Thienopyridines or Aspirin to Prevent Stroke and Other Serious Vascular Events in Patients at High Risk of Vascular Disease?

A Systematic Review of the Evidence From Randomized Trials

Graeme J. Hankey, MD, FRCP, FRACP; Cathie L.M. Sudlow, BM BCh, MRCP (UK); David W. Dunbabin, MBBS, FRACP

Background and Purpose—Aspirin is the most widely studied and prescribed antiplatelet drug for patients at high risk of vascular disease. We aimed to establish how the thienopyridines (ticlopidine and clopidogrel) compare with aspirin in terms of effectiveness and safety.

Methods—We did a systematic review of all unconfounded randomized trials comparing either ticlopidine or clopidogrel with aspirin for patients at high risk of vascular disease. The primary outcome was vascular events (stroke, myocardial infarction, or vascular death). Adverse outcomes were intracranial and extracranial hemorrhage, upper and lower gastrointestinal disturbances, neutropenia, thrombocytopenia, and skin rash.

Results—In 4 trials among 22,656 patients (including 9840 presenting with a transient ischemic attack/ischemic stroke), the thienopyridines reduced the odds of a vascular event by 9% (odds ratio 0.91, 95% CI 0.84 to 0.98; 2P < 0.01), preventing 11 (95% CI 2 to 19) events per 1000 patients treated for ≈2 years. The thienopyridines produced significantly less gastrointestinal hemorrhage and upper gastrointestinal upset (indigestion/nausea/vomiting) than did aspirin. Both thienopyridines increased the odds of skin rash and of diarrhea (ticlopidine by ≈2-fold and clopidogrel by approximately one third). Only ticlopidine increased the odds of neutropenia.

Conclusions—The thienopyridines appear modestly more effective than aspirin in preventing serious vascular events in high-risk patients. Clopidogrel appears to be safer than ticlopidine and as safe as aspirin, making it an appropriate, but more expensive, alternative antiplatelet drug for patients unable to tolerate aspirin. However, there is insufficient information to determine which particular types of patients would benefit most, and which least, from clopidogrel instead of aspirin. (Stroke. 2000;31:1779-1784.)

Key Words: cardiovascular diseases ■ cerebrovascular disorders ■ meta-analysis ■ platelet aggregation ■ randomized controlled trials

Aspirin is the most widely studied and prescribed antiplatelet agent. It inhibits platelet activation by irreversibly inhibiting platelet cyclooxygenase and thromboxane production and prevents about a quarter of serious vascular events (ie, stroke, myocardial infarction [MI], or vascular death) among patients at high risk of vascular disease. In the Antiplatelet Trialists’ (APT) overview of randomized trials of antiplatelet therapy, no antiplatelet regimen was shown to be definitely more effective than aspirin in the prevention of vascular events, but small differences could not be excluded. The thienopyridine derivatives, ticlopidine and clopidogrel, are antiplatelet drugs that act through a mechanism different from that of aspirin, by inhibiting the binding of ADP to its platelet receptor. In the APT overview, ticlopidine, when compared directly with aspirin among almost 3500 patients, produced a promising but nonsignificant reduction in the odds of a vascular event of 10% (95% CI -1 to 24). The results of a large randomized trial comparing the new thienopyridine agent, clopidogrel, with aspirin among almost 20,000 patients at high risk of vascular disease have since added substantially to the available evidence from randomized trials for the effects of the thienopyridines versus aspirin.

Therefore, we carried out a systematic review of the randomized evidence for the effectiveness and safety of the thienopyridines (ticlopidine and clopidogrel) compared with aspirin for the prevention of vascular events among patients at high risk of vascular disease. We considered both thienopyridines together,
because they are chemically very similar and act on platelets through the same mechanism. Because of our particular interest in the management of patients with cerebrovascular disease, we also considered specifically those patients with a previous transient ischemic attack (TIA) or ischemic stroke.

Subjects and Methods

Identification of Trials

We sought all unconfounded randomized trials comparing either ticlopidine or clopidogrel with aspirin among patients at high risk of vascular disease (those with symptoms of ischemia of the cerebral, coronary, or peripheral circulations) who were followed up for at least 1 month for the occurrence of vascular events. We searched the specialized trial registers of the Cochrane Stroke Group and the Antithrombotic Trialists’ Collaboration, Medline, and Embase and contacted Sanofi, the pharmaceutical company that developed and manufactures ticlopidine and clopidogrel.

