Duplice terapia antiaggregante entro le 72 ore da un ictus ischemico

Risultati del trial INSPIRES

Background

Patients with acute mild ischemic stroke or transient ischemic attack (TIA) have a risk of recurrent stroke of approximately 5 to 10% within 90 days after the onset of the initial event.

Guidelines recommend dual antiplatelet therapy with clopidogrel combined with aspirin in patients who have a minor ischemic stroke (defined as a NIHSS score of ≤3) and who can be treated within 24 hours.

The 24-hour time window and low NIHSS score threshold have limited the application of dual antiplatelet therapy in patients with ischemic stroke.

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Background

A time-course analysis of the POINT trial indicated that combined clopidogrel–aspirin therapy may be beneficial in preventing recurrent stroke when it is initiated as long as 3 days after stroke onset.

Meta-analyses have suggested the same for noncardioembolic ischemic stroke or TIA.

In an exploratory analysis of the THALES trial, patients with mild ischemic stroke (NIHSS score of 4 or 5) treated with ticagrelor and aspirin within 24 hours had a lower risk of subsequent stroke than those treated with aspirin alone, without a higher risk of severe bleeding.

The effectiveness of dual antiplatelet therapy potentially varies depending on the pathogenesis of ischemic stroke; in particular, patients with large-artery atherosclerotic stenosis or multiple acute infarctions may benefit from dual treatment.

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Dual Antiplatelet Treatment up to 72 Hours after Ischemic Stroke

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Aim of the study

- In the Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial, the authors tested the hypothesis that DAPT with clopidogrel and aspirin initiated within 72 hours after onset would be superior to aspirin alone with regard to the risk of new ischemic or hemorrhagic stroke among patients with mild ischemic stroke or high-risk TIA presumably caused by atherosclerosis (stenosis of extracranial or intracranial artery ipsilateral to the ischemic field) or multiple infarctions with nonstenotic atherosclerotic plaque ipsilateral to the ischemic field

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Methods

- 222 hospitals in China
- double-blind, randomized, placebo-controlled, two-by-two factorial trial
- Patients with **mild ischemic stroke (NIHSS ≤3) or high-risk TIA (ABCD score ≥4) of presumed atherosclerotic cause who had not undergone thrombolysis or thrombectomy**.
- 1:1 randomization within 72 hours after symptom onset to
  - clopidogrel (300 mg on day 1 and 75 mg daily on days 2 to 90) plus aspirin (100 to 300 mg on day 1 and 100 mg daily on days 2 to 21)
  - matching clopidogrel placebo plus aspirin (100 to 300 mg on day 1 and 100 mg daily on days 2 to 90).
- No interaction between this component of the factorial trial design and a second part that compared immediate with delayed statin treatment (not reported).
- The **primary efficacy outcome** was new stroke at 90 days
- The **primary safety outcome** was moderate-to-severe bleeding at 90 days.

