Primary Care Cardiovascular Journal

PCCJ

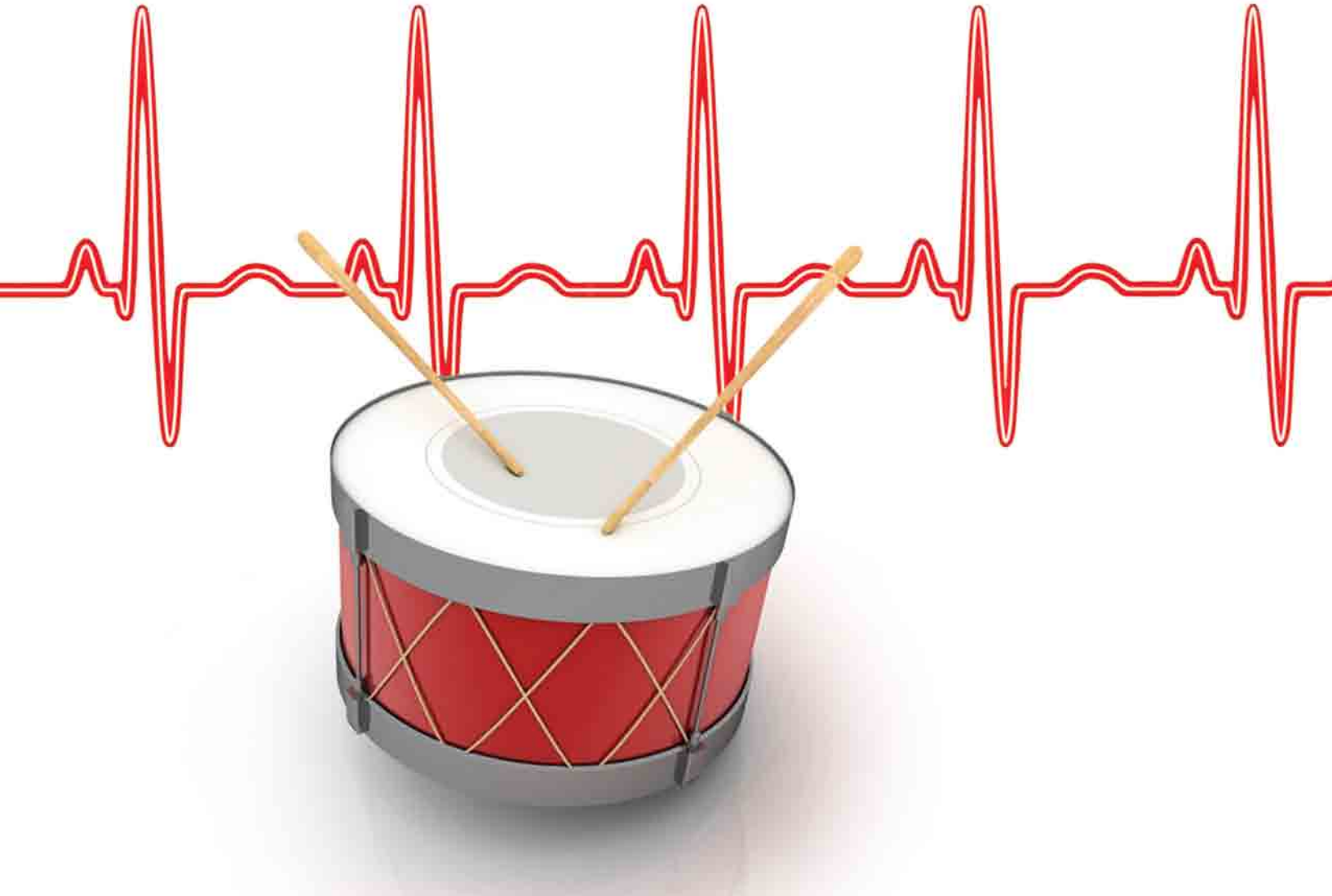
Keeping up to date with CVD and diabetes

Special supplement
October/November/December 2010

Official Journal of
The Primary Care Cardiovascular Society
The UK Stroke Forum

This special supplement is supported by Boehringer Ingelheim Ltd

Atrial fibrillation and stroke: optimising prevention and treatment



Primary Care Cardiovascular Journal
PCCJ
Keeping up to date with CVD and diabetes

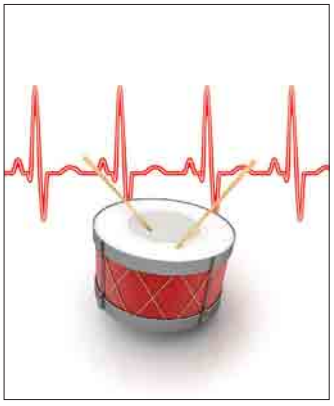
Official Journal of
PCCS
STROKE FORUM

Official journal of
The Primary Care Cardiovascular Society
The UK Stroke Forum

Printed in the UK by Caric Print Ltd, Ferndown, Dorset, in association with Stephens & George Magazines Limited. Printed on acid-free paper.

ISSN 1756-5138 (Print)
ISSN 1756-5146 (Online)

CONTENTS



Atrial fibrillation and stroke: optimising prevention and treatment

The *Primary Care Cardiovascular Journal* approached Boehringer Ingelheim Ltd to fund the production of this supplement. The company was not involved in its development, although it was asked to review it for technical accuracy just prior to printing. Editorial control has remained with the *Primary Care Cardiovascular Journal* at all times.

Moving stroke prevention up the healthcare agenda

Dr Damian Jenkinson

National Clinical Lead, NHS Stroke Improvement Programme, and Consultant Stroke Physician, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust

Prim Care Cardiovasc J 2010; **3**: S2-S3

doi: 10.3132/pccj.2010.043

"There are lots of really powerful examples around of things we can do to improve quality while improving productivity"

This statement from David Nicholson, the NHS Chief Executive, appears on the NHS Evidence website, where the recognition and optimal treatment of atrial fibrillation (AF) is given as one of the top six Quality, Innovation, Productivity and Prevention (QIPP) examples from across the entire NHS.

Uniquely, AF is an eminently preventable cause of stroke with a simple and highly effective treatment. AF is common and affects over 600,000 patients in England (1.2%). It is a major predisposing factor for stroke, and strokes caused by AF can be particularly severe and disabling. The annual risk of stroke is five to six times greater in AF patients, but treatment with warfarin can reduce the risk of stroke by 50-70%, and the safety and efficacy of warfarin in older people has been clearly demonstrated.

Despite this persuasive evidence, fewer than 50% of people with AF who could benefit from anticoagulation are receiving this therapy, and there has been little change in the rates of anticoagulation in the past 10 years. The two major challenges are case identification – about one-third of people with the arrhythmia are unaware of it – and appropriate management, with risk stratification and treatment. If we could put in place the right systems to screen for AF, and the correct culture and attitude to anticoagulate all eligible candidates, the £55 million cost of screening and treating would be more than offset by the £198 million saved by prevention of stroke (4,500 strokes prevented, at an average estimated cost of £44,000 per stroke).

This is why we have dedicated this supplement of the *Primary Care Cardiovascular Journal (PCCJ)* to the important and topical subject of AF. The National Clinical Lead for NHS Improvement and practising GP Matt Fay begins the issue by outlining the underlying pathogenesis of stroke in AF, reviewing the evidence for warfarin versus aspirin in stroke prevention in AF, and highlighting the critical role primary care has to play in AF management.

David Jones, Fellow in Cardiac Electrophysiology at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College, and colleagues describe the effective management of AF, emphasising that treatment needs to be tailored for individuals, and reviewing the evidence for rate versus rhythm control strategies. They also consider the contribution of pacemakers and atrioventricular (AV) node ablation, and provide a summary of who should be referred to secondary and tertiary care.

Mike Kirby, Editor of *PCCJ*, takes a broader view on cardiovascular prevention by describing how we might reduce the burden of stroke further by improving the management of people with transient ischaemic attack (TIA). One in five people who suffer a stroke experience a preceding TIA, with the risk of stroke as high as 10% in the first week, and 20% in the first month after TIA. Early assessment and intervention has been shown to reduce the risk of stroke by a huge 80%, so both the public and professionals need to treat TIA as a medical emergency.

David Fitzmaurice, Professor of Primary Care at the University of Birmingham, scrutinises the literature on thromboprophylaxis for AF, concluding that treatment with aspirin, or other platelet inhibitors, is substantially less effective in stroke prevention for patients with AF when compared with warfarin. He emphasises that the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study has eradicated anxieties about the use of warfarin in older people, demonstrating that warfarin is 65% more effective than aspirin in the over-75s, with no difference in major haemorrhage rates.

The risk of stroke in people with AF is not uniform, and the decision determining therapy choice should be guided by risk stratification tools. Duncan Petty, Lecturer Practitioner at the University of Leeds, compares the widely used $CHADS_2$ tool with the more recently

developed CHA_2DS_2-VASc scoring system. The latter includes additional stroke risk factors not considered in the $CHADS_2$ score (female gender, age 65-74 and evidence of vascular disease) to overcome the deficiency of $CHADS_2$, whereby a significant proportion (1.4%) of those categorised as low-risk go on to suffer a thromboembolic event. The CHA_2DS_2-VASc score therefore has the added benefit of identifying 'truly low-risk' patients.

The number of catheter ablation procedures performed for AF worldwide has increased steadily over the past decade. Ross Hunter and Richard Schilling, from St. Bartholomew's and The London NHS Trust, explain that ablation achieves long-term freedom from symptomatic and asymptomatic arrhythmias in 90% of people with paroxysmal AF, and 70-80% of those with persistent AF, although 20-50% require a second procedure. The procedure remains primarily a treatment for symptoms, as there is no proven prognostic benefit.

Lastly, but importantly, John Camm and Irene Savelieva, from St. George's, University of London, look to the future. Although AF is becoming an epidemic, because of the ageing population and the increasing prevalence of underlying cardiovascular disease, new drug therapies and devices bring new promise.

The time for taking a nihilistic approach to the detection and management of AF has passed. The severe complications of unrecognised and untreated AF are largely preventable, but such prevention requires a leap in knowledge, awareness and attitude on the part of both clinicians and the public.

Atrial fibrillation: a significant risk factor for stroke

Matthew Fay MB ChB
General Practitioner, Westcliffe Medical Practice;
GPwSI Cardiology, Westcliffe Cardiology Service;
National Lead, NHS Improvement Stroke

Prim Care Cardiovasc J 2010; **3**: S4-S8

doi: 10.3132/pccj.2010.025

Atrial fibrillation (AF) is the commonest sustained arrhythmia, affecting 1.2% of the population, which equates to more than 600,000 people in England. The prevalence of AF increases with age, with 8.4% of the over-65 age-group affected[1] and also it is increasing in incidence and prevalence.[2]

Each year there are 150,000 strokes in the UK. Nearly one in five (18%) of the people presenting with a stroke are in AF at the time of presentation, and one in six strokes are directly attributable to AF.[3]

The risk of stroke in AF is reduced by two-thirds with oral anticoagulation, while antiplatelet therapy reduces stroke by one-fifth.[4] The reduction with antiplatelet therapy is broadly consistent with the stroke reduction seen with this therapy in patients with vascular disease or risk factors, and, given that AF largely coexists with vascular disease, the effect of antiplatelet therapy would probably reflect this. The risk of stroke is similar with paroxysmal or permanent AF, in the presence of associated risk factors.

THROMBOGENESIS IN AF

Much of the education for general clinicians on vascular problems focuses on the nature of atheroma, plaque rupture and myocardial infarction, making the role of antiplatelet agents clear. The need to reduce platelet activity when the thrombophilic cholesterol core of an atheromatous plaque is exposed in order to prevent myocardial infarction (MI) is obvious. Translating this information to a concept of stroke as a 'brain attack' also explains the role for antiplatelet agents.

However, antiplatelet agents are substantially less effective in preventing stroke in patients with AF. This is because stroke caused by AF is embolic in nature, with the clot forming in the fibrillating atria, particularly in the left atrial appendage. The pathogenesis of the clot formation is multifactorial and is not dependent solely on blood stasis in the poorly functioning atria. The clot in AF is mostly fibrin-rich ('red clot') in comparison with the clot seen in coronary arteries, which is mostly platelet-rich ('white clot').

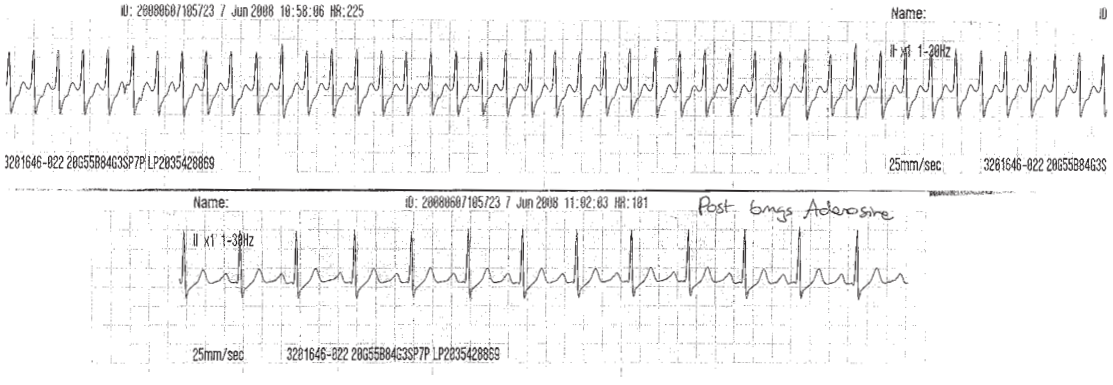
The pathogenesis of the thrombus formation (thrombogenesis) in AF follows the triad of abnormalities first proposed by Rudolf Virchow more than 150 years ago, characterised by changes to the vessel wall, blood flow and blood constituents.[5]

The atria each have a blind-ended passage referred to as the appendage. The left atrial appendage is the most common site for intra-atrial thrombus, even in sinus rhythm. Endothelial damage in atrial fibrillation is well described, being most marked in the left atrial appendage, especially in AF and associated mitral valve stenosis, which is the category of patients at highest risk for stroke.

Key points:

- Atrial fibrillation (AF) is the commonest sustained arrhythmia, affecting 1.2% of the population
- AF increases with age, with 8.4% of the over-65 age-group affected
- Nearly one in five (18%) of the people presenting with a stroke are in AF at the time of presentation, and one in six strokes are directly attributable to AF
- Patients with AF should be systematically assessed for their risk of stroke using a recognised schema, such as the $CHADS_2$ Score

ECG in atrial fibrillation



Abnormal blood flow:
The failure of atrial contraction seems to promote stasis – as visualised by spontaneous echo contrast on a trans-oesophageal echocardiogram – as well as progressive left atrial enlargement.[6] Low left atrial appendage Doppler velocities are evident in such patients.