Outcome Measures

The primary outcome of effectiveness was vascular events, defined as stroke, MI, or death, from a vascular cause. This composite outcome encapsulates all serious events that are likely to be affected by antiplatelet drugs and thus increases the statistical power to detect any true difference in effectiveness between the thienopyridines and aspirin. Secondary effectiveness outcomes were any stroke (ischemic or hemorrhagic), ischemic stroke, MI, vascular death, or all-cause mortality. We classified deaths as vascular if they were due to ischemic stroke, intracranial hemorrhage, MI, or other vascular causes (including extracranial hemorrhage) or as being of unknown cause.

The main adverse outcomes were intracranial hemorrhage, extracranial hemorrhage, gastrointestinal hemorrhage, neutropenia, and thrombocytopenia. Other adverse outcomes were skin rash, diarrhea, and the composite outcome of indigestion, nausea, or vomiting (to capture upper gastrointestinal upset).

We used each trial’s own definitions of the various outcome events.

Data Collection and Analysis

Two reviewers (G.J.H., C.L.M.S.) independently extracted methodological details and relevant data from trial reports. We resolved any disagreements by discussion and consensus. We obtained additional unpublished data from the principal investigators of the largest trial.2 We analyzed data by intention to treat and used the Peto observed-minus-expected method in Cochrane review software3 to obtain a weighted estimate of the odds ratio (OR) for each outcome event. We assessed statistical heterogeneity with a standard χ² test. We calculated absolute risk reductions by the difference in risk observed-minus-expected method in Cochrane review software.4

Results

We identified 4 completed trials, involving a total of 22 656 patients. The qualifying event was a recent TIA or ischemic stroke in 9840 patients, a recent MI in 6302 patients, and symptomatic peripheral arterial disease in 6514 patients. Aspirin was compared with ticlopidine in 3 trials (3471 patients)4–6 and with clopidogrel in 1 trial (19 185 patients).2 The duration of follow-up varied between ≈1 and 3 years, with an average of ≈2 years. The average age of the patients included was ≈63 years, approximately two thirds were male, and most were white. The main characteristics of the trials included are summarized in the Table.

All Patients at High Risk of Vascular Disease

Effects on Serious Vascular Events (Stroke, MI, or Vascular Death)

Compared with allocation to aspirin, allocation to a thienopyridine was associated with a modest, yet statistically significant, reduction in the odds of a serious vascular event (12.0%
for thienopyridine versus 13.0% for aspirin; OR 0.91, 95% CI 0.84 to 0.98; 2\(P\) = 0.01), corresponding to the prevention or delay of 11 (95% CI 2 to 19) vascular events per 1000 patients treated for \(\approx 2\) years (Figure 1).

The patients in the thienopyridine group also experienced a significant reduction in the odds of any stroke (5.7% for thienopyridine versus 6.4% for aspirin; OR 0.88, 95% CI 0.79 to 0.98), corresponding to the prevention or delay of 7 (95% CI 1 to 13) strokes per 1000 patients treated for 2 years (Figure 2). There was also a nonsignificant trend toward a reduction in ischemic stroke (OR 0.90, 95% CI 0.81 to 1.01), MI infarction (OR 0.88, 95% CI 0.76 to 1.01), vascular or unknown cause of death (OR 0.93, 95% CI 0.82 to 1.06), and death from any cause (OR 0.95, 95% CI 0.85 to 1.05) (Figure 2).

### Adverse Effects

There was no clear difference between the thienopyridines and aspirin in the odds of experiencing an intracranial hemorrhage (0.3% for thienopyridine versus 0.4% for aspirin; OR 0.82, 95% CI 0.53 to 1.27) or an extracranial hemorrhage (8.8% for thienopyridine versus 8.9% for aspirin; OR 1.00, 95% CI 0.91 to 1.09). The thienopyridines were associated with a significant reduction in the odds of gastrointestinal hemorrhage (1.8% for thienopyridine versus 2.5% for aspirin; OR 0.71, 95% CI 0.59 to 0.86) and of indigestion/nausea/vomiting (14.8% for thienopyridine versus 17.1% for aspirin; OR 0.84, 95% CI 0.84 to 0.98) but with an increased odds of diarrhea and of skin rash (Figure 3). There was substantial heterogeneity between the results for ticlopidine and clopidogrel for diarrhea (\(\chi^2 = 17.9, 2P = 0.00002\)) and for skin rash (\(\chi^2 = 13.4, 2P = 0.0003\)) (Figure 3). Hence, compared with aspirin, ticlopidine produced an \(\approx 2\)-fold increase in the odds of skin rash (11.8% for ticlopidine versus 5.5% for aspirin; OR 2.2, 95% CI 1.7 to 2.9) and of diarrhea (20.4% for ticlopidine versus 9.9% for aspirin; OR 2.3, 95% CI 1.9 to 2.8), whereas clopidogrel produced a smaller increase of approximately one third in the odds of skin rash (6.0% for clopidogrel versus 4.6% for aspirin; OR 1.3, 95% CI 1.2 to 1.5) and of diarrhea (4.5% for clopidogrel versus 3.4% for aspirin; OR 1.3, 95% CI 1.2 to 1.6) (Figure 3).

