Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial

One-Year Outcomes

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Background—The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial showed that the combined treatment of clopidogrel and aspirin decreases the 90-day risk of stroke without increasing hemorrhage in comparison with aspirin alone, but provided insufficient data to establish whether the benefit persisted over a longer period of time beyond the trial termination. We report the 1-year follow-up outcomes of this trial.

Methods and Results—The trial was a randomized, double-blind, placebo-controlled trial conducted at 114 centers in China. We randomly assigned 5170 patients within 24 hours after onset of minor stroke or high-risk transient ischemic attack to clopidogrel-aspirin therapy (loading dose of 300 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day for 90 days, plus 75 mg of aspirin per day for the first 21 days) or to the aspirin-alone group (75 mg/d for 90 days). The primary outcome was stroke event (ischemic or hemorrhagic) during 1-year follow-up. Differences in outcomes between groups were assessed by using the Cox proportional hazards model. Stroke occurred in 275 (10.6%) patients in the clopidogrel-aspirin group, in comparison with 362 (14.0%) patients in the aspirin group (hazard ratio, 0.78; 95% confidence interval, 0.65–0.93; P=0.006). Moderate or severe hemorrhage occurred in 7 (0.3%) patients in the clopidogrel-aspirin group and in 9 (0.4%) patients in the aspirin group (P=0.44).

Conclusions—The early benefit of clopidogrel-aspirin treatment in reducing the risk of subsequent stroke persisted for the duration of 1-year of follow-up.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00979589.

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Key Words: clopidogrel ■ ischemic attack, transient ■ patient outcome assessment ■ stroke

The early risk of recurrence of stroke following index transient ischemic attack (TIA) or minor ischemic stroke is very high, even in patients treated with aspirin.[1–3] The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial was designed to assess whether the combination treatment of clopidogrel and aspirin taken soon after a TIA or minor stroke could reduce the early risk of stroke.[4] The original study termination of the CHANCE trial was 90 days from randomization, and the results showed that clopidogrel-aspirin treatment decreases the 90-day risk of stroke (hazard ratio, 0.68, 95% confidence interval [CI], 0.57–0.81; P<0.001) but does not increase the risk of hemorrhage in comparison with aspirin alone.[5]

Clinical Perspective on p 46

Trials of clopidogrel in the acute phase after stroke or TIA were suggested to follow up beyond the cessation of clopidogrel for the concern about rebound increase in risk of recurrence of stroke.[6–8] We performed an additional

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1-year visit for the CHANCE trial and patients in both treatment groups were followed up between October 2010 and July 2013 to establish whether the early benefit in the clopidogrel-aspirin group would persist over a longer period of time, or whether the clopidogrel-aspirin group would have a high rate of late strokes that would eliminate or even inverse the early efficacy gap between the 2 groups. We report the 1-year follow-up results of the CHANCE trial in this article.

Methods

Study Design and Subjects

Details on the rationale, design, and early results have been published previously.[4,5] The CHANCE trial was a randomized, double-blind, placebo-controlled trial funded by the Ministry of Science and Technology of the People's Republic of China, and conducted at 114 centers in China between October 2009 and July 2012.

Eligible patients were ≥40 years of age, had a diagnosis of an acute minor stroke or high-risk TIA, and were able to start the study drug within 24 hours after symptom onset. Acute minor stroke was defined by the National Institutes of Health Stroke Scale at the time of randomization ≤3. High-risk TIA was defined as a neurological deficit lasting <24 hours owing to focal brain ischemia plus a moderate-to-high risk of stroke recurrence ($ABCD^2$ [scores assessing the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes mellitus] at the time of randomization ≥4). Exclusion criteria included hemorrhage; other conditions, such as vascular malformation, tumor, abscess, or other major nonischemic brain disease; isolated sensory symptoms, isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline computed tomography or MRI of the head; modified Rankin Scale >2; a clear indication for anticoagulation therapy (presumed cardiac source of embolus, such as atrial fibrillation or prosthetic cardiac valve) or a contraindication to clopidogrel or aspirin. No patients included in the study were treated with thrombolysis around the time of randomization. Other eligibility criteria were provided in the study protocol.[4] The CHANCE protocol was approved by the ethics committee at each study center. All participants or their legal proxies provided written informed consent.

Randomization and Treatments

Patients enrolled were randomly assigned to 1 of the 2 treatment groups with the use of a double-blind, double-dummy design. The site investigator called into an automated system that randomly assigned a number corresponding to a medication kit stored at the research site, and the medication in the kit was administered to the patient. Clopidogrel and the matching placebo were purchased from Sanofi-Aventis, which had no other role in the study.

