# Recurrent Ischemic Lesions After Acute Atherothrombotic Stroke

## Clopidogrel Plus Aspirin Versus Aspirin Alone

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***Background and Purpose***—In patients with acute ischemic stroke caused by large artery atherosclerosis, clopidogrel plus aspirin versus aspirin alone might be more effective to prevent recurrent cerebral ischemia. However, there is no clear evidence.

***Methods***—In this multicenter, double-blind, placebo-controlled trial, we randomized 358 patients with acute ischemic stroke of presumed large artery atherosclerosis origin within 48 hours of onset to clopidogrel (75 mg/d without loading dose) plus aspirin (300-mg loading followed by 100 mg/d) or to aspirin alone (300-mg loading followed by 100 mg/d) for 30 days. The primary outcome was new symptomatic or asymptomatic ischemic lesion on magnetic resonance imaging within 30 days. Secondary outcomes were 30-day functional disability, clinical stroke recurrence, and composite of major vascular events. Safety outcome was any bleeding.

***Results***—Of 358 patients enrolled, 334 (167 in each group) completed follow-up magnetic resonance imaging. The 30-day new ischemic lesion recurrence rate was comparable between the clopidogrel plus aspirin and the aspirin monotherapy groups (36.5% versus 35.9%; relative risk, 1.02; 95% confidence interval, 0.77–1.35; $P$=0.91). Of the recurrent ischemic lesions, 94.2% were clinically asymptomatic. There were no differences in secondary outcomes between the 2 groups. Any bleeding were more frequent in the combination group than in the aspirin monotherapy group, but the difference was not significant (16.7% versus 10.7%; $P$=0.11). One hemorrhagic stroke occurred in the clopidogrel plus aspirin group.

***Conclusions***—Clopidogrel plus aspirin might not be superior to aspirin alone for preventing new ischemic lesion and clinical vascular events in patients with acute ischemic stroke caused by large artery atherosclerosis.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00814268.

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**Key Words:** antiplatelet drugs ■ aspirin ■ atherosclerosis ■ clinical trial, randomized ■ clopidogrel ■ recurrence ■ stroke

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Dual antiplatelet therapy that simultaneously blocks different platelet-activation pathways would more potently inhibit platelet activation and more effectively reduce the risk of ischemic vascular events compared with antiplatelet monotherapy. In contrast to acute coronary syndrome trials, several large stroke trials and a meta-analysis have failed to demonstrate the superior efficacy of dual antiplatelet therapy over antiplatelet monotherapy, but the risk of major bleeding increased with dual antiplatelet therapy.[1–4] Enrolling patients with a lower risk of recurrence and initiating treatment after a high-risk period might account for the failures.

CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) trial and a following meta-analysis showed that clopidogrel plus aspirin versus aspirin alone initiated in early period significantly reduced risk of recurrent stroke without increasing major bleedings.[5,6] However, the CHANCE trial exclusively enrolled Chinese patients who have a higher risk of stroke compared with other populations, and risk factor control for secondary stroke prevention during the trial was inadequate.[5] Therefore, it has been on debate whether the findings of the CHANCE trial might be applied to other populations.

The risk of recurrent ischemic stroke is high during the early period after stroke onset, and patients with large artery atherosclerosis (LAA) had the highest risk of early recurrence.[7] Early ischemic lesion recurrence on magnetic resonance imaging (MRI) was much more frequent than clinical stroke recurrence,[8,9] and most frequently observed in patients with LAA.[10,11] The pathogenetic mechanisms leading to new ischemic lesion seen on MRI and clinical ischemic stroke recurrence would be almost identical. In addition, new lesion recurrence predicted long-term clinical stroke recurrence.[11] Therefore, MRI end points would be useful for primary end points in proof-of-concept trials testing secondary stroke prevention therapies and acute stroke therapies.[12]

The COMPRESS (Combination of Clopidogrel and Aspirin for Prevention of Recurrence in Acute Atherothrombotic Stroke Study) trial aimed to compare clopidogrel plus aspirin versus aspirin alone for the prevention of recurrent ischemic lesion on MRI within 30 days in patients with acute ischemic stroke of presumed large artery atherothrombotic origin.

# Methods

## Trial Design

In this multicenter, prospective, randomized, double-blind, placebo-controlled trial, we compared clopidogrel plus aspirin with aspirin alone in patients with acute ischemic stroke of presumed large artery atherothrombotic origin within 48 hours of onset. Eligible patients were randomly allocated to clopidogrel (75 mg once daily without loading dose) plus aspirin (loading dose of 300 mg followed by 100 mg once daily) or placebo (matched to clopidogrel for taste, color, and size) plus aspirin (loading dose of 300 mg followed by 100 mg once daily) for 30 days in a 1:1 ratio stratified by centers and time to randomization (<24 versus 24–48 hours). Randomization was performed centrally by a computer-generated randomization sequence. All patients received the best medical therapy recommended by current practice guidelines. Concomitant use of additional antiplatelet agents or anticoagulants was not allowed during the trial.

Before randomization, all study subjects had baseline MRI including diffusion-weighted imaging, conventional T1, gradient-recalled echo, and fluid-attenuated inversion recovery and vascular imaging of intra-/extracranial MR angiography or computed tomographic angiography. At 7 (±2) days and 30 (±5) days, we evaluated new ischemic lesions on diffusion-weighted imaging and fluid-attenuated inversion recovery. MRI sequence parameters were standardized across centers. Clinical assessments including National Institutes of Health Stroke Scale score and the modified Rankin Scale (mRS) score were performed at baseline and at 30 days (Figure I in the online-only Data Supplement).

The trial was approved by the institutional ethics committee of each participating institution, and all patients provided written informed consent. The study was registered with Clinicaltrials.gov registration (NCT00814268) and was conducted and reported with fidelity to the study protocol. The trial was a sponsor-initiated trial and sponsored by Sanofi-Aventis Korea and BMS Korea. Representatives of the sponsors participated in the design and conduct of the trial, but academic investigators were allowed to access to the data after the agreement of confidentiality, took the primary responsibility for the completeness, accuracy, and analysis of the data, wrote the draft, and decided to submit the article after the agreement with the sponsors. The independent data and safety board monitored the study conduct.

## Study Population

Patients were eligible for participation in the trial if they were ≥30 years of age, had acute ischemic stroke confirmed by diffusion-weighted imaging, had atherosclerotic stenosis relevant to the index stroke on MR angiography or computed tomographic angiography (extracranial carotid stenosis >30% by the NASCET [North American Symptomatic Carotid Endarterectomy Trial] method and intracranial stenosis at the discretion of responsible physician), and were able to receive study medications within 48 hours from symptom onset. Key exclusion criteria were presumed cardioembolic stroke or small-vessel occlusion, previous history of nontraumatic intracranial bleeding, coexisting brain lesions such as intracranial bleeding or brain tumor, planned conventional angiography, vascular intervention, or surgery before the end of study, bleeding diathesis or coagulopathy, contraindications to antiplatelet therapy, pregnancy or lactation, or receiving thrombolytic therapy. Detailed inclusion and exclusion criteria are provided in the Table I in the online-only Data Supplement.