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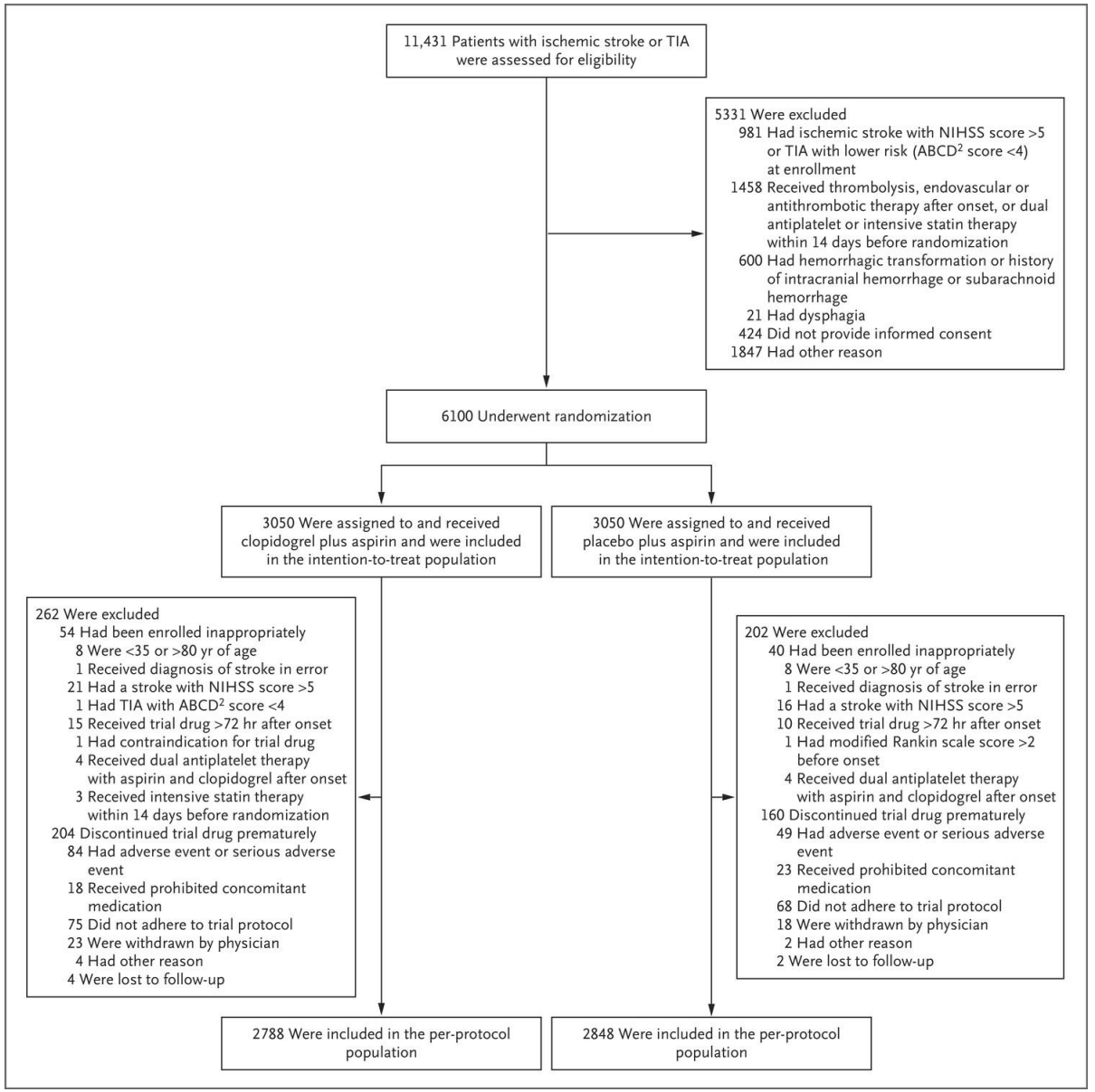
Enrollment and Randomization



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Characteristics of the Patients at Baseline

Characteristic	Clopidogrel–Aspirin (N = 3050)	Aspirin (N = 3050)
Median age (interquartile range) — yr	65 (57–71)	65 (57–71)
Female sex — no. (%)	1063 (34.9)	1122 (36.8)
Medical history — no. (%)		
Hypertension	2047 (67.1)	2036 (66.8)
Diabetes mellitus	830 (27.2)	828 (27.1)
Dyslipidemia	103 (3.4)	123 (4.0)
Previous ischemic stroke	901 (29.5)	908 (29.8)
Current smoking — no. (%)	892 (29.2)	891 (29.2)
Use of agents before qualifying event — no. (%)		
Aspirin	390 (12.8)	403 (13.2)
Clopidogrel	21 (0.7)	22 (0.7)
Lipid-lowering agent	296 (9.7)	291 (9.5)
Qualifying event — no. (%)		
TIA	399 (13.1)	402 (13.2)
Acute single infarction	588 (19.3)	586 (19.2)
Acute multiple infarctions	2063 (67.6)	2062 (67.6)
≥50% symptomatic stenosis — no. (%)†		
Yes	2448/2985 (82.0)	2467/2983 (82.7)
No	537/2985 (18.0)	516/2983 (17.3)
Time to randomization after onset of symptoms — no. (%)		
≤24 hr	401 (13.1)	382 (12.5)
>24 to ≤48 hr	1255 (41.1)	1297 (42.5)
>48 to 72 hr	1394 (45.7)	1371 (45.0)
NIHSS score in qualifying ischemic stroke — no./total no. (%)‡		
≤3	2007/2651 (75.7)	2026/2648 (76.5)
4 or 5	644/2651 (24.3)	622/2648 (23.5)
ABCD² score in qualifying TIA — no./total no. (%)§		
4 or 5	326/399 (81.7)	315/402 (78.4)
>5	73/399 (18.3)	87/402 (21.6)