Patients in the clopidogrel-aspirin group were treated as follows: Day 1, randomized-blind clopidogrel 300 mg, and open-label aspirin at a clinician-determined dose of 75 to 300 mg. Days 2 through 21, randomized-blind clopidogrel 75 mg/d and randomized-blind aspirin 75 mg/d. Days 22 through 90, randomized-blind clopidogrel 75 mg/d, and randomized-blind placebo aspirin daily. After day 90, treatment was at the choice of the clinician and the patient.

Patients in the aspirin-alone group were treated as follows: Day 1, open-label aspirin at a clinician-determined dose of 75 to 300 mg, and randomized-blind placebo clopidogrel. Days 2 through 90, randomized-blind aspirin 75 mg/d and randomized-blind placebo clopidogrel daily. After day 90, treatment was at the choice of the clinician and the patient.

Duration of Follow-Up and Outcomes

The original plan of the CHANCE trial was to follow patients for 90 days. However, we added a visit to follow patients for 1 year after enrollment between October 2010 and July 2013. All follow-up visits were in person by a trained site coordinator. The 1-year visit collected information including assessment of the patient's modified Rankin Scale score at year 1, any end point events, and medicines used beyond day 90. We obtained the patient's medical records for any reported events for review, and confirmed by a central adjudication committee that was unaware of the study-group assignments. The starting time, duration, and dose of antiplatelet agents, including aspirin and clopidogrel, used beyond day 90 were recorded.

The primary efficacy outcome was a new stroke event (ischemic or hemorrhagic) during 1 year of follow-up. Secondary efficacy outcomes included a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), analyzed as a composite outcome and also as individual outcomes. The definitions of ischemic stroke, hemorrhagic stroke, and vascular death were consistent with previously reported 3-month outcomes of the CHANCE trial.[5]

Safety outcomes included moderate-to-severe bleeding event and any bleeding event. Moderate-to-severe bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[9] Severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention. Moderate bleeding was defined as bleeding that required transfusion of blood but did not lead to a hemodynamic compromise requiring intervention.[9]

Statistical Analysis

All analyses were by intention to treat, based on patients who were randomly assigned. Categorical variables were presented as percentages, and continuous variables were presented as median with interquartile because their distribution is not normal. The χ^2 test and Wilcoxon rank sum test were performed for comparison of categorical variables and continuous variables between 2 groups, respectively. Time to randomization was calculated as a group mean. We investigated longitudinal differences in the antiplatelet agents use over time beyond month 3 between the treatment groups by using a marginal model for repeated measurements of categorical data.

Differences between study groups in all end points during the 1-year follow-up period were assessed by using the Cox proportional hazards model, with pooled study centers (≥20 patients) as a random effect. Clopidogrel and aspirin usage over time beyond month 3 were included in the model as time-dependent covariates. Hazard ratios with 95% CIs are reported. When there were multiple events of the same type, the time to the first event was used in the model. Data from patients who had no events during the study were censored at 1 year or death. For each model, the proportional hazards assumption was assessed by testing the treatment by time interaction.

In addition, we preformed 3 sensitivity analyses to generate data of primary end point for patients lost to follow-up[10]: (1) all patients lost to follow-up were considered to have a stroke at last contact; (2) only patients lost to follow-up in the clopidogrel-aspirin group were considered to have a stroke at last contact; and (3) only patients lost to follow-up in the aspirin group were considered to have a stroke at last contact. We tested the interaction effects between group (clopidogrel-aspirin group versus aspirin alone group) and antiplatelet drug use (clopidogrel or aspirin) beyond month 3 in the sensitivity analyses. When the interaction effect was significant, we performed separate analysis by subgroups of patients with or without antiplatelet treatment beyond month 3, respectively. We performed subgroup analyses for prespecified baseline factors with rates of the primary end point by testing the treatment by factor interaction with the use of Cox models.

The α-level of significance was $P<0.05$ 2-sided. All analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Between October 2009 and July 2012, 5170 patients were randomly assigned to treatment: 2586 to the aspirin group and 2584 to the clopidogrel-aspirin group. The baseline characteristics of the 2 groups were well balanced (Table 1). A total of 197 patients were lost to follow-up at 1 year: 111 (4.3%) in the aspirin group and 86 (3.3%) in the clopidogrel-aspirin group (P=0.07). The baseline characteristics of the patients with and without 1-year follow-up were about the same (Table I in the online-only Data Supplement).

The proportion of patients on clopidogrel plus aspirin, clopidogrel alone, and aspirin alone at 3 months was 2.6%, 4.8%, and 77.3% in the aspirin group, and 2.7%, 5.5%, and 77.4% in the clopidogrel-aspirin group, respectively. At 1 year, the proportion declined to 1.4%, 4.8%, and 74.9% in the aspirin group, and 1.4%, 5.8%, and 74.5% in the clopidogrel-aspirin group, respectively. We detected no significant difference of proportion of patients on antiplatelet agents over time beyond month 3 between the 2 groups (P=0.55; Figure 1).

