The secondary prevention of ischemic stroke is aided by the use of antiplatelet therapy, and the predominant current choices are aspirin, aspirin plus extended-release dipyridamole, and clopidogrel. The potential utility of combining platelet antiaggregants with different mechanisms of action proved successful with aspirin plus extended-release dipyridamole, and this approach has been explored with the combination of clopidogrel and aspirin. In the Management of Atherothrombosis With Clopidogrel in High-Risk Patients trial, this combination was compared with clopidogrel alone for secondary prevention in patients with transient ischemic attack and stroke in a high-risk population with a high prevalence of other vascular risk factors. A nonsignificant trend for a reduction of the combined endpoint of ischemic stroke, myocardial infarction, vascular death, and rehospitalization was observed in the combination therapy group ($P = .24$). The frequency of serious, life-threatening bleeding adverse effects was almost doubled in the combination arm. Neurologists need to be aware of these results and avoid the use of clopidogrel plus aspirin in patients with stroke or transient ischemic attack until evidence that the combination is safe in this population is provided. Neurologists faced with patients who have had a stroke or transient ischemic attack and are receiving this combination of antiplatelet agents after coronary stenting should inform their cardiology colleagues of the reported bleeding risk, and they should encourage the use of the combination for as short a time period as possible after such coronary intervention.

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Such data allow neurologists to use evidence-based information in making treatment decisions for their patients with stroke and TIA. With the recent publication of the results of the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) trial, which evaluated the safety and efficacy of clopidogrel in combination with aspirin in the secondary prevention of stroke, neurologists now have new relevant data on which to base important treatment decisions when they are considering this combination of antiplatelet agents.

RESULTS FROM EARLIER CLOPIDOGREL TRIALS

The efficacy and safety of clopidogrel in the secondary prevention of vascular events were investigated in several multicenter trials. The Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events trial was a randomized, double-blind trial that assessed the relative efficacy of a once-daily regimen of either 75 mg of clopidogrel or 325 mg of aspirin in reducing the incidence of ischemic stroke, myocardial infarction (MI), or vascular death in nearly 20,000 patients who had recent ischemic stroke or MI or who currently had symptomatic peripheral arterial disease. The annual risk of ischemic stroke, MI, or vascular death was found to be 5.32% in patients treated with clopidogrel as compared with 5.83% in patients treated with aspirin. This translates into a significant 8.7% relative risk reduction (RRR) for clopidogrel vs aspirin (95% confidence interval [CI], 0.3–16.5; \( P < .001 \))^9 with an absolute risk reduction of 0.5%.

When broken down by diagnostic group, patients with stroke experienced an average annual event rate of 7.15% in the clopidogrel group as compared with 7.71% in the aspirin group, for an RRR of 7.3% in favor of clopidogrel (95% CI, −5.7 to 18.7; \( P = .26 \)). For patients who experienced MI, event rates were 5.03% and 4.84% with clopidogrel and aspirin, respectively, with an RRR of 3.7% favoring aspirin (95% CI, −12.0 to 22.1; \( P = .66 \)). Patients with peripheral arterial disease had average annual event rates of 3.71% and 4.86% with clopidogrel and aspirin, respectively, resulting in an RRR of 23.8% (95% CI, 8.9–36.2; \( P = .003 \)).\(^9\) It is evident that the effectiveness noted in reduction of the primary combined end point of stroke, MI, or vascular death in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial was primarily driven by results from the peripheral arterial disease cohort. Furthermore, in the ischemic stroke cohort, the absolute risk reduction for clopidogrel over aspirin was only 0.6, and although a trend toward significance was found for the RRR in favor of clopidogrel, the wide confidence intervals demonstrate that the risk reduction was not significant (\( P = .26 \)). Severe upper gastrointestinal discomfort, intracranial hemorrhage, and gastrointestinal hemorrhage were more frequent in the aspirin group.\(^9\) Additionally, a few more patients in the aspirin group (0.53%) than in the clopidogrel group (0.39%) experienced validated, nonfatal, primary intracranial hemorrhage or hemorrhagic death.\(^9\)

