ORIGINAL ARTICLE

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

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BACKGROUND

Combination antiplatelet therapy with clopidogrel and aspirin may reduce the rate of recurrent stroke during the first 3 months after a minor ischemic stroke or transient ischemic attack (TIA). A trial of combination antiplatelet therapy in a Chinese population has shown a reduction in the risk of recurrent stroke. We tested this combination in an international population.

METHODS

In a randomized trial, we assigned patients with minor ischemic stroke or high-risk TIA to receive either clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 50 to 325 mg per day) or the same range of doses of aspirin alone. The dose of aspirin in each group was selected by the site investigator. The primary efficacy outcome in a time-to-event analysis was the risk of a composite of major ischemic events, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days.

Population

- Patients who were at least 18 years of age were enrolled if they could undergo randomization within 12 hours after having an acute ischemic stroke with a score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) or a high-risk TIA with a score of 4 or more on the ABCD^2
- They were also required to undergo computed tomography or magnetic resonance imaging to rule out intracranial bleeding or other conditions that could explain the neurologic symptoms or detect any contraindications to a trial treatment.
- Patients with TIA and minor, nondisabling ischemic stroke are generally not considered to be candidates for thrombolysis or endovascular therapy.[10] Additional details regarding the inclusion and exclusion criteria are provided in the protocol.[13]

Table 1. Characteristics of the Patients at Baseline. *

Characteristic	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)
Median age (IQR) — yr	65.0 (55.0–74.0)	65.0 (56.0–74.0)
Female sex — no. (%)	1097 (45.1)	1098 (44.8)
Race — no./total no. (%)†		
White	1774/2360 (75.2)	1781/2378 (74.9)
Black	473/2360 (20.0)	493/2378 (20.7)
Asian	77/2360 (3.3)	67/2378 (2.8)
Other	36/2360 (1.5)	37/2378 (1.6)
Hispanic ethnic group — no./total no. (%)†	144/2320 (6.2)	146/2328 (6.3)
Region — no. (%)		
United States	2014 (82.8)	2029 (82.9)
Other countries	418 (17.2)	420 (17.1)
Medical history — no./total no. (%)		
Ischemic heart disease	257/2426 (10.6)	240/2443 (9.8)
Hypertension	1693/2423 (69.9)	1680/2437 (68.9)
Diabetes mellitus	678/2425 (28.0)	662/2447 (27.1)
Medication use at presentation — no. (%)		
Aspirin	1417 (58.3)	1397 (57.0)
Clopidogrel	48 (2.0)	42 (1.7)
Time from presentation to randomization		
Mean time (±SD) — hr	7.4±3.0	7.3±2.9
Interval — no./total no. (%)		
<6 hr	755/2431 (31.1)	789/2449 (32.2)
≥6 hr	1676/2431 (68.9)	1660/2449 (67.8)
Qualifying event — no. (%)		
TIA	1056 (43.4)	1052 (43.0)
Ischemic stroke	1376 (56.6)	1397 (57.0)
Median qualifying neurologic score (IQR)		
ABCD^2 for TIA‡	5.0 (4.0–6.0)	5.0 (4.0–5.0)
NIHSS for ischemic stroke§	2.0 (1.0–2.0)	2.0 (1.0–2.0)

* There were no significant differences in baseline characteristics between the two groups. IQR denotes interquartile range, and TIA transient ischemic attack.

† Race or ethnic group was determined by the investigator. Hispanic ethnic group was assessed only in patients in the United States; the denominator excludes 233 patients for whom Hispanic status was unknown.