Table 1. Baseline Characteristics of the Patients

Characteristic	Aspirin (n=2586)	Clopidogrel-Aspirin (n=2584)	*P* Value
Age, y, median (IQR)	62 (54–71)	63 (55–72)	0.11
Female sex, n (%)	898 (34.7)	852 (33.0)	0.18
Systolic pressure, mm Hg, median (IQR)	150 (136–161)	150 (136–161)	0.91
Diastolic pressure, mm Hg, median (IQR)	90 (80–100)	90 (80–98)	0.25
Body mass index, median (IQR)	25 (23–27)	25 (23–26)	0.08
Medical history, n (%)			
Ischemic stroke	517 (20.0)	516 (20.0)	0.98
TIA	80 (3.1)	94 (3.6)	0.28
Myocardial infarction	53 (2.0)	43 (1.7)	0.30
Angina	87 (3.4)	97 (3.8)	0.45
Congestive heart failure	38 (1.5)	42 (1.6)	0.65
Known atrial fibrillation or flutter	48 (1.9)	48 (1.9)	1.00
Valvular heart disease	10 (0.4)	4 (0.2)	0.11
Hypertension	1683 (65.1)	1716 (66.4)	0.31
Diabetes mellitus	543 (21.0)	550 (21.3)	0.80
Hypercholesterolemia	283 (10.9)	290 (11.2)	0.75
Pulmonary embolism	1 (<0.1)	0	1.00
Current or previous smoking, n (%)	1105 (42.7)	1116 (43.2)	0.74
Mean time to randomization, h	13	13	0.56
Time to randomization, n (%)			0.70
<12 h	1280 (49.5)	1293 (50.0)	
≥12 h	1306 (50.5)	1291 (50.0)	
Qualifying event, n (%)			0.75
TIA	728 (28.2)	717 (27.7)	
Minor stroke	1858 (71.8)	1867 (72.3)	
$ABCD^2$ score*, median (IQR)	4 (4–5)	4 (4–5)	0.72

IQR indicates interquartile range; and TIA, transient ischemic attack.

*Data are only for the 1445 patients who had a TIA. The $ABCD^2$ assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes mellitus, with scores ranging from 0 to 7 and higher scores indicating greater short-term risk.

Baseline characteristics of the patients in different categories of antiplatelet therapy at 3 months after the cessation of the trial treatment are shown in Tables II and III in the online-only Data Supplement.

Throughout the trial, stroke occurred in 275 patients (10.6%) in the clopidogrel-aspirin group, in comparison with 362 patients (14.0%) in the aspirin group (hazard ratio, 0.78; 95% CI, 0.65–0.93; P=0.006) (Table 2, Figure 2). Beyond month 3, 63 (2.7%) of 2346 patients in the clopidogrel-aspirin group and 59 (2.6%) of 2260 patients in the aspirin group had a stroke (hazard ratio, 0.96; 95% CI, 0.68–1.35; P=0.81) (Figure 2). The results of sensitivity analyses for primary outcome at 1 year were shown in Table 3. The worst-case scenario in which only patients lost to follow-up in the clopidogrel-aspirin group were considered to have a stroke at last contact still resulted in an event rate being numerically lower than that in the aspirin group, although no statistically significant differences were detected.

Table 2 shows the secondary outcomes and safety outcomes in each group. The clopidogrel-aspirin group had lower rates of combined secondary vascular events (hazard ratio, 0.78; 95% CI, 0.65–0.93; P=0.005) and ischemic stroke (hazard ratio, 0.77; 95% CI, 0.64–0.93; P=0.006) in comparison with the aspirin group. No significant difference was detected between the 2 groups for other secondary end points. Moderate-to-severe hemorrhage occurred in 7 patients (0.3%) in the clopidogrel-aspirin group and in 9 patients (0.4%) in the aspirin group (P=0.44).

The reduction in the rate of stroke with clopidogrel and aspirin was consistent across all subgroups (Figure 3). We detected no significant interaction with treatment for any of the prespecified baseline factors (P>0.10 for all comparisons).

Discussion

The early benefit of combination treatment with clopidogrel and aspirin in patients with acute minor stroke and high-risk TIA persisted for the duration of 1 year of follow-up in this trial. The results of 1-year follow-up were consistent with the original 3-month efficacy of this study,[5] suggesting that clopidogrel-aspirin therapy was associated with a decrease of recurrence of stroke without an increase of hemorrhage.