## Outcomes

The primary outcome was new symptomatic or asymptomatic ischemic lesion(s) within 30 days, as confirmed by diffusion-weighted imaging or fluid-attenuated inversion recovery at days 7 and 30. For patients who had clinical stroke or intracranial bleeding before the end of trial, MRI was evaluated at the time of the stroke occurrence. Two investigators (C.H.S. and J.L.) of the independent imaging review core laboratory independently assessed the MRI data blinded to the treatment allocation and clinical data. Discrepancies between the 2 investigators were resolved by consensus. Secondary efficacy outcomes were disability measured by the mRS, clinical stroke recurrence, and composite of stroke, myocardial infarction, and vascular death at 30 days. Safety outcomes were any bleedings, which were further categorized as life-threatening (death related to hemorrhagic complications, decrease of hemoglobin level >5 g/dL, hypovolemic shock because of bleeding, symptomatic intracranial hemorrhage, or requiring the transfusion of ≥4 units of blood), major bleeding (intraocular hemorrhage, significant disability by bleeding, or requiring the transfusion of ≤3 units of blood), or minor bleeding. The independent adjudication committee confirmed clinical events before breaking the randomization codes.

## Statistical Analysis

Based on findings from earlier studies,[8,10,11,13] we assumed that the rate of new ischemic lesion on MRI within 30 days would be 45% in the aspirin monotherapy group, and the absolute reduction with clopidogrel plus aspirin would be 15%. The sample size of 360 patients (180 patients per each arm) was calculated based on 2-sided test with 80% power and a significant level of 0.048 (from the O'Brien and Fleming method taking into account 1 interim analysis using a significance level of 0.005) and the assumption of a dropout rate of 10%.

The primary efficacy analysis was undertaken in the intention-to-treat population, which included randomized patients who took at least 1 dose of study medications, completed final MRI evaluation, and did not withdraw informed consent. In addition, we compared the primary outcome between the 2 groups for prespecified subgroups and examined the effect of treatment-by-subgroup interaction.

Safety analysis included all patients who took at least 1 dose of study medications and was performed based on actual treatment (2 patients who were randomized to clopidogrel plus aspirin but received aspirin monotherapy were included in the aspirin monotherapy group in the safety analysis). In the planned interim analysis conducted after the completion of 180 patients, the primary efficacy outcome did not differ between the 2 groups ($P$=0.754). During the trial, we conducted an unplanned safety analysis for 295 patients because of the safety concern of clopidogrel plus aspirin from the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial that exclusively enrolled lacunar strokes.[3] The rates of any bleeding were not different between the 2 groups ($P$=0.083), and the independent data and safety committee decided to allow further enrollment. All statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

# Results

## Characteristics of the Study Population

Between January 2009 and April 2012, 358 patients were randomized (178 in the clopidogrel plus aspirin group and 180 in the aspirin monotherapy group) at 20 centers in Korea. After randomization, 6 patients did not receive treatment and 3 patients withdrew consent. Of the remaining 349 (clopidogrel plus aspirin, n=174; placebo and aspirin, n=175) patients, 334 patients who completed follow-up MRI (167 patients for each arm) were included in the primary efficacy analysis, and 352 patients (clopidogrel plus aspirin, n=174; placebo and aspirin, n=178) were included in the safety analysis (Figure 1). Detailed data on the numbers of patients included in each outcome analysis are provided in the Table II in the online-only Data Supplement. The baseline demographics and stroke characteristics were well balanced between the 2 groups (Table 1). The mean age was 66.1 (SD, 11.7) years, and 36.4% of the patients were women. The median National Institutes of Health Stroke Scale score at baseline was 3. Ischemic stroke subtypes were LAA in 341 (97.7%) patients and stroke of other determined or undetermined etiology in 8 (2.3%) patients. Of the 349 patients, 238 (68.2%) patients had symptomatic intracranial stenosis, and 76 (21.8%) were randomized with 24 hours from stroke onset. There were no differences in the territory and location of the index stroke and the distribution of arterial stenosis between the 2 groups except for more pontine and cerebellar infarcts in the clopidogrel plus aspirin arm (Tables III–V in the online-only Data Supplement). During the trial, days covered by study medication were comparable between the 2 groups (Table VI in the online-only Data Supplement).

## Primary Outcome

The primary outcome of new symptomatic or asymptomatic ischemic lesions on MRI within 30 days occurred in 61 of the 167 patients in the clopidogrel plus aspirin group (36.5%) and in 60 of the 167 in the placebo and aspirin group (35.9%), and the difference was not statistically significant (relative risk, 1.02; 95% confidence interval [CI], 0.77–1.35; $P$=0.91; Table 2). Of the 121 patients with the recurrent ischemic lesions, 114 (94.2%) were clinically asymptomatic. The recurrent lesions were found in the same vascular territory of the qualifying stroke in 87.6%, <10 mm in diameter size in 69.4%, multiple in 42.1%, and presumed of LAA origin in 88.4%. The characteristics of the recurrent ischemic lesions did not differ between the 2 groups (Table VII in the online-only Data Supplement).

In all predefined subgroups, there were no significant interactions between the treatment and any of the 14 predefined subgroups (Table VIII and Figure II in the online-only Data Supplement). Even in patients randomized within 24 hours, the reduction of primary outcome with clopidogrel plus aspirin compared with aspirin alone was not significant (relative risk, 0.62; 95% CI, 0.32–1.18; $P$=0.14), and there was no interaction between treatment and time to randomization ($P$=0.080).

