

Clopidogrel plus aspirin did not differ from aspirin alone for reducing MI, stroke, and CV death in high-risk atherothrombosis

Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706-17.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆ Cardiology ★★★★★☆ Neurology ★★★★★☆

QUESTION

In patients at high risk for atherothrombosis, is long-term treatment with clopidogrel plus aspirin more effective than aspirin alone for reducing cardiovascular (CV) events?

METHODS

Design: Randomized placebo-controlled trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA]).

Allocation: Concealed.*

Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†.*

Follow-up period: Median 28 months.

Setting: 768 sites in 32 countries.

Patients: 15 603 patients ≥ 45 years of age (median age 64 y, 70% men, 80% white) who had multiple atherothrombotic risk factors (type 1 or 2 diabetes, diabetic nephropathy, ankle-brachial index < 0.9, asymptomatic carotid stenosis ≥ 70% of luminal diameter, ≥ 1 carotid plaque, systolic blood pressure ≥ 150 mm Hg, primary hypercholesterolemia, smoking > 15 cigarettes/d, or men ≥ 65 y or women ≥ 70 y of age), coronary disease, cerebrovascular disease, or symptomatic peripheral arterial disease. Exclusion criteria were long-term use of antithrombotic or nonsteroidal antiinflammatory drugs, indications for clopidogrel therapy, or revascularization.

Intervention: Clopidogrel, 75 mg/d, plus aspirin, 75 to 162 mg/d ($n = 7802$), or matching placebo plus aspirin ($n = 7801$).

Outcomes: Composite endpoint of myocardial infarction (MI), stroke, or CV death; and severe bleeding. Secondary outcomes included the primary composite endpoint or hospitalization for unstable angina, revascularization, or transient ischemic attack (secondary composite endpoint); individual outcomes of the composite endpoints; all-cause and CV mortality; and moderate bleeding. The study had 90% power to detect a 20% relative risk reduction in the primary composite endpoint.

Patient follow-up: 99.5% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the primary composite endpoint or severe bleeding (Table). The clopidogrel group had a lower incidence

of the secondary composite endpoint and nonfatal stroke, but a higher incidence of moderate bleeding than did the placebo group (Table). Groups did not differ for all-cause mortality, CV death, or nonfatal MI.

CONCLUSION

In patients at high risk for atherothrombosis, long-term treatment with clopidogrel plus aspirin did not differ from aspirin alone for reducing the composite endpoint of myocardial infarction, stroke, and cardiovascular death.

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*See Glossary.

†Information provided by author.

Clopidogrel plus aspirin vs aspirin alone for high-risk atherothrombosis at median 28 months‡

Outcomes	Clopidogrel + aspirin	Aspirin alone	RRR (95% CI)	NNT (CI)
Primary composite endpoint§	6.8%	7.3%	7.0% (–5.0 to 17)	Not significant
Secondary composite endpoint	16.7%	17.9%	8.0% (0.5 to 14)	70 (40 to 1119)
Nonfatal stroke	1.9%	2.4%	21% (2.0 to 36)	197 (115 to 2064)
			RRI (CI)	NNH (CI)
Severe bleeding	1.7%	1.3%	25% (–3.0 to 61)	Not significant
Moderate bleeding	2.1%	1.3%	62% (27 to 108)	125 (72 to 287)

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from control event rates and relative risks in article.

§Cardiovascular death, myocardial infarction, or stroke.

||Primary composite endpoint, or hospitalization for unstable angina, transient ischemic attack, or revascularization.

COMMENTARY

Aspirin, which blocks the platelet cyclooxygenase pathway, is effective for preventing vascular events (1). Recent short-term studies combining aspirin with clopidogrel, another antiplatelet drug that blocks the adenosine diphosphate P2Y₁₂ receptor, have shown significant benefit in patients with acute coronary syndromes and those undergoing percutaneous revascularization (2).

The CHARISMA trial by Bhatt and colleagues was designed to determine if long-term therapy with aspirin plus clopidogrel was better than aspirin alone in patients at high risk for atherothrombosis. Overall, there was no benefit in using dual therapy over aspirin alone for the primary outcome and only a small benefit for the secondary outcome. However, it is logical that if dual therapy is effective for short-term therapy in acute coronary syndromes, there may be some patients for whom long-term therapy might also be beneficial. To address this possibility, the authors did a prespecified subgroup analysis, including patients with multiple risk factors alone and those with a his-

tory of vascular events. Dual therapy provided no benefit for patients with multiple risk factors alone but a small risk reduction in the primary endpoint for patients who had established vascular disease (6.9% vs 7.9%). The usual cautions about subgroup analysis apply, and further research is needed to show benefit for long-term dual therapy. Dual therapy is more expensive than aspirin alone, and this trial showed an increased risk for moderate bleeding. For now, clinicians should use aspirin alone for long-term antiplatelet therapy.

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References

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