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Atrial fibrillation, is warfarin the only option for stroke prevention

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Evidence Based Medicine

Atrial Fibrillation, is Warfarin the only option for stroke prevention?

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Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of vascular events-active

Why is this study important and noteworthy?

Atrial fibrillation is the most common cardiac arrhythmia with a potential for serious adverse events like stroke. The annual rate of stroke with AF is around 4.5% and increases in patients older than 75 years of age. Warfarin has long been established as the treatment of choice for stroke prevention in patients with AF. However, there are several issues with oral anticoagulation. Firstly, there is an increased risk of haemorrhagic complications, secondly INR's commonly fall out of range due to drug and food interactions and require major lifestyle adjustment to accommodate frequent testing. As a result investigators have tried to explore options other than Warfarin to prevent cerebrovascular events. Several studies have compared varying doses of Aspirin to oral anticoagulation and a meta-analysis concluded that Warfarin was superior in terms of preventing cerebrovascular events but increased the risk of haemorrhage.

Clopidogrel added to aspirin had been found superior to aspirin in some cardiology trials. Therefore the investigators for ACTIVE also decided to explore whether the combination of clopidogrel and aspirin was any match to warfarin in patients with AF.

The trial had a third arm in which irbesartan which is an ACE inhibitor was given to half the patients in a factorial design, on the pretext that hypertension increases the risk of stroke in patients with AF. The results of this trial are still awaited.

Who were the participants?

ACTIVE included three separate interrelated trials. ACTIVE W was an open label non-inferiority trial in which clopidogrel plus ASA was compared to oral anticoagulation in patients with AF and at least 1 risk factor for stroke. ACTIVE A included patients with AF and at least 1 risk factor for stroke who received ASA because they had a contraindication to oral anticoagulation or because they were unwilling to take an oral anticoagulant and half of them received clopidogrel in a double blind placebo controlled manner. ACTIVE I was a partial factorial, double-blind, placebo-controlled trial of irbesartan in patients participating in ACTIVE A or ACTIVE W.

The study was a multicenter trial performed at 580 centers in 33 countries. Patients were eligible if they had ECG evidence of AF and at least one risk factor for stroke. If they were less than 75 years of age, they had to have either DM or CAD. They were excluded from ACTIVE A if they had any contraindication to clopidogrel and from ACTIVE W if they had contraindication to oral anticoagulation. ACTIVE I is not described here as the results from it are still awaited.

What was the intervention?

In ACTIVE W, 3371 patients were assigned to oral anticoagulation (keeping INR between 2 and 3) and 3335 to a combination of Aspirin 75-100mg and Clopidogrel 75mg. They were followed up for a median of 1.28 years.

ACTIVE A included patients who had had AF and were at increased risk for stroke but were considered unsuitable for oral anticoagulation. In ACTIVE A, 3772 patients were randomized to receive clopidogrel 75mg plus aspirin 75-100mg and 3782 were assigned to placebo plus aspirin 75-100mg. Both groups were followed up for a median of 3.6 years.

What was the outcome?

In ACTIVE W there were 164 primary outcome events (stroke, non-CNS systemic embolus, myocardial infarction, or vascular death) on oral anticoagulation therapy (annual risk 3.9%) compared with 234 events on clopidogrel plus aspirin (annual risk 5.6%; relative risk [RR] 1.44, 95% CI 1.18-1.76; p=0.0003).Oral anticoagulation was most protective against stroke (RR 1.72, 95% CI 1.24-2.37; p=0.001) and non-CNS systemic embolism (4.66, 1.58-13.8; p=0.005). Rates of major haemorrhage were similar in the two groups. However, total as well as minor bleeds were significantly more common with clopidogrel plus aspirin than with oral anticoagulation therapy (RR 1.21 and 1.23 and p=0.001 and p=0.0009 respectively).

In ACTIVE A there were 832 primary outcome events (stroke, MI, systemic embolism and death) in the aspirin plus clopidogrel arm and 924 events in the aspirin plus placebo arm (RR 0.89, p=0.01). The greatest benefit of the combination was seen in stroke with a RR of 0.72 and

p<0.001. However, the rate of major haemorrhage also increased significantly with the combination. Therefore, on combining the major vascular events and major haemorrhages, the number of events in the two groups were not significantly different (A+C 968 vs. A 996 events; p = 0.54). The addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% per year to 6.8%, but the rate of haemorrhage increased from 1.3% to 2.0% per year.

What were the conclusions?

ACTIVE W concluded that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke who do not have contraindications to oral anticoagulation therapy. The trial failed to show mortality benefit with Warfarin. The number needed to be treated for 1 year with anticoagulation to prevent one stroke is about 100.

ACTIVE A concluded that a combination of aspirin and clopidogrel is superior to aspirin alone for preventing all vascular events and particularly strokes. However, this advantage is offset by the risk of excess bleeding with the combination.

How does this impact our clinical practice?

The clear advantage of oral anticoagulation for AF was re-demonstrated in ACTIVE W. Therefore for patients with AF at risk of stroke, and with no contraindications to anticoagulation, Warfarin remains the drug of choice.

In our setting, putting patients on Warfarin is perhaps a bigger challenge than it is in the West. Reasons for this include lack of education regarding the drug, lack of proper follow up, and sub standard medicines and laboratory testing.

For all these reasons, oral anticoagulation is often not safe. For those with a clear cut contraindication to Warfarin, a combination of aspirin and clopidogrel confers greater protection against vascular events compared to aspirin alone. However, given the increased risk of haemorrhage with the combination, this decision should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for an individual patient.

Recommended Reading

1. The ACTIVE steering committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006; 151: 1187-93.
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4. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009; 360: 2066-78.