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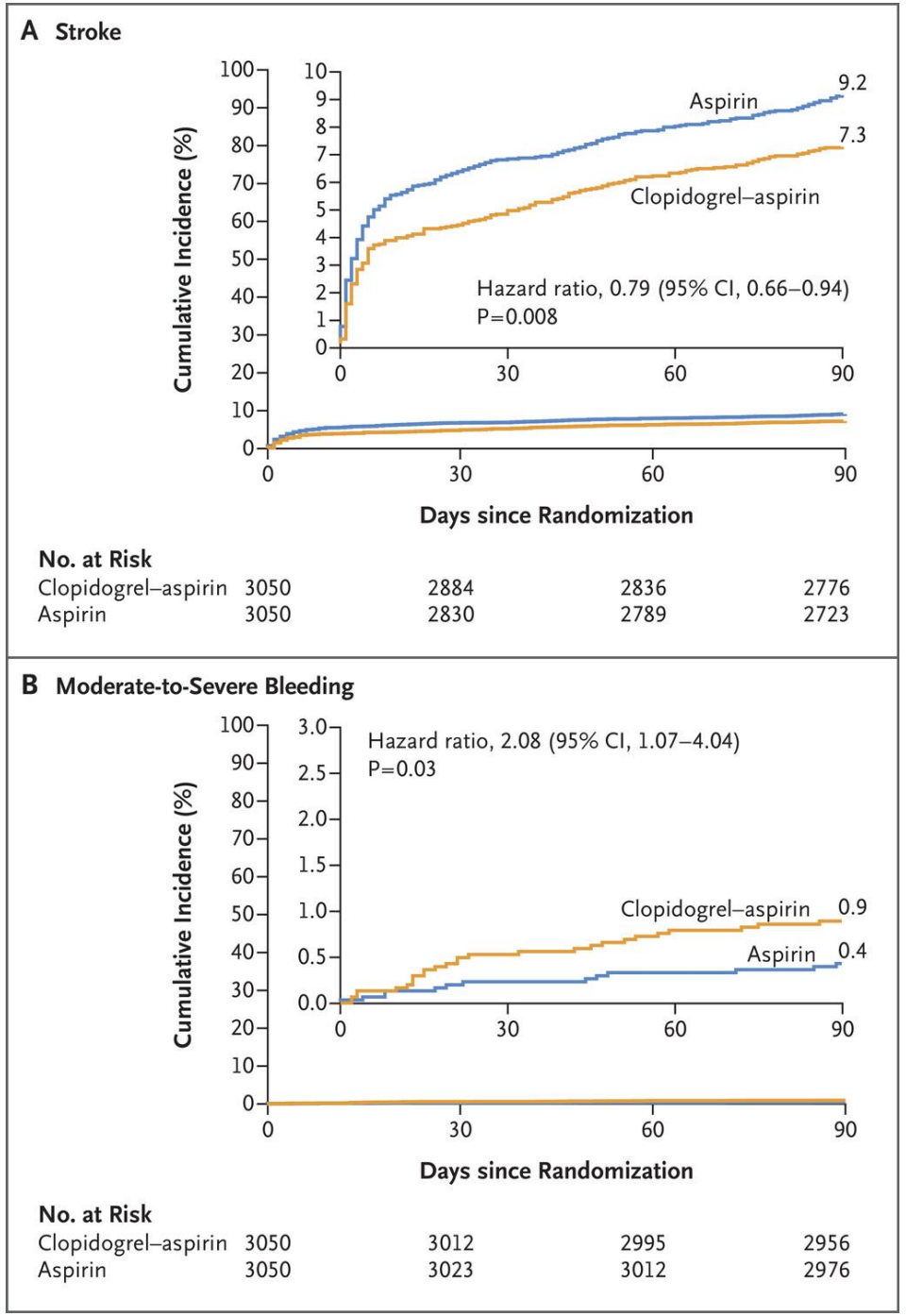
Cumulative Incidence of Stroke (Primary Efficacy Outcome) and Moderate-to-Severe Bleeding (Primary Safety Outcome