Blood constituents:
Increased fibrin turnover has been seen in AF, both acutely and in the chronic state, irrespective of the cause. However, abnormal concentrations of prothrombotic indices are more prominent in patients who have suffered stroke in AF. They are also more prominent in patients with associated stroke risk factors such as diabetes and heart failure and AF than with a single risk factor.[5]

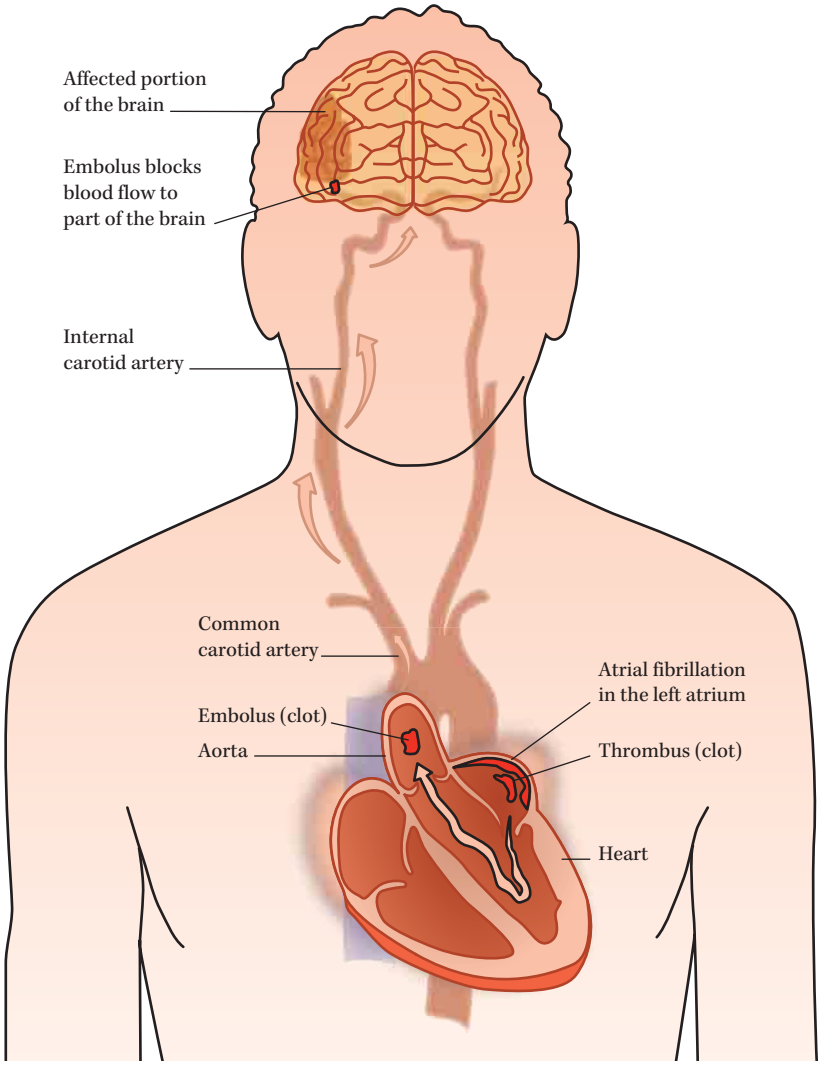
Platelets:
The results of studies looking at a potential role for platelets in AF-associated stroke have generally been conflicting, which may reflect the different aspects of platelet function. Abnormal platelet function occurs in AF but this reflects associated co-morbidities, such as vascular disease or hypertension, rather than AF *per se*.[6]

PREVENTION OF STROKE IN AF

The Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK)[7] included 1,007 patients with AF who were treated with aspirin, warfarin (INR 2.8-4.2) or placebo. Results showed a reduction in stroke in the warfarin cohort of 64% compared with the placebo group, representing an absolute risk reduction of 3.5%. There was also a non-significant decrease in the frequency of strokes in the aspirin cohort. The study was discontinued at interim analysis when the clear superiority of oral anticoagulation was seen.

The Stroke Prevention in Atrial Fibrillation (SPAF-I) randomised trial[8] had two groups – Group 1 included patients who were eligible for warfarin, aspirin or placebo, and Group 2 included those who were not eligible for warfarin for various reasons. Results for Group 1 showed there was only one stroke in patients treated with aspirin compared to 18 in the placebo group, which gave a risk reduction of 94% in the aspirin-treated group. However, results in Group 2 showed there were 25 strokes in the aspirin group compared to 26 in the placebo group, suggesting no difference. Despite the internal heterogeneity within this trial, the outcomes were combined into a final figure of a 42% reduction in stroke with aspirin, which was statistically significant.

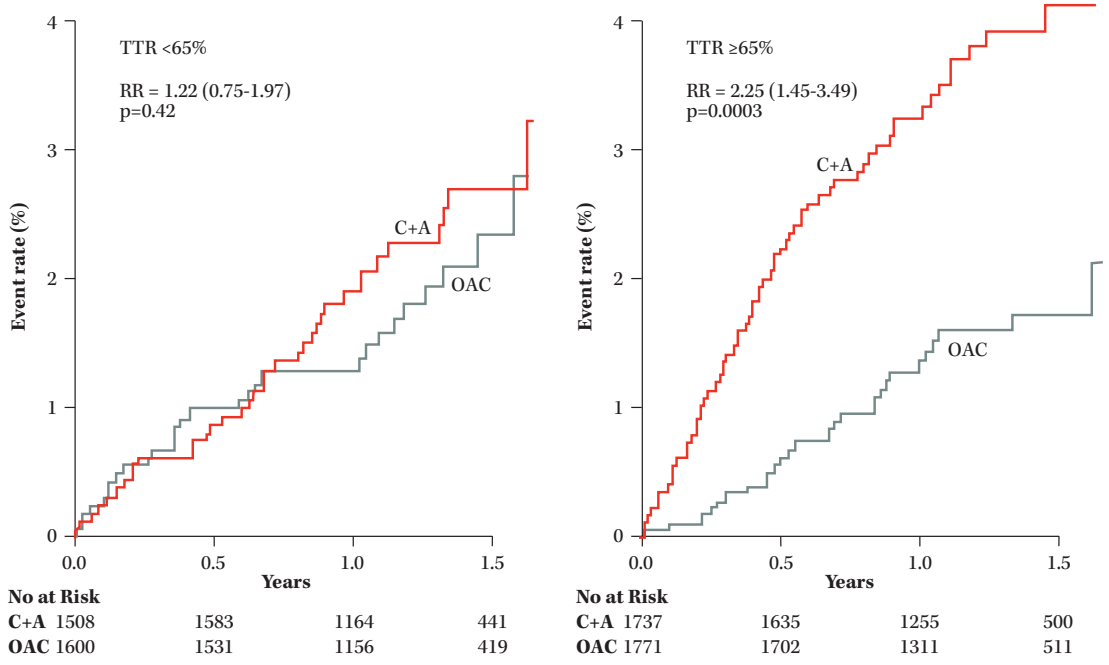
How atrial fibrillation increases the risk of stroke



The benefit with aspirin has not been replicated in subsequent studies; however, this result has driven the data to suggest that aspirin is not as effective as warfarin but is (apparently) 'better than placebo'. The meta-analysis by Hart *et al.*[4] found that trials considering aspirin alone showed a 20% reduction in stroke risk with 95% confidence intervals (CIs) crossing zero (*ie* no benefit).

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events (ACTIVE-W)[9] compared warfarin to a combination of aspirin and clopidogrel. The study was discontinued early because the rate of the primary endpoint of stroke in the aspirin plus clopidogrel group was almost double that with warfarin. In the comparison for aspirin alone

Figure 1: Results from the ACTIVE-W showing time in therapeutic range (TTR) for clopidogrel plus aspirin (C+A) vs OAC (oral anticoagulant)



with aspirin plus clopidogrel the benefit with two antiplatelet agents was slightly greater than with one alone (28% relative risk reduction in stroke, although the absolute difference was small) but at the risk of a more than 50% increase in bleeding with aspirin plus clopidogrel compared to aspirin alone.

The Birmingham Atrial Fibrillation Treatment in the Aged (BAFTA) Study[10] showed a clear superiority of warfarin over aspirin, with no increase in risk of major haemorrhage. The mean age of the population was 81.5 years, so the study confirmed the safety of warfarin in the older population and there was no difference in bleeding between the two groups. Not only were there many more strokes in the aspirin group, but these strokes were more severe than those occurring in patients on warfarin.

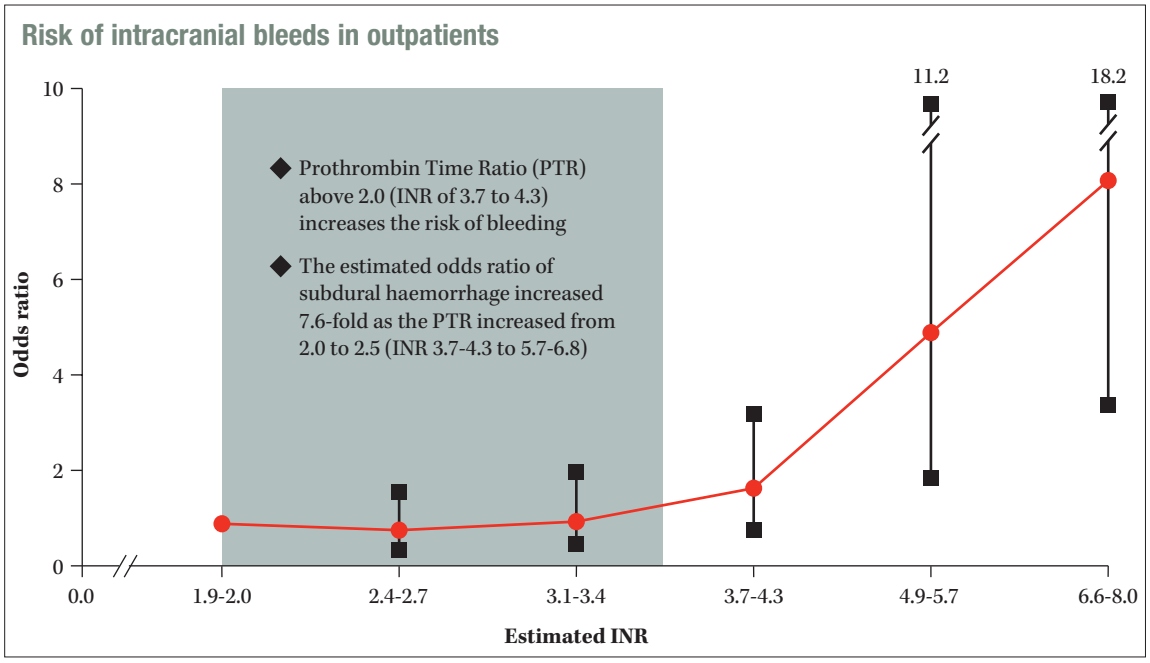
The ACTIVE-W study also provided information on the quality of anticoagulation (see Figure 1). Not only is it important to have high-risk patients on oral anticoagulants but it is important that this anticoagulation is of a high standard. If the time in therapeutic range (TTR) is less than 65% then the advantage of anticoagulant therapy reduces to that of antiplatelet agents.

There will be patients who are unable to use oral anticoagulants despite their high risk of stroke in AF. In this situation, occlusion of the left atrial appendage may be an option. The Watchman occlusion device (a fabric-covered expandable nitinol cage that is placed just distal to the ostium) was studied in the PROTECT AF study[11] and showed non-inferiority against warfarin for stroke prevention. However, there was a higher rate of complications in the intervention group and a period of anticoagulation was required, although this could be stopped after a period of time.

RISK ASSESSMENT FOR STROKE IN AF

Atrial fibrillation is an important risk factor for stroke. Patients over 65 with lone atrial fibrillation have a five-fold increase in ischaemic stroke prevalence. Other risk factors for stroke include diabetes and heart failure. A study of 1,066 patients from three different trials showed that moderate to severe LV systolic dysfunction gave a 2.5% relative risk of stroke.[12] Concurrent hypertension with AF was shown to have an annual stroke risk of 3.6% in the SPAF-III trial.[13]

Age remains an important factor for stroke in patients with AF. Those over 75 years, and with no other risk factors, have an annual stroke risk of 3.5%. This compares with an annual stroke risk of 1.1% in patients aged 65-74. If patients had other risk factors then the annual risk increased to 7.9% in the over-75 age-group and 3.6% in patients aged 65-74 years.



Bringing these risk factors together has produced several schema for scoring the risk of stroke in patients with AF, with the best known being the $CHADS_2$ Score. This gives one point each for concurrent heart failure, hypertension, age over 75 and diabetes and two points for previous history of stroke. People with scores of two or greater are considered high-risk and worthy of consideration for oral anticoagulants.

Oral anticoagulants have been shown to be effective in preventing stroke in patients with AF but this comes with an increased risk of bleeding. This risk is a great concern to clinicians when considering therapeutic options for patients. Hylek *et al.*[14] looked at 121 patients who suffered an intracranial haemorrhage – 77 intracerebral bleeds and 44 subdural haemorrhages – while on warfarin and randomly matched each of them to three controls. In subdural haemorrhage, the risk rose dramatically with international normalised ratios (INRs) above 4 (PTR over 2)[14]. Age was the only other independent risk factor.

It is important to remember that the risk of falls is significant in the population where anticoagulation is an appropriate therapeutic option. Man-Son-Hing and colleagues reviewed prospective cohort studies and retrospective case series and calculated the risk of intracranial bleeding.[15] They calculated the risk of a subdural haemorrhage from falling in patients with an annual stroke risk of 5% ($CHADS_2$ Score of 2-3) and found it would require a patient to fall 295 times for the fall risk to outweigh the stroke reduction benefit of warfarin.

THE ROLE OF PRIMARY CARE

The importance of primary care in the management of atrial fibrillation was recognised in 2006 when 15 points were added to the Quality and Outcomes Framework (QOF) for atrial fibrillation. These were given for three areas:

- AF01: to have a register of patients with AF
- AF02: for the diagnosis to be confirmed on an ECG
- AF03: for a patient with AF on stroke preventive therapy in the form of antiplatelet agents or anticoagulants.

Despite this intervention to improve the management of AF in primary care there has been little change in the anticoagulation rates compared to the preceding years.

It is clear that there are two main issues for the management of atrial fibrillation in primary care. The first is case identification and the second is appropriate management with risk stratification and appropriate treatment with oral anticoagulants.

There is a need for QOF to be improved to ensure better intervention in patients with AF. Ideally, a revised QOF for AF should include:

- AF01: an AF Register
- AF02: % of patients over 65 years with a pulse check
- AF03: Confirmation of AF diagnosis with an ECG
- AF04: A stroke risk assessment performed with a validated schema
- AF05: % of patients receiving oral anticoagulants or left atrial appendage occlusion.

CONCLUSION

Stroke imposes a major burden on the NHS, as well as the patients affected and their families, demonstrating that there is a clear need to focus on improving the identification of patients with AF, appropriate risk stratification and increasing intervention with appropriate therapy.

This significance is recognised by the Department of Health in the Quality and Productivity agenda, but audits warn that fewer than 50% of patients with AF who could benefit from anticoagulation are receiving this therapy. The Quality and Outcomes Framework for AF fails to recognise the importance of risk stratification and equates oral anticoagulants with antiplatelet agents.

To improve the care of patients with AF who are at high risk for stroke clinicians need greater understanding of the effectiveness and safety of oral anticoagulants. There needs to be a shift in the attitude that there is a choice of therapy for stroke protection in patients with AF between antiplatelet agents and oral anticoagulants and these are equipotent. The evidence does not support this view and patients who are at moderate or high risk of stroke should be recommended oral anticoagulation therapy.

References

1. Fitzmaurice DA, Hobbs FDR, Jowett S, *et al.* Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007; **335**: 383.
2. Miyasaka Y, Barnes ME, Gersh BJ, *et al.* Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; **114**: 119-25.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-8.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Int Med* 2007; **146**: 857-67.
5. Weston T, Shantsila E, Lipp GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009; 155-66.
6. Sanfilippo AJ, Abascal VM, Sheenham M. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. *Circulation* 1999; **100**: 87-95.
7. Petersen P, Boysen G, Godtfredsen J, *et al.* Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK Study. *Lancet* 1989; **1**: 175-9.
8. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; **84**: 527-39.
9. 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 The ACTIVE Writing Group on behalf of the ACTIVE Investigators. *Lancet* 2006; **367**: 1903-12.
10. Mant J, Hobbs FDR, Fletcher K, *et al.* on behalf of the BAFTA investigators. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**: 493-503.
11. Holmes DR, Reddy VY, Turi ZG, *et al.* for the PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**: 534-42.
12. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med* 1998; **158;** 1316-20.
13. Rose G, Baxter PJ, Reid DD, McCartney P. Prevalence and prognosis of electrocardiographic findings in middle aged men. *Br Heart J* 1978; **40**: 636-43.
14. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994; **120**: 897-902.
15. Man-Son-Hing M, Nichol G, Lau A, Laupacis A.Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk of falls. *Arch Intern Med* 1999; **159**: 677-85.

Risk stratification for stroke in patients with non-valvular atrial fibrillation – can we improve decision-making for optimal treatment?

Duncan Petty,
PhD, IP, MRPharmS
Lecturer Practitioner, School of Health Care, University of Leeds; Practice-based Pharmacist, Bradford

Prim Care Cardiovasc J 2010; **3**: S9-S12

doi: 10.3132/pccj.2010.027

Key points:
- Warfarin is more effective than aspirin in preventing stroke
- Patients with 'intermediate' risk should be considered for warfarin
- The CHA_2DS_2-VASc scoring system offers a more accurate method for deciding who should be offered warfarin

INTRODUCTION

Antiplatelet (usually aspirin) and anticoagulant (usually warfarin) treatments are available to reduce the risk of stroke in patients with atrial fibrillation (AF) but both have potentially harmful adverse effects and warfarin can be time-consuming and expensive to monitor. Guidance exists for choosing between treatments[1] but is often insufficiently detailed to support an informed choice about the risk and benefits. Prescribers and patients are often left with a choice between aspirin or warfarin, and aspirin – which is perceived to be safer and easy to use – is often chosen. This article explores the evidence for aspirin and warfarin in preventing stroke in patients with AF, and describes how we should change the way that decisions about treatment are made.

