

ORIGINAL ARTICLE

Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke

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ABSTRACT

BACKGROUND

Recurrent stroke is a frequent, disabling event after ischemic stroke. This study compared the efficacy and safety of two antiplatelet regimens — aspirin plus extended-release dipyridamole (ASA-ERDP) versus clopidogrel.

METHODS

In this double-blind, 2-by-2 factorial trial, we randomly assigned patients to receive 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily or to receive 75 mg of clopidogrel daily. The primary outcome was first recurrence of stroke. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. Sequential statistical testing of noninferiority (margin of 1.075), followed by superiority testing, was planned.

RESULTS

A total of 20,332 patients were followed for a mean of 2.5 years. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11). The secondary outcome occurred in 1333 patients (13.1%) in each group (hazard ratio for ASA-ERDP, 0.99; 95% CI, 0.92 to 1.07). There were more major hemorrhagic events among ASA-ERDP recipients (419 [4.1%]) than among clopidogrel recipients (365 [3.6%]) (hazard ratio, 1.15; 95% CI, 1.00 to 1.32), including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11 to 1.83). The net risk of recurrent stroke or major hemorrhagic event was similar in the two groups (1194 ASA-ERDP recipients [11.7%], vs. 1156 clopidogrel recipients [11.4%]; hazard ratio, 1.03; 95% CI, 0.95 to 1.11).

CONCLUSIONS

The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke. (ClinicalTrials.gov number, NCT00153062.)

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This article (10.1056/NEJMoa0805002) was published at www.nejm.org on August 27, 2008.

N Engl J Med 2008;359.

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RECURRENT STROKE IS AN IMPORTANT vascular event affecting the life of survivors of ischemic stroke.¹ Multiple randomized trials have proved the efficacy of antiplatelet agents for the prevention of recurrent stroke after non-cardioembolic stroke.²⁻¹¹ Antiplatelet options for the prevention of recurrent stroke include aspirin (50 mg to 325 mg per day), the combination of low-dose aspirin and extended-release dipyridamole, and clopidogrel alone.^{12,13}

Aspirin has been shown to reduce the risk of stroke recurrence by about 23% as compared with placebo.⁷ Studies of clopidogrel have suggested an 8% relative risk reduction of stroke recurrence, as compared with aspirin, among stroke patients, whereas studies of aspirin plus extended-release dipyridamole have suggested relative risk reductions of 20 to 23% as compared with aspirin alone.^{4,5,10,11} Indirect comparisons suggested that aspirin plus extended-release dipyridamole was superior to clopidogrel in the prevention of recurrent stroke.¹⁴

Although the combination of two antiplatelet agents with different mechanisms of action may be more effective in preventing recurrent stroke than either is alone, increased bleeding may result. Two trials have shown that the combination of aspirin and extended-release dipyridamole is better than aspirin alone for prevention of recurrent stroke — as well as stroke, myocardial infarction, and death from vascular causes — without increasing the risk of major bleeding.^{5,10,11} Among stroke patients with multiple risk factors, the addition of aspirin to clopidogrel is not more efficacious than clopidogrel alone but significantly increases the incidence of bleeding.⁸ Moderate bleeding is increased with the use of clopidogrel and aspirin, as compared with aspirin alone, in secondary and primary prevention.^{15,16}

There is no guideline for using one of these therapies over the other.^{12,17} Thus, in this trial, we aimed to compare the relative efficacy and safety of aspirin plus extended-release dipyridamole with that of clopidogrel among patients who had a recent ischemic stroke.¹⁸

METHODS

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial was a 2-by-2 factorial, double-blind, active and placebo-controlled study of the fixed combination of low-dose aspirin (25 mg) and extended-release dipyridamole

(200 mg) given twice daily as compared with clopidogrel (75 mg) given once daily, and of telmisartan (80 mg once daily) as compared with placebo, in patients with a recent ischemic stroke. This article focuses on the antiplatelet comparison within the factorial design. The antiplatelet part of the factorial design was initially intended to compare clopidogrel plus aspirin with aspirin plus extended-release dipyridamole. The design was modified, after 2027 patients were randomly assigned, when the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent TIA or Ischemic Stroke (MATCH) trial demonstrated an increased risk of bleeding with the combination of clopidogrel and aspirin.⁸ Patients initially assigned to receive clopidogrel plus aspirin had been treated for up to 8 months before they were switched to clopidogrel alone at the time of the protocol amendment; 18,305 patients were subsequently randomly assigned to receive aspirin plus extended-release dipyridamole or clopidogrel alone.

Details of the trial design have been published previously.¹⁸ The steering committee designed and oversaw the trial; data management was performed by the sponsor (Boehringer Ingelheim). A trial management committee, with representatives from the steering committee and the sponsor, met regularly to evaluate progress. The coauthors and the members of the steering committee had complete access to the trial data and prepared the final manuscript, and they vouch for the design, the final statistical analysis, and the completeness, accuracy, and interpretation of the data. The final statistical analyses were conducted simultaneously by the independent statisticians at the Medical University of South Carolina (who provided data and interim analysis reports to the data and safety monitoring committee) and the statisticians from Boehringer Ingelheim.

The protocol was approved by the appropriate regulatory authorities and ethics committees or institutional review boards. All patients provided written informed consent.