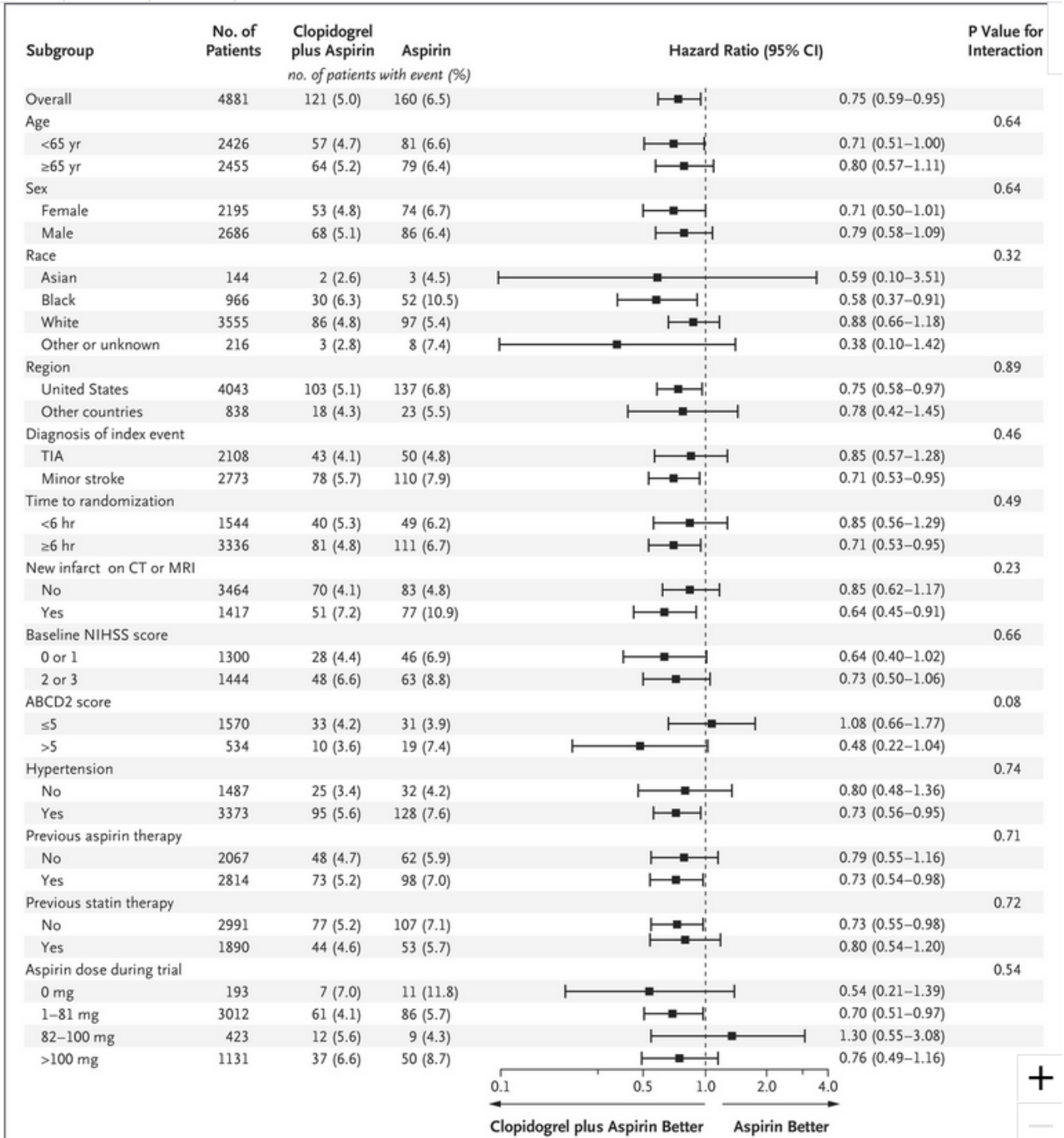
‡ Among patients with TIA, the qualifying score was 4 or more on the ABCD^2 scale, which ranges from 0 to 7, with higher scores indicating a greater risk of stroke. The scale is used to estimate the risk of recurrent stroke after a TIA on the basis of age, blood pressure, clinical features, duration of symptoms, and presence of diabetes. Scores were available for 2104 of the 2108 patients with TIA (1055 patients in the clopidogrel group and 1049 in the aspirin group).