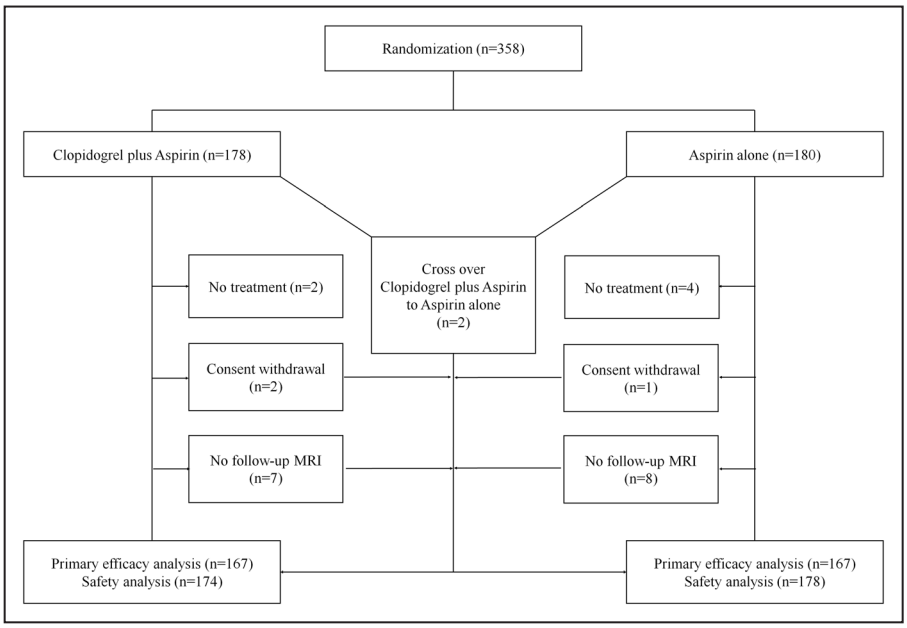


**Figure 1.** Study profile. Clopidogrel plus aspirin group: primary efficacy population (n=167). 167=178 (assigned)–2 (no treatment)–2 (consent withdrawal)–7 (no magnetic resonance imaging follow-up [MRI FU]). Clopidogrel plus aspirin group: safety population (n=174). 174=178 (assigned)–2 (no treatment)–2 (cross over to aspirin alone). Aspirin monotherapy group: primary efficacy population (n=167). 167=180 (assigned)–4 (no treatment)–1 (consent withdrawal)–8 (no MRI FU). Aspirin monotherapy group: safety population (n=178). 178=180 (assigned)–4 (no treatment)+2 (cross over from clopidogrel plus aspirin).

**Table 1. Demographics and Baseline Characteristics**

| | Clopidogrel Plus Aspirin (n=174) | Aspirin (n=175) | *P* Value |
|---|---|---|---|
| Mean age, y, median (range) | 68 (37–96) | 67 (36–89) | 0.70* |
| Male sex, n (%) | 114 (65.52) | 108 (61.71) | 0.46† |
| Body mass index, kg/m$^2$, mean±SD | 23.81±3.19 | 23.79±3.55 | 0.97‡ |
| Systolic blood pressure, mm Hg, median (range) | 140 (93–208) | 135 (94–195) | 0.09* |
| Diastolic blood pressure, mm Hg, median (range) | 80 (52–113) | 80 (53–119) | 0.33* |
| Previous ischemic stroke, n (%) | 20 (11.49) | 16 (9.14) | 0.47† |
| Previous coronary artery disease, n (%) | 8 (4.60) | 8 (4.57) | 0.99† |
| History of hypertension, n (%) | 112 (64.37) | 119 (68.00) | 0.47† |
| History of diabetes mellitus, n (%) | 58 (33.33) | 55 (31.43) | 0.70† |
| History of hypercholesterolemia, n (%) | 59 (33.91) | 50 (28.57) | 0.28† |
| Smoking status, n (%) | | | 0.37§ |
| Current | 71 (40.80) | 63 (36.00) | |
| Former | 30 (17.24) | 25 (14.29) | |
| Baseline scales, median (range) | | | |
| NIHSS at randomization | 3 (0–19) | 3 (0–18) | 0.88* |
| Stroke subtype, n (%) | | | 0.21§ |
| LAA | 168 (96.6) | 173 (98.9) | |
| SOE or SUE | 6 (3.4) | 2 (1.1) | |
| Extracranial carotid stenosis, n (%) | 52 (29.9) | 43 (24.6) | 0.26† |
| Medications at timing of randomization, n (%) | | | |
| Antiplatelet within 3 mo before randomization | 30 (17.24) | 24 (13.71) | 0.30† |
| Antihypertensive agents | 77 (44.25) | 91 (52.00) | 0.23† |
| Antidiabetic agents | 35 (20.11) | 40 (22.86) | 0.53† |
| Lipid-lowering agents | 28 (16.09) | 24 (13.71) | 0.53† |
| Time from onset to randomization, h, mean±SD | 32.63±10.10 | 31.71±11.07 | 0.44* |
| <24 h, n (%) | 36 (20.7) | 40 (22.9) | 0.62† |
| Time from onset to medication, h, mean±SD | 35.19±9.94 | 33.49±11.12 | 0.19‡ |

LAA indicates large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SOE, stroke of other determined etiology; and SUE, stroke of undetermined etiology.

*Wilcoxon rank-sum test.

†$\chi^2$ test.

‡Student *t* test.

§Fisher exact test were used to calculate *P* value for variance.

## Secondary Outcomes

At 30 days, the clopidogrel plus aspirin group versus the aspirin monotherapy group did not differ in the distribution of mRS scores (shift analysis: odds ratio, 1.10; 95% CI, 0.74–1.64; *P*=0.65) and in the proportion of patients who achieved mRS score of 0 to 2 outcome at 30 days (odds ratio for mRS score of ≤2, 0.73; 95% CI, 0.44–1.20; *P*=0.21; Table 2; Figure 2). The composite outcome of recurrent stroke, myocardial infarction, and vascular death occurred in 4 patients (2.40%) in the clopidogrel plus aspirin group and 6 patients (3.61%) in the aspirin monotherapy group (relative risk, 0.66; 95% CI, 0.19–2.31; *P*=0.52). The 2 groups did not differ in the 30-day rate of clinical stroke recurrence (3 strokes [1.80%] including 2 ischemic strokes and 1 hemorrhagic stroke in the clopidogrel plus aspirin group and 5 ischemic strokes [3.01%] in the aspirin monotherapy group; relative risk, 0.59; 95% CI, 0.14–2.46; *P*=0.50). Three patients (1.72%) in the clopidogrel plus aspirin group died (1 death caused by progression of the index stroke, 1 death caused by presumed rupture of aortic aneurysm, and 1 death of unknown cause), whereas there was no death in the aspirin group (*P*=0.12; Table 2.).