ELIGIBILITY

The inclusion criteria were a recent ischemic stroke (within <90 days before randomization), defined by symptoms persisting for more than 24 hours or symptoms of a shorter duration but with evidence of a recent brain infarction on a computed tomographic scan or magnetic resonance imaging; clinical and neurologic stability before randomization; and an age of 55 years or older. Patients

were excluded if they had contraindications to one of the antiplatelet agents or were otherwise unsuitable for randomization.¹⁸ After approximately 6000 patients had been enrolled, a protocol amendment was introduced to enhance recruitment and permit the inclusion of younger patients (50 to 54 years of age) or those with less recent strokes (within 90 to 120 days before randomization) if they also had at least two additional vascular risk factors.¹⁸

RANDOMIZATION AND TREATMENT

Eligible and consenting patients were randomly assigned, through a central telephone randomization system, to receive either aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily or clopidogrel (75 mg daily) and telmisartan (80 mg daily) or placebo. Patients were evaluated in the hospital at the time of discharge or at 1 week after discharge and then at 1, 3, and 6 months and every 6 months thereafter.

OUTCOME EVENTS

The primary outcome was recurrent stroke of any type. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. The tertiary outcomes are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org). The primary and secondary outcomes, and episodes of major bleeding, were adjudicated by a central committee. If a patient had a recurrence of ischemic stroke, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used to classify the event.¹⁹ Three months after the recurrence of stroke, the degree of disability was assessed according to the modified Rankin scale (with scores ranging from 0 to 6 and higher scores indicating greater disability) and the Barthel index (with scores ranging from 0 to 100 and higher scores indicating less disability).^{20,21} Definitions for hemorrhagic events (major, life-threatening, intracranial, and minor) are listed in the Supplementary Appendix.

DATA MONITORING

An independent data and safety monitoring committee regularly monitored the safety and quality of the data of the trial. Two formal interim efficacy analyses were performed with the use of modified Haybittle–Peto²² boundaries to test the null hypotheses of no difference between treatment groups, with thresholds of $P < 0.0001$ when

one third of expected events had occurred and $P < 0.001$ when two thirds of the expected events had occurred.

STATISTICAL ANALYSIS

This event-driven trial was originally designed to test the superiority of aspirin plus extended-release dipyridamole over clopidogrel in 15,500 patients, modified to 20,000 patients after six protocol amendments owing to lower-than-expected numbers of primary outcome events. With this amended sample size, the trial had a statistical power of 82% to detect a 13% relative risk reduction after 1715 strokes had occurred.

A sequential analysis for the antiplatelet comparison was developed and planned to first test the noninferiority of aspirin plus extended-release dipyridamole as compared with clopidogrel. If this condition was satisfied, then the superiority of aspirin plus extended-release dipyridamole over clopidogrel could be assessed in a second test of the conventional null hypothesis of no difference between the two treatments.

Confirmation of noninferiority in this trial involved the prespecification of a hazard ratio for aspirin plus extended-release dipyridamole, as compared with clopidogrel, that is below a predefined margin. The margin was defined in the following way. Using data from the nonfatal stroke outcomes from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial⁴ and from the meta-analysis by the Antithrombotic Trialists' Collaboration,⁷ and following the method of Fisher et al.,²³ we derived an estimated odds ratio for clopidogrel being better than placebo for the outcome of nonfatal stroke: 1.377 (95% confidence interval [CI], 1.155 to 1.645). Thus, to ensure that the aspirin plus extended-release dipyridamole preserved at least half the effect of clopidogrel, the noninferiority margin was set at 1.075, an effect size equal to half the lower limit of the confidence interval. To reject the inferiority null hypothesis, the upper boundary of the 95% confidence interval for the hazard ratio must lie below the value of 1.075 (an increase of 7.5% in the hazard associated with aspirin plus extended-release dipyridamole). With 1715 recurrent strokes, we would have a statistical power of 82% to reject the inferiority null hypothesis, assuming a 6.5% relative risk reduction with aspirin plus extended-release dipyridamole as compared with clopidogrel.

The primary analysis was of the time to the first recurrence of stroke. The Cox proportional-

hazards regression model was prespecified for analysis of this outcome and had as covariates the baseline values for age, diabetes status, use or nonuse of angiotensin-converting-enzyme inhibitors, and score on the modified Rankin scale. Before conducting the antiplatelet comparison, on the basis of data aggregated across the telmisartan and placebo groups, we performed a test of interaction (with a prespecified alpha value of 1%). The antiplatelet noninferiority comparison was then conducted with a one-sided alpha value of 2.5%; the test of superiority was two-sided with an alpha value of 5%. All analyses were performed according to the intention-to-treat principle, involved a time-to-event approach, and included all randomized patients.

Subgroup analyses for the primary outcome and for major vascular events were performed for prespecified baseline features. These included a history of vascular disease, alcohol use, and a stroke risk score generated from the overall trial data (i.e., age, sex, degree of physical activity, baseline systolic blood pressure, and history of hypertension, diabetes, myocardial infarction, atrial fibrillation, peripheral arterial disease, and stroke before the qualifying event).

RESULTS

A total of 20,333 patients were enrolled from 695 centers in 35 countries. One patient who did not give written informed consent was randomized in error but never received a study drug or underwent follow-up and was not included in the study database. Therefore, the data are reported for 20,332 patients: 10,181 recipients of aspirin plus extended-release dipyridamole and 10,151 recipients of clopidogrel. The trial commenced on September 11, 2003, and patients were followed until the end of the trial on February 8, 2008. The mean duration of follow-up was 2.5 years (range, 1.5 to 4.4); 1495 patients (7.4%) died during the study and 125 patients (0.6% in each treatment group) were lost to follow-up.

