Review: Thienopyridines are more effective than aspirin for preventing vascular events in high-risk patients

Hankey GJ, Sudlow CL, Dunbabin DW. **Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients.** Cochrane Review, latest version 24 Aug 1999. In: The Cochrane Library. Oxford: Update Software.*

QUESTION

In patients at high risk for vascular events, are thienopyridine derivatives (ticlopidine and clopidogrel) more effective and safe than aspirin for preventing stroke and other vascular events (myocardial infarction [MI] or vascular mortality)?

DATA SOURCES

Studies were identified by searching the Specialised Register of Controlled Trials of the Cochrane Collaboration Stroke Group, the Antithrombotic Trialists' database, MEDLINE, and EMBASE/Excerpta Medica up to July 1999. Investigators from 1 trial and the manufacturer (Sanofi) were also contacted.

STUDY SELECTION

Randomized controlled trials were selected if patients were at high risk for occlusive arterial disease because of atherosclerotic arterial disease; oral ticlopidine or clopidogrel was compared with aspirin; follow-up was ≥ 1 month; and outcomes of stroke, MI, or vascular mortality were evaluated.

DATA EXTRACTION

Data were extracted on methodologic quality; patient and study characteristics; drug regimens, including compliance; follow-up duration and numbers; and outcomes.

MAIN RESULTS

4 trials of 22 656 patients met the inclusion criteria (mean age 63 y, approximately 66% men, 85% having had a previous vascular event, and follow-up 1 to 3 y). Analysis was by intention to treat. Thienopyridines were associated with a decreased rate of the composite endpoint of stroke, MI, or vascular mortality (P = 0.01) (Table) and all-cause stroke (P = 0.02) (Table) but not ischemic stroke or stroke of unknown pathologic type, hemorrhagic stroke, MI, vascular or unknown cause of death, all-cause mortality, or extracranial hemorrhage. Patients receiving thienopyridines had lower rates of gastrointestinal hemorrhage and indigestion, nausea, or vomiting. Ticlopidine was associated with more neutropenia, skin rash, and diarrhea. Clopidogrel was associated with more skin rash and diarrhea. Subgroup analyses showed that patients with previous transient ischemic attacks or ischemic stroke had similar benefits.

CONCLUSION

Thienopyridines (ticlopidine and clopidogrel) are more effective than aspirin for preventing the combined outcome of stroke, myocardial infarction, and vascular mortality and have lower rates of gastrointestinal hemorrhage but higher rates of skin rash and diarrhea.

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For correspondence: Dr. G. Hankey, Stroke Unit, Department of Neurology, Royal Perth Hospital, Wellington Street, Perth, Western Australia, Australia 6001. FAX 61-8-9224-3323. ■

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Thienopyridines (ticlopidine and clopidogrel) vs aspirin to prevent vascular events in high-risk patients†

Outcomes at 1 to 3 y	Weighted event rates		RRR (95% CI)	NNT (CI)
	Thienopyridines	Aspirin		
Composite‡	12%	13%	8% (2 to 14)	98 (55 to 441)
Stroke	5.8%	6.4%	11% (2 to 20)	177 (87 to 3250)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
‡Stroke, myocardial infarction, or vascular mortality.

COMMENTARY

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study is the world's largest clinical trial in cardiology (1). Hankey and colleagues included this trial, which contributes 85% of the patients and 72% of the events to the meta-analysis. Because the results of the meta-analysis reflect primarily the outcome of the mega-trial, the effect of the results from the smaller trials on this meta-analysis is modest.

2 antiplatelet drugs of the thienopyridine class, ticlopidine and clopidogrel, are analyzed together. Is this justified? Neither beneficial nor adverse effects of drugs in the same class are necessarily interchangeable (2, 3). In the meta-analysis, the beneficial effects of the 2 drugs have been combined, whereas the adverse effects have been analyzed separately. This difference was based on formal statistical tests of heterogeneity. Nevertheless, it would have been useful to see the actual data when the effect of clopidogrel on cardiovascular events is directly compared with ticlopidine.

Clopidogrel proves interesting when applying cost-effectiveness principles in clinical practice. As the CAPRIE results show, when compared with aspirin, an additional 200 patients need to be treated with clopidogrel for 1 year to prevent 1 additional cardiovascular event. The annual marginal cost is about U.S. $800/patient (or $160 000 to prevent 1 additional event). This substantial cost must be balanced by the economic and human costs associated with stroke, MI, or gangrene-related amputation. Clopidogrel causes fewer peptic ulcers than aspirin, although as many as 900 patients need to be treated with clopidogrel rather than aspirin to avoid 1 additional gastrointestinal hemorrhage (l).

Because of the unfavorable cost-effectiveness of clopidogrel, Hankey and colleagues propose it as the second choice in routine clinical practice, mainly for patients who cannot tolerate aspirin. This is sound advice.

Kjell Asplund, MD, PhD
University Hospital
Umea, Sweden

References

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