## Bleeding Events

Any bleeding events were more frequent in the clopidogrel plus aspirin group than in the aspirin monotherapy group, but the difference was not statistically significant (16.7% versus 10.7%; relative risk, 1.59; 95% CI, 0.91–2.68; *P*=0.11). Life-threatening bleeding occurred in 4 patients (2 symptomatic

**Table 2. Efficacy Outcomes**

| | Clopidogrel Plus Aspirin | Aspirin | RR or OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary outcome, n/total n (%) | | | | |
| Newly developed ischemic lesion | 61/167(36.5) | 60/167(35.9) | 1.02 (0.77–1.35) | 0.91* |
| Secondary outcomes | | | | |
| mRS score | | | | |
| mRS score at 30 d, median (range) | 1 (0, 5) | 1 (0, 5) | 1.10 (0.74–1.64) | 0.65† |
| mRS 0–2 at 30 d, n/total n (%) | 103/151 (68.2) | 115/154 (74.68) | 0.73 (0.44–1.20) | 0.21* |
| Composite end point, n/total n (%) | 4/167 (2.40) | 6/166 (3.61) | 0.66 (0.19–2.31) | 0.52‡ |
| Any stroke, n (%) | 3/167 (1.80) | 5/166 (3.01) | 0.59 (0.14–2.46) | 0.50‡ |
| Ischemic stroke, n (%) | 2/167 (1.20) | 5/166 (3.01) | 0.39 (0.07–2.02) | 0.28‡ |
| Hemorrhagic stroke, n (%) | 1/167 (0.60) | 0 (0) | NA | >0.99‡ |
| Myocardial infarction, n (%) | 0 (0) | 1/166 (0.60) | NA | 0.50‡ |
| Vascular death, n (%) | 1/167 (0.60) | 0/166 (0) | NA | 0.50‡ |
| Any death, n (%) | 3/174 (1.72) | 0/178 (0) | NA | 0.12‡ |

All estimates of the clopidogrel plus aspirin vs aspirin monotherapy groups are relative risk (RR; 95% confidence interval [CI]) except for the analysis of modified Rankin Scale (mRS) outcome (odds ratio [OR]).

*$\chi^2$ test.

†Cochran–Mantel–Haenszel test.

‡Fisher exact test were used to calculate *P* value for variance.

intracranial hemorrhages; 1 requiring the transfusion of ≥4 units of blood; and 1 hypovolemic shock because of bleeding) in the clopidogrel plus aspirin group and in 2 patients (1 with decrease of hemoglobin level ≥5 g/dL and 1 requiring the transfusion of ≥4 units of blood) in the aspirin monotherapy group (*P*=0.40). Major bleeding not categorized as a life-threatening bleeding did not occur in the aspirin monotherapy group, but occurred in 3 patients in the clopidogrel plus aspirin group (3 patients had a systemic bleeding requiring transfusion of ≤3 units of blood; Table 3).

## Discussion

In this trial enrolling patients with acute ischemic stroke of presumed large artery atherothrombotic origin within 48 hours of onset, adding clopidogrel to aspirin for 30 days compared with aspirin alone did not reduce the risk of developing new ischemic lesion on MRI, clinical stroke recurrence, composite major vascular events, and functional disability. Although there was no statistical significance, the rates of bleeding event and mortality were numerically higher in the dual antiplatelet group than in the aspirin monotherapy group.

Our negative results are in contrast to the findings observed in CHANCE, which showed the benefit of clopidogrel plus aspirin for 21 days followed by clopidogrel alone over aspirin alone in terms of recurrent stroke and major vascular events. CHANCE enrolled patients with high-risk transient ischemic attack (TIA) or minor stroke (ischemic stroke subtypes were undetermined) within 24 hours (50% within 12 hours) and used a loading dose of 300 mg of clopidogrel. In contrast, our trial used a broader time window of 48 hours because MRI

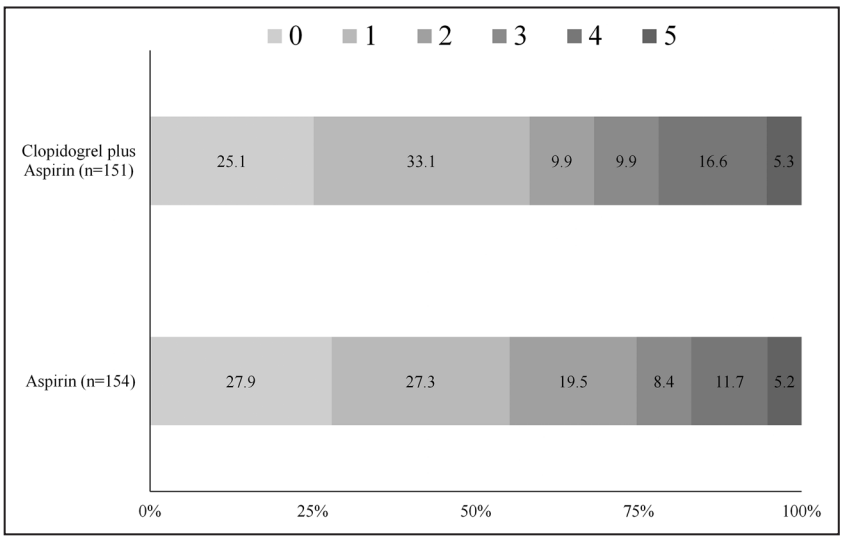


**Figure 2.** Scores on the modified Rankin Scale at 30 days.

**Table 3. Safety Outcomes**

| | Clopidogrel Plus Aspirin (n=174) | Aspirin Alone (n=178) | Relative Risk (95% CI) | *P* Value* |
|---|---|---|---|---|
| Any bleeding, n (%) | 29 (16.7) | 19 (10.7) | 1.59 (0.91–2.68) | 0.11 |
| Life threatening, n (%) | 4 (2.3) | 2 (1.1) | 2.05 (0.38–11.03) | 0.40 |
| Major, n (%) | 3 (1.7) | 0 (0) | NA | 0.19 |
| Minor, n (%) | 22 (12.6) | 17 (9.6) | 1.32 (0.73–2.41) | 0.36 |
| Life threatening or major, n (%) | 7 (4.0) | 2 (1.1) | 3.58 (0.75–17.00) | 0.11 |

*$\chi^2$ test or Fisher exact test were used to calculate *P* value for variance.

and MR angiography/computed tomographic angiography evaluation was required for patient selection. As a result, we were able to randomize only 21.8% of the patients within 24 hours. Although it was not statistically significant, there was a trend of interaction between treatment and time to randomization or time to treatment within 24 versus ≥24 hours (Table VIII in the online-only Data Supplement). In addition, we did not use a clopidogrel loading dose because of safety concern. Without a loading dose, maximum inhibition of ADP-induced platelet aggregation with daily doses of clopidogrel 75 mg has been shown to be achieved after 3 to 7 days in healthy subjects.[14] Therefore, we might miss the highest risk period when the benefit of dual antiplatelet therapy would be greatest.