Baseline characteristics were balanced across the two treatment groups (Table 1). The mean age was 66.1 years, and 36.0% were women. Almost one quarter of the patients had a history of stroke or transient ischemic attack before the index stroke; 74.0% had a history of hypertension, 46.7% of dyslipidemia, 28.2% of diabetes, and 16.3% of ischemic coronary artery disease. The median time from the qualifying stroke to randomization was

15 days, and 39.8% of patients were randomized within 10 days after that event. The most frequent type of ischemic stroke was small-artery occlusion (lacune), in 52.0% of patients, whereas 28.6% had large-artery atherosclerosis.

Premature discontinuation of the study drug was significantly more frequent among patients receiving aspirin plus extended-release dipyridamole (2961 patients [29.1%]) than among those receiving clopidogrel (2290 [22.6%], $P < 0.001$). Medication compliance, defined as taking the study medication more than 75% of the time, was greater in the clopidogrel group (76.8%) than in the group receiving aspirin and extended-release dipyridamole (69.6%).

PRIMARY OUTCOME

Confirmed first recurrence of stroke occurred in 1814 patients. There was no interaction between the treatment benefit of the antiplatelet treatment and telmisartan ($P = 0.35$). The primary outcome of first recurrence of stroke occurred in 916 recipients (9.0%) of aspirin plus extended-release dipyridamole and 898 recipients (8.8%) of clopidogrel (hazard ratio, 1.01; 95% CI, 0.92 to 1.11) (Table 2 and Fig. 1A). Although the hazard ratio is very close to 1.00 (representing equivalence), the upper limit of the confidence interval extends beyond the prespecified noninferiority margin of 1.075.

Ischemic stroke accounted for 87.4% (1585 of 1814) of the recurrent strokes (Fig. 2). Although there were 25 fewer ischemic recurrent strokes in the group receiving aspirin plus extended-release dipyridamole than in the group receiving clopidogrel, recipients of aspirin and extended-release dipyridamole had 5 more recurrent strokes of other or unknown causes and 38 more hemorrhagic strokes. Despite this excess of hemorrhagic strokes, the number of patients with fatal or disabling strokes (defined by a score of ≥ 3 on the modified Rankin scale at 3 months after the recurrence of stroke) was similar in the two groups: 413 (4.1%) in the aspirin-extended-release dipyridamole group and 392 (3.9%) in the clopidogrel group (hazard ratio, 1.05; 95% CI, 0.96 to 1.16). In analyses based on the treatment received, the results for the primary outcome were virtually the same in the two groups, with recurrent stroke occurring in 777 patients (7.6%) receiving aspirin plus extended-release dipyridamole and in 777 patients (7.7%) receiving clopidogrel (hazard ratio, 1.07; 95% CI, 0.97 to 1.18).

Characteristic	Aspirin-ERDP (N=10,181)	Clopidogrel (N=10,151)
Age (yr)	66.1±8.6	66.2±8.5
Female sex (%)	35.9	36.0
Region (%)		
Asia	31.8	31.7
Europe, Israel, or Australia	38.1	38.4
Latin America or South Africa	5.6	5.6
United States or Canada	24.5	24.2
Ethnic group (%)†		
African	4.0	4.1
Chinese	18.1	17.9
South Asian	8.3	8.5
Other Asian	6.2	6.4
White/European	57.7	57.3
Native Latin	4.9	4.9
Other	0.8	0.9
BMI‡	26.8±5.0	26.8±5.0
Waist circumference (cm)	96.2±14.1	96.7±14.0
Tobacco use (%)		
Never	42.5	42.8
Currently	21.3	21.0
Previously	36.2	36.1
Alcohol use (%)		
No regular consumption	64.4	64.9
1–14 drinks/wk	29.6	29.2
15+ drinks/wk	5.4	5.2
Obesity (%)§	25.4	25.9
Exercise category (%)		
Sedentary	35.6	35.7
Some physical activity	31.9	31.8
Intense physical activity	32.0	31.8
Time from qualifying stroke to randomization		
Median (days)	15	15
≤10 days (%)	39.6	40.0
11–30 days (%)	29.1	28.8
31–90 days (%)	27.7	27.5
>90 days (%)	3.3	3.5
TOAST classification of qualifying stroke (%)		
Large-artery atherosclerosis	28.8	28.3
Cardioembolism	1.8	1.8
Small-artery occlusion (lacune)	52.0	52.1
Acute stroke of other determined cause	2.0	2.1
Stroke of undetermined cause	15.4	15.6

Table 1. (Continued.)

Characteristic	Aspirin-ERDP (N=10,181)	Clopidogrel (N=10,151)
Score on modified Rankin scale (%)¶		
0	13.9	14.1
1	37.3	37.3
2	24.9	25.1
3-5	23.9	23.5
Baseline NIHSS score (%)		
0-1	39.6	40.0
2-3	29.3	29.6
4-5	16.7	16.3
6-14	13.6	13.5
>14	0.8	0.7
Previous stroke or TIA (%)	24.2	24.9
Previous stroke	18.1	18.4
TIA	8.6	8.8
Atherosclerotic disease (%)	19.3	19.5
MI	6.7	6.7
Ischemic coronary artery disease	16.1	16.4
PAOD	2.9	3.0
CHF (%)	2.6	2.6
Hypertension (%)	74.4	73.6
Diabetes mellitus (%)	28.5	28.0
Hyperlipidemia (%)	46.5	46.8
Atrial fibrillation (%)	2.7	2.6
Valvular disease (%)	1.7	1.7
Deep-vein thrombosis (%)	1.5	1.5

* Plus-minus values are means \pm SD. P values for all comparisons between the two groups were greater than 0.05 except for waist circumference, for which P=0.02. CHF denotes congestive heart failure, ERDP extended-release dipyridamole, MI myocardial infarction, PAOD peripheral arterial obstructive disease, TIA transient ischemic attack, and TOAST Trial of Org 10172 in Acute Stroke Treatment.