WHAT DOES THE EVIDENCE BASE TELL US ABOUT CURRENTLY AVAILABLE TREATMENTS?

Aspirin

A Cochrane review published in 2005 identified three randomised controlled trials (RCTs), including 1,965 patients, that assessed aspirin in non-valvular AF compared to placebo.[2] The mean duration of follow-up was 1.3 years. Analysis showed that aspirin did not achieve any benefit in terms of reducing all strokes (odds ratio [OR] 0.70, 95% confidence interval [CI] 0.47 to 1.07), or all-cause death (OR 0.75, 95% CI 0.54 to 1.04).

An updated meta-analysis published in 2007 identified seven RCTs, including 3,990 patients, with a mean duration of follow-up over 1.7 years.[3] A relative risk reduction of 19% (95% CI -1% to 35%) was shown for stroke reduction, but as the CI included zero this was not considered significant.

Clopidogrel

There is currently no clinical evidence to support the use of clopidogrel in AF.[4] The benefits of clopidogrel plus aspirin in AF patients with moderate to high risk were studied in the ACTIVE-W study. The incidence of stroke was 3.00% with clopidogrel plus aspirin and 1.75% with warfarin (relative risk [RR] 1.72, 95% CI 1.24–2.37), but there was no difference in all-cause mortality between groups (4.8% clopidogrel plus aspirin vs 4.7% warfarin).[5] The risk of major bleeding with combination therapy was increased by more than 50% compared to aspirin alone, with event rates (2% per year) similar to anticoagulated patients.

Warfarin

A Cochrane review updated in 2004 found five RCTs, including 2,313 patients, assessing the benefits of warfarin.[6] The mean duration of follow-up was 1.5 years. Warfarin had a statistically significant effect in reducing all strokes (OR 0.39, 95% CI 0.26 to 0.59) and death (OR 0.69, 95% CI 0.50 to 0.94) and the combined endpoint of all stroke, myocardial infarction or vascular death (OR 0.56, 95% CI 0.42 to 0.76).

These results suggest that about 25 strokes would be prevented yearly for every 1,000 AF patients given warfarin. Intracranial and extracranial haemorrhages were not significantly increased by warfarin, but the results had wide confidence intervals, suggesting that they need to be treated with some caution.

Warfarin versus aspirin

Comparative studies have shown that warfarin is more effective than aspirin in preventing fatal or disabling stroke in people with AF.[7,8] In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study patients prescribed warfarin [target INR of 2.5], over a mean period of 2.7 years, had a yearly risk of stroke of 1.8%, while those prescribed aspirin (75 mg) had a risk of 3.8%.[7] This represents an absolute risk reduction (ARR) of 2%. The yearly extracranial bleed risk from warfarin (1.4%) was less than that from aspirin 1.6% (ARR 0.2%). For various reasons, the risks with warfarin are likely to be an underestimate. For example, 40% of people entered into the study were already on warfarin so people experiencing problems with warfarin may already have been excluded.[7]

A Cochrane review updated in 2007 found eight RCTs, including 9,598 patients, that compared adjusted-dose warfarin versus aspirin (in dosages ranging from 75 to 325 mg/day) in AF patients without prior stroke or TIA.[8] The mean overall follow-up was 1.9 years. Oral anticoagulants were associated with lower risk of all strokes (OR 0.68, 95% CI 0.54 to 0.85). Warfarin reduced stroke and major vascular events by about one-third compared to aspirin. Thirteen strokes per year would be avoided per 1,000 people treated with warfarin compared to using aspirin. The yearly extracranial bleed risk with warfarin (2.14%) was the same as that with aspirin of 2.12% (OR 0.97, 95% CI 0.74 to 1.28).[8]

These studies demonstrate that, in patients where there are no contraindications [see below], warfarin is the drug of choice for stroke prevention in AF. However, they do not identify which patients are more likely to benefit from treatment with warfarin rather than aspirin.

RISK STRATIFICATION TO DETERMINE THERAPY CHOICES

The risk of stroke in patients with AF is not homogeneous. The decision to prescribe either warfarin or aspirin for patients with non-valvular AF is guided by tools that stratify risk. Two risk assessment tools are commonly used in the UK.

As with many international guidelines, the National Institute for Health and Clinical Excellence (NICE) guidance on the management of AF contains a "stroke risk stratification and thromboprophylaxis" guide.[9] Risk is categorised into three groups – high, moderate or low – depending on the level of risk factors, and was based on the Birmingham 2009 risk schema:

- The low-risk group (patients aged <65 years, with no moderate or high risk factors) should be treated with aspirin (75-300 mg) daily if there are no contraindications
- The moderate-risk group (aged >65 years with no risk factors, or <75 years with hypertension, diabetes or vascular disease) can be offered aspirin or warfarin
- The high-risk group should be offered warfarin (if there are contraindications, they should be offered aspirin if possible)

The $CHADS_2$ risk tool is widely used in primary care and is incorporated into many general practice computer clinical systems. $CHADS_2$ assigns one point each for congestive heart failure (C), high blood pressure (H), age 75 or older (A), and diabetes (D), and two points for a previous stroke or transient ischaemic attack (S_2). The $CHADS_2$ scoring system, shown in Table 1, determines the stroke risk.

The total score ascertains a patient's stroke risk and, as can be seen in Table 2, patients with an intermediate risk can be offered a choice of warfarin or aspirin and those with a low risk are offered aspirin.

One of the deficiencies of the $CHADS_2$ tool is that a significant number of patients with a score of zero or 1 can go on to have a stroke. In the Euro Heart Survey on Atrial Fibrillation a large proportion of patients (60%) had an intermediate $CHADS_2$ score, and were therefore offered either warfarin or aspirin.[10] As there is a common assumption that warfarin is a more dangerous drug to use than aspirin, and it is certainly more cumbersome for healthcare professionals and patients to monitor, then many would choose aspirin in preference. Aspirin (as discussed above) is a less effective choice so a large number of people are likely to be suboptimally treated.

Table 1: $CHADS_2$ Score for determining stroke risk in patients with atrial fibrillation

		Score
C	Congestive heart failure	1
H	Hypertension – high blood pressure	1
A	Age ≥75	1
D	Diabetes mellitus	1
S_2	Stroke or TIA (transient ischaemic attack, called a mini-stroke)	2

Table 2: Treatment recommendations based on $CHADS_2$ Score

Score	Risk	Recommendation
0	Low	Aspirin (75-300 mg) daily
1	Intermediate	Aspirin (75-300 mg) daily or warfarin (INR 2.0–3.0), based on patient preference
2 or more	High ($CHADS_2$ revised) or Intermediate ($CHADS_2$ classic)	Warfarin (INR 2.0-3.0), unless there are reasons to avoid it

A new risk tool has recently been proposed – the CHA_2DS_2-VASc Scoring System or Birmingham 2009 Schema (see Table 3) – which includes additional stroke risk factors not considered in the $CHADS_2$ score (female gender; age 65-74 and vascular diseases: coronary artery disease, myocardial infarction, peripheral artery disease and complex aortic plaque).[10] High risk means a score of 2 or more – and these patients should therefore be offered warfarin.

The authors have also produced a flow chart (see Table 4) to help identify who should be on anticoagulants.

In the flow chart, high risk means having one definitive risk factor, which merits warfarin, or having two or more combination risk factors, in which case warfarin should be considered. Having one combination risk factor is an intermediate risk. But as warfarin is superior to aspirin in people aged 75 years and over, this should be the treatment of choice.

The Birmingham schema classified 15% of patients with AF as intermediate risk (compared with 60% using $CHADS_2$), and 75% were classified as high risk and needing warfarin. No patients classified as low risk with the Birmingham schema had a thromboembolic event (thus identifying 'truly low-risk' patients). In contrast, 1.4% of those categorised as low-risk with $CHADS_2$ had a thromboembolic event.

Table 3: The CHA_2DS_2-VASc Scoring System (2009 Birmingham Schema)

	Risk factor	Score
C	Congestive heart failure/ Left ventricular dysfunction	1
H	Hypertension – treated high blood pressure	1
A	Age ≥75	2
D	Diabetes	1
S_2	Stroke/TIA/TE (thromboembolism)	2
V	Vascular disease – coronary artery disease (CAD), myocardial infarction (heart attack), peripheral artery disease (PAD), or aortic plaque	1
A	Age 65-74	1
Sc	Sex – female gender	1

Table 4: Flow chart to identify patients with AF who should be on anticoagulants

Q1	Age 75 or greater?	Yes – Oral anticoagulant	No – Go to Q2 (OAC)
Q2	History of stroke, TIA, or embolism?	Yes – OAC	No – Go to Q3
Q3	Gender?	Male – Go to Risk Factors	Female – Go to Risk Factors
Risk Factors: • Age 65–74 • Hypertension (high blood pressure) • Vascular disease – coronary artery disease (CAD), myocardial infarction (heart attack), peripheral artery disease (PAD), or aortic plaque • Heart failure • Decreased ejection fraction • Diabetes mellitus		Male + two or more risk factors – OAC	Female + any other risk factors – OAC
OAC = Oral anticoagulant			

PRACTICAL ASPECTS WHEN CONSIDERING WARFARIN

In primary care it is possible to identify patients given an AF diagnosis from the Quality and Outcomes Framework (QOF) database or by running a search on the clinical code for AF. As discussed above, the majority of patients ought to be considered for warfarin treatment. The following checklist provides a simple tool to identify individual patients who should not be invited in to discuss the potential initiation of warfarin.

For each patient, identify, from the clinical record (GP record and hospital letters), the following factors:

1. Has warfarin been given before?

If yes, and it has been stopped, identify and record the reason – such as bleed; poor adherence with tablet taking or attending tests; patient choice etc.

2. Currently on aspirin?

Record if the patient is on aspirin that is either prescribed or bought over the counter. This is useful to know in case the patient cannot be offered warfarin, or if it needs to be stopped once warfarin is started.

3. Contraindications to warfarin

Look for contraindications to warfarin such as:

- Patient refusal – documentation that they have declined to have warfarin in the past
- Falls risk – if the patient has a recent history of falls, consider if the risk is likely to outweigh the benefit
- Adherence risk – the patient may have poor adherence with medicine taking and/or attending appointments, which would put them at risk if they used warfarin
- Bleed risk – this would include any significant risk of bleed that warfarin would exaggerate, such as gastric bleed, intraocular bleed, intracerebral bleed etc
- Other – there may be social/clinical risks that you feel cause warfarin to be contraindicated such as alcoholism, end-stage dementia/poor quality of life, other terminal illness, extreme age etc
- Significant drug interactions where it would not be possible to alter treatment

All other patients may appear "on paper" to be suitable to have warfarin. A face-to-face consultation should be arranged with these patients to discuss prescribing warfarin as an option.

SUMMARY

Current guidance offers a choice of warfarin or aspirin for patients with intermediate (moderate) risk of stroke in non-valvular AF. The evidence shows that warfarin is more effective and the risks are relatively low. As warfarin is more effective than aspirin, all patients with an intermediate risk should be considered for warfarin as first-choice therapy. The new CHA_2DS_2-VASc Scoring System would simplify management given that oral anticoagulants can be considered for those with one or more risk factors (that is, CHA_2DS_2-VASc score ≥1) while those at truly low risk (CHA_2DS_2-VASc score = 0) may not need any antithrombotic therapy.

References

1. Fuster V, Rydén LE, Asinger RW, *et al.* ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J* 2001; **22**: 1852-923.
2. Aguilar MI, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005; **4**: CD001925. doi:.
3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Int Med* 2007; **146**: 857-67.
4. Warfarin superior to clopidogrel plus aspirin in AF: ACTIVE W. MeReC Extra 2006, **24**. National Prescribing Centre.
5. The ACTIVE Writing Group on behalf of the ACTIVE investigators. *Lancet* 2006; **367**: 1903-12.
6. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005; **3**: CD001927. doi: 10.1002/14651858.CD001927.pub2.
7. Mant J, Hobbs R, Fletcher K, *et al.* Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**: 493-503.
8. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2007; **3**: CD006186. doi:10.1002/14651858.CD006186.pub2.
9. The National Institute for Health and Clinical Excellence (NICE) guidance on the management of atrial fibrillation. Quick Reference Guide. *NICE* June 2006.
10. Lip GYH, Nieuwlaat R, Pisters R, *et al.* Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; **137**: 263-72.

Catheter and surgical ablation of cardiac arrhythmias

Ross J Hunter
Research Fellow & Registrar
Cardiology Research Department, Barts and The London NHS Trust and QMUL, St Bartholomew's Hospital, London

Richard J Schilling
Consultant Cardiologist, and Professor of Cardiology & Electrophysiology
Cardiology Research Department, Barts and The London NHS Trust and QMUL, St Bartholomew's Hospital, London

Prim Care Cardiovasc J 2010; **3**: S13-S17

doi: 10.3132/pccj.2010.028

Catheter and surgical ablation of cardiac arrhythmias have evolved rapidly over the last 30 years. Catheter ablation of 'simple' atrial arrhythmias such as supraventricular tachycardias and typical atrial flutter is very successful and low-risk. Catheter ablation of atrial fibrillation (AF) is now also successful in restoring sinus rhythm for the majority of patients. The place of invasive treatment for ventricular arrhythmias in various contexts is also evolving.

Following implementation of the Department of Health's Chapter 8 of the *National Service Framework* in 2005, there has been expansion of arrhythmia services in the UK. In 2010, the capacity of hospitals to treat these arrhythmias is growing rapidly, and perhaps the main barrier to patient access is the limited awareness among would-be referring physicians of which patients should be referred for such treatments. This review article outlines the ways in which arrhythmias can be treated by catheter and surgical ablation, and provides success and complication rates to help the reader determine when, and for whom, these treatments might be appropriate.

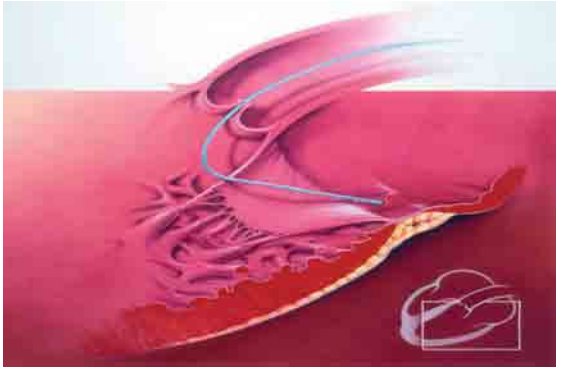
Key points:

- Catheter ablation of 'simple' atrial arrhythmias is very successful and low-risk
- Catheter ablation of AF is now also successful in restoring sinus rhythm for the majority of patients
- It should be offered to those intolerant of drugs or symptomatic despite drug treatment
- It can achieve long-term success in approximately 90% of patients with paroxysmal AF, and 70-80% with persistent AF
- The high success rates and low complication rates for arrhythmias such as atrial flutter and SVT mean they can now be considered first-line therapies

Catheter and surgical ablation of cardiac arrhythmias have emerged really only over the last 30 years. Although they have evolved in parallel, catheter ablation has followed in the footsteps of surgery, trying to offer similar treatment less invasively.

In the early 1980s, surgical destruction of the atrioventricular (AV) node with permanent pacemaker insertion was offered to patients with permanent AF resistant to treatment. The first catheter ablation of the AV node was performed in 1982 using direct current (DC). Similarly, accessory pathway-mediated tachycardias – which enable re-entry between the atria and ventricles by the AV node and an accessory pathway – can be treated with either surgical transection or catheter ablation.

Although direct current was the predominant energy source for catheter ablation in the 1980s, the sudden surge of current and high temperatures reached in the tissue treated meant that there was some collateral damage, and complications including tamponade were common. The use of radiofrequency ablation began in the 1990s, and the use of direct current is now mostly consigned to history. In the last decade, a dizzying array of new energy sources has evolved, including highly focused ultrasound, hot balloons to create circular lesions, liquid nitrogen balloons to damage tissue by freezing, and laser catheters. For now, radiofrequency energy is the mainstay of catheter-based treatment.