Except for CHANCE, no trial demonstrated the clinical benefit of clopidogrel plus aspirin over aspirin alone in acute ischemic stroke. In the FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence) enrolling patients with TIA or minor stroke within 24 hours, clopidogrel plus aspirin was not superior to aspirin alone for reducing recurrent stroke and major vascular events.[15] In an earlier meta-analysis that did not include the CHANCE data, the benefit of clopidogrel plus aspirin over aspirin alone was not significant for recurrent stroke and composite of major vascular event.[16] In the CHANCE trial, the risk factor control rates during the follow-up were insufficient: antihypertensive agents in 35%, lipid-lowering agents in 42%, and antidiabetic agents in 13%, but traditional Chinese drugs in 25%. Therefore, the findings observed in CHANCE might not be replicated in populations with a higher adherence to risk factor control.

In patients with acute coronary syndrome, clopidogrel plus aspirin was superior to aspirin alone for preventing cardiac or major vascular events.[17,18] Among stroke subtypes, ischemic stroke caused by LAA might be most comparable to acute coronary syndrome. In 2 small trials enrolling patients with acute symptomatic large artery stenosis, clopidogrel plus aspirin was superior to aspirin alone in preventing micorembolism detected on transcranial Doppler ultrasound.[19,20] In SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), patients assigned to the medical therapy received clopidogrel plus aspirin for 90 days, and their recurrent stroke risk was much lower than observed among patients treated with aspirin monotherapy in the earlier WASID (Warfarin–Aspirin Symptomatic Intracranial Disease) trial. However, the intensity of risk factor control including high-intensity stain therapy and tight blood pressure control was greater and more comprehensive in SAMMPRIS than in WASID, which were likely to substantially contribute to the lower recurrent stroke risk than expected in the medical therapy group.[21,22] Therefore, in patients with symptomatic large artery stenosis, no randomized trial has confirmed the superiority of clopidogrel plus aspirin over aspirin alone. In the subgroup analysis of the CHANCE trial including 1089 patients with MR angiography images available, clopidogrel plus aspirin was not superior to aspirin alone for preventing recurrent stroke in those with and without intracranial stenosis. Of note, these patients had a lower recurrent stroke rate and higher rates of antihypertensive and lipid-lowering treatment than the overall CHANCE patients.[23] In our trial using an imaging surrogate marker for recurrent cerebral ischemic injury, we could not find any signal of benefit with clopidogrel plus aspirin over aspirin monotherapy in patients with acute ischemic stroke caused by LAA.

In this trial, the risk of life-threatening or major bleeding with clopidogrel plus aspirin compared with aspirin alone increased by >3-fold. Although there was no statistical significance, low statistical power might account for the nonsignificance. In the clopidogrel plus aspirin group, the 30-day rate of life-threatening or major bleeding was 4.0%, which was higher than 0.3% of the clopidogrel plus aspirin group in CHANCE (severe or moderate bleeding by the GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] definition). The 30-day risk of hemorrhagic stroke in the dual therapy group of this study was 0.6%, which was also greater than the 90-day hemorrhagic stroke risk of 0.3% in CHANCE. The differences in stroke severity (median National Institutes of Health Stroke Scale score of 3 versus TIA or minor stroke with National Institutes of Health Stroke Scale score <4) and age (median age, 67 versus 62) between our trial and CHANCE might, in part, account for the difference in bleeding risks.[5] In FASTER, the 90-day rate in the clopidogrel plus aspirin arm was 1.0% for intracranial hemorrhage and 3.0% for any symptomatic hemorrhage.[15] Therefore, the safety of short-term clopidogrel plus aspirin observed in CHANCE might not be generalized to broad range of patients with acute ischemic stroke.

The balance between ischemic and bleeding risks would be critical for choosing antiplatelet strategy. In our study, the 30-day rate of life-threatening or major bleeding in the clopidogrel plus aspirin was 4.0%, which was higher than the 30-day composite of major vascular event risk of 2.4%

in the clopidogrel plus aspirin group and 3.6% in the aspirin group. Therefore, concern remains on clopidogrel plus aspirin for patients with acute ischemic stroke, particularly for Korean patients.

In the current study, we found that overall 35.2% of patients had ischemic lesion recurrence within 30 days: the rate of 36.5% in the clopidogrel plus aspirin arm was higher than expected and that of 35.9% in the aspirin arm was lower than expected. In earlier studies, among patients who had an acute ischemic stroke caused by LAA and performed MRI within 24 hours from onset, the rate of new ischemic lesion recurrence was 50.0% within 7 days[10] and 61.1% within 90 days.[11] Our finding along with those of the earlier studies indicates that patients with acute ischemic stroke with LAA are at high risk of subsequent cerebral ischemic injury. The incidence of lesion recurrence on MRI compared with the recurrent clinical stroke incidence was approximated 15-fold greater in this study and 7.8- to 12-fold greater in earlier studies.[10,11] In a population-based, longitudinal cohort study, elderly people with new ischemic lesion on follow-up MRI had a greater cognitive decline, but only 11.4% of those with new ischemic lesion had a clinical stroke or TIA.[24] Therefore, despite of no apparent clinical stroke recurrence in most cases, recurrent ischemic lesion would be of clinical importance.

This study has several limitations. Any stenosis in the intracranial artery and >30% stenosis in the extracranial artery were eligible if the qualifying ischemic lesion was relevant to the territory of the arterial stenosis, it was not a small subcortical lesion, and no evidence of cardioembolic source was found at the time of randomization. Our broad criteria that were made by the consensus of the investigators would be subject to debate. This is a surrogate marker study, and the findings should be confirmed by a large randomized trial that uses an adequate clinical end point as a primary end point. More than 3 quarters of patients were enrolled between 24 and 48 hours from stroke onset, and we did not use a loading dose of clopidogrel. Therefore, the effect of dual antiplatelet therapy initiated in hyperacute stage was not fully explored. The follow-up duration was 30 days, which might be insufficient to detect a treatment effect for new ischemic lesion and particularly for clinical events. The ongoing POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial, which will enroll 5840 patients with high-risk TIA or minor stroke within 12 hours and uses 600-mg clopidogrel loading, would appropriately determine whether more aggressive antithrombotic therapy with clopidogrel plus aspirin versus aspirin alone, when initiated acutely, is more effective to prevent subsequent ischemic events.[25]

## Summary

In patients with acute ischemic stroke of presumed cause of LAA, clopidogrel plus aspirin might not be superior to aspirin alone for the prevention of recurrent ischemic lesion and clinical vascular events.

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## Disclosures

Dr Hong has received lecture honoraria from Sanofi-Aventis Korea and BMS Korea (modest). Dr Bae has served as a member of a scientific advisory board for BMS Korea and has received lecture honoraria from BMS Korea (modest). Dr Yoon has received lecture honoraria from Sanofi-Aventis Korea (modest). The other authors report no conflicts.