† Ethnic group was self-reported. The term Native Latin refers to Latin American ethnic background.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Obesity was defined as a BMI of 27 or more for Asian patients and 30 or more for all others.

¶ Scores on the modified Rankin scale ranged from 0 to 5, with higher scores indicating greater disability.

|| Higher scores on the National Institutes of Health Stroke Scale (NIHSS) indicate worse stroke severity.

SECONDARY AND TERTIARY OUTCOMES

The numbers of patients with the secondary outcome of stroke, myocardial infarction, or death from vascular causes were identical in the two groups: 1333 patients (13.1%) (hazard ratio for aspirin plus extended-release dipyridamole vs. clopidogrel, 0.99; 95% CI, 0.92 to 1.07) (Table 2 and Fig. 1B). The rates of most tertiary (efficacy) outcomes were similar in the two groups (Table 2). The rate of new or worsening congestive heart failure was significantly lower in the group receiving

aspirin plus extended-release dipyridamole (144 patients [1.4%]) than in the group receiving clopidogrel (182 patients [1.8%]; hazard ratio, 0.78; 95% CI, 0.62 to 0.96). There was no significant difference in the rate of recurrent stroke or major hemorrhagic event between the recipients of aspirin plus extended-release dipyridamole (1194 [11.7%]) and the recipients of clopidogrel (1156 [11.4%]; hazard ratio, 1.03; 95% CI, 0.95 to 1.11). Our post hoc analysis comparing the rates of the secondary outcome or major hemorrhage, like that

Table 2. Hazard Ratios for Primary, Secondary, and Key Tertiary Efficacy and Safety Outcomes.*

Outcome	Aspirin-ERDP (N=10,181)	Clopidogrel (N=10,151)	Hazard Ratio for Aspirin-ERDP (95% CI)
	number (percent)		
Primary outcome: recurrent stroke	916 (9.0)	898 (8.8)	1.01 (0.92–1.11)
Secondary outcome: composite of vascular events (stroke, MI, or death from vascular causes)	1333 (13.1)	1333 (13.1)	0.99 (0.92–1.07)
Tertiary outcome			
MI	178 (1.7)	197 (1.9)	0.90 (0.73–1.10)
Death from vascular causes	435 (4.3)	459 (4.5)	0.94 (0.82–1.07)
Death from any cause	739 (7.3)	756 (7.4)	0.97 (0.87–1.07)
New or worsening CHF†	144 (1.4)	182 (1.8)	0.78 (0.62–0.96)
Other vascular event	533 (5.2)	517 (5.1)	1.03 (0.91–1.16)
First ischemic stroke‡	789 (7.7)	807 (7.9)	0.97 (0.88–1.07)
First recurrence of stroke or major hemorrhagic event	1194 (11.7)	1156 (11.4)	1.03 (0.95–1.11)
Safety outcome			
Major hemorrhagic event§	419 (4.1)	365 (3.6)	1.15 (1.00–1.32)
Life-threatening	128 (1.3)	116 (1.1)	
Non-life-threatening	291 (2.9)	249 (2.5)	
Hemorrhagic event (minor or major)¶	535 (5.3)	494 (4.9)	1.08 (0.96–1.22)
Intracranial hemorrhage	147 (1.4)	103 (1.0)	1.42 (1.11–1.83)
Intracerebral hemorrhage (hemorrhagic stroke)	90 (0.9)	55 (0.5)	
Fatal	28 (0.3)	29 (0.3)	
Nonfatal	62 (0.6)	26 (0.3)	
Intraocular hemorrhage	22 (0.2)	22 (0.2)	
Nonstroke intracranial hemorrhage	35 (0.3)	26 (0.3)	
TTP or neutropenia	7 (0.1)	8 (0.1)	0.89 (0.32–2.44)

* Covariates in the Cox model were baseline values for age, use or nonuse of angiotensin-converting-enzyme inhibitor, score on the modified Rankin scale, and baseline diabetes status. Differences between the treatment groups were not significant unless otherwise stated. CHF denotes congestive heart failure, ERDP extended-release dipyridamole, MI myocardial infarction, and TTP thrombotic thrombocytopenic purpura.

† P=0.02 for the hazard ratio for CHF.

‡ Data on first ischemic stroke are from the 780 patients in the aspirin-ERDP group and the 805 patients in the clopidogrel group, with a stroke contributing to the primary outcome, plus 9 more and 2 more patients, respectively, with an ischemic stroke.

§ Major hemorrhagic event (life-threatening or non-life-threatening) was defined as a hemorrhagic event that resulted in clinically significant disability, symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or the equivalent amount of whole blood, or the need for hospitalization. Life-threatening hemorrhagic events were defined as those that were fatal or that required use of intravenous inotropic medication to maintain blood pressure, surgical intervention, or transfusion of 4 or more units of red cells or the equivalent amount of whole blood. Non-life-threatening hemorrhagic events were defined as those classified as major hemorrhagic events but not as life-threatening.

¶ All hemorrhagic events leading to interruption of therapy were classified as such by the investigator. Bleeding events related to surgical procedures were classified as hemorrhagic events. Bleeding events due to accidental trauma were not classified as hemorrhagic events.

|| P=0.006 for the hazard ratio for intracranial hemorrhage.

performed in the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT; ClinicalTrials.gov number, NCT00161070)¹⁰ showed no differences between the two groups (1572 patients [15.4%] receiving aspirin plus extended-release dipyridamole and 1563 patients [15.4%] receiving clopidogrel; hazard ratio, 1.00; 95% CI, 0.93 to 1.07).

