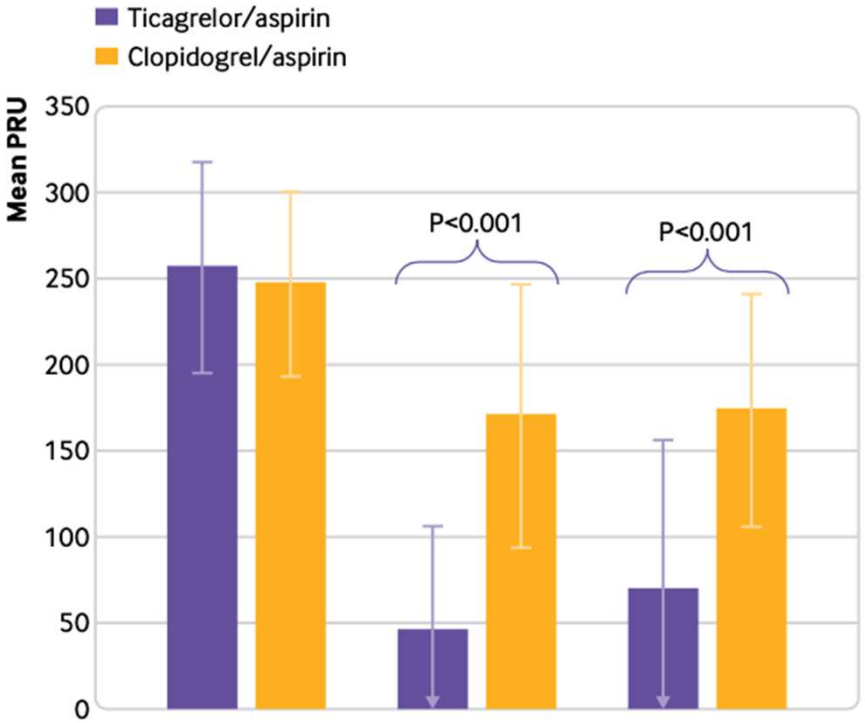
PLATELET REACTIVITY



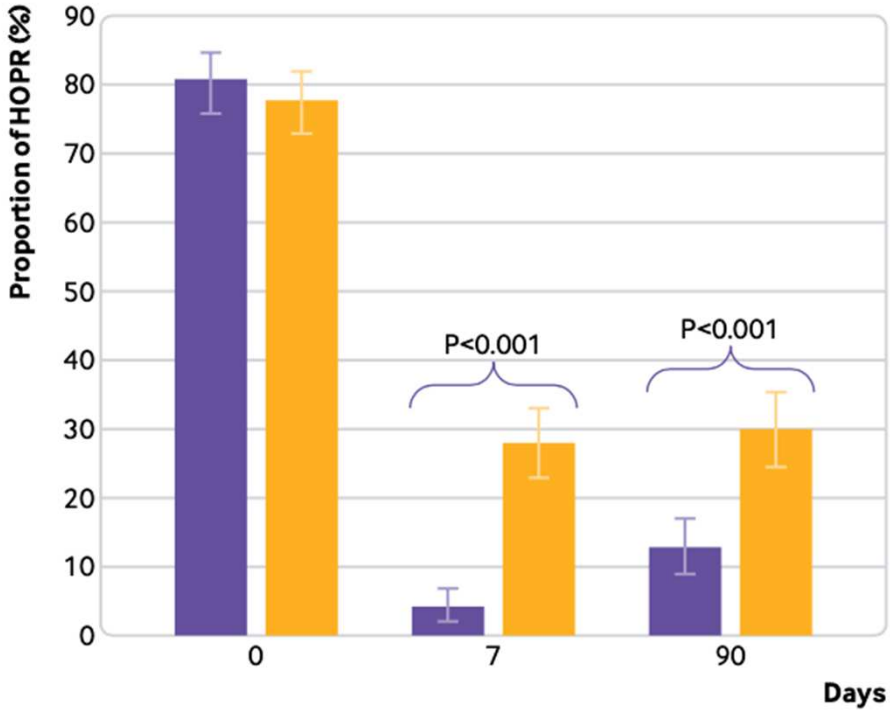


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Table 2 | Effect of ticagrelor/aspirin versus clopidogrel/aspirin on efficacy and safety outcomes in PRINCE trial