Ticlopidine was associated with an excess of neutropenia, <1.2×10^9 neutrophils per liter (2.3% for ticlopidine versus 0.8% for aspirin; OR 2.7, 95% CI 1.5 to 4.8), but clopidogrel was not (0.1% for clopidogrel versus 0.2% for aspirin; OR 0.63, 95% CI 0.29 to 1.36; test for heterogeneity between results for ticlopidine and clopidogrel, \(\chi^2 = 8.9, 2P = 0.003\)) (Figure 3). Nor did clopidogrel produce an excess of thrombocytopenia, <100×10^9 platelets per liter (0.26% versus 0.26%; OR 1.00, 95% CI 0.57 to 1.74) (Figure 3). There were no published trial data available for the frequency of thrombocytopenia associated with ticlopidine compared with aspirin.

### Table: Comparison of the effects on vascular events of thienopyridines vs aspirin in patients at high risk of vascular disease.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Thienopyridine</th>
<th>Aspirin</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE</td>
<td>976 / 9599</td>
<td>1093 / 9580</td>
<td>0.91 (0.84 to 0.98)</td>
</tr>
<tr>
<td>Toghni</td>
<td>8 / 170</td>
<td>16 / 170</td>
<td>0.91 (0.84 to 0.98)</td>
</tr>
<tr>
<td>Schoop</td>
<td>0 / 31</td>
<td>2 / 31</td>
<td>0.91 (0.84 to 0.98)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1364 / 11329</td>
<td>1476 / 11327</td>
<td>0.91 (0.84 to 0.98)</td>
</tr>
</tbody>
</table>

**Figure 1.** Comparison of the effects on the primary outcome of vascular events (stroke, MI, or vascular death) of thienopyridines vs aspirin in patients at high risk of vascular disease. TASS indicates Ticlopidine Aspirin Stroke Study; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events.

**Figure 2.** Comparison of the effects on secondary effectiveness outcomes of thienopyridines vs aspirin in patients at high risk of vascular disease. (Results for individual trials are available in the full electronic version of the present review in the Cochrane Library.)

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*No heterogeneity between results for individual trials with data (p \(\geq 0.1\)).

\# Heterogeneity between 3 trials with data \(\chi^2 = 5.2, p = 0.04\).*
Analyses Restricted to Patients Presenting With Stroke or TIA
Among the 9840 patients with TIA/ischemic stroke, the thienopyridines produced proportional benefits similar to those found overall, in terms of vascular events (16.8% for thienopyridine versus 18.3% for aspirin; OR 0.90, 95% CI 0.81 to 1.00) and in terms of any stroke (10.4% for thienopyridine versus 12.0% for aspirin; OR 0.86, 95% CI 0.75 to 0.97). The absolute reduction of 14 (95% CI 2 to 29) vascular events per 1000 patients treated for >2 years was similar to that observed among all high-risk patients. However, the risk of stroke among patients with a previous TIA or ischemic stroke in the aspirin group (12.0%) was almost twice as high as that for all high-risk patients (6.4%). Therefore, the absolute reduction of 16 strokes (95% CI 3 to 28) per 1000 patients was approximately twice as large as that for all high-risk patients combined.

The results for adverse effects among patients with TIA/ ischemic stroke were similar to those for all patients combined (data not shown).

Discussion
This systematic review considered all of the available evidence from randomized trials of a thienopyridine (either ticlopidine or clopidogrel) versus aspirin, constituting >20 000 patients and >2500 vascular events. Most of the data were from the 2 largest trials. Data were incomplete for several outcome events in only a very small minority of patients, and we would not expect this to alter any of the conclusions of the review.