SUBGROUP ANALYSES

The relative difference with regard to the primary outcome of first recurrence of stroke between the

group receiving aspirin plus extended-release dipyridamole and the clopidogrel group was consistent across multiple prespecified and exploratory subgroups based on baseline characteristics (Fig. 3).

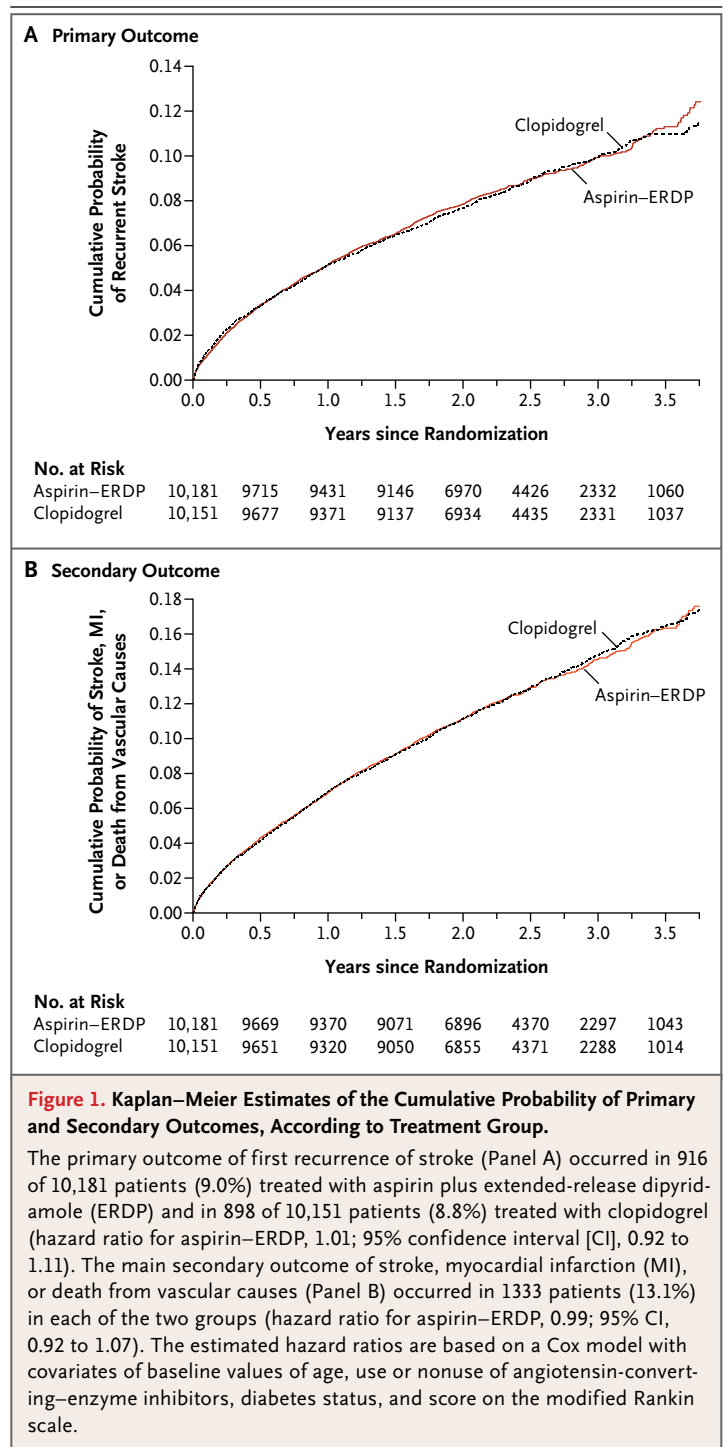
SAFETY OUTCOMES

Major hemorrhagic events occurred more frequently among recipients of aspirin plus extended-release dipyridamole (419 patients [4.1%]) than among recipients of clopidogrel (365 patients [3.6%]; hazard ratio, 1.15; 95% CI, 1.00 to 1.32). Intracranial hemorrhage (including the 128 hemorrhagic strokes counted in the primary outcome) were significantly more frequent in patients receiving aspirin plus extended-release dipyridamole (147 patients [1.4%], vs. 103 patients receiving clopidogrel [1.0%]; hazard ratio, 1.42; 95% CI, 1.11 to 1.83). There were no significant differences between the two groups in the frequency of death, any hemorrhagic event (major or minor), or thrombotic thrombocytopenic purpura or neutropenia (Table 2). The most commonly reported serious adverse events (in at least 0.4% of patients) are reported in the Supplementary Appendix.

Adverse events leading to permanent discontinuation of the study medication were increased in the group receiving aspirin plus extended-release dipyridamole (1650 patients [16.4%]) as compared with the group receiving clopidogrel (1069 patients [10.6%]). Discontinuations due to adverse events occurred earlier with aspirin plus extended-release dipyridamole, with 49.6% of all such discontinuations occurring within the first 2 months as compared with 32.5% of those in the clopidogrel group. Permanent discontinuation of study medication due to headache was more frequent among recipients of aspirin plus extended-release dipyridamole (593 [5.9%]) than among recipients of clopidogrel (87 [0.9%]). Headache also occurred more frequently in the group receiving aspirin and extended-release dipyridamole (30.2% of patients by day 7, vs. 10.2% in the group receiving clopidogrel). Incidence rates for selected adverse events leading to discontinuation are listed in Table 3 (with all occurring in at least 0.1% of patients reported in the Supplementary Appendix).