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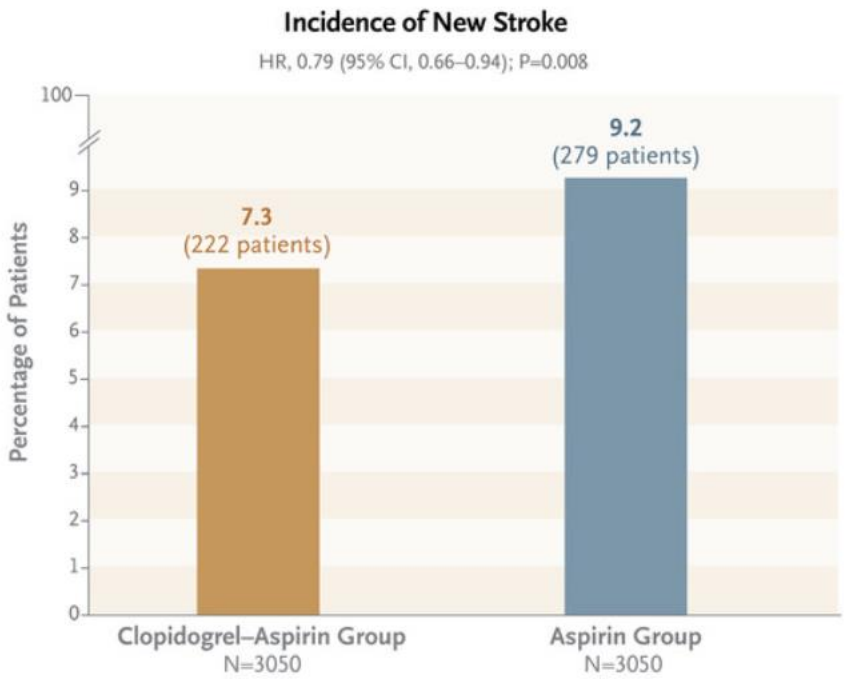
Efficacy outcomes



Outcome	Clopidogrel–Aspirin (N=3050)		Aspirin (N=3050)		Hazard Ratio or Relative Risk (95% CI)*	P Value
	Patients with Event	Incidence†	Patients with Event	Incidence†		
		%		%		
Primary outcome						
Stroke, including ischemic and hemorrhagic stroke — no.	222	7.3	279	9.2	0.79 (0.66–0.94)	0.008
Secondary outcomes						
Composite cardiovascular event (stroke, myocardial infarction, or death from cardiovascular causes) — no.	229	7.5	282	9.3	0.80 (0.67–0.96)	
Ischemic stroke — no.	208	6.8	274	9.0	0.75 (0.63–0.90)	
Recurrent stroke	159	5.3	205	6.8	0.77 (0.62–0.94)	
TIA with infarction	5	0.2	11	0.4	0.45 (0.16–1.29)	
Progressive stroke‡	44	1.5	58	1.9	0.75 (0.51–1.11)	
Hemorrhagic stroke — no.	15	0.5	5	0.2	3.01 (1.09–8.28)	
TIA — no.	21	0.7	39	1.3	0.54 (0.32–0.91)	
Myocardial infarction — no.	5	0.2	2	0.1	2.50 (0.49–12.90)	
Death from cardiovascular causes — no.	21	0.7	15	0.5	1.40 (0.72–2.72)	
Poor functional outcome — no./total no.§	301/3047	9.9	346/3046	11.4	0.87 (0.76–0.99)	
Six-level assessment of new stroke — no./total no.¶					0.76 (0.64–0.91)	
5: Fatal stroke	20/3049	0.7	13/3049	0.4		
4: Severe stroke	28/3049	0.9	27/3049	0.9		
3: Moderate stroke	69/3049	2.3	102/3049	3.3		
2: Mild stroke	104/3049	3.4	136/3049	4.5		
1: TIA	21/3049	0.7	35/3049	1.1		
0: No stroke or TIA	2807/3049	92.1	2736/3049	89.7		