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# Recurrent Ischemic Lesions After Acute Atherothrombotic Stroke: Clopidogrel Plus Aspirin Versus Aspirin Alone

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Inclusion and Exclusion criteria

Inclusion criteria

1. Age of 30 years or older
2. Acute ischemic stroke confirmed by DWI
3. Atherosclerotic stenosis relevant to the index stroke on MRA or CTA:

   Degree of stenosis for the study inclusion was not specified and the decision for inclusion was at the discretion of responsible physician. However, for extracranial carotid stenosis, the stenosis should be more than 30% by the NASCET method
4. Initiation of study medication within 48 hours from stroke onset
5. Informed consent

Exclusion criteria

1. Presumed etiology of cardioembolism or small-vessel occlusion (subcortical lesion less than 2.0 cm on DWI without relevant stenosis)
2. Prior history of non-traumatic intracranial bleeding
3. Co-existing brain lesions such as intracranial bleeding or brain tumor
4. Planned conventional angiography, vascular intervention, or surgery before the end of study
5. Bleeding diathesis or coagulopathy
6. Anemia (Hb <8.0 d/dl) or low platelet count (<100,000/μl)
7. Hepatic dysfunction (AST or ALT>200 IU/L)
8. Renal dysfunction (serum creatinine >3.0 mg/dl)
9. Allergy to aspirin or clopidogrel
10. Thrombolytic treatment for the index stroke
11. Participated in another clinical trial within 30 days prior to screening
12. Pregnancy or lactation
13. Co-morbidity that would interfere study conduct and interpretation of results

14. Inability or unwillingness to comply with study-related procedures

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DWI: Diffusion weighted imaging

NASCET: North American Symptomatic Carotid Endarterectomy Trial

Supplemental Table II. The number of patient included in each analysis and the reasons for exclusion.

| | Clopidogrel plus aspirin | Aspirin alone |
|---|---|---|
| Randomization, n | 178 | 180 |
| No treatment, n | 2 | 4 |
| Consent withdrawal, n | 2 | 1 |
| Cross over, n | 2 (treated with ASA alone) | 0 |
| No follow-up MRI, n | 7 | 8 |
| No mRS evaluation at the end, n | 23 | 21 |
| No NIHSS score evaluation at the end, n | 23 | 21 |
| No data on composite endpoint, n | 7 | 9 |
| No data on recurrent stroke, n | 7 | 9 |
| Primary efficacy population (MRI), n | 167 | 167 |
| Safety population, n | 174 | 178 |
| mRS assessment, n | 151 | 154 |
| NIHSS score assessment, n | 151 | 154 |
| Composite endpoint assessment, n | 167 | 166 |
| Recurrent stroke assessment, n | 167 | 166 |

mRS: modified Rankin Scale, NIHSS: National Institute of Health Stroke Scale

Supplemental Table III. Vascular territory of the index stroke

| | Clopidogrel plus aspirin (n=174) | Aspirin alone (n=175) | p-value |
|---|---|---|---|
| ICA, n (%) | 6 (3.45) | 13 (7.43) | 0.1013[1)] |
| MCA, n (%) | 108 (62.07) | 121 (69.14) | 0.1642[1)] |
| ACA, n (%) | 6 (3.45) | 6 (3.43) | 0.9919[1)] |
| PCA, n (%) | 22 (12.64) | 14 (8.00) | 0.1538[1)] |
| VA, n (%) | 11 (6.32) | 4 (2.29) | 0.0630[1)] |
| SCA, n (%) | 7 (4.02) | 3 (1.71) | 0.2191[2)] |
| AICA, n (%) | 1 (0.57) | 0 (0.00) | 0.4986[2)] |
| PICA, n (%) | 13 (7.47) | 6 (3.43) | 0.0960[1)] |
| Border-zone, n (%) | 7 (4.02) | 10 (5.71) | 0.4630[1)] |
| BA, n (%) | 22 (12.64) | 15 (8.57) | 0.2166[1)] |

ICA: Internal Carotid A, MCA: Middle Cerebral A, ACA: Anterior Cerebral A, PCA: Posterior Cerebral A, BA: Basilar A, SCA: Superior Cerebellar A, AICA: Anterior Inferior Cerebellar A, PCA: Posterior Inferior Cerebellar A, VA: Vertebral A, BG/IC: Basal Ganglia/Internal Capsule

1) Chi-square test; 2) Fisher's exact test

Supplemental Table IV. Lesion location of the index stroke

| | Clopidogrel plus aspirin (n=174) | Aspirin alone (n=175) | P-value |
|---|---|---|---|
| Cortex, n (%) | 104 (59.77) | 104 (59.43) | 0.9482[1)] |
| Corona radiata, n (%) | 65 (37.36) | 68 (38.86) | 0.7728[1)] |
| BG/IC, n (%) | 42 (24.14) | 55 (31.43) | 0.1285[1)] |
| Thalamus, n (%) | 16 (9.20) | 14 (8.00) | 0.6904[1)] |
| Midbrain, n (%) | 3 (1.72) | 2 (1.14) | 0.6848[2)] |
| Pons, n (%) | 25 (14.37) | 12 (6.86) | 0.0227[1)] |
| Medulla, n (%) | 5 (2.87) | 4 (2.29) | 0.7503[2)] |
| Cerebellum, n (%) | 20 (11.49) | 8 (4.57) | 0.0173[1)] |
| Negative, n (%) | 0 (0.00) | 3 (1.71) | 0.2479[2)] |