DISCUSSION

The PROfESS trial provides important evidence regarding the direct comparison of two antiplatelet agents after noncardioembolic stroke. All antiplatelet agents tested in this trial were already



approved for the prevention of recurrent stroke in most of the participating countries. The trial did not meet the predefined statistical criteria for non-inferiority, but it showed similar rates of recurrent stroke in the group receiving aspirin and extended-release dipyridamole and in the group receiving

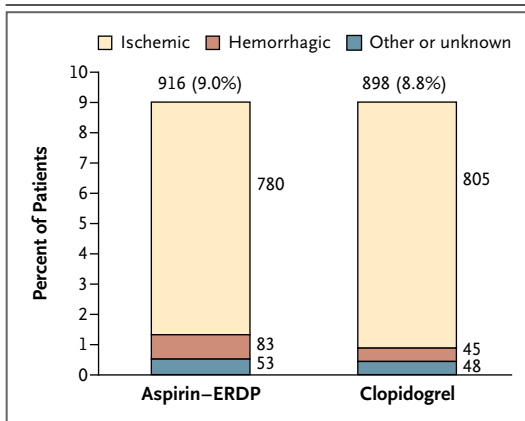


Figure 2. Frequency of Types of Recurrent Stroke among the Study Patients, According to Treatment Group.

The mean follow-up period was 2.5 years. Numbers of patients in each stroke category are given to the right of the bar and total numbers are given on top. The hazard ratio for recurrent stroke among patients receiving aspirin plus extended-release dipyridamole (ERDP), as compared with those receiving clopidogrel, was 1.01 (95% confidence interval, 0.92 to 1.11).

clopidogrel. Therefore, the study does not show that either aspirin plus extended-release dipyridamole or clopidogrel is superior to the other in the prevention of recurrent stroke.

There were more hemorrhagic strokes with aspirin plus extended-release dipyridamole than with clopidogrel. However, there was no significant difference in the risk of fatal or disabling stroke. Although indirect evidence from previous randomized trials with aspirin as a comparison drug had suggested that aspirin plus extended-release dipyridamole was more effective than clopidogrel for the prevention of stroke recurrence, direct comparisons within a randomized trial are the most valid estimates of comparative treatment efficacy. The trial results emphasize the need for direct comparisons between active antiplatelet agents in the context of prevention of recurrent stroke. Indirect comparisons are limited by differences in antiplatelet trial designs, populations of patients, choice of drugs to compare with aspirin, and definitions of the primary outcomes.²⁴

Despite similar rates of recurrent stroke in our two treatment groups, we were not able to make a claim of noninferiority. The trial was designed to demonstrate the superiority of aspirin plus extended-release dipyridamole, assuming a 13% relative risk reduction with 82% power. Given

Figure 3 (facing page). Hazard Ratios for the Primary Outcome of First Recurrence of Stroke, According to Prespecified and Post Hoc Baseline Characteristics.

The hazard ratios are for recurrent stroke among patients receiving aspirin plus extended-release dipyridamole (ERDP) as compared with those receiving clopidogrel. The sizes of the squares are proportional to the number of events. All tests for interaction between treatment group and subgroup had P values greater than 0.05, except for history of hypertension, for which P=0.05. See the Supplementary Appendix for the calculation of stroke risk score. Ethnic group was self-reported. ACE denotes angiotensin-converting enzyme, TIA transient ischemic event, and TOAST Trial of Org 10172 in Acute Stroke Treatment.

the uncertainty about indirect comparisons, we added a noninferiority test with a conservative delta value as a precursor to the superiority test. Power calculations showed that the trial would have a statistical power of 82% to show noninferiority if the relative risk reduction for aspirin plus extended-release dipyridamole as compared with clopidogrel was only 6.5%. Given equivalent efficacies of the two treatments, the trial was substantially underpowered (with only 30% power) to show noninferiority. Furthermore, we chose a very conservative noninferiority margin of 7.5%. Although some statistical guidelines for the derivation of a noninferiority margin have been published,²⁵⁻²⁷ the choice of margin is still controversial.^{28,29} If noninferiority is declared, then the clinician may conclude that one treatment is as good as or better than the other. If noninferiority is not found, the clinician cannot be confident, within the specified noninferiority margin, that the treatment of interest is at least as good as the other. Nor can the clinician conclude that the comparison treatment is noninferior to or better than the treatment of interest.

The rates of the composite outcome of stroke, myocardial infarction, or death from vascular causes were identical in the two treatment groups, with narrow confidence intervals, suggesting that there is little likelihood for a clinically important difference between the two regimens with regard to these events. The rates of primary and secondary outcomes were consistent across multiple baseline risk factors. Our trial adds to the evidence that recurrent stroke is the most frequent vascular event among survivors of stroke. Randomized trials involving aspirin added to clopidogrel as compared with aspirin alone have suggested stronger effects

