Antiplatelet Drugs In the Secondary Prevention After Stroke
Differential Efficacy in Large Versus Small Vessel Disease? A Subgroup Analysis From ESPS-2

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Background and Purpose—Arterial disease resulting in cerebral ischemia can be classified into large vessel disease (LVD) and small vessel disease (SVD). We assessed whether antiplatelet drugs were more efficacious in large than in small vessel cerebrovascular disease.

Methods—Individual patient data of the second European Stroke Prevention Study (n=6602), in which patients with a previous transient ischemic attack or ischemic stroke were randomized to aspirin, dipyridamole, their combination, or placebo, were reanalyzed. Type of vessel disease was classified according to clinical symptoms or physical examination. Presence of a lacunar syndrome was considered typical for SVD and evidence of cortical dysfunction for LVD. Vascular events (nonfatal stroke, nonfatal myocardial infarction, nonfatal other vascular event, or vascular death) were taken as outcome. Cox regression analyses were performed.

Results—A total of 419 first vascular events occurred in 2600 patients with SVD and 367 in 1816 patients with LVD (mean follow-up 1.7 years). For aspirin versus placebo, the hazard ratio (HR) was 0.86 (95% CI, 0.66 to 1.11) in patients with SVD and 0.80 (95% CI, 0.61 to 1.06) in those with LVD (Pinteraction=0.74). For dipyridamole versus placebo, the HR was 0.86 (95% CI, 0.67 to 1.12) in patients with SVD and 0.90 (95% CI, 0.68 to 1.19) in patients with LVD (Pinteraction=0.84). Similar observations were made for the outcome stroke only.

Conclusions—Our findings do not concur with the hypothesis that aspirin, dipyridamole, or the combination may be especially effective in preventing vascular events in patients with previous cerebral ischemia that was caused by LVD compared with SVD. (Stroke. 2006;37:134-138.)

Key Words: aspirin ■ dipyridamole ■ vascular disease

Antiplatelet therapy achieves a relative risk reduction in recurrent vascular events of ≈25% among all types of high-risk patients, including those with a previous myocardial infarction, transient ischemic attack (TIA) or stroke, and peripheral vascular disease.1 If such analyses were restricted to the use of aspirin only in patients with cerebrovascular disease, the relative risk reduction is only 13%.2,3 However, cerebrovascular disease consists of a mixture of pathophysiological entities. Cerebral ischemia of arterial origin can be broadly classified into large vessel disease (LVD) and small vessel disease (SVD).4,5 SVD accounts for 25% and LVD for up to 50% of all ischemic strokes.6,7 The difference between SVD and LVD is usually made with the help of neuroimaging, but it can also be made reliably on the basis of history alone.8 Patients with SVD have a lower case fatality and better functional outcome on the short term than patients with LVD, which is probably explained by the difference in amount of brain tissue that is damaged.9 However, in the long term, there may be an excess risk of death and recurrent stroke in patients with SVD.10

Given the difference in underlying atherosclerotic disease, patients with LVD and patients with SVD may respond differently to antiplatelet drugs. This is supported by the fact that the 25% risk reduction of major vascular complications achieved by aspirin was achieved mainly in patients with LVD, especially of coronary arteries.1 Trials in which the efficacy of aspirin was evaluated in patients with previous cerebrovascular disease of arterial origin contained ≈50% of patients with LVD and 50% with SVD because patients with known source of emboli in the heart were excluded from these trials.5 The aim of the present study was to assess whether antiplatelet drugs (aspirin or dipyridamole) are more efficacious in patients with previous cerebral ischemia associated with LVD than in patients with previous cerebral ischemia from SVD.

Methods
Patients and Treatment Allocation
Data of the second European Stroke Prevention Study (ESPS-2) were reanalyzed. The ESPS-2 study was a randomized, placebo-controlled,
double-blind trial to investigate the safety and efficacy of antplatelet drugs for secondary prevention after transient or minor disabling cerebral ischemia. Patients with previous minor ischemic stroke or TIA were randomized between treatment with aspirin alone (2×25 mg per day; n=1649), modified-release dipyridamole alone (2×200 mg per day; n=1654), the 2 agents in a combined formulation (n=1650), or placebo (n=1649). Patients were followed for 2 years. Details on the background, design, and results of the trial have been reported previously.11,12

Criteria for LVD and SVD

The classification of type of vessel disease was based on previous studies.5,6,8,13,14 Patients were classified as having SVD if they had signs or symptoms of 1 of the classical lacunar syndromes (pure motor stroke, pure sensory stroke, ataxic hemiparesis, or dysarthria clumsy hand syndrome) on the basis of symptoms at time of their classifying event or at clinical examination at the time of randomization: motor or sensory deficit of arm, leg, or face (2 or 3 of 3) without evidence of cortical dysfunction. Classification of SVD or LVD was done without knowledge of subsequent vascular events.

Patients were classified as having LVD if they had evidence of cortical dysfunction based on symptoms at time of the ischemic event or at clinical examination at time of randomization. Dysphasia, dyspraxia, hemianopia, or a decreased level of consciousness at time of clinical examination was considered evidence of a cortical syndrome.

Patients without evidence of either LVD or SVD were excluded from the present analyses. Also, patients with evidence for LVD in their history at the time of qualifying event and evidence of SVD at physical examination or vice versa were excluded from the analyses. Patients with stupor or coma at the time of the qualifying event or patients with symptoms of brain stem dysfunction at clinical examination were excluded from the analyses because we considered classification of these conditions as either SVD or LVD would lack a solid scientific basis. In addition, we excluded patients with atrial fibrillation because we wanted to limit the study to cerebral ischemia of presumed arterial origin.