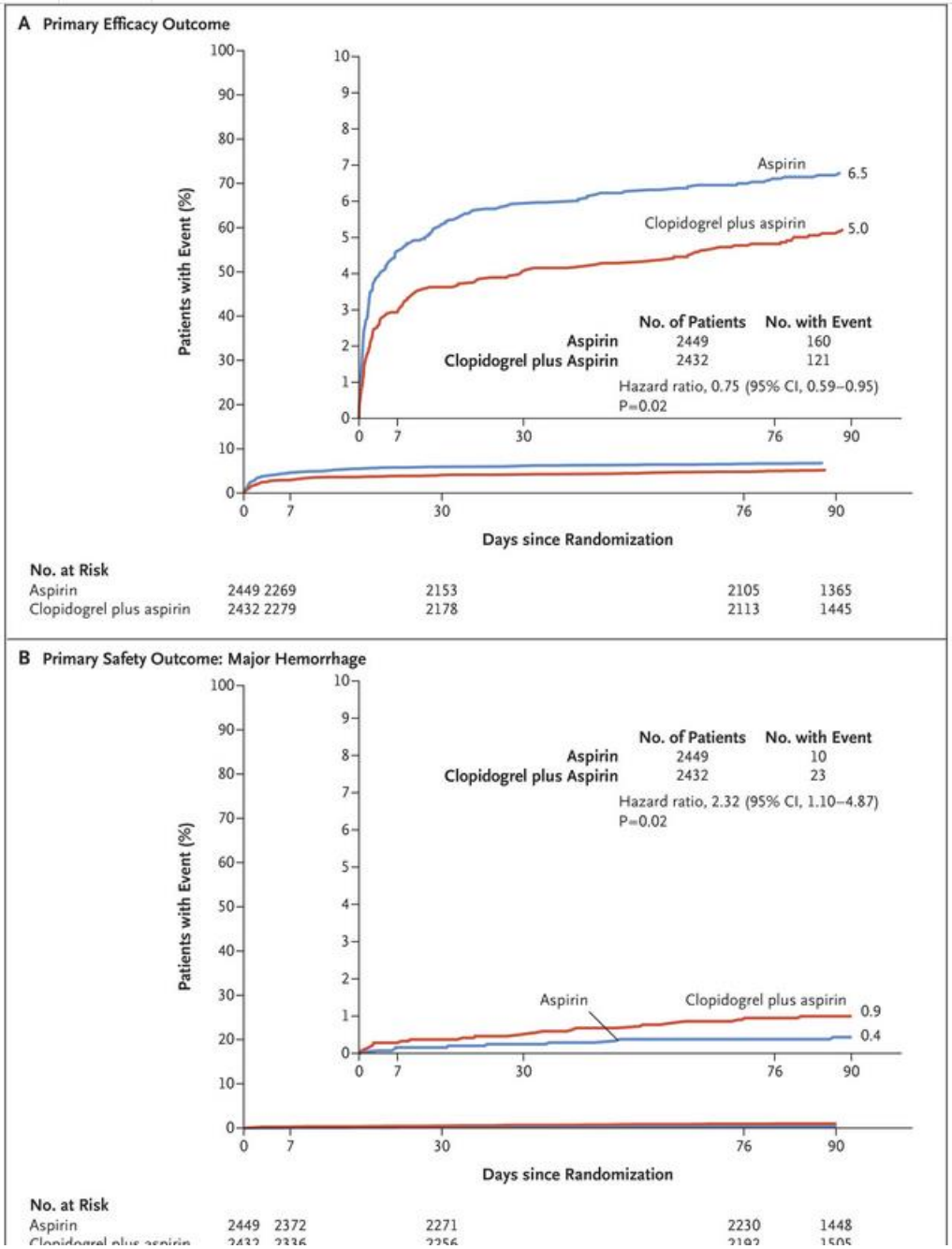
§ Among patients with ischemic stroke, the qualifying score was 3 or less on the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 to 42, with higher scores indicating a greater stroke severity. Scores were available for 2750 of the 2773 patients with ischemic stroke (1365 patients in the clopidogrel group and 1385 in the aspirin group).

Outcomes

- The primary outcome was the risk of a composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes (major ischemic events) on the basis of standard definitions.[13]
- The primary safety outcome was the risk of major hemorrhage, which was defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage.[15,16]

- Key secondary efficacy end points were each component of the primary efficacy outcome, a composite of the primary efficacy outcome and major hemorrhage, and the total number of ischemic and hemorrhagic strokes.
- Secondary safety outcomes included hemorrhagic stroke, symptomatic intracerebral hemorrhage, other symptomatic intracranial hemorrhage, major hemorrhage other than intracranial hemorrhage, minor hemorrhage that included asymptomatic intracranial hemorrhage, and death from any cause