Radiofrequency ablation

Treatment of the commonest cause of cardiac arrhythmia – atrial fibrillation (AF) – was restricted to palliation by AV node ablation and pacing until the advent of the surgical maze procedure by James Cox in the early 1990s.[1] Although it was very successful, it was associated with significant mortality and morbidity. Similarly, attempts to re-create the surgical maze with catheter ablation resulted in long procedures with low success rates and high complication rates. The late 1990s saw the realisation that a more limited lesion set, creating scar tissue surrounding the pulmonary veins to electrically isolate them, could effectively treat AF. The last decade has seen exponential growth of catheter ablation for AF, with success rates increasing and complication rates falling as techniques and equipment evolve.[2,3]

Now that catheter ablation of AF and other 'simple' atrial arrhythmias such as supraventricular tachycardias (SVTs) has become more successful, it has become a large part of the workload of all tertiary centres, and is spilling over into UK district general hospitals. Following implementation of the Department of Health's Chapter 8 of the *National Service Framework* in 2005, there has been expansion of arrhythmia services in the UK. In 2010, the capacity of hospitals to treat these arrhythmias is growing rapidly, and perhaps the main barrier to patient access is the limited awareness among would-be referring physicians of which patients should be referred for such treatments. It is therefore an ideal time to review the ways in which arrhythmias can be treated by catheter and surgical ablation, and outline the success and complication rates to help determine when, and for whom, these treatments might be appropriate. A summary of the indications and success rates for catheter ablation of different arrhythmia is shown in Table 1, with the possible complications listed in Table 2.

SUPRAVENTRICULAR TACHYCARDIA

Although, technically, SVT includes all arrhythmias originating above the ventricles, the treatments for AF and atrial flutter (specifically, cavo-tricuspid isthmus dependent flutter) differ significantly from other forms of SVT, and so are discussed separately. The common remaining SVTs include:

(i) AV nodal re-entrant tachycardia or AVNRT (where the re-entry circuit is confined to the AV node)
(ii) AV re-entrant tachycardia or AVRT (where the re-entry circuit makes use of the AV node and an accessory pathway to travel between the atria and ventricles), and
(iii) atrial tachycardia, which involves activation from a focus or re-entry circuit confined entirely to the atrium.

SVTs can now all be treated by catheter ablation, with cases that require surgery being vanishingly rare. Although there is a wide range of different SVTs, their management is effectively the same until patients reach the catheter laboratory.

Catheter ablation is now the treatment of first choice for SVT because it is successful in 96-98% of patients[4] (although the less common varieties of SVTs may have lower long-term success rates around 80%).[5-7,4] The procedure is carried out on a day-case basis under sedation and local anaesthesia, with three to five thin electrode catheters passed up to the right heart from the femoral veins. This takes approximately two hours, most

Table 1: Indications, success rates and complication rates for catheter ablation of cardiac arrhythmias

Arrhythmia	Indication	Success rate (%)	Major complication rate (%)
Atrial fibrillation (AF)			
Paroxysmal AF	Failed drug treatment	90%	2-3%
Persistent AF		75%	2-3%
Atrial flutter	First line/ recurrence after DC cardioversion	95%	<1%
Ventricular tachycardia (VT)			
RVOT VT	Failure of one drug, or patient choice instead of drugs	90%	1-2%
VT & structural disease	Failed drug treatment	70-90%	4-5%
Ventricular ectopics (VE)	Failed drug treatment	90%	1-2%

Indications, success and complication rates from the literature discussed. Major complications are those that delay discharge or have long-standing sequelae.

Table 2: Complications following catheter ablation of cardiac arrhythmias

Arrhythmia	Major complications
SVT	Total <1% Heart block (requiring pacemaker) <1% If ablation in left atrium (in 20%) then stroke 0.1% Tamponade 0.1% Venous access complication <1%
Atrial fibrillation (Paroxysmal or persistent)	Total 2-3% Stroke 0.5% Tamponade 1% Venous access complication <1% (although haematoma is common) Death 0.1%
Atrial flutter	Total <1% Tamponade 0.1% Heart block (requiring pacemaker) 0.1% Venous access complication <1%
Ventricular tachycardia (VT) **RVOT VT** **VT & structural disease**	Total 4-5% (1-2% for RVOT) Stroke 1% (not for RVOT) Tamponade 1% Venous access complication <1% Death 0.5% (not for RVOT)
Ventricular ectopics (VE)	Total 1-2% Stroke 1% (if originating from left ventricle) Tamponade 1% Venous access complication <1%

Approximate complication rates and their incidence from the literature discussed in the text. Minor complications, such as bruising or haematoma, are not included. Serious venous access complications are similar for all these procedures requiring central venous access and include deep vein thrombosis, pseudo-aneurysm, arterial-venous fistula formation and retroperitoneal haematoma (although these rarely have long-term sequelae).

of which is spent confirming the precise diagnosis, with minimal or no discomfort during a minute or two of ablation of the target. The complication rate is very low, with major complications occurring in less than 1% of patients.[6,7] The majority of SVT patients can be ablated from the right atrium, but in the 20% or so who require ablation in the left atrium, a small risk (approximately 0.1%) of thrombus formation and stroke is introduced.

ATRIAL FIBRILLATION

The number of catheter ablation procedures performed for AF worldwide has increased steadily over the last decade. Isolation of the pulmonary veins has emerged as the cornerstone of catheter ablation for AF. This is achieved by creating small lesions side by side to form continuous lines of scar around the pulmonary vein ostia. Although pulmonary vein isolation is usually sufficient to treat paroxysmal AF, additional ablation is needed for persistent AF, usually in the form of left atrial linear lesions and/or modifying the atria by targeting tissue with abnormal or 'fractionated' electrograms. Several randomised controlled trials have demonstrated the superiority of catheter ablation over medical treatment for AF in terms of maintenance of sinus rhythm and improved symptoms.[8-12]

Catheter ablation can now achieve long-term success (*ie* freedom from all symptomatic or asymptomatic atrial arrhythmias) in approximately 90% of patients with paroxysmal AF, and 70-80% with persistent AF.[3,13,15] However, 20-50% of patients will need a second procedure.[3,13,15] Reconnection of the pulmonary veins due to gaps in the lines of scar appears to be the most common cause of recurrent arrhythmia, and targeting these gaps achieves freedom from arrhythmias for the majority.[16] As catheter ablation of AF is a relatively recent treatment, long-term follow-up data are only recently emerging. There was initially concern that the procedure may be palliative, with late recurrence being inevitable. However, recurrence of atrial arrhythmias more than two years post-ablation occurs in only 3% of patients per year, with follow-up data reaching up to seven years.[13-15]

Complication rates were initially high but have now improved, with more recent studies reporting major complication rates of 2-3%.[13,15] These consist of stroke/TIA or tamponade, and, although these are potentially serious, the majority resolve or are treated without sequelae. The procedural mortality is very low, at approximately 0.1%.[13,17]

As there is no proven prognostic benefit of catheter ablation for AF, it remains a treatment for symptoms. Success rates are now good, particularly for paroxysmal AF, and the complication rates are acceptable but not trivial. Therefore, catheter ablation for AF is usually reserved for patients who are intolerant of drug treatment or who remain symptomatic despite medical treatment with at least one antiarrhythmic drug.

Surgery for AF analogous to the original maze procedures described previously has been performed for some time in patients undergoing cardiac surgery for other reasons, such as valve repair/replacement. There has been considerable interest in minimally invasive or thoracoscopic procedures involving pulmonary vein isolation for 'stand alone' AF (*ie* with no concomitant surgery). Several series have been published, some with comparable results to catheter ablation.[18,19] However, the complication rates remain high (including a small mortality), and a small fraction results in open chest procedures. These problems may resolve with further experience and refinement in equipment, and a place may well evolve for this technique in subsets of patients.

"The number of catheter ablation procedures performed for AF worldwide has increased steadily over the last decade"

ATRIAL FLUTTER

Typical atrial flutter is a re-entry circuit that revolves around the tricuspid annulus. There is a narrow isthmus of tissue between the tricuspid annulus and the inferior vena cava, which means typical atrial flutter can be treated very easily by catheter ablation in this region, with a success rate of 90-95%.[4] This is performed as a day-case procedure taking 30-40 minutes, with a major complication rate below 1%.

Although it used to be said that atrial flutter could be treated in the same way as AF, with rate or rhythm control and long-term anticoagulation if needed, with such an effective treatment available, most now believe that sinus rhythm should simply be restored. Catheter ablation of atrial flutter results in better maintenance of sinus rhythm, improved quality of life, and fewer hospital admissions than in patients managed medically.[20] For this reason, cardiologists with an interest in heart rhythm management will universally consider patients for catheter ablation of typical atrial flutter almost regardless of age or co-morbidity.

VENTRICULAR ARRHYTHMIAS

The context in which ventricular arrhythmias occur is of crucial importance. In patients with structural heart disease, ventricular ectopics (VEs) and ventricular tachycardia (VT) are ominous and herald an increased risk of sudden death. However, in a structurally and functionally normal heart, VEs and VT are of little

prognostic significance, and treatment is mostly symptomatic. There are also several distinct patterns of ventricular arrhythmia, with the most common being ischaemic/scar-related VT, but others include VT in non-ischaemic cardiomyopathy and VT due to automatic foci such as in right ventricular outflow tract tachycardia (RVOT). The aims of treatment and the methods used vary in these different forms of ventricular arrhythmias.

In patients with structural heart disease, particularly in those with poor left ventricular function, ventricular arrhythmias can cause sudden arrhythmic death. Hence a reliable treatment is desirable. In this context, an implantable cardioverter defibrillator that can effectively terminate arrhythmias is the mainstay of treatment. However, there is now an expanding population of patients who might previously have died from their ventricular arrhythmias, who are presenting with recurrent shocks from their ICD. The efficacy of medications in alleviating symptoms due to VT or the frequency of shocks is often disappointing. This population forms a growing pool of patients who should be considered for catheter ablation of VT.

Patients first undergo an assessment of their cardiac status, particularly for the presence of ischaemic heart disease and the need for revascularisation, or for whether there are biochemical abnormalities. The procedure is carried out with local anaesthesia and sedation, with two to three catheters introduced to the heart usually via the femoral veins/artery. Ablation of the ventricular tissue supporting VT or ventricular fibrillation does not impair left ventricular function because the area targeted is mostly scar already.

The procedure is usually well tolerated, can be performed as an emergency (in extremely ill patients), and usually takes 1-4 hours. The complication rates vary between series, depending on the cases included. Patients can be desperately sick with VT storm (in which case failure to control VT will often result in death) or having ablation electively due to ICD shocks. Accordingly, major complication rates have been as high as 8% in some cohorts,[21] or 2-3% in others.[22,23] An average major complication rate is perhaps 4-5%, with freedom from VT/ICD shocks achieved in 70-90% in most series.[24]

In the structurally normal heart there is no risk of sudden arrhythmic death. Treatment is directed at symptom control. This can sometimes be achieved with medications such as beta-blockers. Catheter ablation is very successful in this context, rendering approximately 90% of patients free of ventricular arrhythmia subsequently.[24] Catheter ablation can therefore be used as second line for patients with symptoms refractory to drug treatment, and is increasingly being requested by younger patients who prefer not to continue lifelong medication.

CONCLUSION

Catheter ablation of cardiac arrhythmias has evolved and expanded massively over the last 30 years. The high success rates and low complication rates for arrhythmias such as atrial flutter and SVT mean catheter ablation can now be considered first-line therapies. Ablation for AF is much more successful than previously, and should be offered to those intolerant of drugs or symptomatic despite drug treatment. Catheter ablation for ventricular arrhythmias is a diverse area, offering excellent results for those with structurally normal hearts, and reducing ICD shocks in those with structural heart disease.

“The high success rates and low complication rates for arrhythmias such as atrial flutter and SVT mean catheter ablation can now be considered first-line therapies”

References

1. Cox JL, Schuessler RB, D'Agostino HJ Jr, *et al.* The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991; **101**: 569-83.
2. Cappato R, Calkins H, Chen SA, *et al.* Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005; **111**: 1100-5.
3. Cappato R, Calkins H, Chen SA, *et al.* Up-dated worldwide survey on the methods, efficacy and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3**: 32-8.
4. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, *et al.* ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias). *Circulation* 2003; **108**: 1871-1909.
5. Showkathali R, Earley MJ, Gupta D, *et al.* Current case mix and results of catheter ablation of regular supraventricular tachycardia: are we giving unrealistic expectations to patients? *Europace* 2007; **9**: 1064-8.
6. Clague JR, Dagres N, Kottkamp H, *et al.* Targeting the slow pathway for atrioventricular nodal reentrant tachycardia: initial results and long-term follow-up in 379 consecutive patients. *Eur Heart J* 2001; **22**: 82-8.
7. Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. *Pacing Clin Electrophysiol* 2000; **23**: 1020-8.
8. Pappone C, Augello G, Sala S, *et al.* A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol* 2006; **48**: 2340-7.
9. Jais P, Cauchemez B, Macle L, *et al.* Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008; **118**: 2498-505.
10. Oral H, Pappone C, Chugh A, *et al.* Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006; **354**: 934-41.
11. Wazni OM, Marrouche NF, Martin DO, *et al.* Radiofrequency ablation *vs* antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005; **293**: 2634-40.
12. Stabile G, Bertaglia E, Senatore G, *et al.* Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J* 2006; **27**: 216-21.

13. Bhargava M, Di BL, Mohanty P, *et al.* Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: Results from a multicenter study. *Heart Rhythm* 2009; **6**: 1403-12.
14. Pappone C, Rosanio S, Augello G, *et al.* Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol* 2003; **42**: 185-97.
15. O'Neill MD, Wright M, Knecht S, *et al.* Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J* 2009; **30**: 1105-12.
16. Rajappan K, Kistler PM, Earley MJ, *et al.* Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: a prospective characterization of anatomical sites. *Pacing Clin Electrophysiol* 2008; **31**: 1598-1605.
17. Cappato R, Calkins H, Chen SA, *et al.* Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2009; **53**: 1798-1803.
18. Edgerton JR, McClelland JH, Duke D, *et al.* Minimally invasive surgical ablation of atrial fibrillation: six-month results. *J Thorac Cardiovasc Surg* 2009; **138**: 109-13.
19. Beyer E, Lee R, Lam BK. Point: Minimally invasive bipolar radiofrequency ablation of lone atrial fibrillation: early multicenter results. *J Thorac Cardiovasc Surg* 2009; **137**: 521-6.
20. Natale A, Newby KH, Pisano E, *et al.* Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. *J Am Coll Cardiol* 2000; **35**: 1898-1904.
21. Calkins H, Epstein A, Packer D, *et al.* Catheter ablation of ventricular tachycardia in patients with structural heart disease using cooled radiofrequency energy: results of a prospective multicenter study. Cooled RF Multi Center Investigators Group. *J Am Coll Cardiol* 2000; **35**:1905-14.
22. Reddy VY, Reynolds MR, Neuzil P, *et al.* Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007; **357**:2657-65.
23. Tanner H, Hindricks G, Volkmer M, *et al.* Catheter ablation of recurrent scar-related ventricular tachycardia using electroanatomical mapping and irrigated ablation technology: results of the prospective multicenter Euro-VT-study. *J Cardiovasc Electrophysiol* 2010; **21**: 47-53.
24. Aliot EM, Stevenson WG, Almendral-Garrote JM, *et al.* EHRA/HRS Expert consensus on catheter ablation of ventricular arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). *Europace* 2009; **11**: 771-817.

What is the real role of anticoagulants in atrial fibrillation and stroke?

Professor David Fitzmaurice
Professor of Primary Care,
Primary Care Clinical Sciences
The University of Birmingham,
Edgbaston, Birmingham, B15 2TT

Prim Care Cardiovasc J 2010;
3: S18-S21

doi: 10.3132/pccj.2010.026

Key points:

- Aspirin or other platelet inhibitors are substantially less effective in preventing stroke compared to warfarin
- Warfarin reduces the incidence of all strokes by 68%, representing an absolute annual reduction of 3.1% ($p<0.001$)
- All patients with AF should be considered for oral anticoagulation (with a target INR of 2.5), apart from those under 65 years with no other risk factors
- Patients who cannot tolerate oral anticoagulation therapy should be considered for aspirin
- The disadvantages with warfarin are that it requires regular monitoring and can be associated with significant haemorrhagic events

The majority (84%) of people with AF are over the age of 65 years.[1] In the UK, the prevalence of AF is 7.2% for patients aged 65 and over.[2] AF is a particularly important risk factor for stroke in the elderly. 15% of all strokes are associated with the arrhythmia, increasing to 36% in people over the age of 80. The prevalence of AF is higher in men at all ages, although the overall number of patients with AF is approximately equal between the sexes because of unequal death rates. In overall terms, approximately 50% of patients with AF are 75 or over, and over half of these are women.

