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Stroke reduction in patients with atrial fibrillation

B Vezi
Staff Cardiologist, Department of Medicine, Groote Schuur Hospital, Cape Town, South Africa

TITLE 1 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

AUTHORS 1 ACTIVE Writing Group on behalf of the ACTIVE Investigators, Connolly SJ, Pogue J et al.

JOURNAL 1 *Lancet* 2006; 367:1903–12

TITLE 2 Effect of clopidogrel added to aspirin in patients with atrial fibrillation

AUTHORS 2 ACTIVE Investigators, Connolly SJ, Pogue J et al.

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***Correspondence to* B Vezi, Department of Medicine, E25 Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa**

***tel.* +27 21 404 6084**
***e-mail* brianvez@ialch.co.za**

SUMMARY

These papers report the first two trials (ACTIVE A and ACTIVE W) of a trilogy of interrelated strategies to reduce vascular events in patients with atrial fibrillation (AF). ACTIVE W compared dual antiplatelet therapy with oral anticoagulation therapy (OAC), while ACTIVE A compared single versus dual antiplatelet therapy. The third trial, ACTIVE I, is an ongoing comparison of irbesartan with placebo.

The inclusion criteria and main outcomes for both trials were similar, with the exception that in ACTIVE A patients were considered ineligible for OAC. In ACTIVE W, 6,706 patients were randomly allocated to receive clopidogrel (75 mg per day) plus aspirin (75–100 mg per day) or OAC. The primary outcome was first occurrence of stroke, non-central nervous system systemic embolus, myocardial infarction or vascular death. The study was stopped early because of clear evidence of the superiority of OAC. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3.93%) and 234 in those on clopidogrel plus aspirin (annual risk 5.60%). The endpoint was primarily driven by stroke; OAC reduced the rate of stroke by 42% compared with the clopidogrel/aspirin combination.

The ACTIVE A trial enrolled 7,554 patients who were unable to take OAC. Patients were randomised to aspirin or clopidogrel/aspirin. The addition of clopidogrel to aspirin reduced the primary endpoint from 7.6% per year to 6.8% per year. Again, the difference was primarily due to a reduction in the rate of stroke. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year); relative risk (RR) 0.72; 95% confidence interval (CI) 0.62–0.83; p<0.001. Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year); RR 1.57; 95% CI 1.29–1.92; p<0.001.

TABLE 1 Summary of the stroke and major bleeding rates from the ACTIVE W and ACTIVE A trials

	ACTIVE A annual event rates		**ACTIVE W** annual event rates	
	aspirin	aspirin/ clopidogrel	aspirin/ clopidogrel	OAC
Stroke	3.3%	2.4%	2.39%	1.40%
Major bleeding	1.3%	2.8%	2.42%	2.21%
Fatal bleeding	0.2%	0.3%	0.17%	0.26%

OPINION

These two trials add significantly to our knowledge of stroke risk reduction in patients with AF. There are two important messages. Firstly, in patients at moderate to high risk of stroke who are able to take either anti-platelet therapy or OAC, OAC is clearly the more effective form of stroke prevention. However, the downside is a substantial risk of major bleeding, which can occasionally be fatal.

Secondly, in patients who are *absolutely* unable to take OAC, the aspirin/clopidogrel combination offers modest additional stroke reduction compared with aspirin alone. Again, it should be noted that the downside is an important additional risk of major bleeding, similar to the risk of OAC.

When assessing a patient with AF we need to estimate the individual's risk of stroke. We know this is related to other clinical features, including the aetiology of AF,

hypertension, left ventricular function, age, diabetes and history of previous stroke.[1] Following this, the patient's potential benefit from antiplatelet therapy and OAC should be estimated. Finally, and perhaps most tricky, the patient's risk of major bleeding should be assessed. Future research should try to develop more robust methods to predict the individual risk of stroke and major bleeding.

REFERENCE

1 Gage BF, Waterman AD, Shannon W et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285:2864–70.

Severe anaemia in sub-Saharan Africa

T Latham
VSO Visiting Lecturer in Haematology, College of Medicine, Blantyre, Malawi, and Honorary Clinical Senior Lecturer, University of Edinburgh, UK

TITLE Severe anemia in Malawian children

AUTHORS Calis JCJ, Phiri KS, Faragher EB et al.

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Correspondence to ***T Latham, Department of Haematology, College of Medicine, Private Bag 360, Chichiri, Blantyre, Malawi***

tel. ***+265 995629062***
e-mail ***tom.latham@ed.ac.uk***

Kanthu n'kavumbu, kavumbula mende pachisa
(Something is revealed, stirring up the rat in the nest) – Malawian (Chewa) idiom

SUMMARY

In one of the most comprehensive studies published to date of the aetiology of severe anaemia in the developing world, Calis et al. compare the prevalence of factors associated with severe anaemia in 382 children aged between six and 60 months of age with haemoglobin (Hb) <5.0 g/dL, and 759 apparently healthy matched controls. Subjects were recruited from an urban teaching hospital in Malawi and a rural district hospital. Two groups of control patients, one from the community and one consisting of surgical outpatients, were studied.

The control group data illustrate the public health importance of anaemia and its causes, and the difficulty of inferring causation from uncontrolled studies in populations with widespread poor health. Even among the community control groups, the mean Hb was 9.9g/dL. Deficiencies of iron, vitamin B12, vitamin A and generalised malnutrition as suggested by wasting were common in the control group as a whole (69.4%, 15.6%, 65.6% and 6.2% respectively); folate deficiency was not found. Infective causes were also very prevalent (malaria [*Plasmodium falciparum*] 42.8%, human immunodeficiency virus [HIV] 6%, hookworm 1.9%, Epstein-Barr virus [EBV] 18%). Haemoglobinopathies were rare (Hb S/S 1.0%; β thalassaemia and α0 thalassaemias have not been described in Malawi), although the prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency was 9%.

Factors positively associated with severe anaemia in a multivariate analysis were deficiencies of vitamins A and B12, infection with HIV, EBV, *P. falciparum* and hookworm, bacteraemia (most commonly with non-typhi Salmonella species), and G6PD deficiency. Low maternal education levels were also associated with severe anaemia. Counterintuitively, iron deficiency was less common among children with severe anaemia than in the control group, especially for children from an urban area. The authors note an inverse association between bacteraemia and iron deficiency and suggest that a protective role of iron deficiency against bacteraemia may have a net effect of protecting against severe anaemia.

A subsequent follow-up of patients in the study[1] showed an in-hospital mortality of 6.4% and an 18-month all-cause mortality of 12.6%. This compares with a 1.4% all-cause mortality for the community controls (which is distressingly high in itself). HIV infection was the strongest predictor of subsequent mortality in patients with severe anaemia.

OPINION

One of the first observations that strikes any doctor working in the developing world is the frequency and severity of anaemia both in hospital patients and the community. Based on World Health Organization criteria