Thienopyridine Derivatives Versus Aspirin for Preventing Stroke and Other Serious Vascular Events in High Vascular Risk Patients

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Cardiovascular disease is an enormous burden on society, and the prevention of serious vascular events in high-risk individuals is one strategy to reduce this burden. Aspirin is the most widely studied and prescribed antiplatelet agent for preventing serious vascular events, reducing the odds of such events among high vascular risk patients by approximately one quarter. Thienopyridine derivatives, including clopidogrel and ticlopidine, inhibit platelet activation by a different mechanism and so may be more effective. This article is an update1 of a Cochrane review first published in 2000.2,3

Methods

Study Objective
The objective of this study was to determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for preventing serious vascular events (stroke, myocardial infarction, or death from a vascular cause) in patients at high risk.

Search Methods
To update a previous comprehensive search, we searched the trials registers of the Stroke, Heart, and Peripheral Vascular Diseases Cochrane Review Groups (last searched July 2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 3, 2008), MEDLINE (1966 to August 2008), and EMBASE (1980 to August 2008). We also searched reference lists of relevant papers and contacted other researchers and the pharmaceutical company Sanofi-BMS (December 2008).

Selection Criteria
We selected all unconfounded, double blind, randomized trials directly comparing a thienopyridine derivative with aspirin in high vascular risk patients (ie, those with previous transient ischemic attack, ischemic stroke, myocardial infarction, angina, or peripheral arterial disease).

Data Collection and Analysis
Two review authors independently extracted the data and assessed trial quality. We sought additional data from the principal investigators of the largest trials. We calculated a weighted estimate of the odds ratio for each outcome using the Peto fixed-effect method.

Results
Ten trials involving 26 865 high vascular risk patients were included. The trials were generally of high quality. Aspirin was compared with ticlopidine in 9 trials (7633 patients) and with clopidogrel in 1 trial (19 185 patients) (Figure, a). Compared with aspirin, allocation to a thienopyridine produced a modest, just statistically significant, reduction in the odds of a serious vascular event (11.6% vs 12.5%; odds ratio=0.92; 95% CI, 0.85 to 0.99), corresponding to the avoidance of 10 (95% CI, 0 to 20) serious vascular events per 1000 patients treated for 2 years. However, the wide confidence interval includes the possibility of negligible additional benefit. This proportional reduction in the odds of serious vascular events associated with thienopyridines was similar in the subgroup of patients with previous transient ischemic attack/ischemic stroke. Compared with aspirin, thienopyridines significantly reduced gastrointestinal adverse effects. However, thienopyridines increased the odds of skin rash and diarrhea, ticlopidine more so than clopidogrel. Allocation to ticlopidine, but not clopidogrel, significantly increased the odds of neutropenia (Figure, b).

Conclusions
The addition of 6 new trials (4209 participants) since the last version of the review has not changed the main conclusions. The thienopyridine derivatives are at least as effective as aspirin in preventing serious vascular events in patients at high risk and possibly somewhat more so. However, the size of any additional benefit is uncertain and could be negligible. Of the thienopyridines included in the trials, clopidogrel has a more favorable safety and tolerability profile than ticlopidine.
Figure. Meta-analysis of randomized trials of a thienopyridine derivative (clopidogrel or ticlopidine) vs aspirin in high–vascular risk patients, showing (a) effectiveness outcomes (stroke and other serious vascular events) and (b) safety outcomes/adverse effects. Results are expressed as Peto odds ratios and 95% CIs. An odds ratio <1 suggests that the thienopyridine derivative is superior to aspirin.
Implications for Practice
The data support the use of thienopyridine derivatives, in particular clopidogrel, as an alternative to aspirin. However, because clopidogrel is substantially more expensive than aspirin and not clearly more effective, it should generally only be used in patients genuinely intolerant of or allergic to aspirin.

Implications for Research
Future large trials are needed to address two important unresolved issues. The first is what clinicians should do about antiplatelet treatment when high vascular risk patients have further vascular events while taking aspirin alone. The second is whether combining a thienopyridine derivative with aspirin is safe and more effective than either alone in the early very high risk period after ischemic stroke/transient ischemic attack.

Disclosures
Prof Graeme Hankey has received honoraria for lecturing at scientific symposia sponsored by Sanofi Aventis, Bristol Meyers Squibb, and Boehringer Ingelheim and has received fees for consulting from Sanofi Aventis, Bristol Meyers Squibb, and Boehringer Ingelheim. All of the remaining authors report no conflicts of interest.

References

Key Words: antiplatelet drugs □ aspirin □ stroke □ thienopyridines □ vascular events
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