No published data on the long-term efficacy of dual-antiplatelet agents are available from the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial,[11] the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial,[12] and the Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) pilot,[13] because follow-ups were not continued after the termination of the trials. In our study, the curves for hazard of stroke were particularly steep in the first few days, but persistently smooth subsequently until 1 year. Sixty-three (2.7%) of 2346 patients in the clopidogrel-aspirin group and 59 (2.6%) of 2260 patients in the aspirin group had a stroke during 3 months to 1 year, and the absolute risk reduction of stroke was 3.5% at 3 months and 3.4% at 1 year. These data suggested that there was no obvious rebound or

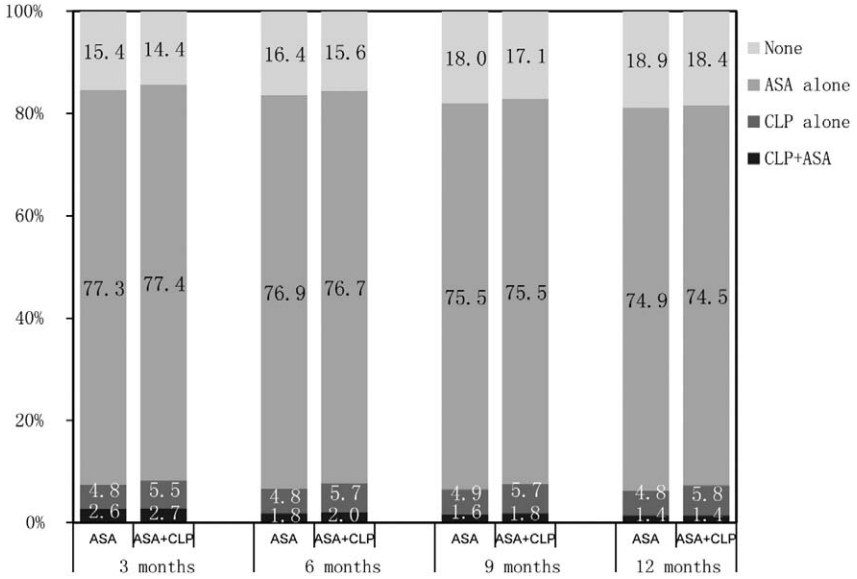


Figure 1. Proportion of patients on antiplatelet agents from day 90 to 1 year in 2 groups. ASA indicates aspirin; and CLP, clopidogrel.

drop of recurrence of stroke, and the efficacy gap between the 2 groups did not narrow over time after the termination of the trial treatment. One possible explanation is that the rebound effect of clopidogrel cessation in this trial may not occur, which was similar to the other previous studies on stroke and TIA reported.[14,15] In addition, >80% of the patients were still under the protection of at least 1 kind of antiplatelet agent over time beyond month 3.

Concerns have been raised that the antiplatelet agents used beyond the trial termination in the CHANCE trial may confound the efficacy of the trial treatments. Antiplatelet therapy beyond month 3 likely affects the recurrence of stroke during 3 months to 1 year, because it has been well proved to be effective for secondary stroke prevention.[16–18] However, after 3 months, patients took clopidogrel or aspirin or neither according to decisions they and their clinicians made, because the protocol made no treatment specification after the first 90 days. Actually, there was no significant difference in the proportion of patients on antiplatelet agents over time beyond month 3 between the 2 groups. In addition, the effects of the antiplatelet agents used beyond the trial termination were adjusted as time-dependent covariates in the Cox model.

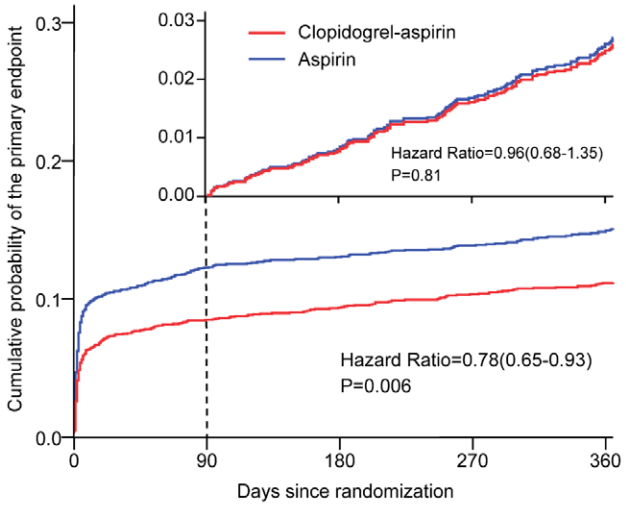
Although clopidogrel-aspirin therapy seems to have substantially reduced the risk of stroke in these patients in comparison with aspirin-alone therapy, there is still a large