AF AND RISK OF STROKE

The Framingham Study identified AF as an independent risk factor for stroke, even in the absence of mitral valve disease (non-valvular atrial fibrillation).[3] This form of AF may be referred to as non-rheumatic atrial fibrillation (NRAF). The relative risk for stroke associated with NRAF must be a primary consideration when making decisions about therapy, given that oral anticoagulation carries its own risks. The Whitehall study[4] and the British Heart study[5] confirmed the increased risk of stroke associated with NRAF; however, the relative risks differed somewhat as did the underlying rate of stroke within the control population (relative risk = 2.3-6.9).[6]

In clinical practice, the risk of stroke is assumed to be constant between paroxysmal and persistent AF. The presence of angina was found to be a risk factor within individual studies; however, its significance was lost in the multivariate analysis.

THROMBOPROPHYLAXIS FOR AF

Warfarin

Eight randomised studies were published in the 1980s and 1990s[8-15] that informed the debate over the selection of patients for oral anticoagulation, the relative merits of anticoagulation versus antiplatelet agents, and the risk stratification for patients with AF with and without other risk factors for stroke. However, interpreting the results of these studies is problematic because different levels of anticoagulant intensity were employed and the actual levels of intensity achieved were either not stated or not subject to direct comparison (using prothrombin ratios rather than INR).

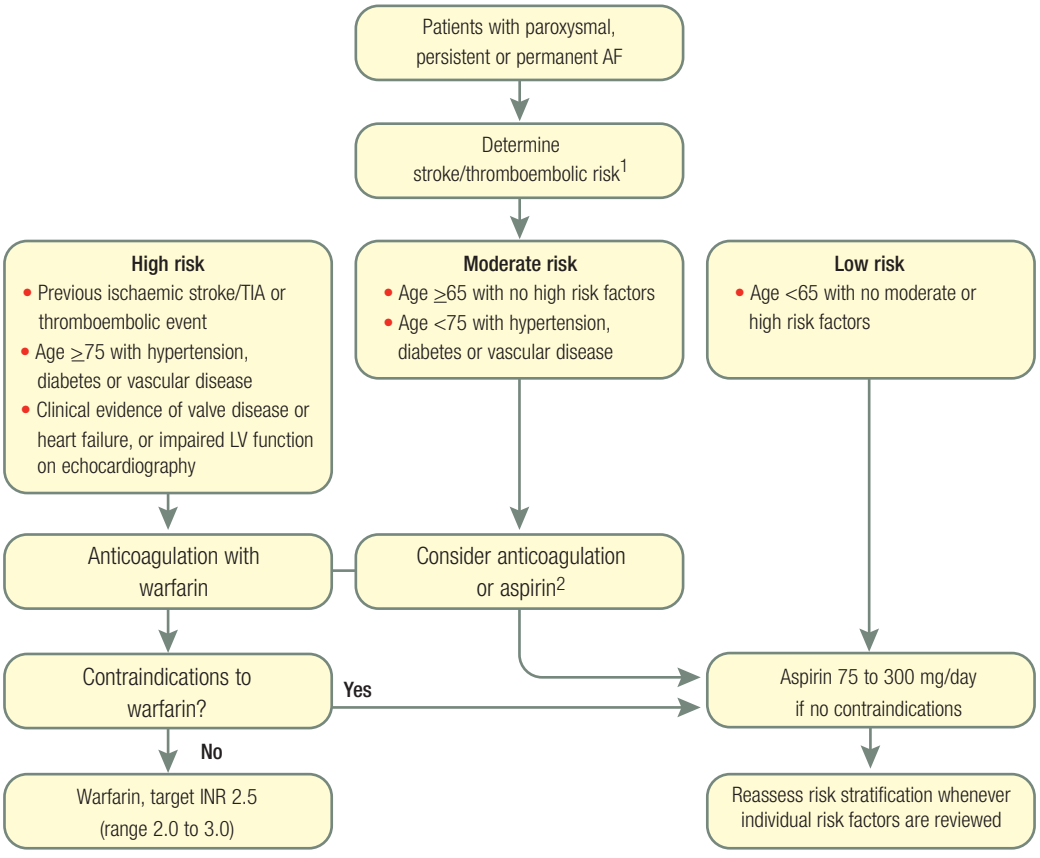
Meta-analysis of the five primary prevention studies (comparing warfarin with placebo) covered 1,889 patient-years for those receiving warfarin and 1,802 in

Risk factors associated with stroke in NRAF

Multivariate analysis[7] revealed the following factors as significant additional risk factors in prediction of stroke for patients with NRAF:

- Age: the annual risk of stroke in patients with NRAF younger than 65 with no other risk factors was 1.0%. This increased to 8.1% for patients older than 75 with one or more other risk factors. Warfarin reduced the risk of stroke in all subgroups except those younger than 60 with no other risk factors in whom the incidence of stroke was <1%.
- History of hypertension: this gives a relative risk (RR) of stroke of 1.6 (95% CI 1.3-2.8)
- History of diabetes: RR = 1.7 (1.2-3.6)
- History of prior stroke or transient ischaemic attack (TIA): RR = 2.5 (1.2-5.3)
- History of myocardial infarction: RR = 1.7 (1.1-2.7)
- History of congestive heart failure: RR = 1.7 (1.1-2.5)

NICE Guidelines: Treatment algorithm based on stroke risk



1 Note that risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. Since the incidence of a stroke and thromboembolic events in patients with thyrotoxicosis appears similar to that in patients with other aetiologies of AF, antithrombotic treatments should be chosen based on the presence of validated stroke risk factors.

2 Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risks and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more moderate stroke risk factors. Referral and echocardiography may help in cases of uncertainty.

National Institute for Health and Clinical Excellence (2006) CG 36 *Atrial fibrillation: the management of atrial fibrillation* London: NICE. Available from www.nice.org.uk/CG036. Reproduced with permission.

the control group.[7] For the aspirin-placebo comparison there were 1,132 patient-years experience with aspirin and 1,133 with placebo. Primary endpoints were ischaemic stroke and major haemorrhage.

Patients in the control groups who had no history of transient ischaemic attack (TIA) or stroke, hypertension or congestive heart failure, diabetes, angina or myocardial infarction had an annual incidence of stroke of 1.5%.

Warfarin was found to be consistently effective for the prevention of ischaemic stroke with a reduction in the incidence of all strokes of 68% (95% CI, 50% to 79%), representing an absolute annual reduction of 3.1% (p<0.001). This risk reduction has to be viewed in the light of a reported low incidence of side-effects, particularly haemorrhagic stroke, which may represent selection bias. The absolute reduction in risk, however, may have been underestimated as the analysis was performed on an intention-to-treat basis, when in fact eight of the 27 patients in the warfarin group who had a stroke were not receiving warfarin at the time. Warfarin also decreased the rate of death by 33% (95% CI, 9% to 51%; p=0.10) and the rate of the combined outcome of stroke, systemic embolism, or death by 48% (95% CI, 34% to 60%; p<0.001).

Warfarin or aspirin for NRAF?

Four studies randomised patients to receive aspirin or oral anticoagulant.[8,9,12,14] The Danish AFASAK trial[8] (using a 75 mg per day dose) showed a non-statistically significant reduction in stroke rate when compared to placebo. The SPAF study,[9] however, showed a reduction of 44% (95% CI, 7% to 66%) in the incidence of stroke at a dose of 325 mg per day. Meta-analysis of these studies[14] confirmed that oral anticoagulation is twice as effective as aspirin therapy for the prevention of ischaemic stroke in atrial fibrillation patients. Furthermore the beneficial effects of aspirin do not appear to be dose-related.[16]

The EAFT study[12] was a secondary prevention study and used aspirin at a dose of 300 mg per day compared to warfarin or placebo. No statistically significant reduction in thromboembolic disease was observed in the aspirin-treated group when compared to placebo, whereas warfarin did achieve statistically significant improvement. The conclusion is that treatment with aspirin or other platelet inhibitors is substantially less effective in stroke prevention for patients with AF when compared to warfarin.

In combination with warfarin, aspirin has little role to play in the prevention of stroke for patients with atrial fibrillation, as shown by the SPAF III study.[15] This study had to be discontinued after a mean follow-up period of 1.1 years because of the increased incidence of primary events (ischaemic stroke and systemic embolism) for patients given combination therapy ($p<0.0001$) compared to adjusted-dose warfarin.

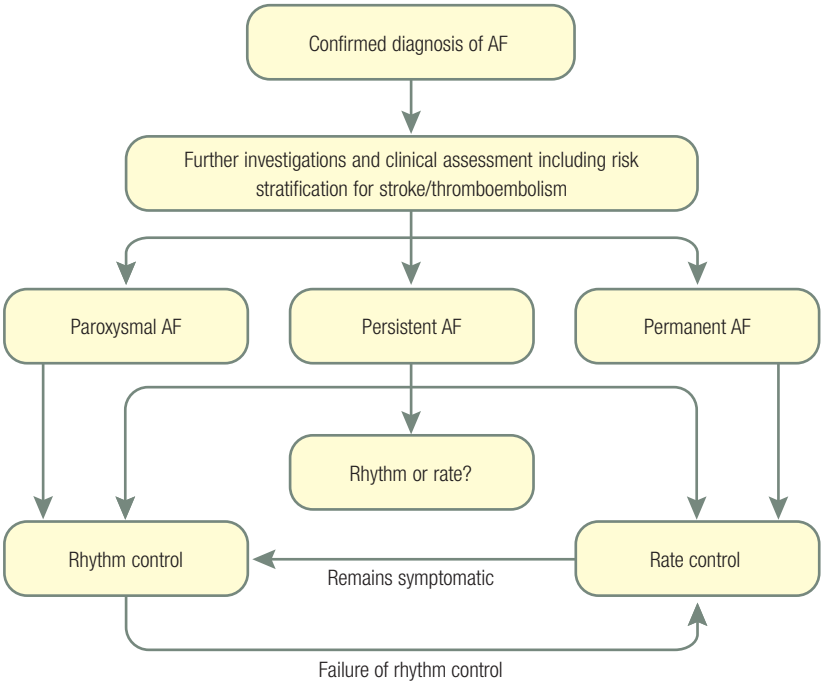
Cost-effectiveness analysis using US data supports the view that warfarin is to be preferred to aspirin or no treatment in terms of quality-adjusted life years for all patients with NRAF.[17] Aspirin does appear to minimally increase the risk of haemorrhagic stroke. Meta-analysis of randomised controlled trials using aspirin found that at a mean dose of 273 mg per day, there was an absolute risk increase in haemorrhagic stroke of 12 events per 10,000 people.[18] This is incredibly small and must be weighed against the relative risk reductions of myocardial infarction (137 events per 10,000) and ischaemic stroke (39 events per 10,000).

Nevertheless, for patients with AF under 65 with no other risk factors, there is minimal benefit with warfarin as compared to no therapy, because of the low underlying risk of stroke. Treatment decisions ultimately depend on the patient's perception of the inconvenience and harm associated with taking warfarin.[17] While aspirin is an alternative to warfarin therapy it should be reserved only for those patients who genuinely cannot tolerate warfarin.

STROKE RISK STRATIFICATION

It is increasingly recognised that treatment decisions need to be based on individual risk assessment. The NICE guideline in the UK includes a formal algorithm that is problematic in that the majority of patients are assessed as moderate risk and the recommendation is to use either oral anticoagulation or aspirin.[19] A more widely used assessment tool is the $CHADS_2$ system which gives a point each for congestive heart failure, hypertension, age greater than 75, and diabetes, and two points for a history of stroke or transient ischaemic attack, with risk of stroke increasing with the number of points acquired.[20] While $CHADS_2$ is simple to use its predictive value is less than ideal and there are ongoing attempts to improve its efficacy. Patients should also be assessed for bleeding risk.

NICE Guidelines: Treatment strategy decision tree



National Institute for Health and Clinical Excellence (2006) CG 36 *Atrial fibrillation: the management of atrial fibrillation* London: NICE. Available from www.nice.org.uk/CG036. Reproduced with permission.

THROMBOPROPHYLAXIS IN THE ELDERLY

Patients aged over 75 years were under-represented in the original trials, so concern remained that the bleeding risks with warfarin may outweigh the benefits of treatment. This led to physician uncertainty as to whether aspirin was a safer option in this population, supported by a meta-analysis of *post hoc* analyses of those over 75 from the warfarin versus aspirin trials.[21] Importantly, the BAFTA study has now also demonstrated that warfarin is 65% more effective than aspirin in an elderly population (over-75s), with no difference in major haemorrhage rates.[22]

THE DESIRED THERAPEUTIC RANGE FOR ORAL ANTICOAGULATION IN NRAF

The risk of stroke for patients with AF rises steeply below an INR of 2.0,[23] while the risk of haemorrhage increases rapidly at levels of INR greater than 4.0.[24] Interpretation of these data has been consistent with regard to the lower level of intensity recommended, with an INR of 2.0 being almost universally accepted.[25] The upper limit of intensity is more widely debated, ranging between 3.0 and 4.0. It may be argued that the aim is to keep INR below 4.0; however, this is unlikely to be successfully achieved unless the *target* INR is set at 3.0, given the weaknesses associated with current models. The target for INR should, therefore, be 2.5.

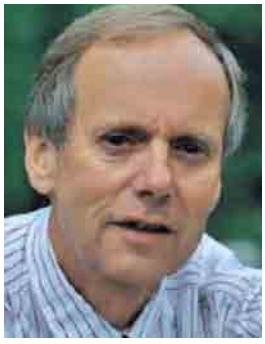
Based on current evidence, all patients with AF should be considered for oral anticoagulation (with a target INR of 2.5), apart from those patients younger than 65 years of age with no other risk factors. Patients who cannot tolerate oral anticoagulation therapy should be considered for aspirin.

SUMMARY

Stroke risk assessment and appropriate thrombo-prophylaxis, usually with warfarin, can reduce the risk of stroke in patients with AF. Patients should be warned of potential adverse effects before initiating any medication. New drugs that are potentially more convenient in terms of dosing and monitoring are emerging for the prevention of stroke in AF.

References

1. Feinberg WM, Blackshear JL, Laupacis A, *et al.* Prevalence, age distribution, and gender of patients with atrial fibrillation. *Arch Intern Med* 1995; **155**: 469-73.
2. Fitzmaurice DA, Hobbs FDR, Jowett J, *et al.* Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007; **335**: 383-6, doi:10.1136/bmj.39280.660567.55 (published 2 August 2007).
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-8.
4. Reid DD, Brett GZ, Hamilton PJS, *et al.* Cardiorespiratory disease and diabetes among middle-aged male civil servants. *Lancet* 1974; **1**: 469-73.
5. Rose G, Baxter PJ, Reid DD, McCartney P. Prevalence and prognosis of electrocardiographic findings in middle aged men. *Br Heart J* 1978; **40**: 636-43.
6. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet* 1987; **1**: 526-9.
7. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449-57.
8. Petersen P, Boysen G, Godtfredsen J, *et al.* Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989; **1**: 175-8.
9. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation* 1991; **84**: 527-39.
10. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990; **323**: 1505-11.
11. Connolly SJ, Laupacis A, Gent M, *et al.* Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991; **18**: 349-55.
12. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; **342**: 1255-62.
13. Ezekowitz ND, Bridge SL, James KE, *et al.* Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. *N Engl J Med* 1992; **327**: 1406-12.
14. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke Prevention in Atrial Fibrillation II study. *Lancet* 1994; **343**: 687-91.
15. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348**: 633-8.
16. Albers GW. Atrial fibrillation and stroke. Three new studies, three remaining questions. *Arch Intern Med* 1994; **154**: 1443-8.
17. Cage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; **274**: 1839-45.
18. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke. *JAMA* 1998; **280**: 1930-5.
19. http://www.nice.org.uk/Guidance/CG36
20. Go AS, Hylek EM, Chang Y, *et al.* Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003; **290**: 2685-92.
21. van Walraven C, Hart RG, Singer DE, *et al.* Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation. An individual patient meta-analysis. *JAMA* 2002; **288**: 2441-8.
22. Mant J, Hobbs FDR, Fletcher K, *et al.* Warfarin versus aspirin for stroke prevention in an elderly population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**: 493-503.
23. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996; **335**: 540-6.
24. Hylek EM, Singer DE. Risk factors for intracranial haemorrhage in out-patients taking warfarin. *Ann Intern Med* 1994: **120**: 897-902.
25. Lancaster T, Mant J, Singer DE. Stroke prevention in atrial fibrillation. *BMJ* 1997; **314**: 1563-64.



Professor Michael Kirby

Editor of *PCCJ*
Visiting Professor, Faculty of Health and Human Sciences, Centre for Research in Primary and Community Care (CRIPACC), and the Clinical Trials Coordinating Centre, University of Hertfordshire, Hatfield, UK.

