Efficacy of Aspirin Plus Extended-Release Dipyridamole in Preventing Recurrent Stroke in High-Risk Populations

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Objective: To assess the efficacy of aspirin plus extended-release dipyridamole compared with aspirin alone for the prevention of recurrent stroke among high-risk groups.

Design: A post hoc analysis was conducted using data from the European Stroke Prevention Study 2. Rates of annual strokes and vascular events were determined for the aspirin plus extended-release dipyridamole group (n=1650) and the aspirin-only group (n=1649), and were stratified by risk subgroup and univariate risk factors. Stroke models from the Framingham Study and the Stroke Prognostic Instrument II were applied to subjects in the European Stroke Prevention Study 2 to categorize patients into risk groups.

Results: Compared with aspirin alone, aspirin plus extended-release dipyridamole demonstrated a more pronounced efficacy in reducing the risk for stroke and vascular events among patients younger than 70 years; those with hypertension, prior stroke, or transient ischemic attack; current smokers; and those with any prior cardiovascular disease. Relative hazard reductions favored the combination of aspirin plus extended-release dipyridamole, and were greatest for the high-risk Framingham Study group and the moderate-risk Stroke Prognostic Instrument II subgroup.

Conclusion: Aspirin plus extended-release dipyridamole is more effective than aspirin alone at preventing stroke, and the difference in efficacy increases in higher-risk patients.

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STROKE IS THE THIRD LEADING cause of death in most developed countries and a leading cause of serious long-term disability.1 In the United States, 750000 persons have a stroke annually, of whom about 200000 have recurrent stroke.1 Among patients with a first stroke, 80% to 85% survive.2,3 These patients face a 5% to 15% risk for recurrent stroke in the first year following the acute stroke, during which the highest risk exists in the weeks immediately following the initial event.2 Because age is an important nonmodifiable risk factor for stroke, the decline in stroke-related mortality combined with the increase in life expectancy for the US population will certainly increase the number of persons at risk for recurrent stroke and stroke’s related disability and medical care costs.2

Fortunately, observational epidemiological studies and controlled clinical trials have provided substantial evidence that the risk of recurrent ischemic stroke can be reduced.3 Various modifiable risk factors, such as hypertension, cardiac disease, and dyslipidemias, can be controlled to help reduce the risk for recurrent stroke. Four antiplatelet agents have demonstrated efficacy for preventing recurrent stroke, including aspirin, ticlopidine hydrochloride, clopidogrel bisulfate, and aspirin plus extended-release dipyridamole.6 The studies that produced these findings have resulted in updates to the guidelines for secondary stroke prevention from the American Heart Association and the American College of Chest Physicians.5,7

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Despite the revised recommendations, expert opinion varies considerably regarding the relative efficacy of antiplatelet agents for prevention of recurrent stroke.6 This uncertainty is largely a result of the absence of direct comparisons of combination antiplatelet therapy and the marked variability in the choice of primary end points for individual trials.8 Moreover, certain agents or combinations of agents may be pre-
The ESPS-2 was a multicenter, randomized, placebo-controlled, double-blind, 2-by-2 factorial trial designed to assess the safety and efficacy of low-dose aspirin, extended-release dipyridamole, and the 2 agents combined for the secondary prevention of ischemic stroke. The full details of the study design are described by Diener and colleagues, in brief, the study population comprised 6602 patients older than 18 years (mean age, 66.7 years) who had experienced a transient ischemic attack (TIA) (24%) or an ischemic stroke (76%) within the preceding 3 months. Patients were randomly assigned to receive aspirin alone (30 mg/d), extended-release dipyridamole alone (400 mg/d), the 2 agents in a combined formulation, or placebo, and were followed up every 3 months for 2 years. Primary end points were stroke (fatal and nonfatal) and death from all causes.

At baseline, various data were collected regarding demographics and vascular risk factors, such as history of hypertension, diabetes mellitus, myocardial infarction (MI), cigarette smoking, stroke, or TIA. These variables were defined by history through subject interview and baseline medical record review. Any cardiovascular disease was defined as persons having experienced cardiac failure or having hypertension, ischemic heart disease, or peripheral vascular disease. Definitions of vascular risk factors from ESPS-2 are listed in Table 1.