Outcomes	Trial participants (No with event/total No (%))		Hazard ratio or risk ratio (95% CI)*	P
	Ticagrelor/aspirin	Clopidogrel/aspirin		
Primary efficacy outcomes†				
Baseline	268/333 (80.5)	260/336 (77.4)	1.04 (0.96 to 1.13)	0.33
7+2 days	12/306 (3.9)	89/321 (27.7)	0.14 (0.07 to 0.23)	<0.001
90±7 days	35/280 (12.5)	86/290 (29.7)	0.40 (0.28 to 0.56)	<0.001
Secondary efficacy outcomes				
Stroke	21/336 (6.3)	30/339 (8.8)	0.70 (0.40 to 1.22)	0.20
Composite events‡	22/336 (6.5)	32/339 (9.4)	0.68 (0.40 to 1.18)	0.17
Ischaemic stroke	18/336 (5.4)	28/339 (8.3)	0.64 (0.35 to 1.16)	0.14
Haemorrhagic stroke	3/336 (0.9)	2/339 (0.6)	1.52 (0.25 to 9.08)	0.65
Myocardial infarction	0/336 (0.0)	1/339 (0.3)	—	—
Death from cardiovascular causes	1/336 (0.3)	2/339 (0.6)	0.50 (0.05 to 5.55)	0.58
Death from any cause	3/336 (0.9)	2/339 (0.6)	1.50 (0.25 to 9.00)	0.65
Transient ischaemic attack	1/336 (0.3)	2/339 (0.6)	0.50 (0.05 to 5.53)	0.57
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 haemorrhage	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
Dyspnoea	14/336 (4.2)	0/339 (0.0)	—	<0.001
Epistaxis	6/336 (1.8)	0/339 (0.0)	—	0.04

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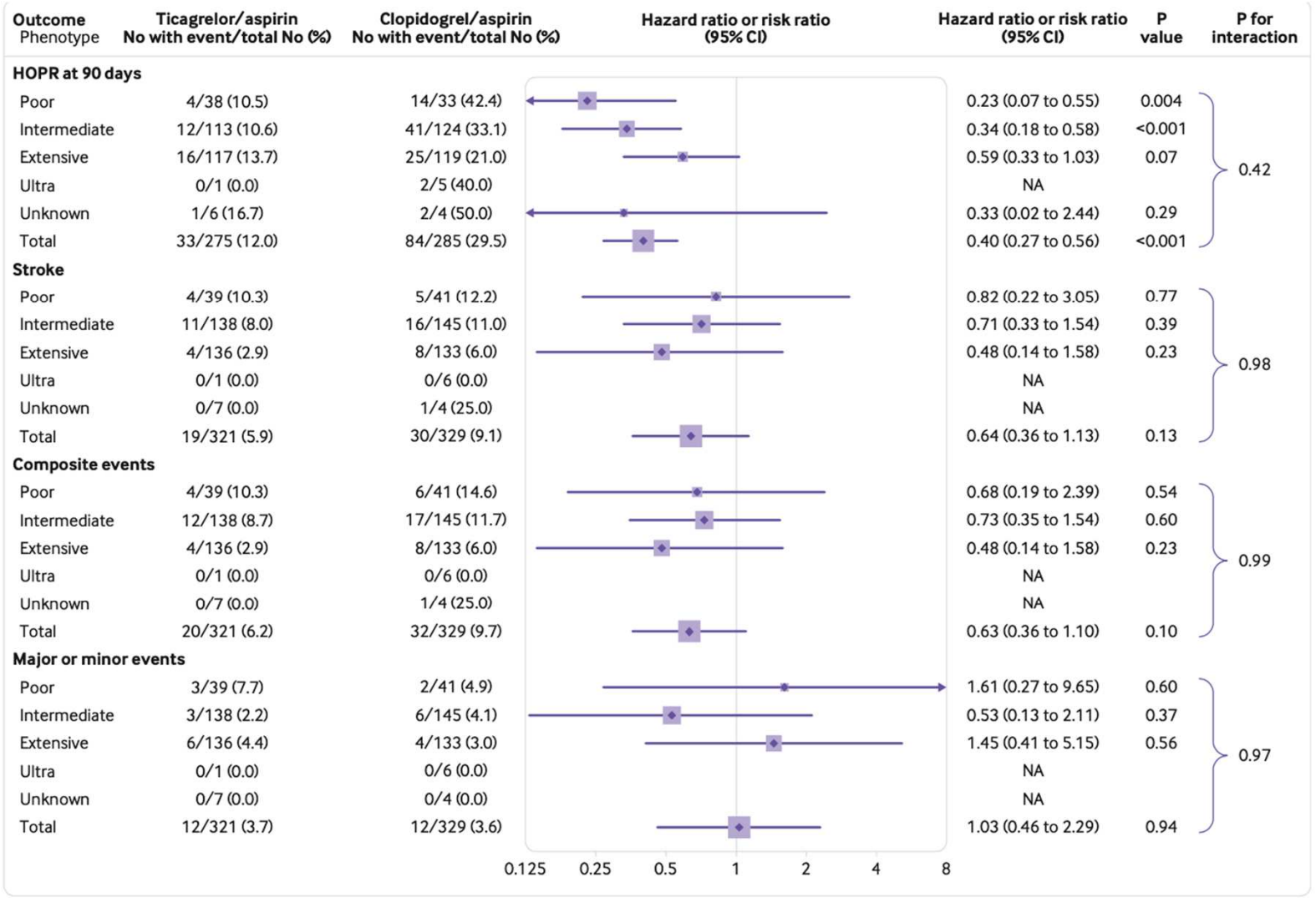
Metaboliser phenotype:

- **Poor**: two *2 or *3 alleles (*2/*2, *2/*3, *3/*3)
- **Intermediate**: one *2 or *3 allele (*1/*2 or *1/*3)
- **Extensive**: without a *2, *3, or *17 allele (*1/*1)
- **Ultra**: single *17 allele (*1/*17) and *17 homozygotes



Outcome Phenotype	Ticagrelor/aspirin No with event/total No (%)	Clopidogrel/aspirin No with event/total No (%)	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	0.42
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	
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	
Stroke					
Poor	4/39 (10.3)	5/41 (12.2)	0.82 (0.22 to 3.05)	0.77	0.98
Intermediate	11/138 (8.0)	16/145 (11.0)	0.71 (0.33 to 1.54)	0.39	
Extensive	4/136 (2.9)	8/133 (6.0)	0.48 (0.14 to 1.58)	0.23	
Ultra	0/1 (0.0)	0/6 (0.0)	NA		
Unknown	0/7 (0.0)	1/4 (25.0)	NA		
Total	19/321 (5.9)	30/329 (9.1)	0.64 (0.36 to 1.13)	0.13	
Composite events					
Poor	4/39 (10.3)	6/41 (14.6)	0.68 (0.19 to 2.39)	0.54	0.99
Intermediate	12/138 (8.7)	17/145 (11.7)	0.73 (0.35 to 1.54)	0.60	
Extensive	4/136 (2.9)	8/133 (6.0)	0.48 (0.14 to 1.58)	0.23	
Ultra	0/1 (0.0)	0/6 (0.0)	NA		
Unknown	0/7 (0.0)	1/4 (25.0)	NA		
Total	20/321 (6.2)	32/329 (9.7)	0.63 (0.36 to 1.10)	0.10	
Major or minor events					
Poor	3/39 (7.7)	2/41 (4.9)	1.61 (0.27 to 9.65)	0.60	0.97
Intermediate	3/138 (2.2)	6/145 (4.1)	0.53 (0.13 to 2.11)	0.37	
Extensive	6/136 (4.4)	4/133 (3.0)	1.45 (0.41 to 5.15)	0.56	
Ultra	0/1 (0.0)	0/6 (0.0)	NA		
Unknown	0/7 (0.0)	0/4 (0.0)	NA		
Total	12/321 (3.7)	12/329 (3.6)	1.03 (0.46 to 2.29)	0.94	