Table 2. Efficacy and Safety Outcomes at 1 Year

	Aspirin (n=2586)		Clopidogrel-Aspirin (n=2584)			
	Patients With Event, n	Event Rate, %	Patients With Event, n	Event Rate, %	Hazard Ratio (95% CI)	*P* Value
Primary outcome						
Stroke	362	14.0	275	10.6	0.78 (0.65–0.93)	0.006
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	370	14.3	282	10.9	0.78 (0.65–0.93)	0.005
Ischemic stroke	349	13.5	263	10.2	0.77 (0.64–0.93)	0.006
Hemorrhagic stroke	13	0.5	13	0.5	1.00 (0.46–2.15)	0.99
Myocardial infarction	8	0.3	5	0.2	0.61 (0.19–2.00)	0.41
Death from cardiovascular causes	11	0.4	11	0.4	0.98 (0.42–2.29)	0.97
Death from any cause	36	1.4	28	1.1	0.70 (0.42–1.17)	0.18
Transient ischemic attack	62	2.4	57	2.2	0.90 (0.63–1.29)	0.57
Safety outcome						
Moderate-to-severe bleeding*	9	0.4	7	0.3	0.67 (0.24–1.87)	0.44
Any bleeding	46	1.8	64	2.5	1.39 (0.95–2.04)	0.09

CI indicates confidence interval; and TIA, transient ischemic attack.

*Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.



Number at risk

Aspirin	2586	2260	2174	2149	1771
Clopidogrel-aspirin	2584	2346	2269	2240	1854

Figure 2. Cumulative probability of a stroke (ischemic or hemorrhagic stroke) by treatment. The inset shows the curves for the landmark analysis from 3 months to 1 year after the deletion of the events that occurred within 3 months.

proportion of patients at high risk of stroke despite clopidogrel treatment. China has a high prevalence of genetic polymorphisms that may affect the metabolism of clopidogrel.[19] Clopidogrel resistance, with poor clopidogrel metabolizer phenotypes, seems to be associated with a higher probability of experiencing ischemic cerebral vascular events, implying that personalized therapy is needed.[19–22] Future research should focus on the development of new therapies to reduce the risk of stroke in these high-risk patients, such as new antiplatelet agents (eg, ticagrelor and prasugrel), which are effective in atherothrombotic acute coronary syndrome.[23,24]

Our study has some limitations. First, the CHANCE trial was performed in China and the participants enrolled were restricted to Chinese patients. It is not known whether dual-antiplatelet treatment will be shown to be similarly effective in other populations. The external generalizability of the findings of the CHANCE trial needs further validation in Western populations. The Platelet-Oriented Inhibition in the New TIA and Minor Ischemic Stroke (POINT) trial (ClinicalTrials.gov, Unique identifier: NCT00991029) sponsored by the National Institutes of Health, assessing the efficacy of dual-antiplatelet treatment with a higher loading dose of clopidogrel (600 mg) and a narrower time window (treatment within 12 hours after symptom onset) than were used in our study, is now enrolling patients at sites primarily in the United States.[25] Second, the characteristics of patients enrolled in the CHANCE trial were different from those of a typical TIA sample from population-based cohorts.[26,27] Females were a minority in our study (33%). However, this is not unprecedented in secondary stroke prevention trials; for instance, the United Kingdom Transient

Table 3. Sensitivity Analyses for Primary Outcome at 1 Year

		Aspirin			Clopidogrel-Aspirin					
Model	Effect	n	Patients With Event, n	Event Rate, %	n	Patients With Event, n	Event Rate, %	Hazard Ratio (95% CI)	*P* Value	P_{int} Value
Model 1*	Total	2586	450	17.4	2584	349	13.5	0.77 (0.67–0.89)	<0.001	0.25
	Subgroup 1†	2084	290	13.9	2129	222	10.4	0.73 (0.61–0.87)	<0.001	
	Subgroup 2‡	502	160	31.9	455	127	27.9	0.87 (0.68–1.12)	0.28	
Model 2§	Total	2586	362	14.0	2584	349	13.5	1.01 (0.86–1.19)	0.89	<0.001
	Subgroup 1†	2084	290	13.9	2129	222	10.4	0.73 (0.61–0.87)	<0.001	
	Subgroup 2‡	502	72	14.3	455	127	27.9	1.82 (1.34–2.47)	<0.001	
Model 3‖	Total	2586	450	17.4	2584	275	10.6	0.60 (0.51–0.70)	<0.001	<0.001
	Subgroup 1†	2084	290	13.9	2129	222	10.4	0.73 (0.61–0.87)	<0.001	
	Subgroup 2‡	502	160	31.9	455	53	11.7	0.38 (0.27–0.53)	<0.001	

CI indicates confidence interval.