Subgroup
No. of Patients
Clopidogrel plus Aspirin
Aspirin
no. of patients with event (%)
Hazard Ratio (95% CI)
P Value for Interaction
Overall 4881 121 (5.0) 160 (6.5) 0.75 (0.59–0.95)
Age 0.64
<65 yr 2426 57 (4.7) 81 (6.6) 0.71 (0.51–1.00)
≥65 yr 2455 64 (5.2) 79 (6.4) 0.80 (0.57–1.11)
Sex 0.64
Female 2195 53 (4.8) 74 (6.7) 0.71 (0.50–1.01)
Male 2686 68 (5.1) 86 (6.4) 0.79 (0.58–1.09)
Race 0.32
Asian 144 2 (2.6) 3 (4.5) 0.59 (0.10–3.51)
Black 966 30 (6.3) 52 (10.5) 0.58 (0.37–0.91)
White 3555 86 (4.8) 97 (5.4) 0.88 (0.66–1.18)
Other or unknown 216 3 (2.8) 8 (7.4) 0.38 (0.10–1.42)
Region 0.89
United States 4043 103 (5.1) 137 (6.8) 0.75 (0.58–0.97)
Other countries 838 18 (4.3) 23 (5.5) 0.78 (0.42–1.45)
Diagnosis of index event 0.46
TIA 2108 43 (4.1) 50 (4.8) 0.85 (0.57–1.28)
Minor stroke 2773 78 (5.7) 110 (7.9) 0.71 (0.53–0.95)
Time to randomization 0.49
<6 hr 1544 40 (5.3) 49 (6.2) 0.85 (0.56–1.29)
≥6 hr 3336 81 (4.8) 111 (6.7) 0.71 (0.53–0.95)
New infarct on CT or MRI 0.23
No 3464 70 (4.1) 83 (4.8) 0.85 (0.62–1.17)
Yes 1417 51 (7.2) 77 (10.9) 0.64 (0.45–0.91)
Baseline NIHSS score 0.66
0 or 1 1300 28 (4.4) 46 (6.9) 0.64 (0.40–1.02)
2 or 3 1444 48 (6.6) 63 (8.8) 0.73 (0.50–1.06)
ABCD2 score 0.08
≤5 1570 33 (4.2) 31 (3.9) 1.08 (0.66–1.77)
>5 534 10 (3.6) 19 (7.4) 0.48 (0.22–1.04)
Hypertension 0.74
No 1487 25 (3.4) 32 (4.2) 0.80 (0.48–1.36)
Yes 3373 95 (5.6) 128 (7.6) 0.73 (0.56–0.95)
Previous aspirin therapy 0.71
No 2067 48 (4.7) 62 (5.9) 0.79 (0.55–1.16)
Yes 2814 73 (5.2) 98 (7.0) 0.73 (0.54–0.98)
Previous statin therapy 0.72
No 2991 77 (5.2) 107 (7.1) 0.73 (0.55–0.98)
Yes 1890 44 (4.6) 53 (5.7) 0.80 (0.54–1.20)
Aspirin dose during trial 0.54
0 mg 193 7 (7.0) 11 (11.8) 0.54 (0.21–1.39)
1–81 mg 3012 61 (4.1) 86 (5.7) 0.70 (0.51–0.97)
82–100 mg 423 12 (5.6) 9 (4.3) 1.30 (0.55–3.08)
>100 mg 1131 37 (6.6) 50 (8.7) 0.76 (0.49–1.16)
0.1
0.5
1.0
2.0
4.0
Clopidogrel plus Aspirin Better
Aspirin Better


A Primary Efficacy Outcome
Patients with Event (%)
Aspirin
6.5
Clopidogrel plus aspirin
5.0
No. of Patients
No. with Event
Aspirin 2449 160
Clopidogrel plus Aspirin 2432 121
Hazard ratio, 0.75 (95% CI, 0.59–0.95)
P=0.02
Days since Randomization
No. at Risk
Aspirin 2449 2269 2153 2105 1365
Clopidogrel plus aspirin 2432 2279 2178 2113 1445
B Primary Safety Outcome: Major Hemorrhage
Patients with Event (%)
No. of Patients
No. with Event
Aspirin 2449 10
Clopidogrel plus Aspirin 2432 23
Hazard ratio, 2.32 (95% CI, 1.10–4.87)
P=0.02
Aspirin
Clopidogrel plus aspirin
0.9
0.4
Days since Randomization
No. at Risk
Aspirin 2449 2372 2271 2230 1448

Results

- A total of 4881 patients were enrolled at 269 international sites. The trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days.
- Major ischemic events occurred in 121 of 2432 patients (5.0%) receiving clopidogrel plus aspirin and in 160 of 2449 patients (6.5%) receiving aspirin plus placebo (hazard ratio, 0.75; 95% confidence interval [CI], 0.59 to 0.95; P=0.02), with most events occurring during the first week after the initial event.
- Major hemorrhage occurred in 23 patients (0.9%) receiving clopidogrel plus aspirin and in 10 patients (0.4%) receiving aspirin plus placebo (hazard ratio, 2.32; 95% CI, 1.10 to 4.87; P=0.02).

Conclusions

In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone. (Funded by the National Institute of Neurological Disorders and Stroke;