Editorial

Warfarin in atrial fibrillation: underused in the elderly, often inappropriately used in the young

In the past decade, much has been learned about antithrombotic prophylaxis to prevent stroke in patients with non-valvar atrial fibrillation (AF). Adjusted dose warfarin is highly efficacious, aspirin is modestly efficacious (reducing primarily non-disabling, non-cardioembolic strokes in AF), warfarin is much more efficacious than aspirin, and low intensity warfarin (international normalised ratios (INR) < 1.5) alone or combined with aspirin offers minimal protection.¹ The absolute risk of stroke varies widely in patients with AF, from < 1% to 12% per year, depending on age and coexisting vascular disease.^{2,3} Selection of antithrombotic prophylaxis should consider the inherent risk of stroke and the absolute risk reductions afforded. It is my view that many AF patients, including most younger than 75 years, do not substantially benefit from treatment with adjusted dose warfarin.

Two observational studies in this issue address this important, controversial issue.^{4,5} Perez and colleagues surveyed a sample of patients with AF randomly drawn from outpatient clinics.⁴ Applying a scheme for stratifying stroke risk, only about half of those deemed high risk and who had no apparent contraindications for anticoagulation were being treated with warfarin, while a quarter of those presumed at low risk were receiving anticoagulants. Warfarin was particularly underused among high risk AF patients older than 75 years: only about 20% were being anticoagulated. The second study by Deplanque and the SAFE I (stroke in atrial fibrillation ensemble) Study Investigators examined the use of antithrombotic agents before hospitalisation among 213 AF patients with acute stroke or transient ischaemic attack.⁵ Their results suggest considerable room for improvement but are more difficult to interpret as the risk of stroke in those not given antithrombotic agents in the population from which these cases were drawn cannot be estimated, and risk stratification was not examined. The mean age of outpatients with AF in Perez *et al*'s study was 68 years,⁴ while the mean age of AF patients with cerebral ischaemia was nearly a decade older in the SAFE I study.⁵ Both studies found advancing age to be inversely correlated with warfarin use.^{4,5}

Underuse of warfarin in patients with AF older than 75 years

About 50% of people with non-valvar AF in population based surveys are > 75 years, and the bulk of AF associated stroke occurs in this age group. The risk of major bleeding during anticoagulation, including devastating intracranial haemorrhage, is higher in the very elderly,⁶ but the risks do not offset the substantial benefits for most high risk AF patients if anticoagulants are carefully administered.^{2,7} While INRs between 2 and 3 appear to provide optimal protection against stroke for most AF patients,⁸ targeting the lower end of this range may be sensible for primary prevention in those > 75 years to minimise major and minor haemorrhage, the latter frequently leading to discontinuation of warfarin.⁹ More studies are needed on the safety of anticoagulation and tolerance over time for AF patients > 75 years treated in clinical practice. Nevertheless, it seems clear that warfarin is underused in

elderly, high risk AF patients, neglecting an important opportunity for stroke prevention.¹⁰

Predicting stroke risk in AF patients

Warfarin reduces stroke for all patients with AF, but the magnitude of reduction is small for the many patients with low inherent risks for stroke (table 1). The number of AF patients who would need to be treated with warfarin instead of aspirin for one year to prevent one stroke (the number needed to treat) is about 14 for high risk AF patients with recent cerebral ischaemia compared with nearly 250 for AF patients at low risk for stroke.

Can stroke risk in AF patients be reliably predicted? Four schemes have been generated by multivariate analyses of prospectively studied clinical trial cohorts (table 2).^{11–14} While criteria overlap, the differences importantly influence patient management. Depending on which scheme is used, the fraction of an AF cohort categorised as high risk can vary from 33–88%.¹⁵ Most AF patients over age 75 years (66–100%) are predicted to be high risk compared with as few as 6% of younger AF patients without prior stroke, depending on the criteria.¹³ In one scheme, results of precordial echocardiography did not contribute to risk stratification,¹³ although this remains controversial.¹⁰ Whether transoesophageal echocardiography contributes to risk characterisation is also unsettled.¹⁶ The SPAF (stroke prevention in atrial fibrillation) study criteria have been shown reliably to identify low risk AF patients in two independent test cohorts.^{12,17} The criteria from the atrial fibrillation investigators were derived from pooled analysis of participants in five trials, perhaps enhancing their generalisability.¹¹ Validation of these schemes outside clinical trial cohorts is needed¹⁷ as community based cohorts are generally older and have a higher proportion of women. There is some evidence that existing risk stratification schemes may be age sensitive.¹⁵