*Model 1: all patients lost to follow-up were considered to have a stroke at last contact.

†Subgroup 1: patients with clopidogrel or aspirin treatment beyond month 3.

‡Subgroup 2: patients without clopidogrel or aspirin treatment beyond month 3.

§Model 2: only patients lost to follow-up in clopidogrel and aspirin group were considered to have a stroke at last contact.

‖Model 3: only patients lost to follow-up in aspirin group were considered to have a stroke at last contact.

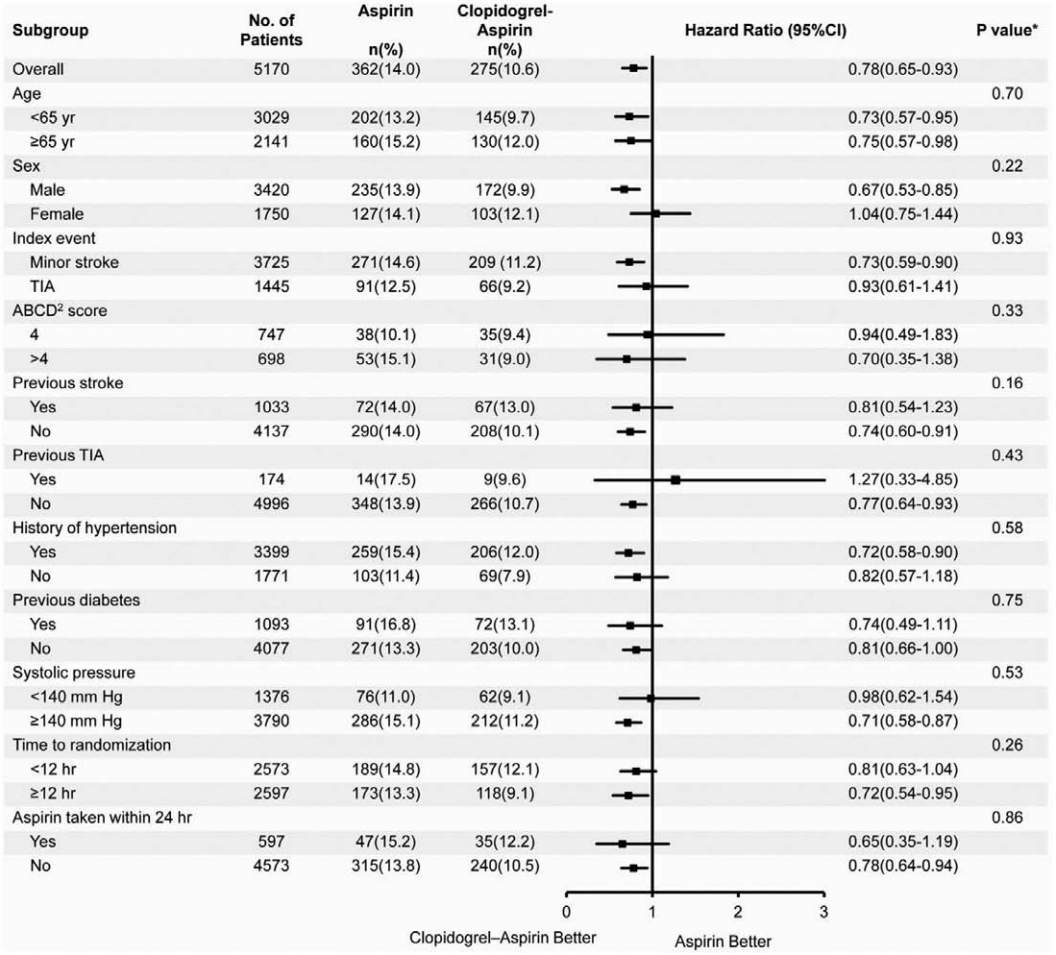


Figure 3. Hazard ratio for the primary outcome in prespecified subgroups. **P* value for interaction of treatment and the factor. There were no significant interactions in any of the 11 predefined subgroups (*P*>0.1 for all comparisons). ABCD² indicates score assessing the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes mellitus; CI, confidence interval; and TIA, transient ischemic attack.

Ischemic Attack (UK-TIA) trial was 27% female.[28] Our trial enrolled only high-risk TIA patients (ABCD² scores≥4). This may have resulted in high event rates. Our findings may not apply to other populations of patients.

Conclusions

In summary, our study shows that among patients with acute high-risk TIA or minor ischemic stroke, the benefit of treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for 90 days, in reducing the risk of subsequent stroke persisted over the duration of 1 year of follow-up.

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Disclosures

Dr Johnston is the principal investigator of the POINT trial, a National Institutes of Health–sponsored trial with clopidogrel and placebo donated by Sanofi. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The previously published results of the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial have shown that treatment with clopidogrel plus aspirin for 21 days followed by clopidogrel alone for 90 days decreases the 90-day risk of stroke without increasing the risk of hemorrhage in patients with acute minor stroke or high-risk transient ischemic attack. This article reported the 1-year follow-up results of the CHANCE trial and found that the results of 1-year follow-up were similar to the original 3-month efficacy of this study. These data suggested rebound increase in the risk of recurrence of stroke may not occur after the cessation of clopidogrel in the trial, and the early benefit of combination treatment of clopidogrel and aspirin persisted over the duration of 1 year of follow-up. We found that most of the stroke recurrences occurred at the early stage after the onset of the event. Early aggressive dual-antiplatelet therapy may be of benefit to patients with acute minor stroke or high-risk transient ischemic attack for a long time.

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Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial: One-Year Outcomes

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SUPPLEMENTAL MATERIAL

Table I. Baseline Characteristics of the Patients with and without 1 year follow-up

Characteristic	Without follow-up (N=197)	With follow-up (N=4973)	p value
Age (yr), median (IQR)	62 (54-72)	62 (55-71)	0.82
Female sex, n(%)	63(32.0)	1687(34.0)	0.57
Systolic pressure (mm Hg) , median (IQR)	150(140-160)	150(135-161)	0.90
Diastolic pressure (mm Hg) , median (IQR)	90(80-95)	90(80-100)	0.61
Body-mass index, median (IQR)	24(22-26)	24(23-26)	0.06
Medical history, n(%)			
Ischemic stroke	34(17.3)	999(20.1)	0.33
TIA	7(3.6)	167(3.4)	0.88
Myocardial infarction	1(0.5)	95(1.9)	0.25
Angina	8(4.1)	176(3.5)	0.70
Congestive heart failure	5(2.5)	75(1.5)	0.39
Known atrial fibrillation or flutter	3(1.5)	93(1.9)	0.93
Valvular heart disease	0(0.0)	14(0.3)	0.46
Hypertension	120(60.9)	3279(65.9)	0.15
Diabetes mellitus	35(17.8)	1058(21.3)	0.24
Hypercholesterolemia	26(13.2)	547(11.0)	0.34
Pulmonary embolism	0(0.0)	1(<0.1)	1.00
Current or previous smoking, n(%)	87(44.2)	2134(42.9)	0.73
Mean time to randomization (hr), median (IQR)	11(6.5-19.5)	12(6.5-19.5)	0.53
Time to randomization, n(%)			0.11
<12 hr	109(55.3)	2464(49.5)	
≥12 hr	88(44.7)	2509(50.5)	
Qualifying event, n(%)			0.15
TIA	133(67.5)	3592(72.2)	
Minor stroke	64(32.5)	1381(27.8)	

TIA indicates transient ischemic attack; IQR, Interquartile Range.

Table II. Baseline Characteristics of the Patients in Subgroups of Non-antiplatelet and Aspirin Alone Therapy at 3 Months.

Characteristic	Non-antiplatelet at 3 months			Aspirin alone at 3 months		
	ASA*(N=378)	ASA+CLP*(N=358)	p value	ASA*(N=1902)	ASA+CLP*(N=1924)	p value
Age (yr), median (IQR)	62(54-73)	63(55-72)	0.86	62(54-71)	63(55-72)	0.12
Female sex, n(%)	136(36.0)	119(33.2)	0.44	666(35.0)	641(33.3)	0.27
Systolic pressure (mm Hg) , median (IQR)	150(140-162)	150(140-170)	0.27	150(135-160)	150(135-160)	0.68
Diastolic pressure (mm Hg) , median (IQR)	90(80-100)	90(80-100)	0.16	90(80-100)	90(80-97)	0.08
Body-mass index, median (IQR)	24(22-26)	25(23-27)	0.08	25(23-27)	24(23-26)	0.001
Medical history, n(%)						
Ischemic stroke	59(15.6)	70(19.6)	0.16	395(20.8)	394(20.5)	0.83
TIA	7(1.9)	9(2.5)	0.54	63(3.3)	73(3.8)	0.42
Myocardial infarction	8(2.1)	8(2.2)	0.91	43(2.3)	27(1.4)	0.048
Angina	8(2.1)	16(4.5)	0.07	70(3.7)	63(3.3)	0.49
Congestive heart failure	4(1.1)	3(0.8)	1.00	29(1.5)	33(1.7)	0.64
Known atrial fibrillation or flutter	7(1.9)	6(1.7)	0.86	39(2.1)	31(1.6)	0.31
Valvular heart disease	0(0.0)	0(0.0)	1.00	9(0.5)	4(0.2)	0.16
Hypertension	225(59.5)	226(63.1)	0.32	1252(65.8)	1269(66.0)	0.93
Diabetes mellitus	59(15.6)	65(18.2)	0.36	416(21.9)	403(21.0)	0.49
Hypercholesterolemia	35(9.3)	33(9.2)	0.99	196(10.3)	202(10.5)	0.84
Pulmonary embolism	0(0.0)	0(0.0)	1.00	1(0.1)	0(0.0)	0.50
Current or previous smoking, n(%)	155(41.0)	168(46.9)	0.11	811(42.6)	808(42.0)	0.69
Mean time to randomization (hr) , median (IQR)	12(6.7-19.0)	12(6.0-19.8)	0.74	12(6.5-19.7)	12(6.3-19.5)	0.45
Time to randomization, n(%)			0.84			0.51
<12 hr	183(48.4)	176(49.2)		929(48.8)	960(49.9)	
≥12 hr	195(51.6)	182(50.8)		973(51.2)	964(50.1)	

Qualifying event, n(%)			0.55		0.51
TIA	266(70.4)	259(72.4)		1364(71.7)	1398(72.7)
Minor stroke	112(29.6)	99(27.7)		538(28.3)	526(27.3)

TIA indicates transient ischemic attack; IQR, Interquartile Range.

* ASA indicates aspirin group in CHANCE trial, ASA+CLP indicates clopidogrel-aspirin group in CHANCE trial.

Table III. Baseline Characteristics of the Patients in Subgroups of Clopidogrel Alone and Aspirin Plus Clopidogrel Therapy at 3 Months.

Characteristic	Clopidogrel alone at 3 months			Aspirin- clopidogrel at 3 months		
	ASA*(N=117)	ASA+CLP*(N=137)	p value	ASA*(N=65)	ASA+CLP*(N=68)	p value
Age (yr), median (IQR)	60(53-71)	62(56-70)	0.16	65(55-71)	64(58-71)	0.73
Female sex, n(%)	39(33.3)	43(31.4)	0.74	16(24.6)	16(23.5)	0.88
Systolic pressure (mm Hg) , median (IQR)	152(136-170)	150(138-161)	0.17	150(140-169)	155(145-169)	0.43
Diastolic pressure (mm Hg) , median (IQR)	90(80-95)	85(80-92)	0.18	88(80-96)	90(80-100)	0.40
Body-mass index, median (IQR)	24(23-27)	25(23-27)	0.47	25(24-26)	26(23-28)	0.81
Medical history, n(%)						
Ischemic stroke	25(21.4)	26(19.0)	0.64	12(18.5)	13(19.1)	0.92
TIA	3(2.6)	5(3.7)	0.89	3(4.6)	2(2.9)	0.96
Myocardial infarction	1(0.9)	4(2.9)	0.47	1(1.5)	3(4.4)	0.64
Angina	1(0.9)	5(3.7)	0.29	4(6.2)	7(10.3)	0.39
Congestive heart failure	3(2.6)	2(1.5)	0.86	0(0.0)	1(1.5)	1.00
Known atrial fibrillation or flutter	1(0.9)	4(2.9)	0.47	0(0.0)	3(4.4)	0.26
Valvular heart disease	0(0.0)	0(0.0)	1.00	0(0.0)	0(0.0)	1.00
Hypertension	80(68.4)	107(78.1)	0.08	48(73.9)	55(80.9)	0.33
Diabetes mellitus	32(27.4)	41(29.9)	0.65	15(23.1)	22(32.4)	0.23
Hypercholesterolemia	24(20.5)	30(21.9)	0.79	12(18.5)	11(16.2)	0.73
Pulmonary embolism	0(0.0)	0(0.0)	1.00	0(0.0)	0(0.0)	1.00
Current or previous smoking, n(%)	53(45.3)	63(46.0)	0.91	33(50.8)	34(50.0)	0.93
Mean time to randomization (hr) , median (IQR)	12(6.0-18.5)	10(6.0-19.3)	0.94	11(6.5-19.5)	12(7.6-17.8)	0.87
Time to randomization, n(%)			0.43			0.54
<12 hr	60(51.3)	77(56.2)		35(53.9)	33(48.5)	
≥12 hr	57(48.7)	60(43.8)		30(46.2)	35(51.5)	

Qualifying event, n(%)			0.10		0.89
TIA	91(77.8)	94(68.6)		50(76.9)	53(77.9)
Minor stroke	26(22.2)	43(31.4)		15(23.1)	15(22.1)

TIA indicates transient ischemic attack; IQR, Interquartile Range.

* ASA indicates aspirin group in CHANCE trial, ASA+CLP indicates clopidogrel-aspirin group in CHANCE trial.

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