Another study, Clopidogrel in Unstable Angina to Prevent Recurrent Events,\(^15\) evaluated daily administration of aspirin (75–325 mg) plus either 75 mg of clopidogrel or placebo to more than 12,000 patients who had presented within 24 hours of onset with an acute coronary syndrome without ST-segment elevation. Primary outcomes included a composite of death from cardiovascular causes, nonfatal MI, or stroke, along with the previous composite end point of refractory ischemia.\(^12\) The composite end point occurred in 9.3% of the clopidogrel group as compared with 11.4% of the placebo group, for a relative risk of 0.80 (RRR, 20.0%; absolute risk reduction, 2.1%; 95% CI, 0.72–0.90; \( P < .001 \)).\(^12\) The second primary outcome (ie, the first primary outcome or refractory ischemia) was also higher in the placebo group than in the clopidogrel group—18.8% vs 16.5%, respectively. This resulted in an RRR of 14.0% and an absolute risk reduction of 2.3% (95% CI, 0.79–0.94; \( P < .001 \)).\(^12\) When the data were broken down by type of event, the greatest difference in favor of clopidogrel was for MI, with a relative risk of 0.77 (95% CI, 0.67–0.89); the relative risk for stroke was 0.86 (95% CI, 0.63–1.18).\(^12\) Major bleeding was significantly more common in the group that received clopidogrel plus aspirin (3.7%) than in the group that received aspirin alone (2.7%) (relative risk, 1.38; 95% CI, 1.13–1.67; \( P = .001 \)).\(^12\) This represents a 38% relative excess of major bleeding complications for clopidogrel plus aspirin.\(^4\) The incidence of minor bleeding episodes was also higher in the group that received clopidogrel with aspirin (5.1%) than in the group that received aspirin alone (2.4%) (\( P < .001 \)).\(^12\) However, no difference was noted between the 2 therapies in terms of fatal bleeding events.\(^6\)

RESULTS OF THE MATCH TRIAL

The efficacy and safety of the combination of clopidogrel plus aspirin needed to be investigated directly in a stroke or TIA population. Toward that end, the MATCH trial randomly assigned 7599 high-risk patients who had a stroke (79%) or a TIA (21%) to clopidogrel (75 mg daily) plus aspirin (75 mg daily) or clopidogrel (75 mg daily) plus placebo.\(^11\) The primary end point of the study was ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event.

Primary end point analysis revealed a nonsignificant RRR of 9.5% for the group that received clopidogrel plus aspirin for the composite end point as compared with the group that received clopidogrel alone (95% CI, −2.0 to 19.6; \( P = .24 \)).\(^11\) The combination of clopidogrel plus aspirin also showed a slightly favorable effect on event rates in most patient subgroups, including patients with diabetes mellitus, previous ischemic stroke or TIA, previous MI, or peripheral arterial disease (Table 1).\(^11\) Secondary end point analysis showed a nonsignificant RRR of 7.1% for ischemic stroke (fatal or not) for clopidogrel plus aspirin vs clopidogrel alone (95% CI, −8.5 to 20.4; \( P = .35 \)), and an RRR of 2.0% for the combination vs monotherapy for any stroke (95% CI, −13.8 to 15.6; \( P = .79 \)) (Table 2).\(^11\)

However, the combination of clopidogrel plus aspirin resulted in a significantly greater incidence of serious, life-threatening bleeding complications than was observed with clopidogrel alone (\( P < .001 \)).\(^11\) Although the frequency of fatal bleeding events was similar in the 2 groups, life-threatening bleeding occurred in almost twice
as many patients receiving combination therapy as those receiving clopidogrel alone (96 patients vs 49 patients, respectively; relative risk, 1.26; \(P = 0.001\)) (Table 3).

Some have argued that the design of the MATCH trial resulted in the enrollment of a very high-risk population and that bleeding complications might be less frequent in a lower-risk population. It is clear that patients in the MATCH trial were at high risk. Persons with hypertension constituted 78% of the population, and those with diabetes mellitus, 68%. In all, 56% of patients had hypercholesterolemia, 26% had an ischemic stroke before the time of the qualifying event, and 19% had a previous TIA. Thus, it was suggested that clopidogrel plus aspirin may have therapeutic value in nondiabetic, lower-

### Table 1. Primary End Point Analysis of the Management of Atherothrombosis With Clopidogrel in High-Risk Patients Trial*

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin and Clopidogrel, No. (%) (n = 3797)</th>
<th>Placebo and Clopidogrel, No. (%) (n = 3802)</th>
<th>Absolute Risk Reduction, % (95% CI)</th>
<th>Relative Risk Reduction, % (95% CI)</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome‡</td>
<td>596 (16)</td>
<td>636 (17)</td>
<td>1.0 (−0.6 to 2.7)</td>
<td>6.4 (−4.6 to 16.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or not)</td>
<td>59 (2)</td>
<td>62 (2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ischemic stroke (fatal or not)</td>
<td>299 (8)</td>
<td>319 (8)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Other vascular death</td>
<td>69 (2)</td>
<td>74 (2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rehospitalization for acute ischemic event</td>
<td>169 (4)</td>
<td>181 (5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable.
*Adapted from Diener et al11 with permission from Elsevier.
†Log-rank test.
‡Only the first event was counted. For every component of the primary end point, only the event regarded as the first outcome from the composite was counted.