We conducted our post hoc analysis with external stroke models from the Framingham Study and the Stroke Prognostic Instrument II (SPI-2) to compute estimated risk categories based on the ESPS-2 baseline variables. We converted the risk variables to risk scores using the method in the Framingham Study. The Framingham stroke risk score was developed from the Framingham cohort to calculate an estimated probability of stroke (primarily first stroke) in men and women. For the Framingham Study model, the 10-year stroke probability was classified as low (<0.15) or high (>0.15) using the following variables: age, systolic blood pressure, antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. The SPI I was developed specifically to predict stroke or death among stroke or TIA survivors. The SPI-2 model, which uses new predictive variables and recalculated point scores for all component variables, was developed from the Women's Estrogen for Stroke Trial cohort, and its enhanced performance has been demonstrated and validated in other external cohorts. The SPI-2 score was classified as low (0-3), middle (4-7), or high (8-15) using the following variables: congestive heart failure, diabetes mellitus, prior stroke, older than 70 years, stroke for enrollment event, severe hypertension, and coronary artery disease. Stroke risk scores were calculated according to these models for each subject in ESPS-2, and subjects were categorized into risk strata based on these scores.

The new analyses examined the annual stroke and vascular event rates for the aspirin-alone group (n=1649) and the aspirin plus extended-release dipyridamole group (n=1630), stratified by the patient's risk subgroup and univariate risk factors. Subjects with missing baseline data (n=103) for risk model stratification (Framingham Study or SPI-2) were eliminated from this analysis. Annual event rates were defined as the number of first events divided by the total number of patient-years in the study. The primary focus of the study was stroke outcomes (fatal or nonfatal). Stroke or vascular events were defined as the first occurrence of nonfatal stroke, nonfatal MI, or vascular death. Vascular death was defined as fatal stroke, fatal MI, death due to other vascular events or cardiac failure usually within 30 days of the event, sudden death, hemorrhagic death (noncerebral fatal bleeding), or death of uncertain or un-

Table 1. Definitions of Vascular Risk Variables in the European Stroke Prevention Study 2 Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Prior cerebrovascular event</td>
<td>Prior stroke or TIA</td>
</tr>
<tr>
<td>IHD</td>
<td>A history of ischemic heart disease or MI or electrocardiographic evidence of coronary ischemic signs or residual signs of previous infarction</td>
</tr>
<tr>
<td>PVD</td>
<td>A history of PVD, the absence of 1 or more peripheral pulse (carotid, radial, femoral, or popliteal artery), or the presence of 1 or more vascular murmurs (carotid or femoral artery)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>A history of hypertension, baseline systolic blood pressure &gt;160 mm Hg, baseline diastolic blood pressure &gt;95 mm Hg, or current antihypertensive treatment at baseline (centrally acting antihypertensive agents, angiotensin-converting enzyme inhibitors, diuretics in the absence of cardiac failure, β-blockers in the absence of IHD, or calcium channel blockers in the absence of IHD)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>A history of hypercholesterolemia, a baseline cholesterol level &gt;290 mg/dL, (&gt;7.5 mmol/L), or current treatment with hypolipidemic agents at baseline</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>IHD, PVD, cardiac failure, or hypertension</td>
</tr>
<tr>
<td>TIA</td>
<td>A focal disturbance of the cerebral circulation that resulted in a clinical neurological deficit recovering within 24 h without functional impairment at standard clinical neurological examination</td>
</tr>
<tr>
<td>Stroke</td>
<td>A focal disturbance of the cerebral circulation that resulted in a functional neurological deficit lasting &gt;24 h</td>
</tr>
<tr>
<td>Sudden death</td>
<td>Death occurring within approximately 24 h after the appearance of symptoms; other cardiovascular deaths included deaths attributable to cardiac arrhythmia, hemorrhage, and peripheral vasculopathy; and other nonvascular deaths included those attributable to miscellaneous causes, such as diabetes mellitus and renal failure</td>
</tr>
<tr>
<td>Vascular event</td>
<td>First of nonfatal stroke, nonfatal MI, or vascular death, where vascular death includes fatal stroke, fatal MI, death due to other vascular events or cardiac failure usually within 30 d of the event, sudden death, hemorrhagic death (noncerebral fatal bleeding), or death of uncertain or unknown cause occurring within 24 h after the onset of symptoms</td>
</tr>
</tbody>
</table>

Abbreviations: IHD, ischemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack.
known cause occurring within 24 hours after the onset of symptoms. Relative hazard reductions were calculated using Cox proportional hazards models.