AF patients categorised as having a moderate risk of stroke (about 3% per year given aspirin) engender the most uncertainty about antithrombotic prophylaxis. Existing criteria for moderate risk are the most variable; it is unclear how reliably this subgroup can be characterised, the durability of classification, and the validity outside of clinical trials. Those doubting the reliability of currently available schemes to distinguish moderate from high risk generally advocate warfarin for all but the lowest risk patients.

Table 1 Magnitude of benefit according to inherent stroke risk in non-valvar atrial fibrillation

	Primary prevention			Secondary prevention
	Low	Moderate	High	
Intrinsic rate (no treatment)	1%/year	3.5%/year	6%/year	12%/year
Number of strokes prevented/year/1000 treated				
Adjusted dose warfarin <i>v</i> none	6	21	36	84
Aspirin <i>v</i> none	2	7	12	12
Warfarin <i>v</i> aspirin	4	14	24	72

General estimates to illustrate the effect of risk stratification on the magnitude of treatment effects. Relative risk reductions are 60% for warfarin *v* none; 20% for aspirin *v* none; and 40% for warfarin *v* aspirin for primary prevention with corresponding reductions of 70%, 10%, and 60% for secondary prevention.¹

Table 2 Schemes for stratification of stroke risk in non-valvular atrial fibrillation

	High risk	Moderate risk	Low risk
<i>Untreated patients</i>			
Atrial Fibrillation Investigators (1994) ¹¹	Age ≥ 65 years History of hypertension Diabetes Prior stroke/TIA 5.1%/year	NA	Age < 65 years No high risk features
Observed stroke rate			1.0%/year
American College of Chest Physicians Consensus (1998) ¹⁴	Age > 75 years History of hypertension Prior stroke/TIA Left ventricular dysfunction* > 1 moderate risk factor NA	Age 65-75 years Diabetes Coronary disease Thyrotoxicosis	Age < 65 years No risk factors
Observed stroke rate		NA	NA
<i>Aspirin treated patients</i>			
Stroke Prevention in Atrial Fibrillation (1995) ¹²	Women > 75 years Systolic BP > 160 mm Hg Prior stroke/TIA Left ventricular dysfunction† 7.7%/year	History of hypertension No high risk features	No high risk features No history of hypertension
Observed stroke rate		3.6%/year	1.1%/year
SPAF Exploratory Analysis (1999) ¹³	Women > 75 years Systolic > 160 mm Hg Hypertension plus age > 75 Prior stroke/TIA 7.1%/year	Hypertension and age ≤ 75 years Diabetes No high risk features 2.6%/year	No high or moderate risk features 0.9%/year

*Moderate to severe left ventricular systolic dysfunction on echocardiography or recent congestive heart failure.

†Impaired left ventricular function included recent congestive heart failure or fractional shortening ≤ 25% by M mode echocardiography.
TIA, transient ischaemic attack.

Patient values and preferences after explanation of the benefits and risks of anticoagulation are particularly important in this risk stratum, although patient choices can be subtly—and not so subtly—influenced by physician perceived fears, both warranted and exaggerated, of anticoagulation.

Appropriate use of warfarin in AF

Considering the rapid pace of developments and lack of general consensus defining appropriate use, it is not surprising that many surveys have documented suboptimal use of warfarin, despite its potential to confer important benefits for many AF patients. Additional efforts to achieve consensus in this confusing area are needed. Additional data concerning prediction of stroke risk are required, including pathophysiological correlates and application of risk stratification schemes in clinical practice. Now that the efficacy and safety of warfarin and aspirin for prevention of stroke in AF patients have been reasonably well defined,¹ reliable prediction of stroke risk to identify those who can benefit most and least from lifelong anticoagulation is presently the salient clinical issue, as emphasised by the two studies in this issue.^{4,5} All patients with AF should carefully be evaluated for factors conferring additional risk, and their stroke risk estimated. Those deemed high risk and many of those presumed at moderate risk should be considered for anticoagulation, regardless of age.

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