### Table 2. Frequency of Secondary End Point Events of the Management of Atherothrombosis With Clopidogrel in High-Risk Patients Trial*

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin and Clopidogrel, No. (%) (n = 3797)</th>
<th>Placebo and Clopidogrel, No. (%) (n = 3802)</th>
<th>Absolute Risk Reduction, % (95% CI)</th>
<th>Relative Risk Reduction, % (95% CI)</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, ischemic stroke, and vascular death</td>
<td>445 (12)</td>
<td>473 (12)</td>
<td>0.7 (−0.7 to 2.2)</td>
<td>5.9 (−7.1 to 17.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or not)</td>
<td>73 (2)</td>
<td>68 (2)</td>
<td>−0.1 (−0.7 to 0.5)</td>
<td>−7.7 (−49.8 to 22.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Ischemic stroke (fatal or not)</td>
<td>309 (8)</td>
<td>333 (9)</td>
<td>0.6 (−0.6 to 1.9)</td>
<td>7.1 (−8.5 to 20.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Vascular death</td>
<td>124 (3)</td>
<td>121 (3)</td>
<td>0.1 (−0.9 to 0.7)</td>
<td>−2.4 (−31.5 to 20.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischemic stroke (fatal or not) and vascular death</td>
<td>401 (11)</td>
<td>430 (11)</td>
<td>0.8 (−0.7 to 2.2)</td>
<td>6.6 (−0.7 to 18.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Any stroke (ischemic stroke, primary intracranial hemorrhage, or nonclassifiable stroke [fatal or not])</td>
<td>339 (9)</td>
<td>347 (9)</td>
<td>0.2 (−1.1 to 1.5)</td>
<td>2.0 (−13.8 to 15.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>201 (5)</td>
<td>201 (5)</td>
<td>−0.01 (−1.0 to 1.0)</td>
<td>0.1 (−21.5 to 17.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>NontFatal myocardial infarction, nont Fatal ischemic stroke, rehospitalization for acute ischemic event</td>
<td>505 (13)</td>
<td>546 (14)</td>
<td>1.1 (−0.5 to 2.6)</td>
<td>7.6 (−4.3 to 18.2)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Adapted from Diener et al11 with permission from Elsevier.
†First event counted (independently from the first outcome from the composite of the primary end point).

### Table 3. Patients With Bleeding Events in the Management of Atherothrombosis With Clopidogrel in High-Risk Patients Trial*

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin and Clopidogrel, No. (%) (n = 3759)</th>
<th>Placebo and Clopidogrel, No. (%) (n = 3781)</th>
<th>Difference Between Aspirin and Placebo, % (95% CI)</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening bleeding</td>
<td>96 (3)</td>
<td>49 (1)</td>
<td>1.26 (0.64–1.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>16 (&lt;1)</td>
<td>11 (&lt;1)</td>
<td>0.13 (−0.14 to 0.40)</td>
<td>NA</td>
</tr>
<tr>
<td>NontFatal bleeding</td>
<td>81 (2)</td>
<td>38 (1)</td>
<td>1.15 (0.59–1.71)</td>
<td>NA</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage‡</td>
<td>40 (1)</td>
<td>25 (1)</td>
<td>0.40 (−0.01 to 0.82)</td>
<td>NA</td>
</tr>
<tr>
<td>Primary intracranial hemorrhage</td>
<td>32 (1)</td>
<td>17 (&lt;1)</td>
<td>0.40 (0.04–0.76)</td>
<td>NA</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>73 (2)</td>
<td>22 (1)</td>
<td>1.36 (0.86–1.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>120 (3)</td>
<td>39 (1)</td>
<td>2.16 (1.51–2.81)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available.
*Adapted from Diener et al11 with permission from Elsevier.
†Pearson \(X^2\) test.
‡All of the symptomatic (and thus primary) intracranial hemorrhages were life-threatening bleeding.
risk population whereas patients entering the ESPS2 trial had fewer risk factors. Although 60.5% of the ESPS2 study population had hypertension as compared with 78.0% in the MATCH population, the difference between the 2 study populations in terms of percentages of patients with diabetes mellitus was much greater than this (68.0% for MATCH and 15.3% for ESPS2). It could be questioned whether aspirin plus extended-release dipyridamole would work as well in a high-risk population. Recently, a post hoc analysis of ESPS2 data that stratified data by risk subgroup and univariate risk factors addressed this question. It is interesting to note that Sacco et al found that the difference in efficacy rates between aspirin alone and combination therapy increased as the level of patient risk increased, with the greatest efficacy of the combination observed in those at highest risk. Another valid criticism of the Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events, ESPS2, and MATCH trials is that little attempt was made to subtype the patients with stroke who were included, so it remains unclear how different stroke subtypes responded to the antiplatelet agents used in these trials. In the future, providing such information could help to target antiplatelet therapy to particular stroke subtypes if differential effects are observed.