Prim Care Cardiovasc J 2010; **3**: S22-S26

doi: 10.3132/pccj.2010.029

Management and early treatment of transient ischaemic attack (TIA)

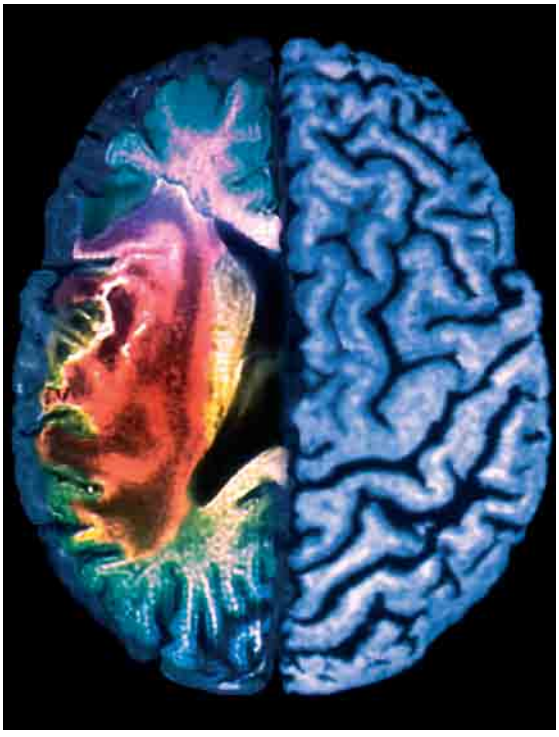
The White Paper, *Saving lives: our healthier nation* (1999), set out a target to reduce the death rate from coronary heart disease and related illnesses such as stroke by 40% in the under-75s by 2010;[1] recent trends indicate that this target will be met. Although the past forty years have seen a significant reduction in age-standardised stroke mortality rates, stroke still accounts for around 53,000 deaths each year in the UK, with more than 9,500 of these occurring in the under-75s.[2] This article reviews how we might reduce the huge burden of stroke by improving the management of transient ischaemic attack (TIA).

TIAs are estimated to affect 35 people per 100,000 each year, and are associated with a very high risk of stroke in the first month of the event and up to one year afterwards.[3] NICE defines TIA as stroke signs and symptoms that resolve within 24 hours.[4] However, the symptoms of TIA usually resolve within minutes or a few hours at most, and anyone with continuing neurological signs when first assessed should be assumed to have had a stroke.

The World Health Organization (WHO) has defined stroke as 'a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin'.[5]

DIAGNOSING TIA

Like a stroke, the symptoms of a TIA will depend on which part of the brain is affected. In people with a sudden onset of neurological symptoms, current guidance recommends a validated tool such as Face Arm Speech Test (FAST) for use outside hospital to diagnose stroke or TIA.[4]



© Zephyr, Science Photo Library

Coloured magnetic resonance imaging (MRI) scan of the brain of a patient after a cerebrovascular accident (CVA, or stroke)

Key points:

- A TIA can be an important warning sign of impending stroke
- Identification of patients at highest and lowest risk of stroke aids effective intervention in those who need it most
- Preventative strategies involve the combination of pharmacological treatments with lifestyle modification

Risk factors for TIA

Non-modifiable risk factors

- Increasing age
- Male sex
- Family history of TIA
- Previous TIA or heart attack
- African American race

Modifiable risk factors

- Smoking
- High blood pressure
- High cholesterol
- Obesity/overweight
- Diabetes
- Inactivity
- Poor nutrition
- Carotid artery disease
- Heart disease
- Excessive alcohol consumption
- Sleep apnoea
- Drug abuse
- Contraceptive pill use

The FAST test[6]

- Facial weakness – Has the mouth or eyelid drooped and can they smile?
- Arm weakness – Can they raise both arms?
- Speech problems – Can they understand what you say and speak clearly?
- Time – If any of the above are present, it's time to seek urgent medical attention

Other symptoms of TIA may include weakness, numbness, clumsiness or pins and needles on one side of the body, loss of vision or blurred vision in one or both eyes.

Figure 1: The $ABCD_2$ score for TIA risk assessment[8]

Assess each of the following five factors when the patient presents, and assign the scores shown. For C and D you will need to ask the patient or a witness to the event. Add up the score to find if the patient is high or low risk.

Age:	60 years or above – 1 point below 60 years – 0 points
Blood pressure:	140/90 mmHg or above – 1 point below 140/90 mmHg – 0 points
Clinical features:	unilateral weakness – 2 points speech disturbance with no weakness – 1 point no clinical features – 0 points
Duration of symptoms:	60 minutes or longer – 2 points 10 to 59 minutes – 1 point less than 10 minutes – 0 points
Diabetes:	presence of diabetes – 1 point no diabetes – 0 points

Score 4 or above – high risk
Score 3 or below – low risk

If a patient reports having two or more episodes in a week, they should be considered and treated as high risk, even though their $ABCD_2$ score may be 3.

SCORING FOR RISK OF STROKE AFTER TIA

TIAs can be an important warning sign of impending stroke and should not be ignored. Any patient presenting with transient neurological symptoms suggestive of a cerebrovascular event should be considered to have had a TIA.[7] The identification of patients at the highest and lowest risk of stroke following a TIA allows effective interventions in those most likely to benefit from them, although it must be taken into account that these are costly and potentially risky. Current guidance recommends that stroke risk following a TIA is assessed using a validated scoring system such as $ABCD_2$.[4,7]

$ABCD_2$ SCORE

The $ABCD_2$ score (see Figure 1) was generated by multivariate logistic regression analysis of individual risk factors in both the ABCD and California scores. It has been shown to have greater predictive value for early risk of stroke after TIA than the previous scores.[8] The $ABCD_2$ score can be used in routine clinical practice to classify individuals who need emergency investigation and treatment into low, moderate and high-risk groups.

Patients with scores of 0-3 are at low risk (1%) of stroke over the next two days, those with scores of 4-5 are at moderate risk of stroke (4.1%) and scores of 6-7 are associated with a high risk (8.1%) of stroke over the next two days. Although the $ABCD_2$ score is optimised to predict the risk of stroke within two days, higher scores were associated with greater risk of stroke during days 2, 7, 30 and 90 after a TIA.[8]

Basic work-up of the TIA patient

Laboratory studies

- Full blood count
- Serum chemistry, including creatinine
- Erythrocyte sedimentation rate (ESR)
- Lipid profile
- Blood glucose for hyperglycaemia and hypoglycaemia
- Cardiac enzymes
- Estimated glomerular filtration rate (eGFR)

Clinical examination

- Blood pressure (BP) and pulse
- Chest examination
- Heart sounds
- Neck and peripheral pulses
- Central nervous system (CNS) examination
- Electrocardiogram (ECG)

> **TIAs can be an important warning sign of impending stroke and should not be ignored**

The $ABCD_2$ score benefits the management of TIA in several ways:

- By focusing public attention on the importance of the early identification and treatment of TIA
- To assist primary or emergency care in the rapid and reliable assessment of stroke risk and the subsequent urgency of specialist referral
- To allow specialist physicians to triage referrals
- To encourage the modification of the policy of management of TIA patients with high $ABCD_2$ scores, so patients are referred and managed as an inpatient emergency rather than simply being seen in an outpatient clinic.

THE MANAGEMENT OF PATIENTS WITH TIA

TIAs should be treated as a medical emergency. The risk of a full-blown stroke is highest soon after a TIA and may be as high as 10% in the first week after the event, and 20% in the first month.[7] The EXPRESS study showed that early initiation of existing treatments after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke.[3] Appropriate secondary prevention of cardiovascular events should therefore begin as soon as possible.

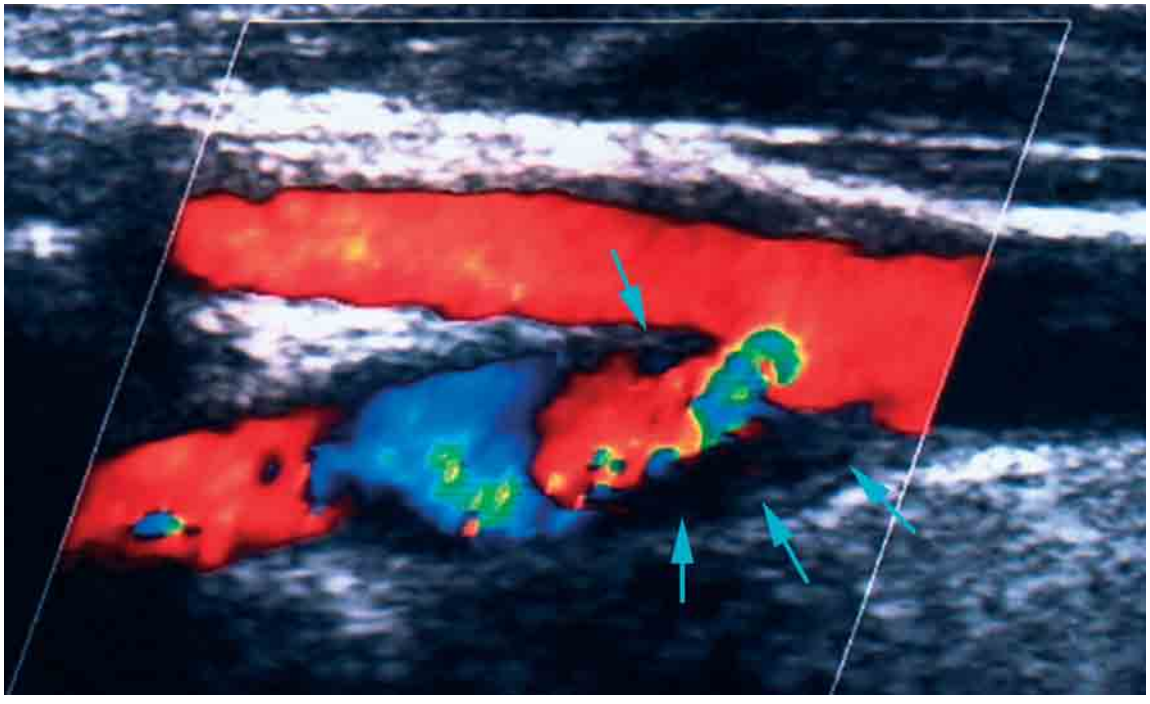
Current guidance recommends that patients who have a history compatible with TIA should be immediately started on 300 mg aspirin daily (unless contraindicated or not tolerated, in which case an alternative antiplatelet agent such as clopidogrel should be used).[4,7] Aspirin in combination with clopidogrel carries an excess risk of bleeding and should not be used routinely.[9] Aspirin in combination with modified-release dipyridamole has been shown to be superior to aspirin alone[10] and this combination is recommended. Anticoagulation is important if atrial fibrillation is present.[4,7]

Patients with a history of TIA who are at lower risk of stroke ($ABCD_2$ <4) should then receive:[4,7]

- Specialist investigation within one week
- Best medical treatment (*eg* blood pressure control, antiplatelet drugs, cholesterol lowering through diet and drugs, smoking cessation)
- Carotid imaging if the patient is a candidate for carotid intervention within one week of symptom onset
- Brain imaging within one week of symptom onset if vascular territory or pathology is uncertain
- Carotid endarterectomy within two weeks if the level of symptomatic carotid stenosis is between 70% and 99% (according to the European Carotid Surgery Trial [ECST] criteria).

Patients who have had a TIA, but present later than one week after their last symptom resolved, should be considered at lower risk of stroke and managed as such.[7]

> **“The EXPRESS study showed that early initiation of existing treatments after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke”**



Coloured Doppler ultrasound scan of blood flow through a stricture (arrowed) at the junction of the right common carotid artery. This stricture is due to atheroma, a fatty plaque deposit caused by atherosclerosis.

Immediate management of patients with suspected TIA

Assess for risk using $ABCD_2$
Start on 300 mg aspirin daily
Give driving advice (see below)

Then:

- High risk ($ABCD_2$ ≥4, or more than two episodes in a week): refer for specialist assessment and investigation within 24 hours
- Low risk ($ABCD_2$ ≤3): refer for specialist assessment and investigation as soon as possible but definitely within one week of onset
- Late presentation: (*ie* more than one week after their last symptoms) treat as low risk

Driving advice

- It is a Driver and Vehicle Licensing Agency (DVLA) requirement that people should not drive for 28 days after a stroke or TIA. Anyone having two or more events in a week needs to contact the DVLA and may be told not to drive for three months. Patients should, therefore, be told not to drive until they have been seen by a specialist. Importantly, they should not drive themselves to their TIA specialist appointment.

Patients with a history of TIA who are at high risk of stroke ($ABCD_2$ ≥4) should then receive:[4,7]

- Specialist assessment and investigation within 24 hours of first symptoms
- Best medical treatment (*eg* blood pressure control, antiplatelet drugs, cholesterol lowering through diet and drugs, smoking cessation)
- Carotid imaging if the patient is a candidate for carotid intervention within 1 week of symptom onset
- Urgent brain imaging within 24 hours of symptom onset where vascular territory or pathology is uncertain
- Carotid endarterectomy within 2 weeks if the level of symptomatic carotid stenosis is between 70% and 99% (according to the European Carotid Surgery Trial [ECST] criteria)

Patients with crescendo TIA (two or more TIAs in one week) should be treated as high risk, even if they have an $ABCD_2$ score of 3 or less.[4]

Every patient who has had a TIA should receive an individualised and long-term management strategy for stroke prevention, including provision of information on stroke and its risk factors, regular review of risk factors, and information on their medications for secondary prevention.[7]

QOF indicators for stroke and transient ischaemic attack (TIA)

Indicator	Points	Payment stages
Records		
Stroke 1. The practice can produce a register of patients with stroke or TIA	2	
Stroke 13. The percentage of new patients with a stroke or TIA who have been referred for further investigation	2	40-80%
Ongoing management		
Stroke 5. The percentage of patients with TIA or stroke who have a record of blood pressure in the notes in the preceding 15 months	2	40-90%
Stroke 6. The percentage of patients with a history of TIA or stroke in whom the last blood pressure reading (measured in the previous 15 months) is 150/90 or less	5	40-70%
Stroke 7. The percentage of patients with TIA or stroke who have a record of total cholesterol in the last 15 months	2	40-90%
Stroke 8. The percentage of patients with TIA or stroke whose last measured total cholesterol (measured in the previous 15 months) is 5mmol/L or less	5	40-60%
Stroke 12. The percentage of patients with a stroke shown to be non-haemorrhagic, or a history of TIA, who have a record that an antiplatelet agent (aspirin, clopidogrel, dipyridamole or a combination), or an anticoagulant is being taken (unless a contraindication or side-effects are recorded)	4	40-90%
Stroke 10. The percentage of patients with TIA or stroke who have had influenza immunisation in the preceding 1 September to 31 March	2	40-85%

Stroke/TIA – rationale for inclusion of indicator set

Stroke is the third most common cause of death in the developed world. One-quarter of stroke deaths occur under the age of 65. There is evidence that appropriate diagnosis and management can improve outcomes.

Source: Quality and Outcomes guidance for GMS contract 2009/10, available at: http://www.nhsemployers.org/Aboutus/Publications/DocumentsQOF_Guidance_2009_final.pdf

LONGER-TERM MANAGEMENT

All patients who have had a TIA should be treated with a statin unless contraindicated. Targets are total cholesterol <4.0 mmol/L and LDL cholesterol <2.0 mmol/L, or a 25% reduction in total cholesterol and a 30% reduction in LDL cholesterol, whichever is greatest.[7] Hypertension is a major risk factor for stroke. An optimal blood pressure target of 130/80 mmHg is advised for patients with cardiovascular disease, although a slightly higher target (*eg* systolic 150 mmHg) may be more appropriate for patients with bilateral severe internal carotid artery stenosis.[7] ACE inhibitors and thiazide diuretics are first-line therapies.

Lifestyle modification is important in reducing the risk of stroke and patients should be advised on and supported in the following:[7]

- Smoking cessation
- Taking regular cardiovascular exercise sufficient to become slightly breathless for 20-30 minutes each day
- Eating a healthy diet low in salt and saturated fat and rich in fruit, vegetables, oily fish and wholegrains
- Achieving and maintaining a healthy weight
- Moderating alcohol consumption to no more than three units per day for men and two units per day for women.

Waist circumference targets for the prevention of cardiovascular disease are <102 cm and <88 cm in white Caucasian men and women, respectively, and <90 cm and <80 cm in Asian men and women, respectively. Body mass index (BMI) should be <25 kg/m^2.[11]

For the secondary prevention of cardiovascular events in people with diabetes, treatment is aimed at maintaining a blood glucose concentration of 4-11 mmol/L.[4] Cardiovascular risk can be reduced by 10-15% for every 1% reduction in HbA_{1c} and NICE recommends a target HbA_{1c} of 6.5% for people at macrovascular risk.[12]

CONCLUSION

TIAs precede a significant number of strokes. To aid early presentation, the public needs to be educated about the symptoms of TIA and the necessity to seek urgent medical attention. The early diagnosis of TIAs followed by secondary prevention strategies to reduce the risk of subsequent strokes is crucial in reducing morbidity and mortality.

