Clopidogrel plus aspirin was effective but increased bleeding in acute coronary syndromes without ST-segment elevation

The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. **Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.** N Engl J Med. 2001 Aug 16;345:494-502.

QUESTION

What are the efficacy and safety of early and long-term use of clopidogrel plus aspirin and aspirin alone in patients with acute coronary syndromes without ST-segment elevation?

DESIGN

Randomized (allocation concealed*), blinded {patients, health care providers, data collectors, outcome assessors, monitoring committee, statisticians, and manuscript writers}†,* placebo-controlled trial with follow-up to 12 months (Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE] Trial).

SETTING

482 centers in 28 countries.

PATIENTS

12 562 patients (mean age 64 y, 62% men) who were hospitalized within 24 hours of symptom onset, had either electrocardiographic changes or elevated levels of cardiac enzymes, and did not have ST-segment elevation. Exclusion criteria were contraindications to antithrombotic or antiplatelet therapy, high risk for bleeding or severe heart failure, oral anticoagulant use, coronary revascularization in the previous 3 months, or intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous 3 days. Follow-up was 99.9%.

INTERVENTION

6259 patients were allocated to an immediate loading dose of oral clopidogrel, 300 mg, followed by 75 mg/d for 3 to 12 months; 6303 patients were allocated to placebo. All patients received aspirin, 75 to 325 mg/d.

MAIN OUTCOME MEASURES

Main outcomes were a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or stroke and a composite of death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia. Safety outcomes included major and minor bleeding.

MAIN RESULTS

Analysis was by intention to treat. Patients in the clopidogrel group had lower rates of the 2 composite outcomes ($P < 0.001$) but higher rates of major and minor bleeding ($P < 0.001$) than did patients in the aspirin-alone group (Table).

CONCLUSION

Clopidogrel plus aspirin was more effective than aspirin alone in patients with acute coronary syndromes without ST-segment elevation, but it increased bleeding.

Sources of funding: Sanofi-Synthelabo and Bristol-Myers Squibb.

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*See Glossary.

†Information provided by author.

Clopidrogrel plus aspirin vs aspirin alone for acute coronary syndromes without ST-segment elevation‡

Outcomes at 12 mo	Clopidrogrel plus aspirin	Aspirin alone	RRR (95% CI)	NNT (CI)
Composite 1	9%	11%	20% (10 to 28)	48 (32 to 96)
Composite 2	17%	19%	14% (6 to 21)	44 (28 to 104)
			RRI (CI)	NNH (CI)
Major bleeding	3.7%	2.7%	38% (13 to 67)	100 (62 to 252)
Minor bleeding	5.1%	2.4%	112% (75 to 156)	37 (30 to 49)

‡Composite 1 = composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or stroke; composite 2 = death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

The findings of the CURE trial are impressive, showing a statistically significant reduction in the primary composite end point of death from cardiovascular causes, nonfatal MI, or stroke in patients treated with clopidogrel and aspirin. More than that, the incidence of Q-wave MI, which is unarguably an important adverse outcome of acute coronary syndromes, was also substantially decreased. This benefit was not observed in previous trials (1–3) that assessed other antiplatelet strategies for acute coronary syndromes.

Increased major and minor bleeding in patients who received clopidogrel plus aspirin is an important concern. 17% of patients had coronary artery bypass grafting (CABG). When CABG was done within 5 days of clopidogrel therapy ($n = 912$), the incidence of major bleeding was higher than in control-group patients (9.6% vs 6.3%, $P = 0.06$). In the 910 patients who had surgery > 5 days after stopping clopidogrel, no additional risk for bleeding was found. Thus, at least some bleeding complications can be prevented by delaying surgery. With this precaution in mind, the use of early and long-term clopidogrel and aspirin in patients with acute coronary syndromes and clinical characteristics similar to those of the patients enrolled in the CURE trial is appropriate. Patients who do and do not have revascularization should benefit.

The addition of clopidogrel to the regimen of such patients will increase expenses by approximately $1500/patient per year. The increased costs may be offset by a reduction in expensive complications. A cost-effectiveness analysis is under way. The utility of continuing clopidogrel therapy beyond 1 year requires additional study.

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