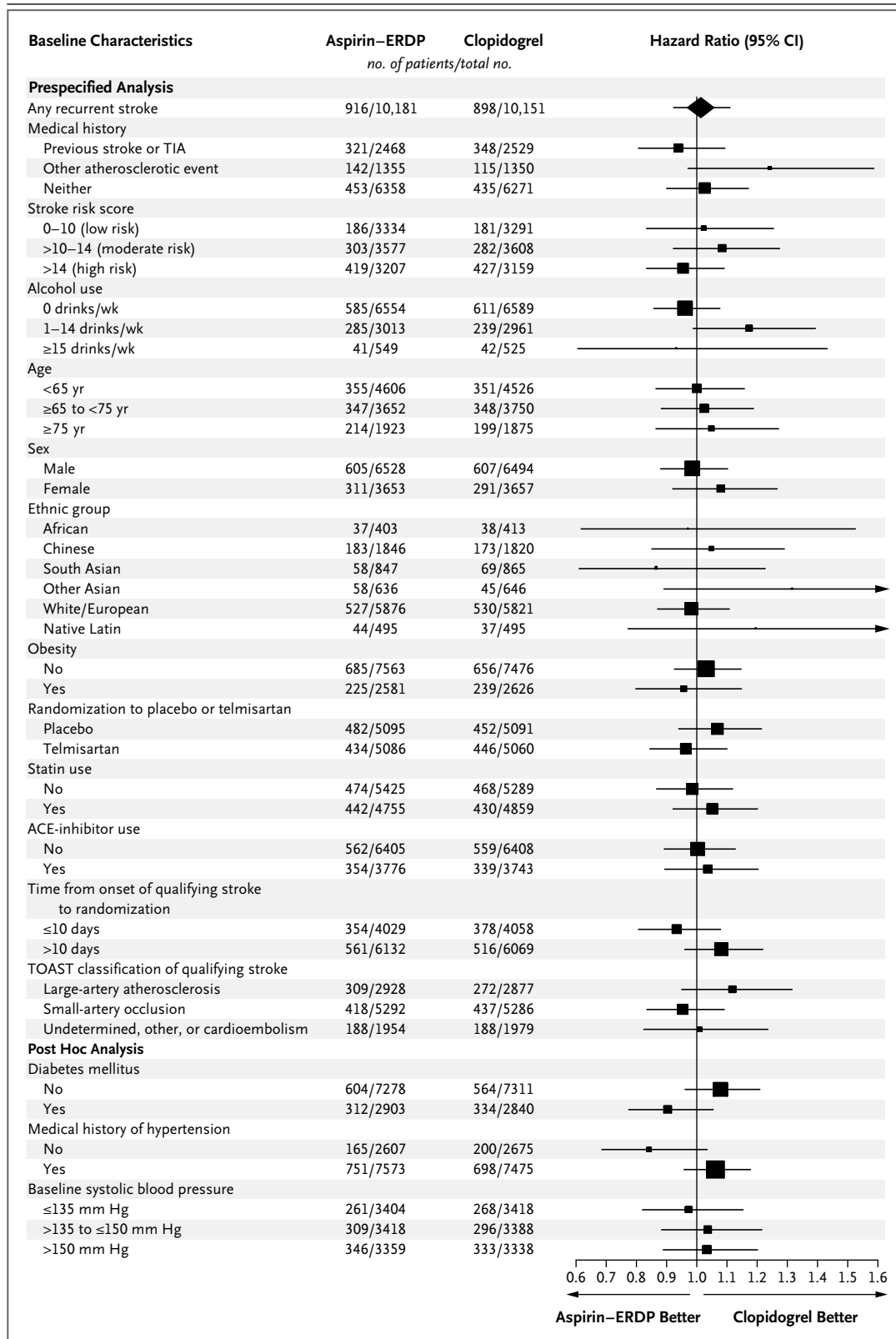


Table 3. Incidence of Selected Adverse Events Leading to Permanent Discontinuation of Study Medications.*

Variable	Aspirin-ERDP	Clopidogrel
	number (percent)	
Patients receiving antiplatelet medication	10,055 (100.0)	10,040 (100.0)
Patients with adverse events leading to treatment discontinuation	1,650 (16.4)	1,069 (10.6)
Headache	593 (5.9)	87 (0.9)
Vomiting	158 (1.6)	37 (0.4)
Nausea	155 (1.5)	58 (0.6)
Dizziness	134 (1.3)	52 (0.5)
Atrial fibrillation	122 (1.2)	143 (1.4)
Diarrhea	102 (1.0)	42 (0.4)
Hypotension	54 (0.5)	35 (0.3)

* ERDP denotes extended-release dipyridamole.

of the combination for reducing the composite end point of stroke, myocardial infarction, or death from vascular causes — particularly among patients with acute coronary syndromes¹⁵ — and some have questioned the efficacy of aspirin plus extended-release dipyridamole in the prevention of myocardial infarction. Our trial results show that therapy with aspirin plus extended-release dipyridamole and therapy with clopidogrel have similar effects on reduction of the composite of vascular events after stroke, including myocardial infarction.

The trial showed no significant difference in the tertiary outcome of first recurrence of stroke or major hemorrhagic event, but there was an increased risk of intracranial bleeding (including intracerebral hemorrhages, 128 of which were also counted toward the primary outcome of recurrent stroke) among patients treated with aspirin plus extended-release dipyridamole, as compared with patients treated with clopidogrel. Trials of clopidogrel plus aspirin have shown greater risks of life-threatening bleeding as compared with monotherapy.^{8,16} In both the European Stroke Prevention Study 2 (ESPS2) and ESPRIT, there was no significant increase in the risk of major hemorrhage in the aspirin-plus-dipyridamole group as compared with the aspirin group.^{5,10,11}

The rates of permanent discontinuation of study treatment due to headache were much lower in this study than in previous trials, probably owing to counseling of patients and the option to adjust the dose over a period of days if necessary. Despite this finding, there was a difference in the rates of discontinuation, with more recipients of

aspirin plus extended-release dipyridamole than recipients of clopidogrel stopping early.