Prevention of Vascular Events
A combined analysis of all of the evidence showed the thienopyridines to be modestly, yet significantly, more effective than aspirin in preventing serious vascular events among patients at high risk of vascular disease, with no heterogeneity between the results for ticlopidine and clopidogrel. However, there is considerable uncertainty about the size of the additional benefit: the wide 95% CI suggests that among high risk patients in general, the proportional reduction in the odds of a vascular event might be as small as 2% or as large as 16%, so that treatment with a thienopyridine rather than aspirin for >2 years might prevent or delay anywhere between 2 and 19 vascular events per 1000 patients.

This overall uncertainty means that the magnitude of the additional benefit for particular types of patients is even more uncertain, and the results of subgroup analyses must be
Adverse Effects

There were no clear differences between the thienopyridines and aspirin in the risks of either intracranial or extracranial bleeding. Aspirin produced more gastrointestinal hemorrhage and upper gastrointestinal upset than did the thienopyridines. However, although evidence from randomized trials shows that aspirin doses ranging from 75 to 1500 mg daily are similarly effective in the long-term prevention of vascular events, the adverse effects of aspirin on the gastrointestinal tract are more frequent at higher doses. Because the doses of aspirin used in the trials ranged from 325 to 1500 mg daily (Table), it is conceivable that a lower daily aspirin dose might compare more favorably with the thienopyridines in terms of these adverse gastrointestinal effects. The thienopyridines produced more skin rash and diarrhea than did aspirin, and indirect comparisons between the results for the 2 thienopyridines suggested that the excess risks of both of these were greater with ticlopidine than with clopidogrel.

Data from the CAPRIE study2 showed clopidogrel to be at least as safe as aspirin (325 mg daily). Because severe episodes of skin rash and diarrhea occurred very infrequently, the excess of each among patients given clopidogrel rather than aspirin was only ≈1 or 2 per 1000 patients over 2 years. The excess risks of severe gastrointestinal bleeding and of severe upper gastrointestinal upset with aspirin were of similar magnitude: ≈2 or 3 per 1000 patients.2 Ticlopidine was also associated with an excess of neutropenia. In addition, observational studies have shown ticlopidine to be associated with both thrombocytopenia and thrombotic thrombocytopenic purpura.8–10 By contrast, clopidogrel has not (so far) been associated with adverse hematological problems, either during the CAPRIE trial or subsequently on the open market. The preliminary results of a direct randomized comparison between the safety profiles of ticlopidine and clopidogrel used in combination with aspirin among ≈1000 patients undergoing coronary artery stenting also suggested the safety and tolerability of clopidogrel to be superior to that of ticlopidine.11

Conclusions and Implications for Clinical Practice and for Future Research

The main conclusions of the present review are as follows: (1) On average, the thienopyridines provide slightly more protection than does aspirin against vascular events among high-risk patients, but the extent of added benefit is uncertain, both overall and especially for individual patients. (2) Clopidogrel appears to be safer than ticlopidine. (3) Clopidogrel is at least as safe as aspirin.

If an alternative antiplatelet drug to aspirin is to be used, clopidogrel is therefore the most appropriate choice. However, clopidogrel is much more expensive than aspirin; the cost of treating 1000 patients for 2 years with clopidogrel instead of aspirin is currently ≈$1.6 million (US dollars).12 Substituting aspirin with clopidogrel among all high-risk patients might prevent as many as 19 vascular events at a cost of ≈$85 000 per event prevented or as few as 2 vascular events at ≈$800 000 per event prevented. Thus, the prescribing costs may well exceed the cost of a vascular event (eg, in Australia the estimated annual cost of a stroke is ≈$35 000).12 At present, it seems prudent to infer that clopidogrel should not replace aspirin as the first-choice antiplatelet agent for all patients at high risk of vascular disease. Cost-effectiveness might be improved by using clopidogrel among those patients considered to be at highest risk of vascular events, perhaps including those who suffer recurrent ischemic events on aspirin, because they are likely to derive the greatest absolute benefit. But, this is speculative, and an analysis based on individual patient data would be required to address the issue of which types of patients benefit most (and which least) from thienopyridines compared with aspirin. However, clopidogrel would seem to be an appropriate alternative antiplatelet drug for patients who are intolerant of, or allergic to, aspirin, provided that we accept the lack of direct evidence among such patients, because they were excluded from the trials.

A further important question not addressed by the present review is whether the combination of clopidogrel and aspirin is both safe and more effective than either drug alone. Because aspirin and clopidogrel have different mechanisms of action on platelets, the addition of clopidogrel to aspirin might well lead to greater additional benefit than replacing aspirin with clopidogrel.13 Several ongoing randomized trials are now comparing the combination with aspirin alone in a range of high vascular risk conditions.

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