### RESULTS

Overall, the ESPS-2 results demonstrated that the combination of aspirin plus extended-release dipyridamole compared with aspirin alone among TIA or stroke patients was superior in reducing the risk of stroke (relative risk reduction, 23%; 95% confidence interval, 9%-37%; \( P = .006 \)) and stroke or vascular events (relative risk reduction, 22%; 95% confidence interval, 7%-36%; \( P = .003 \)). The efficacy of aspirin plus extended-release dipyridamole compared with aspirin alone for various baseline subgroups is shown for the outcome of stroke in Table 2 and for the outcome of stroke or vascular events (including vascular death) in Table 3. Compared with aspirin alone, treatment with aspirin plus extended-release dipyridamole resulted in substantial relative hazard reductions for stroke within some of the specific risk factor subgroups. Relative hazard rates favored the combination therapy in each of these subgroups, with a more pronounced efficacy observed among those younger than 70 years; those with hypertension, prior MI, prior stroke or TIA, and any prior cardiovascular disease; and current smokers. The greatest relative hazard reduction (44.6%) was found among patients with a stroke or TIA before the qualifying event. Patients with a history of MI who were treated with aspirin plus extended-release dipyridamole had a 36.8% relative hazard reduction of stroke compared with those taking aspirin alone. Patients with any prior cardiovascular disease had a 27.3% lower stroke hazard while taking aspirin plus extended-release dipyridamole compared with aspirin alone. The relative hazard reduction for stroke was 11.2% for those with TIA as a qualifying event and 27.8% for those randomized after stroke.

The combined outcome of stroke or vascular events is shown in Table 3. The results show that patients using aspirin plus extended-release dipyridamole experience substantial relative hazard reductions for the end points of stroke or vascular events. Greater relative hazard reductions were found among those with prior stroke or TIA, previous MI, and among current smokers. The relative hazard reduction was 24.8% for those with TIA as a qualifying event and 18.6% for those randomized after stroke. Some subgroups, such as those with atrial fibrillation, were small, which resulted in wide confidence intervals.

The baseline ESPS-2 cohort stratified into low- and high-risk groups according to the Framingham stroke risk.
The annual risk for recurrent stroke among those treated with aspirin increased from 3.8% in the low-risk group to 10.1% in the high-risk group for the Framingham score, and from 3.7% to 13.2% for the SPI-2 score. Relative hazard reductions favored the combination of aspirin plus extended-release dipyridamole in all the subgroups, and were greatest for the high-risk Framingham group and the moderate-risk SPI-2 subgroup. Numbers in the highest-risk group, however, were small. Results were similar for the stroke or vascular events outcome, as shown in Table 5.

**COMMENT**

Guidelines from the American Heart Association, the American College of Chest Physicians, and the European Stroke Initiative state that aspirin alone, aspirin plus extended-release dipyridamole, or clopidogrel is an ac
ceptable option for first-line therapy to prevent recurrent stroke.\textsuperscript{5,7,13} Few data are available regarding how these recommendations translate into clinical practice and which factors affect the choice of antiplatelet drugs in patients with a recent ischemic cerebrovascular event. In a recent study from the Vienna Stroke Register,\textsuperscript{14} investigators determined that the most important factor promoting the use of clopidogrel was therapy with aspirin before the index event. High interhospital variability was found regarding the use of aspirin plus extended-release dipyridamole. The relationship between aspirin and clopidogrel also varied significantly between departments within a hospital. Thus, the most prominent factor influencing the use of clopidogrel or aspirin plus extended-release dipyridamole was the practitioners’ divergent interpretation of the existing evidence. Other main factors were higher costs (clopidogrel), individual experiences, and adverse effects (aspirin plus extended-release dipyridamole).

For the secondary prevention of stroke, alternatives exist for aspirin. Clopidogrel and aspirin plus extended-release dipyridamole are more effective than aspirin alone.\textsuperscript{9,15,16} Adding dipyridamole to aspirin or substituting aspirin with clopidogrel is more expensive than aspirin alone in preventing stroke, but these changes in therapy could be more cost-effective in high-risk patients, if these patients can be identified.\textsuperscript{17} It seems that in the long term, aspirin plus extended-release dipyridamole is more effective and less costly compared with aspirin alone.\textsuperscript{18} Thus, the type of outcome to be prevented, such as recurrent stroke, MI, or other vascular events, and the relative impact of other concomitant risk factors also enter into the physician’s decision-making process.

Clinicians should assess the stroke patient’s greatest risk before determining long-term treatment to prevent vascular events. The most common vascular event during the first few years following a stroke or TIA is a recurrent nonfatal stroke, which often results in significant disability and reduction in quality of life.\textsuperscript{8} Recent antiplatelet studies, such as the Canadian American Ticlopidine Study, the Ticlopidine Aspirin Stroke Study, the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial, and ESPS-2, have clearly demonstrated the high risk for recurrent stroke, compared with the lower risk for MI.\textsuperscript{8} Therefore, from a clinical perspective, treatment must focus on preventing subsequent ischemic strokes. Consequently, the antiplatelet agent that is most effective for preventing stroke will likely result in the greatest benefit for patients with a history of stroke or TIA.

