Clopidogrel plus aspirin was inferior to oral anticoagulation for preventing vascular events in atrial fibrillation

The ACTIVE Writing Group on behalf of the ACTIVE Investigators; Connolly S, Pogue J, Hart R, et al. **Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial.** Lancet. 2006;367:1903-12.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Hematol/Thrombo ★★★★★★★

QUESTION

In patients with atrial fibrillation (AF), is clopidogrel plus aspirin noninferior to oral anticoagulation for preventing vascular events?

METHODS

Design: Randomized controlled trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events [ACTIVE W]).

Allocation: Concealed.*

Blinding: Blinded (outcome assessors and monitoring committee).*

Follow-up period: Median 1.28 years.

Setting: 30 clinical centers worldwide.

Patients: 6706 patients (mean age 70 y, 66% men) with AF and ≥ 1 of the following criteria: age ≥ 75 years; receiving treatment for systemic hypertension; previous stroke, transient ischemic attack, or non–central nervous system (non-CNS) systemic embolus; left ventricular dysfunction with left ventricular ejection fraction < 45%; peripheral arterial disease; or age 55 to 74 years with diabetes mellitus requiring drug therapy or previous coronary artery disease. Exclusion criteria were contraindication to clopidogrel or oral anticoagulant, documented peptic ulcer disease within the previous 6 months, previous intracerebral hemorrhage, significant thrombocytopenia, or mitral stenosis.

Intervention: Clopidogrel, 75 mg/d plus aspirin, 75 to 100 mg/d (n = 3335), or oral anticoagulation (n = 3371). Patients in the oral anticoagulation group received a vitamin K antagonist and were monitored to keep the international normalized ratio (INR) between 2.0 and 3.0. The dose of oral anticoagulation was managed by study investigators or by local anticoagulation clinics.

Outcomes: A composite endpoint of the first occurrence of stroke, non-CNS systemic embolism, myocardial infarction, or vascular death. Secondary outcomes included total stroke, total mortality, and hemorrhage.

Patient follow-up: 99.7% (intention-to-treat analysis).

MAIN RESULTS

The trial stopped early (median 1.28 y) because clopidogrel plus aspirin was clearly inferior to oral anticoagulation therapy (Table). Clopidogrel plus aspirin also led to greater rates of total stroke and total hemorrhage (Table). Groups did not differ for total mortality and major hemorrhage (Table).

CONCLUSION

In patients with atrial fibrillation, clopidogrel plus aspirin was inferior to oral anticoagulation for preventing vascular events.

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*See Glossary.

Clopidogrel plus aspirin vs oral anticoagulation to prevent vascular events in atrial fibrillation at median 1.28 years†

Outcomes	Clopidogrel plus aspirin	Oral anticoagulation	RRI (95% CI)	NNH (CI)
Composite endpoint‡	7.0%	4.9%	44% (18 to 76)	47 (27 to 114)
Total stroke	3.0%	1.8%	72% (25 to 137)	78 (41 to 223)
Total mortality	4.8%	4.7%	1.0% (–19 to 26)	Not significant
Major hemorrhage	3.0%	2.8%	10% (–17 to 45)	Not significant
Total hemorrhage	19%	16%	21% (8 to 35)	30 (18 to 79)

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from relative risks in article.
‡Non–central nervous systemic embolus (0.5% vs 0.1%), myocardial infarction (1.1% vs 0.7%), stroke (3.0% vs 1.8%), and vascular death (2.4% vs 2.3%).

COMMENTARY

Stroke is a serious complication of valvular and nonvalvular AF. Oral anticoagulation with vitamin K antagonists (INR 2 to 3) and aspirin, 325 mg (in patients ineligible for oral anticoagulants), are associated with reductions in stroke risk of two thirds and one fifth, respectively, compared with placebo (1). However, oral anticoagulants are difficult to use and monitor and subject to interactions with disease states, medications, and foods. Currently, there are no proven alternatives to aspirin, including dual antiplatelet therapy with aspirin and clopidogrel (2).

The ACTIVE W trial by Connolly and colleagues was designed to determine whether aspirin and clopidogrel were not inferior to oral anticoagulation with vitamin K antagonists for the prevention of vascular events in patients with AF at high risk for stroke. 77% of patients were receiving oral anticoagulants at the time of randomization. The trial was stopped early because of clear superiority of oral anticoagulants for the primary outcome, without an increase in major hemorrhages or mortality. While total stroke was significantly higher in the aspirin and clopidogrel group, the effect of oral anticoagulants was greatest for preventing nondisabling strokes (0.4% vs 1.0% per y). In addition, minor hemorrhages were more common in patients receiving aspirin and clopidogrel.

This well-conducted study has limitations. First, the rates of stroke and other vascular events were lower than in other trials, resulting in small absolute differences in events between groups. Second, some bias probably existed in favor of oral anticoagulants because most enrolled patients were already taking oral anticoagulants and thus were more likely to benefit from and tolerate them. A randomized trial comparing the 2 treatment regimens in patients naïve to both is needed. The ongoing ACTIVE A trial will determine whether aspirin plus clopidogrel is better than aspirin alone in patients with AF.

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References

1. **van Walraven C, Hart RG, Singer DE, et al.** JAMA. 2002;288:2441-8.
2. **Fuster V, Rydén LE, Cannom DS, et al.** Eur Heart J. 2006;27:1979-2030.