The ongoing Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial may help investigators determine whether clopidogrel plus aspirin is more efficacious in the general stroke population than aspirin alone and whether this combination leads to a higher rate of bleeding events than aspirin alone. This double-blind trial has randomly assigned 15,603 patients to either clopidogrel (75 mg daily) or placebo given in combination with aspirin (75-162 mg daily), but results will not be available for several years.

**OTHER COMBINATION THERAPY**

In contrast, the combination of aspirin and extended-release dipyridamole was shown to be more effective than aspirin alone for secondary prevention of stroke after an initial stroke or TIA. The double-blind, placebo-controlled ESPS2 trial randomly assigned 6602 patients to aspirin alone (25 mg twice daily), extended-release dipyridamole (200 mg twice daily), a combination of these 2 agents, or placebo. This study determined that the RRR for stroke was 18.1% (*P* = .01) with aspirin therapy, 16.3% (*P* = .004) with extended-release dipyridamole, and 37.0% (*P* < .001) for combination therapy as compared with placebo. Risk reduction for TIA was 21.9% (*P* < .01), 18.3% (*P* < .01), and 35.9% (*P* < .001) for aspirin, dipyridamole, and combination therapy, respectively, as compared with placebo. A comparison of combination therapy with aspirin or dipyridamole alone found RRrs of 23.1% (*P* = .006) and 24.7% (*P* = .002), respectively. In terms of numbers of patients needed to be treated to prevent 1 stroke, 17.2 patients would have to be treated for 2 years with aspirin plus extended-release dipyridamole for 1 event to be prevented as compared with 34.5 or 38.5 patients with aspirin or dipyridamole alone, respectively.

Although bleeding episodes occurred significantly more often in patients receiving either aspirin-containing regimen, little difference was noted between the rates of bleeding episodes in the group that received aspirin alone (8.2%) and the group that received aspirin plus extended-release dipyridamole (8.7%). Unfortunately, the MATCH trial did not have an aspirin-only arm. Thus, no data are available for use in comparing the increased risk of bleeding associated with combination therapy of aspirin plus clopidogrel with the risk of aspirin alone. However, the Clopidogrel in Unstable Angina to Prevent Recurrent Events study did show a 38% increased probability of bleeding events for clopidogrel plus aspirin over aspirin alone in patients with cardiac problems, whereas the increase in bleeding events with aspirin plus extended-release dipyridamole as compared with aspirin alone was only 6.7% in the ESPS2 trial.

A valid criticism of a comparison of the ESPS2 and MATCH data is that the MATCH trial enrolled a high-risk population whereas patients entering the ESPS2 trial had fewer risk factors. Although 60.5% of the ESPS2 study population had hypertension as compared with 78.0% in the MATCH population, the difference between the 2 study populations in terms of percentages of patients with diabetes mellitus was much greater than this (68.0% for MATCH and 15.3% for ESPS2). It could be questioned whether aspirin plus extended-release dipyridamole would work as well in a high-risk population. Recently, a post hoc analysis of ESPS2 data that stratified data by risk subgroup and univariate risk factors addressed this question. It is interesting to note that Sacco et al found that the difference in efficacy rates between aspirin alone and combination therapy increased as the level of patient risk increased, with the greatest efficacy of the combination observed in those at highest risk. Another valid criticism of the Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events, ESPS2, and MATCH trials is that little attempt was made to subtype the patients with stroke who were included, so it remains unclear how different stroke subtypes responded to the antiplatelet agents used in these trials. In the future, providing such information could help to target antiplatelet therapy to particular stroke subtypes if differential effects are observed.

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**CONCLUSIONS**

The MATCH trial results that are now available indicate that clopidogrel plus aspirin should not be used for secondary prevention in patients with stroke or TIA unless some other compelling factor is involved, such as a recent coronary stenting. Even then, this combination should be used for a limited time only. For patients who have found aspirin therapy ineffective but who are not aspirin intolerant, aspirin plus extended-release dipyridamole offers a reasonable alternative for secondary prevention.

For patients who are aspirin intolerant, clopidogrel alone should be used. Head-to-head comparator trials of currently available antiplatelet agents for secondary stroke prevention are urgently needed, and a trial comparing clopidogrel with aspirin plus extended-release dipyridamole is ongoing.

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