

Addition of oral anticoagulation to antiplatelet therapy did not reduce CVD events in peripheral arterial disease

The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357:217-27.

Clinical impact ratings: Cardiology ★★★★★☆ Hematol/Thrombo ★★★★★★ Neurology ★★★★★☆

QUESTION

In patients with peripheral arterial disease, is oral anticoagulant plus antiplatelet therapy better than antiplatelet therapy alone for preventing cardiovascular disease (CVD) events?

METHODS

Design: Randomized controlled trial (Warfarin Antiplatelet Vascular Evaluation [WAVE] trial).

Allocation: Concealed.*

Blinding: Blinded (central adjudication committee).*

Follow-up period: Mean 35 months.

Setting: 80 centers in Canada, Poland, Hungary, Ukraine, China, the Netherlands, and Australia.

Patients: 2161 patients 35 to 85 years of age (mean age 64 y, 74% men) with peripheral arterial disease (atherosclerosis of the arteries of the legs, carotid arteries, or subclavian arteries) who, during the run-in phase with oral anticoagulant plus antiplatelet therapy, achieved a stable international normalized ratio between 2.0 and 3.0, adhered to therapy, and had no side effects. Exclusion criteria included indication for oral anticoagulant therapy, high risk for active bleeding, stroke in the previous 6 months, and need for dialysis.

Intervention: Oral anticoagulant (warfarin or acenocoumarol) plus antiplatelet (aspirin, ticlopidine, or clopidogrel) therapy

($n = 1080$) or antiplatelet therapy alone ($n = 1081$).

Outcomes: Composite endpoint 1 (myocardial infarction [MI], stroke, or death from CVD causes), composite endpoint 2 (as above, or severe ischemia of peripheral or coronary arteries leading to urgent intervention), and bleeding.

Patient follow-up: 99.9% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for either composite endpoint (Table). Bleeding at all levels of severity was more frequent in the anticoagulant plus antiplatelet group (Table).

CONCLUSION

In patients with peripheral arterial disease, oral anticoagulant plus antiplatelet therapy was not more effective than antiplatelet therapy alone for preventing cardiovascular disease events and was associated with a 3-fold higher risk for bleeding.

Sources of funding: Canadian Institutes of Health Research; Heart and Stroke Foundation of Ontario; Population Health Research Institute.

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*See Glossary.

Oral anticoagulant plus antiplatelet therapy vs antiplatelet therapy alone for peripheral arterial disease at mean 35 months†

Outcomes	Anticoagulant plus antiplatelet	Antiplatelet alone	RRR (95% CI)	NNT
MI, stroke, or CVD death	12%	13%	8% (-16 to 27)	Not significant
MI, stroke, CVD death, or severe ischemia	16%	17%	9% (-12 to 26)	Not significant
			RRI (CI)	NNH (CI)
Life-threatening bleeding	4.0%	1.2%	241% (84 to 535)	36 (24 to 68)
Moderate bleeding	2.9%	1.0%	182% (43 to 458)	54 (32 to 139)
Minor bleeding	39%	11%	263% (201 to 338)	4 (4 to 5)

†MI = myocardial infarction; CVD = cardiovascular disease; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

Peripheral arterial disease is common and frequently accompanies coronary artery disease. Accordingly, coronary artery disease risk-factor modification and antiplatelet therapy are the mainstays of treatment. The WAVE trial examined the use of combination anticoagulant and antiplatelet therapy to decrease the incidence of CVD complications in patients with peripheral arterial disease.

Previous work has demonstrated an important bleeding risk with combination therapy. WARIS II studied patients after MI and found a 29% relative decrease in a composite endpoint of death, nonfatal MI, or thromboembolic stroke with warfarin plus aspirin compared with aspirin alone (1). However, this benefit was outweighed by a > 3-fold annual increase in major bleeding risk (0.62% vs 0.17%, $P < 0.001$). Similarly, a recent retrospective analysis showed that combined use of aspirin and warfarin increased risk for gastrointestinal bleeding more than warfarin alone, with an adjusted relative risk of 6.48 (2). Finally, a meta-analysis comparing aspirin plus warfarin with warfarin alone showed that combination therapy increased risk for major bleeding (odds ratio 1.43, 95% CI 1.00 to 2.02) without reducing CVD events in patients with coronary artery disease or atrial fibrillation (3).

The WAVE trial did not show any benefit of combination therapy over antiplatelet therapy alone, and risks for bleeding at all severity levels were increased 3-fold in the combination therapy group.

Furthermore, high rates of bleeding occurred despite the exclusion of high-risk patients, such as those with long-term nonsteroidal anti-inflammatory drug use, previous gastrointestinal bleeding, or recent stroke.

The WAVE trial should serve as a caution to physicians that use of combined anticoagulant and antiplatelet therapy confers considerable bleeding risk and probably should be reserved for high-risk patients, such as those who develop atherothrombotic events despite adequate antiplatelet or anticoagulant therapy. Further research is needed to determine the optimal dosing and duration of combination antithrombotic therapy, particularly in patients with drug-eluting stents who typically receive aspirin and clopidogrel and may also have an indication for oral anticoagulant therapy.

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