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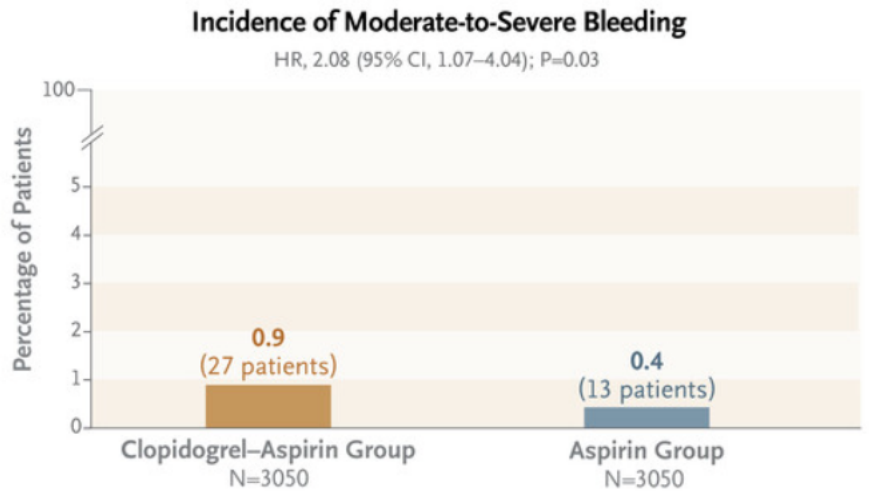
Safety outcomes



Outcome	Clopidogrel–Aspirin (N=3050)		Aspirin (N=3050)		Hazard Ratio or Relative Risk (95% CI)*	P Value
	Patients with Event	Incidence† %	Patients with Event	Incidence† %		
Primary safety outcome						
Moderate-to-severe bleeding — no.	27	0.9	13	0.4	2.08 (1.07–4.04)	0.03
Secondary safety outcomes						
Hepatotoxic effects — no.**	39	1.3	32	1.0	1.22 (0.86–1.74)	
Muscle toxic effects — no.††	2	0.07	1	0.03	2.00 (0.18–22.04)	
Death from any cause — no.	37	1.2	30	1.0	1.24 (0.76–2.00)	
Any bleeding — no.	94	3.1	63	2.1	1.50 (1.09–2.06)	
Intracranial hemorrhage	17	0.6	8	0.3	2.13 (0.92–4.93)	
Mild bleeding	70	2.3	51	1.7	1.38 (0.96–1.97)	