Outcome Events

The primary outcome was the occurrence of the first vascular event. This could be nonfatal stroke, nonfatal myocardial infarction, a nonfatal other vascular event (deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, or venous retinal vascular events), or vascular death. A secondary outcome was the occurrence of a new stroke only.

Figure 1. Pathway of inclusion of patients in the current study.
Statistical Analyses
Cox proportional hazard modeling was used to analyze the association between aspirin or dipyridamole versus placebo and risk of vascular events or stroke in patients with SVD and in those with LVD. To study the interaction of type of vessel disease with treatment, aspirin or dipyridamole versus placebo, type of vessel disease, and the interaction term of type of vessel disease with treatment were included in the models.

Results
Figure 1 shows the flow chart of the inclusion of patients for the present study. We included 4416 patients of whom 2600 were classified as having SVD and 1816 as LVD. In each of these 2 groups, about one quarter received treatment with the combination (aspirin and dipyridamole), one quarter dipyridamole, one quarter aspirin, and one quarter placebo. The distribution of the baseline characteristics was similar across the treatment regimens, indicating that randomization was successful (Table 1).

We compared the patients classified with cerebral ischemia caused by LVD on the basis of symptoms at the time of the qualifying event with the classification on the basis of the clinical examination and found a 78% correspondence. For patients with SVD, this correspondence was 95%.

The annual risk of a vascular event was 9.2% in all patients with SVD compared with 11.9% in all patients with LVD (Table 1 and Figure 2 show these data according to allocated treatment). The hazard ratio (HR) for the risk of a vascular event in patients who received aspirin alone versus those who received placebo was 0.86 (95% CI, 0.66 to 1.11) in patients with SVD and 0.80 (95% CI, 0.61 to 1.06) in patients with LVD. The \( P \) value for interaction was 0.74 (Table 2).

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Table 2. HRs of Aspirin, Dipyridamole, or the Combination of These Two vs Placebo for the Risk of a Vascular Event or Stroke in Patients With SVD and LVD

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. Crude annual risks of vascular events in patients with SVD vs LVD according to 4 different treatments. ASA indicates aspirin; DIP, dipyridamole; PLAC, placebo. Bars with upper limit of 95% CI.
0.68 to 1.19) in those with LVD. The P value for interaction was 0.84.

The annual risk of stroke was 6.2% in patients with SVD and 7.9% in patients with LVD (Table 1). The pattern of HRs for the risk of stroke alone according to the different treatment comparisons within the strata of type of vessel disease was essentially the same as that for the risk of vascular events (Table 2, lower half).

Discussion
Our findings do not concur with the hypothesis that aspirin is more effective in the prevention of vascular events in patients with LVD than in patients with SVD; nor was a differential effect observed for dipyridamole or the combination of aspirin and dipyridamole. There was also no difference in the prevention of stroke. Assuming that a greater efficacy of antiplatelet drugs in LVD would mainly be achieved by the inhibition of platelet aggregation in patients who have atherosclerotic lesions in their larger arteries, it is remarkable that we did not find this trend for the drugs studied.

Several limitations of this study can be addressed. First, we classified type of vessel disease based on clinical symptoms and not on imaging data. However, the advantage of the ESPS-2 study is that detailed information on type of symptoms at the time of the qualifying event was recorded and that at baseline, a detailed clinical examination was performed. In a previous study, we have shown that the differentiation between SVD and LVD can also be made reliably on the basis of history alone. Furthermore, for application in practice, a classification based on symptoms and not on computed tomography data is useful for immediate application before imaging data are available. Moreover, in patients with transient or minor disabling neurological deficit, relevant ischemic lesions accompany only a fraction of all ischemic cerebral events. We evaluated in detail whether our clinical classification was valid and found that the agreement between the classification based on symptoms at time of qualifying event and the classification based on clinical examination was good. Furthermore, patients with LVD were at higher risk of vascular events and stroke separately than those with SVD, which is in accordance with short-term follow-up results (up to 2 years) from previous studies. Classification on basis of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria would have been an alternative approach in our study. However, this was not feasible because the ESPS-2 data did not provide sufficient detail to use it. Moreover, a recent review and accompanying editorial were critical about this classification system. Nevertheless, diffusion-weighted imaging studies may identify multiple lesions in up to 16% of patients presenting with classical lacunar syndromes, suggesting an embolic pathogenesis.

A second limitation is that the ESPS-2 trial was not powered to perform these subgroup analyses. Therefore, it might be that our findings are caused by chance, and a true differential efficacy cannot be ruled out with complete certainty. A third limitation may be that we decided in advance to compare only the patients with either well-defined SVD or well-defined LVD. Hence, we excluded all patients who had had clinical or neuroradiological features of SVD and LVD. We consider this to be appropriate in a study aiming at a better understanding of the effects of antiplatelet drugs in 2 different subtypes of cerebral ischemia. Finally, our analyses had a post hoc nature: they were planned after completion of ESPS-2; however, we specified an analysis plan before embarking on the current study. It is of note that an analysis according to “lacune” versus “no lacune” as the qualifying event was pursued already in the early 1980s by French trialists.

Our hypothesis that antiplatelet drugs are more effective in patients with LVD than in those with SVD was not supported by the findings of the present study. In further research, it still may be worthwhile to test a possible differential efficacy in response to aspirin between patients with LVD and those with SVD because of its important consequences for secondary prevention after cerebral ischemia and for the design of future secondary prevention trials.

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References
11. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic...