University. I also receive reimbursement for educational activities or consulting fees from Acumed, Amylin, the Annenberg Center, Avalere Health, Bayer, Biogen, Boehringer Ingelheim, Boston Scientific, Brandeis University, Five Prime, GlaxoSmithKline, Johnson & Johnson, Heart.org (Conceptis), Kowa Research Institute, Eli Lilly, Medtronic, Merck, Nitrox LLC, Novartis Pharmaceutical, Roche, Sanofi-Aventis, Schering Plough, Scius, Targacept, the University of Florida, Vertex, and Vivus; all revenues from educational activities are paid to Duke University, and all income from consulting activities is donated to non-profit organisations (most being donated to the clinical research fellowship fund of the Duke Clinical Research Institute). I hold equity in Nitrox LLC.

1 Mark DB, Van de Werf FJ, Simes RJ, et al. Cardiovascular disease on a global scale: defining the path forward for research and practice. *Eur Heart J* 2007; **28:** 2678–84.
2 Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009; **301:** 831–41.
3 Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009; **360:** 816–23.

Who is ineligible for warfarin in atrial fibrillation?

Stroke is a disastrous complication of atrial fibrillation. Patients with atrial fibrillation have a five times higher stroke risk than those without this common arrhythmia.[1] Thromboembolism from the functionally asystolic left atrium is thought to cause the stroke. Oral anticoagulation with vitamin K antagonists, mainly warfarin, reduces the stroke risk to a third of that seen without antithrombotic therapy.[2] However, anticoagulants are patient-unfriendly, difficult to monitor, and are associated with a risk of severe bleeding of at least 1% per year. Alternative anticoagulant therapy with the oral direct thrombin inhibitor ximelagatran was shown to be equally effective in two megatrials,[3] but showed unacceptable liver toxicity that prohibited regulatory approval. The only other antithrombotic strategy available in atrial fibrillation is aspirin, which showed efficacy against thromboembolism versus placebo but proved to be inferior to warfarin.[2] In atrial fibrillation, aspirin, although inexpensive, patient-friendly, and relatively safe, is indicated only in warfarin-ineligible patients. A more intense antiplatelet therapy (ie, aspirin plus clopidogrel, which is a successful treatment for acute coronary syndromes with and without ST-segment elevation[4–6]) has been tested in the large ACTIVE-W trial.[7] In that study double antiplatelet therapy proved to be inferior to warfarin in stroke prevention in atrial fibrillation, and was associated with an at least as high bleeding risk. Thus there was no clear alternative for high-risk patients with atrial fibrillation, who for one reason or another are ineligible for warfarin.

Recently, the ACTIVE-A trial was published.[8] In total, 7554 patients who had atrial fibrillation and were ineligible for oral anticoagulation were randomised to double antiplatelet therapy (clopidogrel 75 mg plus aspirin 75–100 mg daily) or to aspirin alone, and were followed up for 3·6 years. The endpoint of disabling or fatal stroke was reduced by 26% by the double antiplatelet strategy (1·6% per year) compared with aspirin alone (2·1% per year, p<0·001). Major bleeding was significantly increased by 57% from 1·3% per year with aspirin alone to 2·0% per year with double antiplatelet treatment. Also the rate of haemorrhagic stroke doubled (0·2% per year *vs* 0·4% per year, respectively, p<0·001). Vascular mortality was not affected by double antiplatelet therapy.

ACTIVE-A clearly showed that more intense antiplatelet therapy is better than single antiplatelet treatment for stroke prevention in atrial fibrillation, which suggests an important role for platelets in the pathogenesis of stroke in patients with atrial fibrillation. The benefit against ischaemic stroke outweighs the risk of severe bleeding and therefore patients who are ineligible for warfarin should be treated with double antiplatelet therapy rather than single antiplatelet treatment.

But the question is: how ineligible is ineligible for warfarin? In the ACTIVE-A trial, 50% of the candidates for the trial were considered ineligible for warfarin by their physicians, a quarter by the patients themselves,

	ACTIVE-A (warfarin ineligible)		ACTIVE-W (warfarin eligible)	
	Aspirin (n=3782)	Aspirin+clopidogrel (n=3722)	Aspirin+clopidogrel (n=3335)	Warfarin (n=3371)
$CHADS_2$ score	2·0	2·0	2·0	2·0
Mean age (years)	70	70	71	71
Total strokes (per year)	3·3	2·4*	2·4	1·4*
Disabling and fatal strokes (per year)	2·1	1·6*	1·7	1·3†
Major bleeds (per year)	1·3	2·0	2·0	2·2
Strokes or major bleed (per year)	2·5	1·2*	1·0	0·6*

*p<0·01, aspirin *vs* aspirin+clopidogrel. †p<0·05, aspirin+clopidogrel *vs* warfarin.