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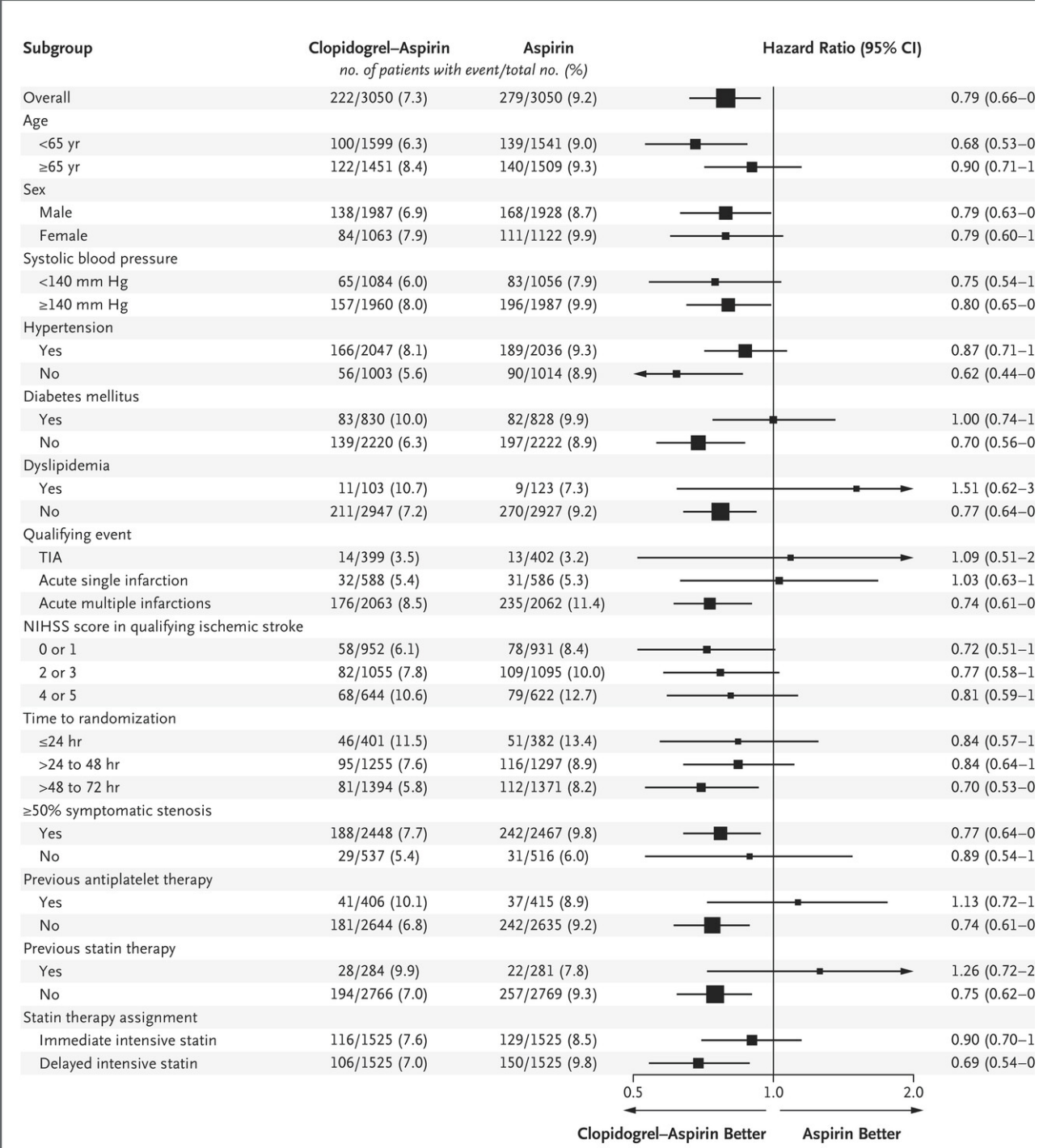

Hazard Ratios for Stroke in Prespecified Subgroups

The trial was not powered to allow definite conclusions on the basis of the results of the subgroup analyses

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Limitations

- Some important populations of patients with stroke or TIA were excluded, such as patients with stroke of presumed cardioembolic origin, those with moderate or severe stroke (NIHSS score, >5), and those who had undergone thrombolysis or thrombectomy.
- 98.5% of the enrolled patients were Han Chinese; the higher proportion of intracranial artery stenosis in this population than in other populations may have contributed to the benefit from dual antiplatelet therapy. The results cannot necessarily be generalized to White and Black patients with stroke.
- Clopidogrel is known to require hepatic cytochrome P450 enzymes to generate active metabolites for its antiplatelet effects; however, the genotype of drug metabolism was not included in the criteria for enrollment in this trial

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Conclusions

- In this trial conducted in China that involved patients with mild ischemic stroke or high-risk TIA from presumed intracranial or extracranial atherosclerosis, treatment with clopidogrel and aspirin initiated within 72 hours after symptom onset (continued for 21 days followed by only clopidogrel) led to a lower risk of new stroke but a higher risk of moderate-to-severe bleeding than treatment with aspirin alone over a period of 90 days.

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