New Data on Long-Term Antiplatelet Therapy

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The Antiplatelet Trialist Collaboration overview of the randomized clinical trials in patients at risk of vascular events established the efficacy of antiplatelet therapy in reducing the risk of death, non-fatal myocardial infarction and non-fatal stroke and formed the basis for their use in patients with unstable angina, myocardial infarction, transient cerebral ischaemia, stroke and atherosclerotic peripheral arterial disease. Aspirin is the most widely used antiplatelet agent but has a number of limitations. Several new antiplatelet drugs are available. Glycoprotein IIb/IIIa receptor bockers including the monoclonal antibody abciximab, the peptide inhibitor eptifibatide and the non-peptide inhibitor tirofiban are effective following coronary revascularization and in patients with unstable angina. Oral glycoprotein IIb/IIIa receptor blockers have proved disappointing. The thienopyridine agents, ticlopidine and clopidogrel that block ADP-induced aggregation have been shown to be more effective than aspirin in patients at risk for vascular events. Two important studies of clopidogrel in the treatment of acute coronary ischaemia have recently been completed. The CURE study[1] evaluated the efficacy and safety of clopidogrel when given with aspirin in patients with acute coronary syndromes without ST-segment elevation. In CURE, 12,562 patients who had presented within 24 hours after the onset of symptoms were randomly assigned to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) (6259 patients) or placebo (6303 patients) in addition to aspirin for 3-12 months. The results of the study showed that the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke occurred in 9.3% of the patients in the clopidogrel plus aspirin group and 11.4% of the patients in the placebo plus aspirin group (relative risk with clopidogrel 0.80; 95% confidence interval, 0.72-0.90; P<0.001). The second primary outcome, the first primary outcome or refractory ischaemia, occurred in 16.5% of the patients in the clopidogrel plus aspirin group and 18.8% of the patients in the placebo plus aspirin group (relative risk, 0.86, P<0.001). In addition, the percentages of patients with in-hospital refractory or severe ischaemia, heart failure and revascularization procedure were significantly lower with clopidogrel. However, there were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7% vs 2.7%; relative risk, 1.38; P=0.001), but there were no more episodes of life-threatening bleeding (2.1% vs 1.8%, P=0.13) or haemorrhagic strokes with clopidogrel. The CURE trial, therefore, showed that clopidogrel had beneficial effects in patients with acute coronary syndromes without ST-segment elevation but with a slightly increased risk of major bleeding. PCI-Cure[2] was a prospectively designed study of patients randomized to double-blind therapy with clopidogrel or placebo in the CURE trial who underwent PCI. Of the 12,562 patients in CURE, 2658 patients underwent PCI of whom 1313 received clopidogrel and 1345 placebo. PCI was performed during the initial hospital stay in 1730, and the remaining 928 after discharge. Patients were pretreated with aspirin and clopidogrel or placebo for a median of 6 days before PCI during the initial hospital admission, and a median of 10 days overall. After PCI, most patients received open label thienopyridine (either clopidogrel or ticlopidine) for 4 weeks after which they took

study drug again for a mean of 8 months. In the main CURE trial, GP IIb/IIIa inhibitors were discouraged except during PCI and when the patient developed refractory ischaemia. The primary endpoint of PCI-Cure was a composite of cardiovascular death, MI or urgent target-vessel revascularization (TVR). Patients treated with clopidogrel plus aspirin had significantly fewer primary endpoint events (between PCI and 30 days) than those on aspirin. Most of this benefit was derived from pretreatment with clopidogrel and aspirin versus aspirin alone. Among patients receiving clopidogrel over the long term, there were significantly lower rates of CV death, MI or any revascularization and of CV death or MI compared to placebo. Overall in PCI-CURE there was a 31% reduction in cardiovascular death or myocardial infarction. While in CURE there was a significant increased risk of major but not life-threatening bleeding with clopidogrel plus aspirin compared to aspirin alone, the excess in major bleeding in PCI-CURE did not reach significance. Life-threatening bleeding was similar between the two treatment groups in PCI-Cure. However, minor bleeding was significantly more common in the clopidogrel group between PCI and follow-up. Among patients who received GP IIb/IIIa inhibitors, no increase in major bleeding (p=0.97) or life-threatening bleeding (p=0.98) was seen between those randomized to receive combination treatment.

The results of these two studies with clopidogrel in non-ST segment elevation ischaemia will apply to most patients who present with unstable angina or non-Q-wave MI and will result in a widespread change in patterns of practice. Additional studies are required to determine the role of combination GPIIb/IIIa/clopidogrel treatment in this setting.

References

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