Table: **Baseline features and outcome of the two major trials of double antiplatelet therapy in stroke prevention in atrial fibrillation**

and for the rest by perceived increased bleeding risk. The last was based on inability to comply with monitoring by international normalised ratio, predisposition to falling or head trauma, persistent blood pressure above 160/100 mm Hg, previous serious bleeding on warfarin, severe alcohol misuse for more than 2 years, peptic ulcer disease, thrombocytopenia, or the need for chronic use of a non-steroidal anti-inflammatory drug. Clearly, these criteria were rather loose, being put forward by either the physician or the patient. Therefore double antiplatelet therapy cannot been seen as an alternative to warfarin for patients with atrial fibrillation in general. Are the patients in ACTIVE-A very different from the patients in ACTIVE-W? The strong risk factors for stroke, such as age and $CHADS_2$ score, a clinical predictor for stroke in atrial fibrillation,[9] were almost identical (table). As expected, the stroke rate in patients on double antiplatelet therapy was also similar in the double antiplatelet therapy groups in both ACTIVE-A and ACTIVE-W, which strongly suggests that the patients also had the same baseline bleeding risk. So it seems that the populations of patients in both trials were similar. The lowest stroke rate per year was seen in the warfarin group in ACTIVE-W, with a similar major bleeding rate as double antiplatelet therapy in both ACTIVE-A and ACTIVE-W.

Although ACTIVE-A underscores the role of platelets in stroke in patients with atrial fibrillation, double antiplatelet therapy for stroke prevention should be given only to patients who are definitely ineligible for warfarin. This group could include patients who refuse to undergo monitoring or those mentally not able to take the various doses of warfarin mandated by the monitoring. Perceived unacceptably high risk of bleeding itself cannot make patients ineligible for warfarin, as clearly shown in the published ACTIVE trials, because the bleeding rate with double antiplatelet therapy in both studies were very similar to the bleeding rate with warfarin. Therefore warfarin should remain the cornerstone of stroke prevention in atrial fibrillation.

Freek W A Verheugt
Department of Cardiology, Onze Lieve Vrouwe Gasthuis, 1091 AC Amsterdam, Netherlands
f.w.a.verheugt@olvg.nl

I have received departmental research funding and consultancy fees from Sanofi-Aventis and speakers' honoraria from AstraZeneca.

1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke: the Framingham Study. *Arch Intern Med* 1987; **147:** 1561–64.
2 Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. *BMJ* 2002; **325:** 1022–25.
3 Verheugt FWA. Can we pull the plug for warfarin in atrial fibrillation? *Lancet* 2003; **362:** 1686–87.
4 CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.
5 Sabatine M, Cannon CP, Montalescot G, et al, for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.
6 COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1607–21.
7 ACTIVE Investigators. Randomized controlled trial of clopidogrel plus aspirin versus oral anticoagulation in patients with atrial fibrillation: The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE). *Lancet* 2006; **367:** 1903–12.
8 ACTIVE Investigators. Effect of clopidogrel added to aspirin in atrial fibrillation. *N Engl J Med* 2009; **360:** 2066–78.
9 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285:** 2864–70.

Insulin glargine and malignancy: an unwarranted alarm

Published **Online**
July 20, 2009
DOI:10.1016/S0140-6736(09)61307-6

See **Correspondence** page 521

Insulin glargine is a recombinant insulin analogue that has become widely used, largely because of a lower risk of hypoglycaemia and prolonged stable action. Synthetic insulins differ from human insulins in both metabolic and cell-growth activities, which raises legitimate concerns about risk of malignancy.[1] A recent observational study claimed an increased cancer incidence in people using glargine insulin compared with other human insulins, but this effect was only apparent after adjusting for dose.[2] Subsequently, three further observational studies[3-5] and one randomised trial[6] have investigated whether insulin glargine is associated with cancer incidence.

Although observational studies from health databases can usefully detect unexpected drug effects in everyday practice, there is potential for biased conclusions.[7] The problem is that clinical decisions determining each patient's treatment are not random: people are prescribed different therapies for health-related reasons. Thus health outcomes might differ between people taking different therapies even if the therapies themselves have no such effect. Despite adjustment for confounders, residual selection bias might distort any true (lack of) differences between treatments.[8]