A significant reduction in the risk of new or worsening congestive heart failure was found with aspirin plus extended-release dipyridamole as compared with clopidogrel. The explanation for this finding is not known, but it may relate to an increase in adenosine level and augmentation of coronary collateralization.³⁰

The PROfESS trial showed that, among patients with a noncardioembolic ischemic stroke, the risks of recurrent stroke or the composite of stroke, myocardial infarction, or death from vascular causes are similar with aspirin plus extended-release dipyridamole and with clopidogrel. Despite the increased risk of hemorrhagic strokes with aspirin plus extended-release dipyridamole as compared with clopidogrel, the net benefit with regard to the risk of recurrent stroke or major hemorrhagic event was similar in the two groups. Furthermore, there was no significant difference between the two treatments in the risk of fatal or disabling strokes. The large number and international representation of patients, who were from 35 countries or regions, enhances the generalizability of our findings. These findings provide additional safety and efficacy data physicians need in making individual treatment decisions for prevention of recurrent stroke or the combined end point of stroke, myocardial infarction, or death from vascular causes in their patients with stroke.

Supported by Boehringer Ingelheim (which manufactures Aggrenox, a combination of extended-release dipyridamole [200 mg] and aspirin [25 mg], and Micardis [telmisartan, 80 mg]). In selected countries, the telmisartan comparison of the PROfESS study was supported by Bayer Schering Pharma and GlaxoSmithKline.

Dr. Sacco reports receiving consulting fees from Boehringer Ingelheim, GlaxoSmithKline, and Sanofi-Aventis and lecture fees from Boehringer Ingelheim; Dr. Diener, honoraria and consulting and lecture fees from Abbott, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, D-Pharm, Fresenius, GlaxoSmithKline, Janssen Cilag, Merck Sharp & Dohme, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi and grant support from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Janssen-Cilag, and Sanofi-Aventis; and Dr. Yusuf, consulting and lecture fees from Boehringer Ingelheim, Sanofi-Aventis, Bristol-Myers Squibb, AstraZeneca, and GlaxoSmithKline and grant support from Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline. Mr. Cotton, Dr. Öunpuu, Mr. Lawton, Dr. Gu, Dr. Hermansson, Dr. Hilbrich, Dr. Machnig, Dr. VanderMaelen, and Dr. Voigt report being employees of Boehringer Ingelheim. Drs. Palesch, Martin, Bath, Chen, De Keyser, and Estol report receiving consulting fees from Boehringer Ingelheim; Dr. Albers, consulting and lecture fees from Boehringer Ingelheim and grant support from Boehringer Ingelheim, NMT Medical, Parexel International, AstraZeneca, and Forest Research Institute; Dr. Dahlöf, consulting

fees from Boehringer Ingelheim, Daiichi-Sankyo, and Novartis and lecture fees from Boehringer Ingelheim, Novartis, and Pfizer; Dr. Donnan, Mr. Roberts, and Dr. Kaste, consulting and lecture fees from Boehringer Ingelheim; Dr. Gorelick, consulting fees from Boehringer Ingelheim, Bayer, TAP Pharmaceutical Products, Myriad, Pfizer, Takeda, Daiichi Sankyo, Novartis, Merck, Brainsgate, and D-Pharm and lecture fees from Boehringer Ingelheim and diaDexus; Dr. Pais, consulting fees and grant support from Boehringer Ingelheim; Dr. Teal, consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Boehringer Ingelheim, and Bayer and lecture fees from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim; Dr. Toni, consulting fees from Boehringer Ingelheim and lecture fees from Boehringer Ingelheim, Sanofi-Aventis, and Novo Nordisk; and Dr. Weber, consulting fees and speakers' fees or honoraria from Novartis, Bristol-Myers Squibb, Daiichi-Sankyo, Boehringer Ingelheim, GlaxoSmithKline, and Forest Laboratories, consulting fees from Gilead and Takeda, and speakers' fees or honoraria from Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

We thank Vicky Hinstridge for technical assistance and Karuna Bellamkonda and Michael Pannucci for programming support.

APPENDIX

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REFERENCES

- Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology* 2006;66:641-6.
- Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;1:1215-20.
- Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;321:501-7.
- CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;348:1329-39.
- Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1-13.
- Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444-51.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324: 141.]
- Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-7.
- Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352: 1305-16.
- The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;367:1665-73. [Erratum, *Lancet* 2007;369:274.]
- Idem*. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol* 2007;6:115-24.
- Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for health-care professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577-617.
- European Stroke Organization (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457-507.
- Thijss V, Lemmens R, Fieuwis S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. *Eur Heart J* 2008;29:1086-92.
- The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
- Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
- Hirsh J, Guyatt G, Albers GW, Schünemann HJ. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: evidence-based guidelines. *Chest* 2004;126:Suppl:172S-173S.
- Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS). *Cerebrovasc Dis* 2007;23:368-80.
- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19: 604-7.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61-5.
- Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793-7.
- Fisher LD, Gent M, Büller HR. Active-control trials: how would a new agent compare with placebo? A method illustrated with clopidogrel, aspirin, and placebo. *Am Heart J* 2001;141:26-32.
- Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA* 2003;289:2947-57.
- Laster LL, Johnson MF. Non-inferiority trials: the 'at least as good as' criterion. *Stat Med* 2003;22:187-200.
- Wang S-J, Hung HMJ. TACT method for non-inferiority testing in active controlled trials. *Stat Med* 2003;22:227-38.
- Fleming TR. Current issues in non-inferiority trials. *Stat Med* 2008;27:317-32.
- James Hung HM, Wang S-J, Tsong Y, Lawrence J, O'Neil RT. Some fundamental issues with non-inferiority testing in active controlled trials. *Stat Med* 2003;22: 213-25.
- D'Agostino RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues — the encounters of academic consultants in statistics. *Stat Med* 2003;22:169-86.
- Akhtar M, Ordovas K, Martin A, Higgins CB, Michaels AD. Effect of chronic sustained-release dipyridamole on myocardial blood flow and left ventricular function in patients with ischemic cardiomyopathy. *Congest Heart Fail* 2007;13: 130-5.

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