1) Chi-square test; 2) Fisher's exact test

BG/IC: Basal Ganglia/Internal Capsule

Supplemental Table V. Distribution of arterial stenosis

| | Clopidogrel plus aspirin (n=174) | Aspirin alone (n=175) | P-value |
|---|---|---|---|
| Intracranial ICA_Right, n (%) | | | 0.6570[2)] |
| Normal | 153 (87.93) | 158 (90.29) | |
| Stenosis | 16 (9.20) | 14 (8.00) | |
| Occlusion | 5 (2.87) | 3 (1.71) | |
| Intracranial ICA_Left, n (%) | | | 0.6829[2)] |
| Normal | 158 (90.8) | 156 (89.14) | |
| Stenosis | 14 (8.05) | 18 (10.29) | |
| Occlusion | 2 (1.15) | 1 (0.57) | |
| Extracranial ICA_Right, n (%) | | | 0.0517[1)] |
| Normal | 146 (83.91) | 158 (90.29) | |
| Stenosis | 23 (13.22) | 10 (5.71) | |
| Occlusion | 5 (2.87) | 7 (4.00) | |
| Extracranial ICA_Left, n (%) | | | 0.6362[2)] |
| Normal | 144 (82.76) | 150 (85.71) | |
| Stenosis | 25 (14.37) | 22 (12.57) | |
| Occlusion | 5 (2.87) | 3 (1.71) | |
| M1_Right, n (%) | | | 0.2946[1)] |
| Normal | 134 (77.01) | 129 (73.71) | |
| Stenosis | 22 (12.64) | 32 (18.29) | |
| Occlusion | 18 (10.34) | 14 (8.00) | |
| M1_Left, n (%) | | | 0.8417[1)] |
| Normal | 134 (77.01) | 139 (79.43) | |
| Stenosis | 28 (16.09) | 26 (14.86) | |
| Occlusion | 12 (6.90) | 10 (5.71) | |
| MCA BRANCH_Right, n (%) | | | 0.2950[1)] |
| Normal | 156 (89.66) | 147 (84.00) | |
| Stenosis | 13 (7.47) | 20 (11.43) | |
| Occlusion | 5 (2.87) | 8 (4.57) | |
| MCA BRANCH_Left, n (%) | | | 0.1921[1)] |
| Normal | 159 (91.38) | 149 (85.14) | |
| Stenosis | 10 (5.75) | 18 (10.29) | |
| Occlusion | 5 (2.87) | 8 (4.57) | |
| ACA_Right, n (%) | | | 0.1507[2)] |
| Normal | 170 (97.7) | 163 (93.14) | |
| Stenosis | 3 (1.72) | 9 (5.14) | |
| Occlusion | 1 (0.57) | 3 (1.71) | |
| ACA_Left, n (%) | | | 0.0900[2)] |
| Normal | 163 (93.68) | 170 (97.14) | |
| Stenosis | 11 (6.32) | 4 (2.29) | |
| Occlusion | 0 (0.00) | 1 (0.57) | |
| PCA_Right, n (%) | | | 0.3424[2)] |
| Normal | 164 (94.25) | 158 (90.29) | |
| Stenosis | 6 (3.45) | 12 (6.86) | |
| Occlusion | 4 (2.30) | 5 (2.86) | |
| PCA_Left, n (%) | | | 0.2836[1)] |
| Normal | 157 (90.23) | 161 (92.00) | |
| Stenosis | 9 (5.17) | 11 (6.29) | |
| Occlusion | 8 (4.60) | 3 (1.71) | |

| | | | |
|---|---|---|---|
| BA, n (%) | | | 0.2930[2)] |
| Normal | 146 (83.91) | 157 (89.71) | |
| Stenosis | 26 (14.94) | 17 (9.71) | |
| Occlusion | 2 (1.15) | 1 (0.57) | |
| VA_Right, n (%) | | | 0.7874[2)] |
| Normal | 156 (89.66) | 160 (91.43) | |
| Stenosis | 14 (8.05) | 12 (6.86) | |
| Occlusion | 4 (2.30) | 3 (1.71) | |
| VA_Left, n (%) | | | 0.3319[2)] |
| Normal | 147 (84.48) | 156 (89.14) | |
| Stenosis | 22 (12.64) | 17 (9.71) | |
| Occlusion | 5 (2.87) | 2 (1.14) | |

1) Chi-square test; 2) Fisher's exact test

ICA: Internal Carotid A, MCA: Middle Cerebral A, ACA: Anterior Cerebral A, PCA: Posterior Cerebral A, BA: Basilar A, SCA: Superior Cerebellar A, AICA: Anterior Inferior Cerebellar A, PCA: Posterior Inferior Cerebellar A, VA: Vertebral A

Supplemental Table VI. Aspirin loading dose and adherence to study medications by treatment group

| | Clopidogrel plus Aspirin (N=174) | Placebo plus Aspirin (N=175) | *p*-value |
|---|---|---|---|
| Aspirin loading, n (%) | 159 (91.38) | 153 (87.43) | 0.23* |
| Aspirin loading dose (mg), median (range) | 300 (100, 600) | 300 (100, 500) | 0.82† |
| Aspirin treatment days during the trial, median (range) | 29 (1, 37) | 28 (2, 35) | 0.58† |
| Clopidogrel or placebo treatment days during the trial (days), median (range) | 29 (1, 36) | 28 (2, 35) | 0.74† |

*Chi-square test and †Wilcoxon rank sum test were used to calculate *p*-value for variance.

Supplemental Table VII. Characteristics of recurrent ischemic lesions

| | Clopidogrel plus Aspirin (n=61) | Aspirin alone (n=60) | P-value* |
|---|---|---|---|
| Same vascular territory, n (%) | 57 (93.4%) | 49 (83.1) | 0.93 |
| Size in diameter <10 mm, n (%) | 43 (70.5%) | 41 (69.5%) | 0.99 |
| Multiplicity, n (%) | 28 (45.9%) | 23 (39.0%) | 0.46 |
| Stroke mechanism | | | 0.49 |
| LAA, n (%) | 56 (91.8%) | 51 (86.4%) | |
| CE, n (%) | 0 (0%) | 2 (3.4%) | |
| SVO, n (%) | 0 (0%) | 1 (1.7%) | |
| Others, n (%) | 0 (0%) | 0 (0%) | |
| Undetermined, n (%) | 5 (8.2%) | 5 (8.5%) | |

*Fisher's exact test

LAA: large artery atherosclerosis, CE: cardioembolism, SVO: small vessel occlusion