Stroke patients often have other vascular conditions, such as MI or prior stroke, and multiple risk factors, such as hypertension and diabetes mellitus. When choosing alternative antiplatelet therapy, the severity of vascular risk factors can influence the clinician to consider more aggressive medications. Our post hoc analysis of the ESPS-2 data shows that the combination of aspirin plus extended-release dipyridamole is significantly more effective than aspirin alone in the prevention of recurrent stroke and stroke or vascular events for various baseline risk factors. Patients with prior stroke or TIA, those who experienced a previous MI, and current smokers who used aspirin plus extended-release dipyridamole had greater hazard reductions for stroke and stroke or vascular events than those who took aspirin alone. The reductions observed among patients with prior cardiovascular disease are noteworthy because some have claimed that aspirin plus extended-release dipyridamole is less effective among patients with other cardiovascular conditions.

In addition, aspirin plus extended-release dipyridamole seems to provide greater protection for those patients with a higher risk for stroke based on predicted stroke probabilities from external stroke models. For diabetes mellitus and atrial fibrillation, we did not observe a significant benefit for aspirin plus extended-release dipyridamole compared with aspirin alone. It is difficult to make any conclusions about the atrial fibrillation subgroup because the numbers of patients randomized were small. Moreover, the results of the European Atrial Fibrillation Trial that demonstrated the efficacy of oral anticoagulants led to a protocol modification and change in practice in many of the participating ESPS-2 sites during the conduct of the trial. Analysis of the ESPS-2 data set has shown that the 2-year risk of first stroke for baseline atrial fibrillation subjects was greatest among those treated with placebo (23.4%) compared with aspirin alone (19.2%) and extended-release dipyridamole plus aspirin (17.3%).

Limitations of our post hoc analysis exist. The definitions of the baseline vascular risk factors were based on data available at randomization into ESPS-2 and may be skewed because of older classification schemes. The

### Table 5. Annual Combined Stroke or Vascular Event Rates and RHRs by Risk Group in Subjects in the European Stroke Prevention Study 2 Trial Treated With Aspirin Alone or Aspirin Plus Extended-Release Dipyridamole

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of Subjects</th>
<th>Aspirin Plus Extended-Release Dipyridamole*</th>
<th>Aspirin Alone*</th>
<th>RHR (Lower, Upper CL), %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham stroke risk score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1453</td>
<td>4.1</td>
<td>5.0</td>
<td>17.4 (-17.8, 42.1)</td>
<td>.29</td>
</tr>
<tr>
<td>High</td>
<td>1743</td>
<td>11.4</td>
<td>14.3</td>
<td>20.6 (2.7, 35.2)</td>
<td>.03</td>
</tr>
<tr>
<td>SPI-2 risk score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1426</td>
<td>4.2</td>
<td>4.9</td>
<td>13.8 (-23.3, 39.7)</td>
<td>.42</td>
</tr>
<tr>
<td>Moderate</td>
<td>1471</td>
<td>9.5</td>
<td>13.1</td>
<td>27.5 (8.1, 42.7)</td>
<td>.008</td>
</tr>
<tr>
<td>High</td>
<td>299</td>
<td>19.8</td>
<td>21.5</td>
<td>7.6 (-37.9, 38.1)</td>
<td>.70</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 4.
*Data are given as annual percentage of subjects in each group who experienced a stroke or vascular event.
use of the Framingham model to stratify patients into low and high risk may have some limitations because it was originally designed to predict first stroke. Some of the variables in the original Framingham model were not available in the baseline ESPS-2 data set and may have reduced the accuracy of the stroke risk scores. The model, however, seemed to competently discriminate the risk for stroke recurrence among the treatment groups. Although the risk of stroke recurrence increased across the 3 categories of the SPI-2, it was originally designed to predict stroke or any death. The lower efficacy of extended-release dipyridamole plus aspirin vs aspirin alone among the highest-risk group may reflect the lower impact of antiplatelet agents on any death after stroke.

This post hoc analysis of ESPS-2 data adds to the growing information supporting the efficacy of combination therapy with antiplatelet agents, particularly in higher-risk stroke patients. Aspirin plus extended-release dipyridamole is more effective than aspirin alone at preventing stroke, and the difference in efficacy increases in higher-risk patients. The baseline vascular risk for the stroke patient is one important consideration when making decisions regarding the most effective antiplatelet regimen to prevent a stroke.

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REFERENCES