Role of antiplatelet agents in cardioprotection

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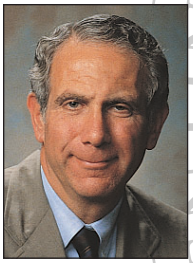

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In addition to beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and HMG-CoA reductase inhibitors (statins), the other class of drugs which have demonstrated cardioprotective effects in large clinical trials are the antiplatelet agents.

Platelets play a key role in the genesis of acute vascular events. Platelet adhesion, activation, and aggregation are essential steps in thrombus formation and occlusive disease. Platelet inhibition is a standard form of treatment for patients with atherosclerotic disease or at risk for such disease.

Aspirin

In the Antiplatelet Trialists' Collaboration, a meta-analysis of 145 trials that included more than 73,000 patients, aspirin therapy was associated with widespread benefit in patients at risk of complications from vascular disease.[1] Among patients with acute myocardial infarction (MI), the incidence of vascular events was reduced from 14% in the patients taking placebo to 10% in those taking aspirin. Patients with a history of MI had a similar reduction in events with aspirin treatment compared with controls. Among the patients with a history of stroke or transient ischemic attack, 18% of those taking antiplatelet therapy and 22% of controls had vascular events.

The reductions in vascular events were about 25% in each of the risk groups analyzed, and the benefit of aspirin was apparent in middle-aged and older patients, men and women, hypertensive and normotensive patients, and in those with or without diabetes. In most of the studies included, the dosage of aspirin was 75 to 325 mg daily. The optimal duration of aspirin therapy is unknown, although the meta-analysis established that benefit continues after 1 year of treatment.

The Antiplatelet Trialists' Collaboration demonstrated protection in a wide range of patients who are at risk for vascular disease and suggested that antiplatelet therapy should be considered for almost all patients with suspected acute MI or a history of MI, unstable angina, stroke, or transient ischemic attack, and in those who have undergone coronary artery bypass surgery or angioplasty.

No evidence was obtained that aspirin is beneficial for primary prevention in persons who are at low risk for vascular disease. Most of the data on aspirin for this purpose have come from studies using doses of 165 to 325 mg/day; relatively few data are available on 81 mg/day. In patients with atrial fibrillation, low-dose aspirin has been no different from placebo in terms of embolus prevention.

A recent meta-analysis of primary prevention trials showed that aspirin reduces the risk of MI but increases the risk of gastrointestinal and intracranial bleeding.[2] The authors concluded that the net benefit of aspirin increases with increasing risk for coronary heart disease and that the decision to use aspirin chemoprevention should be based on the individual patient's risk factors and expected outcomes.

Some controversy exists over the use of aspirin in patients with heart failure, especially in those who are taking ACE inhibitors. An aspirin–ACE inhibitor interaction is biologically plausible; ACE inhibitors exert at least some of their effect by increasing vasodilator prostaglandins, whereas aspirin can block production of prostaglandins by inhibiting cyclo-oxygenase.[3]

The uniformity of aspirin's effects has been questioned. Aspirin resistance may approach 10% in men and 50% in women.

In a recent study, patients who were aspirin resistant, as shown by a high level of thromboxane in their urine, had a 3.5 times higher risk of cardiovascular death than patients with the lowest level.[4] The increased risk was independent of other risk factors, including hypertension, elevated cholesterol levels, obesity, smoking, and diabetes.

Aspirin's mechanism of action is through inhibition of thromboxane A_2, a platelet activator. Other mechanisms are involved in platelet activation and aggregation.

Clopidogrel

Clopidogrel, a thienopyridine derivative, selectively and irreversibly inhibits the binding of adenosine diphosphate to its platelet receptor, thereby inhibiting platelet aggregation. The first large-scale trial of clopidogrel was the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study.[5] CAPRIE was a multicenter study of 19,185 patients who had recent ischemic stroke, recent MI, or established peripheral arterial disease. They were randomized to either a single daily dose of 325 mg of aspirin or 75 mg of clopidogrel. In the intent-to-treat analysis, the annual rate of the combined end point of stroke, MI, or vascular death was 5.83% in the aspirin-treated group compared with 5.32% in the clopidogrel-treated group. The 8.7% relative risk reduction in favor of clopidogrel was statistically significant ($p = .043$).

The safety profile of clopidogrel was comparable to that of aspirin. The overall rate of bleeding was similar between the aspirin- and clopidogrel-treated patients, but the rate of any gastrointestinal hemorrhage and serious gastrointestinal hemorrhage was significantly lower with clopidogrel. Neutropenia was rare in both aspirin- and clopidogrel-treated patients.

Recently, the addition of clopidogrel to standard therapy for acute coronary syndromes was found to reduce the risk of early and late cardiovascular events in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial.[6] The CURE study included 12,562 patients with unstable angina or non–Q-wave MI who were already being treated with aspirin and various other standard cardiovascular therapies that could include beta blocking agents, statins, ACE inhibitors, and heparin. Patients were randomized to placebo or a 300-mg loading dose of clopidogrel followed by 75 mg daily.

At 9 months, the combined end point of cardiovascular death, MI, or nonfatal stroke was reduced by 20% in the group randomized to clopidogrel compared with placebo (11.5% versus 9.3%; $p < .001$). Significant reductions in cardiovascular death, MI, and stroke were also observed with clopidogrel. The incidence of major bleeding was 2.7% in the placebo group compared with 3.6% in the clopidogrel group ($p = .003$). A nonsignificant 15% increase in the incidence of life-threatening bleeds also occurred in the clopidogrel group. The authors concluded that clopidogrel and aspirin have a synergistic antiplatelet effect.

A substudy of CURE analyzed the effect of clopidogrel and aspirin in 2,658 patients with non–ST-segment elevation acute coronary syndrome who underwent percutaneous coronary intervention (PCI-CURE).[7] The investigators found that long-term administration of clopidogrel was associated with a significant 30% ($p = .03$) reduction in the primary end point of the composite of cardiovascular death, MI, or urgent target vessel revascularization within 30 days of percutaneous intervention.

It appears from these trials that clopidogrel should be used with aspirin and continued for at least 9 months in patients with acute coronary syndrome who are not at high risk for bleeding. ■

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