References

1. Department of Health. *Saving lives: our healthier nation 1999*. Available at http://www.archive.official-documents.co.uk/document/cm43/4386/4386-06.htm (Accessed 18.01.10).
2. British Heart Foundation. Stroke Statistics 2009. Available at: http://www.heartstats.org/datapage.asp?id=8615 (Accessed 18.01.10).
3. Rothwell PM, Giles MF, Chandratheva A, *et al.* Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; **370**: 1432-42. doi:10.1016/S0140-6736(07)61448-2.
4. The National Collaborating Centre for Chronic Conditions. National clinical guidelines for diagnosis and management of acute stroke and transient ischaemic attack (TIA). National Institute for Health and Clinical Excellence. 2008. Available at: http://www.rcplondon.ac.uk/pubs/contents/9c4488ac-d8f1-43d8-b9da-b801441bcdfb.pdf (Accessed 18.01.10).
5. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bulletin of the World Health Organisation* 1976; **54**: 541-53.
6. Stroke Association. Transient ischaemic attack (TIA) Factsheet 1. April 2009. Available at: http://www.stroke.org.uk/information/our_publications/factsheets/az_list_of_factshee.html (Accessed 19.01.10).
7. Intercollegiate Stroke Working Party. National Clinical Guidelines for Stroke. Third edition. July 2008. Available at http://www.rcplondon.ac.uk/pubs/contents/6ad05aab-8400-494c-8cf4-9772d1d15301b.pdf. (Accessed 18.01.10).
8. Johnston SC, Rothwell PM, Nguyen-Huynh MN, *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; **369**: 283-92. doi:10.1016/S0140-6736(07)60150-0.
9. Diener HC, Bogousslavsky J, Brass LM, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364**: 331-7. doi:10.1016/S0140-6736(04)16721-4.
10. Halkes PH, van Gijn J, Kappelle LJ, *et al.* Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367**: 1665-73. doi:10.1016/S0140-6736(06)68734-5.
11. Joint British Societies' Guidelines (JBS2) on the prevention of cardiovascular disease in clinical practice. *Heart* 2005, **91**; 5: v1-v52. doi:10.1136/hrt.2005.079988.
12. NICE guideline CG66. Type 2 diabetes 2008. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf (Accessed 25.01.10).

“The early diagnosis of TIAs followed by secondary prevention strategies to reduce the risk of subsequent strokes is crucial in reducing morbidity and mortality”

Effective management of atrial fibrillation

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, and has a significant impact on morbidity and mortality. Treatment is tailored to the individual. This article will review the rhythm-management strategies for patients with atrial fibrillation, and discuss the roles of secondary and tertiary care.

David Jones
Fellow in Cardiac Electrophysiology, Royal Brompton & Harefield NHS Foundation Trust and Imperial College London

Tom Wong
Consultant Cardiologist, Royal Brompton & Harefield NHS Foundation Trust and Imperial College London

Diana Gorog
Consultant Cardiologist, East & North Hertfordshire NHS Trust and Imperial College London

Vias Markides
Consultant Cardiologist, Royal Brompton & Harefield NHS Foundation Trust and Imperial College London

Prim Care Cardiovasc J 2010; **3**: S27–S30

doi: 10.3132/pccj.2010.036

Key points:

- Treatment of AF should be tailored to the individual
- In asymptomatic individuals, rate control may suffice
- A rhythm control strategy is generally recommended in symptomatic patients, particularly those with paroxysmal AF
- Catheter ablation is an effective therapy for symptomatic patients who fail or cannot tolerate antiarrhythmic drugs

A discussion on thromboprophylaxis is beyond the scope of this article, however anticoagulation is recommended for a significant proportion of patients with AF, based upon appropriate stroke-risk assessment.

ACUTE SYMPTOMATIC AF

For many cases of AF, relatively stable clinical status at presentation allows initial management to take place in primary care.

Sudden onset AF, whether first-presenting or recurrent, associated with severe symptoms of dizziness, breathlessness, or palpitation should be considered for management in an acute secondary care setting. In particular, patients with a ventricular rate greater than 150 beats per minute (bpm), ongoing chest pain, or signs of critical hypoperfusion need emergency admission. Those with life-threatening haemodynamic instability should be treated by emergency electrical cardioversion. This particularly applies to the rare but life-threatening condition of preexcited (broad complex) AF in the context of Wolff-Parkinson-White (WPW) syndrome – an irregular broad complex tachycardia, which may be the first presentation of some WPW patients.

If the patient can be stabilised by medical therapy (including acute rate control), consideration is then given to duration of AF:

- Greater than 48 hours or uncertain, the strategy should be anticoagulation and rate control in the first instance, with a view to cardioversion after >3 weeks at therapeutic INR (target 2.5)
- Less than 48 hours, attempts to restore sinus rhythm (typically intravenous flecainide if no structural heart disease, amiodarone otherwise) can be made.

RATE CONTROL

Drugs achieve control of the ventricular rate during AF by acting on the atrioventricular (AV) node to reduce the number of impulses that get through. Ideally, rate-controlling agents should control the heart rate both at rest and during activity in a graded manner, as is the physiological norm in sinus rhythm. Although such an ideal does not exist, patients with otherwise good cardiac function may tolerate this state of 'rhythm failure' if excessive rate swings are prevented.

Suggested targets for rate control are a resting heart rate of 60-80 bpm, and 90-115 on moderate exercise.[1] Although many cardiologists would use the guidelines – particularly in such symptomatic patients (before accepting that the 'rate control strategy' has failed), it remains uncertain how strict the goals should be. The recently reported RACE II trial results suggest that 'lenient' (target <110 bpm at rest) and 'strict' (<80 rest, <110 on moderate exercise) rate-control strategies are associated with similar prognostic outcomes.[2] However it is apparent that many, but not all, symptomatic patients benefit from so-called 'strict' rate control, and an individualised approach is recommended.

DRUG THERAPY FOR RATE CONTROL

When possible, rate-controlling drugs are generally given once daily in the morning – medicating predominantly at night can lead to excess nocturnal bradycardia with suboptimal daytime control.

Beta-blockers

Beta-blockers control the ventricular rate at rest and on exertion, improve symptoms, and are particularly useful as combination therapy with digoxin.[3] They have an excellent safety profile, and are also indicated in the management of co-morbid conditions such as heart failure and ischaemic heart disease. Additionally, there is evidence for some 'rhythm-controlling' effect,[4] perhaps through reducing ectopic triggers of AF. On this basis, beta-blockers can be considered a first-line agent in most patients with AF, regardless of persistence.[5]

Typical drugs include atenolol (25-100 mg once daily) and bisoprolol (2.5-10 mg once daily). In those with significant systolic dysfunction, bisoprolol or carvedilol (3.125-25 mg twice daily) should be up-titrated slowly after introduction, so the patient may take longer to achieve rate control – a decompensated patient with rapid AF and heart failure may need careful acute rate control in a monitored in-patient environment.

Calcium channel blockers

Conduction through the AV node depends largely on calcium currents, which may be suppressed by non-dihydropyridine calcium blockers. These are effective rate controllers, and may be superior to beta-blockers for rate control during exercise.[6]

They are particularly useful in patients with contraindications to, or intolerant of, beta-blockers. The main side-effects are relative hypotension, and occasionally ankle swelling. The available agents are diltiazem (typical AF dose 120-360 mg daily) and verapamil (120-360 mg daily), both in 1-3 doses depending on formulation. Diltiazem may also safely be combined with digoxin, a highly effective combination for rate control at rest and on exercise.

It is recommended that calcium channel blockers are not used for chronic rate control in patients with significant LV dysfunction – digoxin and beta-blockers are then preferred.

Digoxin

Although historically the commonest drug used in atrial fibrillation, the routine use of digoxin for management of AF is no longer recommended for most patients. This is principally because although it controls heart rate modestly at rest, it does so poorly on exercise. However, digoxin is recommended as part of a combination rate-control strategy for those with significant LV dysfunction,[1] given its positive inotropic functions and ability to improve heart failure symptoms, or in elderly, sedentary patients with good renal function and relatively good rate control at baseline.

PACEMAKERS

Rate control is required at both ends of the spectrum. However, transient bradycardia is expected in AF, even when average rates are controlled, and does not necessarily cause symptoms unless profound and/or prolonged.

In general, permanent pacing is not indicated unless the patient has symptomatic bradycardia. If this does occur, in the context of otherwise appropriate rate control, the patient should be referred to a cardiologist for consideration of permanent pacemaker insertion. For permanent AF, single chamber pacemakers are used. For paroxysmal AF, the aim for patients with bradycardia during AF should be maintenance of sinus rhythm. Dual chamber pacing may be indicated in the presence of (spontaneous or drug-induced) sinus node dysfunction associated with non-permanent AF.

AV NODE ABLATION

Patients who require rate control but who remain tachycardic despite optimal pharmacological treatment, have a further option: radiofrequency catheter ablation of the AV node, which achieves both rate control and regularisation of the ventricular rate.[7] This necessitates implantation of, and dependency on, a permanent pacemaker in all cases so is typically reserved for older patients, or those in whom a pacemaker is already in situ.

This 'ablate and pace' strategy is generally effective and well tolerated, with many studies showing an improvement in quality of life and left ventricular function.[7-9] Some patients experience a worsening in symptoms after the procedure, especially if there is underlying ventricular dysfunction, although in some this may be ameliorated by biventricular pacing. Fibrillation of the atria, and risk of thromboembolism, both continue.

RHYTHM CONTROL

The aim of the rhythm control strategy is to restore and maintain sinus rhythm. In general, this strategy is far more likely to involve access to specialist cardiology services. Patients often still require rate control until sinus rhythm is restored, and during any paroxysms that break through the control of antiarrhythmic drugs.

If AF requires cardioversion, this can be achieved pharmacologically or electrically. Each has its merits: acute AF (<48 hours onset) can be treated in hospital with a slowly administered bolus of flecainide without the need for electrical cardioversion, avoiding general anaesthesia or sedation, but this becomes less effective as the paroxysm continues past 24 hours.

If restoration of sinus rhythm is required on haemodynamic grounds, acute electrical cardioversion can be offered. It must be emphasised that if a clear onset of AF within 48 hours of presentation cannot be ascertained, restoration of sinus rhythm should be deferred pending therapeutic anticoagulation for at least three weeks, unless haemodynamic symptoms warrant a strategy of transoesophageal echocardiography to help exclude atrial thrombus followed by direct current (DC) cardioversion.

The efficacy of pharmacological therapy when administered >48 hours after onset of AF is modest and because therapeutic anticoagulation is required for at least three weeks before initiation of such therapy the preferred strategy is that such anticoagulation be followed by DC electrical cardioversion, usually as a day-case hospital admission.

Maintenance of sinus rhythm, *ie* prevention of recurrent AF (either paroxysmal or persistent), usually requires antiarrhythmic drug therapy. After a first AF episode, it is reasonable to await a second episode before commencing antiarrhythmic therapy, because the time to recurrent AF is 'unknown'.

PHARMACOLOGICAL THERAPY

The overall approach should be 'stepwise,' moving from lower-risk interventions with some potential benefit to those that are more effective but carry a greater risk of adverse effects. The first-line agent, including after initial cardioversion, should generally be a standard (non-sotalol) beta-blocker. If, despite maximum tolerable dose-titration, this fails,

the options are class I or III antiarrhythmic drugs. In most cases, it is appropriate for these to be initiated by a cardiologist.

Class I antiarrhythmic drugs, which are sodium channel blockers related to local anaesthetic agents, can be highly effective at maintaining sinus rhythm. The main agents used in the UK are flecainide (100-300 mg daily in divided doses), and propafenone. They are negatively inotropic, have an association with poor outcomes in patients with previous myocardial infarction, and also increase the risk of electrical block in the His-Purkinje system, so patients should be screened for:

- Structural heart disease including previous myocardial infarction, symptomatic coronary artery disease, and cardiac failure
- ECG abnormalities such as bundle branch block, 1st degree heart block, and prolonged QT

Sotalol, a class III antiarrhythmic related to beta-blockers, can also be effective in maintaining sinus rhythm. NICE guidelines recommend it is up-titrated from 80 mg twice daily to 240 mg twice daily. However, we would advise extreme caution when doing this, especially in a primary care setting. There is a risk of pro-arrhythmia due to QT prolongation and torsade de pointes ventricular tachycardia.

Amiodarone has less pro-arrhythmic risk, but is associated with multiple extra-cardiac side-effects, particularly thyroid dysfunction, pulmonary inflammation/fibrosis, and skin problems such as photosensitivity, corneal micro-deposits, and, less commonly, liver and neurological problems. It interacts with warfarin very significantly.

It is the rhythm-control agent of choice in the short-medium term for patients with structural heart disease, especially those with LV dysfunction, but remains generally unsuitable for long-term use. The elderly, in particular, are at risk of bradycardia during initial loading therapy, both in AF and if sinus rhythm is restored; thus caution should be exercised. However, it is probably one of the safest antiarrhythmic agents to be initiated out-of-hospital.

NICE recommendations on initial strategy for treating AF

Rate control	Rhythm control
• minimal or no symptoms	• symptomatic
• persistent AF	• paroxysmal or persistent <1 year
• >65 years old	• younger patients
• coronary artery disease	• first presentation with lone AF
• contraindications to antiarrhythmic drugs	• AF secondary to a treated/corrected precipitant
• unsuitable for cardioversion	• congestive heart failure*
• no congestive heart failure*	

*based on subgroup data from AFFIRM and RACE – not supported (for drug-based rhythm control) by AF-CHF data

NEW ORAL ANTIARRHYTHMICS

Several new oral antiarrhythmics are on the horizon, which offer the potential for greater efficacy with fewer side-effects. The first available new drug, dronedarone, is a non-iodinated derivative of amiodarone with less extra-cardiac toxicity but similar 'broad-spectrum' antiarrhythmic properties. Large clinical trial results look promising[10] and, although its use may not extend to those with heart failure,[11] it is likely to add to the armamentarium of AF therapies, particularly given its apparently improved safety profile, possibly at the expense of efficacy, compared with amiodarone.[12] It has recently been approved for specialist initiation in the UK by NICE.[13]

Rate versus rhythm control

The consensus is that when AF is well tolerated in the over-65s, it can reasonably be treated with a rate-control strategy. If, however, a patient remains symptomatic despite optimal rate control, the rhythm-control strategy is recommended. Appropriate thromboprophylaxis should be given regardless of the strategy.

WHO SHOULD BE REFERRED TO TERTIARY CARE?

NICE guidelines suggest the following patients should be referred to a heart rhythm specialist (cardiac electrophysiologist):

- Those who have failed pharmacological therapy
- Those with lone AF
- Those with ECG evidence of an underlying electrophysiological disorder

Most younger patients, particularly those under the age of 60, should be assessed by an electrophysiologist. In particularly young patients (<40 years) another arrhythmia capable of precipitating AF, such as WPW syndrome or supraventricular tachycardia (which may be easily cured by catheter ablation), can sometimes be identified. However, there also appears to be a distinct group of young (30-50 years) patients (men more frequently than women) with no obvious associated arrhythmias or structural abnormalities (lone AF) who are often quite symptomatic and who tend to require specialist advice/treatment.

WHAT ARE THE SPECIALIST OPTIONS?

A cardiologist with a specialist interest in heart rhythm (cardiac electrophysiologist) can, amongst other things, offer the following therapeutic options:

- Further optimised antiarrhythmic therapy and/or rate control
- Pacemaker insertion, eliminating bradycardias and allowing escalation in pharmacological therapy
- Catheter ablation of the AV node with pacemaker insertion
- Radiofrequency catheter ablation of atrial fibrillation

This last procedure has become established over the last 10 years, and is now an invaluable non-pharmacological rhythm-control option for symptomatic patients unresponsive to, or intolerant of, antiarrhythmic drugs.

