Ever since the Antithrombotic Trialists reported a clear benefit from aspirin in the secondary prevention of vascular disease in patients with a variety of cardiovascular events, there has been a search for more effective antithrombotic agents. The first relatively nontoxic drug to undergo randomized clinical trial was clopidogrel in the CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) where 3 groups of patients (myocardial ischemia (MI), ischemic stroke or peripheral arterial disease) were given either aspirin or the drug. The compound end point of MI, ischemic stroke and vascular death was significantly reduced by clopidogrel compared with patients taking aspirin. However, the substantial benefit on vascular outcome evident in the peripheral vascular group was not shared by either the stroke patients or those with MI.

Because aspirin and clopidogrel have different biochemical pathways inhibiting platelet adhesiveness, a combination of the 2 drugs might be even more effective in secondary prevention of vascular events. In CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) the dual antiplatelet therapy was found even more beneficial than clopidogrel alone in reducing combined cardiac and cerebral ischemic end points, but a group with aspirin alone was not included. This was followed by CREDO (Clopidogrel for the Reduction of Events During Observation), and once again clopidogrel was found more effective than placebo in reducing the compound end points of death and myocardial and cerebral infarction in patients undergoing percutaneous coronary intervention.

However, all these studies failed to show any significant prophylactic effect on the outcome of patients with cerebral ischemia. In the MATCH study (Management of Atherothrombosis with Clopidogrel in High risk patients) a combination of clopidogrel and aspirin was compared with clopidogrel alone specifically in patients with ischemic stroke or transient ischemic attacks (TIAs). The addition of aspirin made no significant difference to reducing subsequent major vascular events but did increase the risk of bleeding.

The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance) was designed to specifically address patients at particularly high vascular risk. Over 15,000 patients with either cardiac, cerebral or peripheral ischemia, or asymptomatic patients (with multiple vascular risk factors) were followed for a mean of 28 months. The results were disappointing. The combination of clopidogrel and aspirin was no more effective than aspirin alone in reducing the rate of subsequent myocardial infarction, stroke or vascular death. Also, as in the MATCH trial, the dual antiplatelet combination caused more frequent and more serious bleeding.

Are these results so surprising? Examining the CAPRIE data, there is no doubt that the compound end points were significantly fewer in the clopidogrel group compared with the aspirin group. However, when the 3 individual outcomes (myocardial ischemia, stroke and peripheral vascular disease) were evaluated separately, only the relative risk reduction (RRR) for peripheral vascular disease (PVD) was effectively reduced: (stroke 7.3%, MI −3.7% and PVD 23.8%) The trialists attributed the discrepancy in the stroke group to the heterogeneity of the disorder, a correct but frequently overlooked observation. Similarly, in the CURE study, when the 3 components of the compound end point are analyzed separately, there is a significantly beneficial effect on MI, but only a nonsignificant beneficial trend in ischemic stroke. In fact, the MI patients had unstable angina, a high risk condition already established by pathological studies to be specifically induced by intramyocardial platelet emboli. Because the MATCH trial showed that the clopidogrel and aspirin combination was no more effective in secondary prevention than clopidogrel alone, and because the risk of serious bleeding complications with dual antiplatelet therapy was 3.0%, use of this combination in patients with stroke or TIA cannot be recommended.

CHARISMA was a well conducted study, with prespecified end points, clearly defined entry criteria, and although sponsored by Industry, there was considerable autonomy in the conduct of the trial by the investigators. However, the lack of any major therapeutic effect is not so surprising.
considering that in CAPRIE the overall RRR of clopidogrel compared with aspirin was only 8.7%, with an absolute risk reduction of only 0.5%, mostly from the effect on PVD. In MATCH, the closest analogous trial, results were similar, with a 5.9% RRR and a mere 0.72% absolute risk reduction.

What have we learned so far from over 20 years of antiplatelet trials? Accumulating evidence indicates that clopidogrel is only marginally more effective than aspirin in secondary prevention of vascular end points, and this effect is predominantly on peripheral vascular disease and those with unstable angina. There is no convincing evidence that clopidogrel (either alone or combined with aspirin) improves the outcome in patients presenting with TIA or stroke, and the cost is 80 times that of aspirin alone. Further antiplatelet studies are currently in progress. However, in spite of over a decade of expensive and time consuming antiplatelet drug wars, the simple fact remains that aspirin is still the first choice of antiplatelet agents in the secondary prevention of stroke.

Also, unlike heart attacks, brain attacks are a misnomer, and include patients with a great variety of different etiologies, all with differing responses to antiplatelet agents. It is time to discard compound end points and conduct trials restricted to clearly defined types of ischemic stroke, even though this may require larger numbers of subjects. Otherwise, history will just keep repeating itself.

Disclosures

None.

References


Key Words: antiplatelet agents ■ antiplatelet drugs ■ clinical trials