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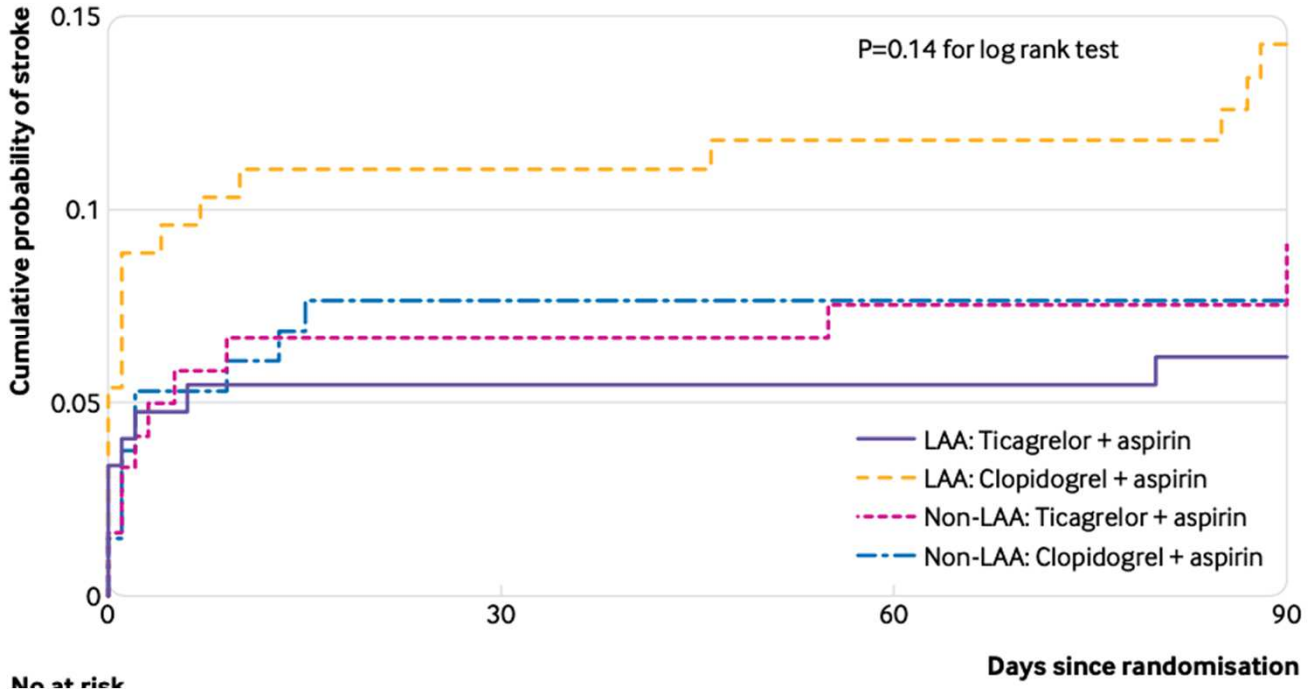
Table 3 | Stroke recurrence at 90 days, by cause

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	—



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LIMITATIONS

- About 15% of patients were lost to follow-up for the evaluation of high platelet reactivity at 90 days.
- Potential selection bias: patients enrolled from sites that were mostly urban hospitals and that had more experts and medical resources.
- The cause of stroke and the genetic differences in the CYP2C19 gene differ between Chinese patients with stroke and European patients with stroke.
- Open label design could have led to a placebo effect

CONCLUSIONS

- This study suggests the efficacy of ticagrelor/aspirin in reducing high platelet reactivity compared with clopidogrel/aspirin, especially in patients with CYP2C19 loss-of-function alleles at 90 days after symptoms onset
- The rate of major or minor haemorrhagic events did not differ between the two groups
- As a phase II trial, these results would need to be replicated and investigated further in larger studies and in different populations in the future