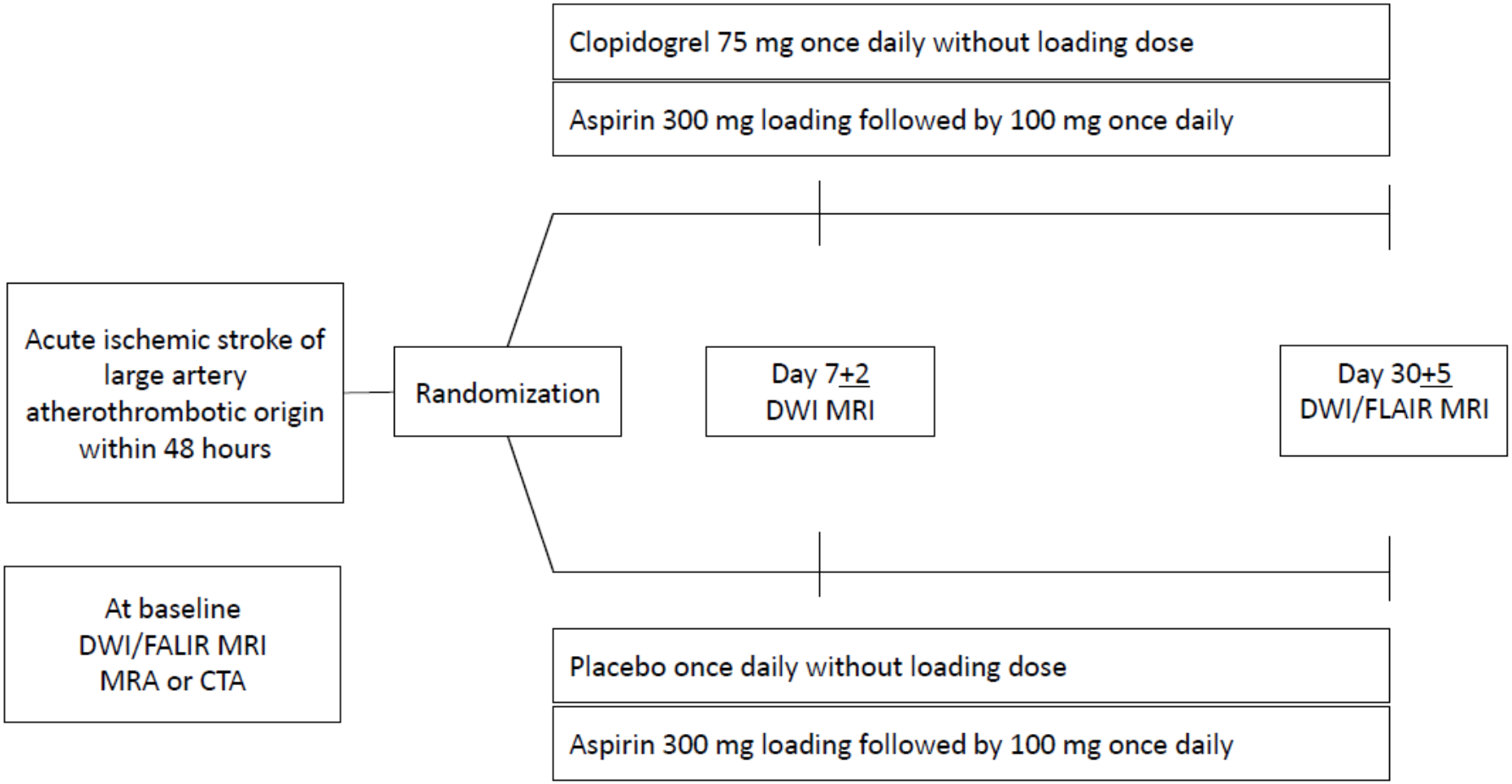
Supplemental Table VIII. Rates and relative risk for the primary endpoint in predefined subgroups

| Characteristics | No. of patients | Event rates, % | | Relative risk (95% CI) | p-value for variance | p-value for interaction |
|---|---|---|---|---|---|---|
| | | Clopidogrel plus Aspirin | Placebo plus Aspirin | | | |
| Overall | 349 | 36.53 | 35.93 | 1.016 (0.765-1.351) | 0.9094 | |
| Age | | | | | | 0.6547 |
| < 65 yr | 146 | 32.88 | 29.41 | 1.118 (0.683-1.830) | 0.6579 | |
| ≥ 65 yr | 203 | 39.36 | 40.40 | 0.9742 (0.689-1.378) | 0.8825 | |
| Sex | | | | | | 0.2731 |
| Male | 222 | 38.96 | 33.96 | 1.145 (0.803-1.634) | 0.4551 | |
| Female | 127 | 32.20 | 39.34 | 0.819 (0.505-1.328) | 0.4173 | |
| History of hypertension | | | | | | 0.3995 |
| Yes | 231 | 38.89 | 41.07 | 0.947 (0.685-1.309) | 0.7413 | |
| No | 118 | 32.20 | 25.45 | 1.265 (0.705-2.2697) | 0.4303 | |
| History of diabetes | | | | | | 0.5131 |
| Yes | 113 | 35.71 | 30.00 | 1.191 (0.687-2.064) | 0.5346 | |
| No | 236 | 36.94 | 38.46 | 0.960 (0.688-1.341) | 0.8124 | |
| History of hypercholesterolemia | | | | | | 0.1885 |
| Yes | 109 | 44.83 | 34.04 | 1.317 (0.807-2.149) | 0.2707 | |
| No | 240 | 32.11 | 36.67 | 0.876 (0.611-1.256) | 0.4704 | |
| History of ischemic stroke | | | | | | 0.1848 |
| Yes | 36 | 55.00 | 30.77 | 1.788 (0.722-4.426) | 0.2093 | |
| No | 313 | 34.01 | 36.36 | 0.935 (0.688-1.272) | 0.6699 | |
| Lipid-lowering agents | | | | | | 0.6729 |
| Yes | 52 | 40.74 | 34.78 | 1.171 (0.570-2.409) | 0.6674 | |
| No | 297 | 35.71 | 36.11 | 0.989 (0.725-1.350) | 0.9444 | |
| Time to randomization | | | | | | 0.0801 |
| < 24 hr | 74 | 28.13 | 45.95 | 0.612 (0.318-1.178) | 0.1419 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥ 24 hr | 272 | 38.35 | 32.56 | 1.178 (0.848-1.636) | 0.3294 | |
| Time to treatment | | | | | | 0.0661 |
| < 24 hr | 63 | 24.00 | 45.71 | 0.525 (0.239-1.152) | 0.1079 | |
| ≥ 24 hr | 286 | 38.73 | 33.33 | 1.162 (0.846-1.597) | 0.3545 | |
| Hospital factor #1 | | | | | | 0.5359 |
| <15 enroll | 80 | 44.44 | 37.50 | 1.185 (0.690-2.037) | 0.5387 | |
| ≥15 enroll | 269 | 34.35 | 35.43 | 0.970 (0.695-1.353) | 0.8553 | |
| Hospital factor #2 | | | | | | 0.2450 |
| <850 beds | 139 | 38.46 | 30.30 | 1.269 (0.787-2.047) | 0.3282 | |
| ≥850 beds | 210 | 35.29 | 39.60 | 0.891 (0.624-1.273) | 0.5264 | |
| Lesion location | | | | | | 0.8575 |
| Cortical only | 92 | 36.59 | 37.50 | 0.976 (0.566-1.681) | 0.9291 | |
| Non-cortical | 257 | 36.51 | 35.29 | 1.034 (0.740-1.446) | 0.8432 | |
| Vascular territory #1 | | | | | | 0.5994 |
| Anterior circulation | 252 | 42.86 | 38.76 | 1.106 (0.815-1.499) | 0.5179 | |
| Posterior circulation | 97 | 23.64 | 26.32 | 0.898 (0.440-1.833) | 0.7679 | |
| Vascular territory #2 | | | | | | 0.2818 |
| MCA | 229 | 44.23 | 38.60 | 1.146 (0.835-1.573) | 0.3988 | |
| Others | 120 | 23.81 | 30.19 | 0.789 (0.432-1.440) | 0.4398 | |

MCA: Middle Cerebral A

Supplemental Figure I. Study design.



Supplemental Figure II. Relative risk for the primary outcome in predefined subgroups