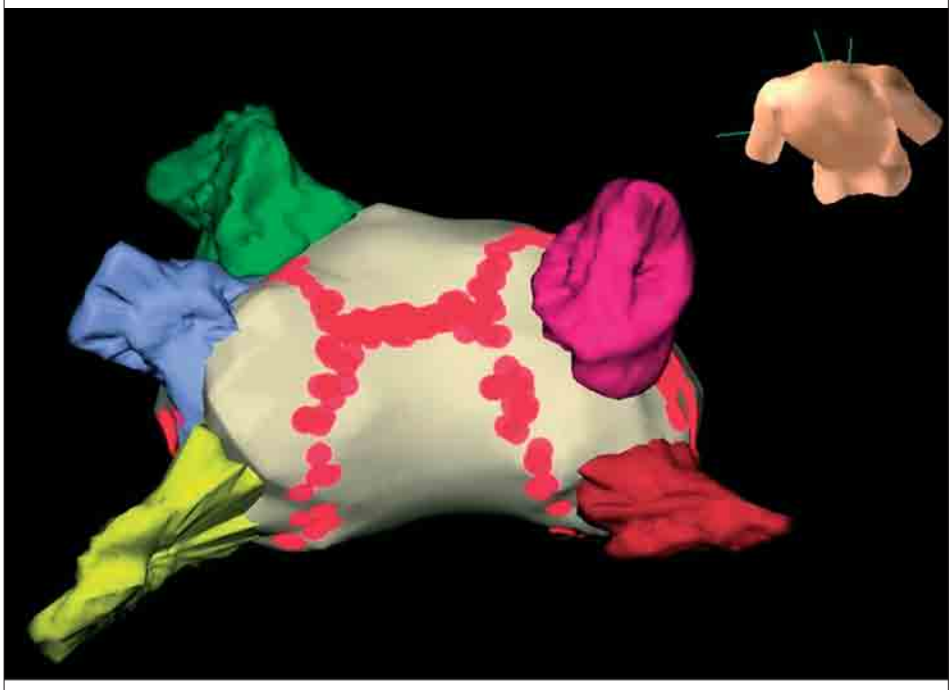
The discovery in the late 1990s that AF could have a focal origin, often in the pulmonary veins, led to the use of minimally invasive radiofrequency catheter ablation techniques to destroy these areas,[14] and later techniques to electrically disconnect the pulmonary veins from the atria – so-called 'pulmonary vein isolation'. Subsequent advances in both understanding of AF pathophysiology, and available technology, including the 3-D reconstruction of the patient's atria and pulmonary veins, have enabled creation of complete encircling and linear atrial lesions (Figure 1), in addition to targeting other areas of pro-fibrillatory activity that contribute to the maintenance of AF.

Long-term freedom from AF can be expected in 70-90% of patients, depending on the duration and complexity of AF, with repeat procedures being necessary to achieve these results in a significant minority of patients. Important complications of the procedure include transient ischaemic attack or stroke (0.5-1.5%, largely dependent on age), tamponade needing drainage (1-3%), symptomatic pulmonary vein stenosis requiring stenting (<0.5%), and right phrenic nerve palsy (0.3%, usually transient). These risks need to be considered in the context of patient symptoms and their risk of stroke with non-intervention, as assessed by the $CHADS_2$ score.

WHO SHOULD BE REFERRED FOR CONSIDERATION OF AF ABLATION?

AF is so common that catheter ablation cannot be offered to all patients. Thankfully, most patients can be managed medically, with appropriate reduction in thromboembolic risk and symptomatic control (with rate or rhythm control) as the cornerstones of treatment. However, ablation can be very useful for patients refractory to, or intolerant of, medical treatment. Younger, highly symptomatic patients with paroxysmal AF are obvious candidates for the procedure as they have the highest success and lowest complication rates, but the application of ablation techniques has been expanded to older patients and patients with long-standing AF.

Figure 1: 3-D reconstruction of left atrium using NavX system



(St Jude Medical, MN, USA). The left atrium is seen from above and behind, with left atrial appendage (green) top left. Circumferential ablation (red dots) has been performed around each pair of pulmonary veins (magenta, red; yellow, blue), resulting in their electrical disconnection from the left atrium, and a line of ablation created on the roof of the left atrium. This map can be navigated in real time allowing reduced use of X-ray fluoroscopy and accurate delivery of treatment.

References

1. Fuster V, Rydén LE, Cannom DS, *et al.* ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Europace* 2006; **8**: 651-745.
2. Van Gelder IC, Groenveld HF, Crijns MD, *et al.* Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010; **362**: 1363-73.
3. Khand AU, Rankin AC, Martin W, *et al.* Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003; **42**: 1944-51.
4. Gronefeld GC, Hohnloser SH. Beta-blocker therapy in atrial fibrillation. *Pacing Clin Electrophysiol* 2003; **26**: 1607-12.
5. Lip GY, Rudolf M. The new NICE guideline on atrial fibrillation management. *Heart* 2007; **93**: 23.
6. Camm AJ, Savelieva I, Lip GY. Rate control in the medical management of atrial fibrillation. *Heart* 2007; **93**: 35-8.
7. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation* 2000; **101**: 1138-44.
8. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992; **69**: 1570-3.
9. Verma A, Newman D, Geist M, *et al.* Effects of rhythm regularization and rate control in improving left ventricular function in atrial fibrillation patients undergoing atrioventricular nodal ablation. *Can J Cardiol* 2001; **17**: 437-45.
10. Hohnloser SH, Crijns HJ, van Eickels M, *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; **360**: 668-78.
11. Kober L, Torp-Pedersen C, McMurray JJV, *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; **358**: 2678-87.
12. Piccini JP, Hasselblad V, Peterson ED, *et al.* Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009; **54**: 1089-95.
13. National Institute for Health and Clinical Excellence (NICE). Final appraisal determination – Dronedarone for the treatment of non-permanent atrial fibrillation. July 2010. Available at: http://www.nice.org.uk/nicemedia/live/11750/49792/49792.pdf
14. Haissaguerre M, Jais P, Shah DC, *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339**: 659-66.

Looking to the future for the management of AF and prevention of stroke

John Camm
Professor of Clinical Cardiology, St. George's, University of London

Irene Savelieva
Lecturer in Clinical Cardiology, St. George's, University of London

Prim Care Cardiovasc J 2010; **3**: S31-S34

doi: 10.3132/pccj.2010.035

Atrial fibrillation (AF) is becoming an epidemic, affecting 1% to 2% of the population in the developed world. Looking to the future, the prevalence of AF will grow dramatically in the coming decades as the elderly population increases. The growing numbers underline the need to improve the detection of patients with AF and measures for reducing their risk of stroke.

The prevalence of atrial fibrillation (AF) is highly age-dependent and is increasing rapidly as the population ages (see Figure 1). However, the rate of increase of AF is greater than can be accounted for by age alone and is probably related to the increasing prevalence of underlying non-fatal cardiovascular disease. Current estimates for the UK, derived from projections of US data, suggest that the number of people with AF may double by 2050, leading to 1.5-2.0 million people with AF.[1]

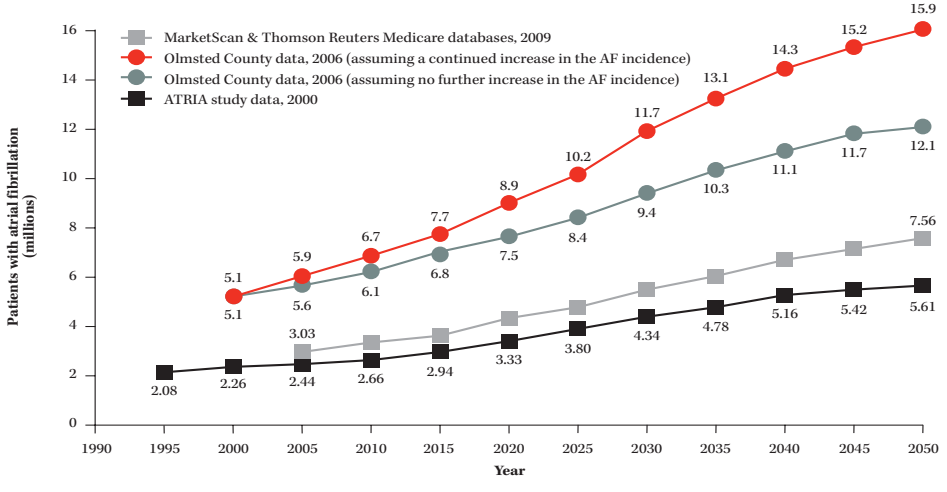
AF is associated with a range of local, systemic and cardiovascular causes as diverse as heart failure, hypertension, valvular disease, carcinoma of the bronchus, alcohol toxicity, endurance athletics and thyrotoxicosis. There are also many other factors that are associated with AF but which may not directly cause the arrhythmia, including: tall stature, long PR interval, obesity, sleep apnoea, and metabolic syndrome. The substrate or triggers for AF may be caused or aggravated by these associated conditions or the link may be due to unknown third factors.

The cardiovascular consequences of AF include stroke, heart failure, tachycardiomyopathy, acute coronary syndrome, all-cause cardiovascular mortality or sudden cardiac death. These may also be directly due to AF

Key points:

- Atrial fibrillation is common and will become more common
- Predicting the imminent development to AF or its progression will allow timely and more successful interventions
- Warfarin will be superseded by new direct thrombin or factor Xa inhibitors
- New antiarrhythmic drugs may provide added value by reducing adverse cardiovascular outcomes
- Left atrial ablation will be an early 'curative' intervention for atrial fibrillation

Figure 1: Predictions of the increase in atrial fibrillation in the US



The prevalence of AF will grow dramatically in the coming decades as the elderly proportion of the population increases. Projected numbers of patients with AF by 2050 are based on current US estimates.

(such as heart failure due to tachycardiomyopathy) or may simply be related to an independent factor that causes both AF and its 'consequences'. In most instances, the contribution to major outcomes from AF and from the causes of AF are not easily distinguished. This is the case with stroke and other cerebral pathologies such as Alzheimer's disease, white matter lesions, and multi-infarct dementia, all of which are associated with AF. This 'marker' versus 'mechanism' concept is fundamental to a proper understanding of how the future of AF management will develop.

AF IS AN INDEPENDENT CV RISK MARKER

It is increasingly clear that AF should be considered as an independent cardiovascular (CV) risk marker. For example, a patient with diabetes or heart failure has a worse outcome if AF is also present. For this reason, it is important to develop methods of predicting if and when AF will develop, especially in groups where its development forecasts a very much worse outcome that could be rescued by an appropriate medical intervention.

Although it is well known that heart failure increases the risk of developing AF by 4-5 fold and that diabetes will increase the likelihood of AF by as much as 50%, the development of comprehensive risk factor schemes have been intrinsically restricted by the limited data that have been collected in epidemiological surveys and clinical trials.

Recent Framingham data have been used to construct a 10-year AF risk prediction score, using a small number of variables, most of which are related to a patient's age and clinical history, but with one additional piece of data – the PR interval from an ECG.[2] Although this is a step forward, a much more accurate, short-term risk calculator is needed to predict the risk of developing AF within the next few days or weeks, if the intention is to justify and implement medical treatment strategies.

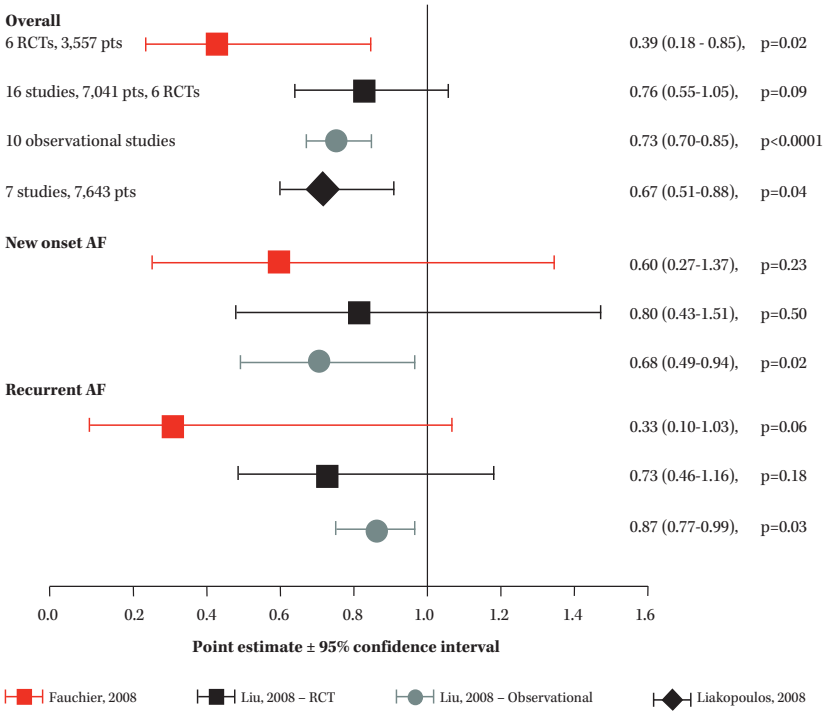
Instead of attempting to predict the first development of AF, it may be more productive to define the likely rate of progression from the first presentation to the development of permanent AF that may then be refractory to treatments aimed at curbing the inexorable deterioration of the atrial substrate for AF.[3] Such a prediction would allow timely interventions that may successfully halt, or even reverse, the progression. A range of 'upstream' therapies are being developed that aim to reduce or eliminate the development of atrial fibrosis. Renin angiotensin system (RAS) inhibitors[4] and statins[5] (see Figure 2) have been extensively investigated, but more specific agents and mechanisms are now being addressed.

For some years, it has been suggested that AF might be cured by reducing the mass, or interrupting the continuity, of atrial tissue. Surgeons, and then interventional cardiologists, attempted to compartmentalise the atria in such a way as to break up the contiguous area of tissue necessary to support multiple waves of re-entry while still preserving sinus/AV nodal conduction to allow sinus rhythm to control the ventricular rate. These techniques have, on the whole, proved to be of limited value.

The discovery of specific triggers of AF[6] (mostly pulmonary vein ectopic activity) prompted their isolation as a major therapeutic strategy. Pulmonary vein isolation (left atrial ablation) has proved to be much more successful, especially in relatively early paroxysmal AF not associated with underlying heart disease, but the appropriate time to intervene, the best lesion set and the most effective ablation energy source (*eg* radiofrequency or cryothermy) for individual patients have not yet been defined. Most importantly, the long-term value of this approach on substantive cardiovascular outcomes, especially in patients with underlying cardiovascular disease, has not been assessed despite considerable enthusiasm for the use of left atrial ablation symptom relief.

> **It is increasingly clear that AF should be considered as an independent cardiovascular risk marker**

Figure 2: Meta-analyses demonstrating the efficacy of statin therapy in the prevention or recurrence of AF[5]



Critically, it has not been established whether a reduction in AF symptoms, and/or AF burden, will be sufficient to impact on the stroke risk associated with AF. However, favourable reports in small numbers of patients who generally have a low absolute stroke risk threaten to destroy the current equipoise and may lead to widespread failure to anticoagulate patients who would otherwise have been considered at high risk.

Antiarrhythmic drugs have generally been helpful for the relief of symptoms associated with AF, but they have not been so successful in reducing the recurrence of AF. Therefore, doctors have not so often been tempted to ignore stroke risk stratification and appropriate anticoagulation. It is not known whether complete and certain eradication of AF would be sufficient in patients at high risk of stroke to allow protection with anticoagulant therapy to be discarded.

The use of a new antiarrhythmic agent, dronedarone, has been associated with a major reduction of stroke events in an elderly population at relatively high risk of stroke.[7] This finding was the result of a *post hoc* analysis and, as the drug is no more effective than other antiarrhythmic agents in suppressing AF, it is possible that the finding is unreliable, or unrelated to the direct antiarrhythmic treatment of AF. Nevertheless, the results will stimulate intensive research in this arena.

STROKE PREVENTION

AF increases the risk of stroke by approximately five fold, and one in six of all strokes is attributable to AF. Strokes associated with AF are more often fatal or disabling than those due to other causes. Blood stasis (*eg* from atrial paralysis), endothelial dysfunction (*eg* inflammation) and abnormal blood constituents (*eg* haemostatic factors) contribute to the high risk of thromboembolism, but the contribution directly from the AF itself is difficult to quantify. Many patients with AF have a myriad of other potential causes for abnormal blood coagulation and/or thromboembolism.

Early placebo-controlled clinical trials and epidemiological registries allowed some risk factors for thromboembolism to be identified. These sources are limited by the data that were collected and the entire basis for stroke risk has not been identified, even when other known clinical, biochemical and echocardiographic risk factors are entered into the model.

At present, the $CHADS_2$ scheme (one point for congestive cardiac failure, hypertension, age ≥75 years, diabetes and two points for stroke/TIA)[8] is most often used to calculate a score that is proportional to thromboembolic risk. A score of two or more warrants treatment with warfarin. No treatment is deemed necessary when the score is zero. Warfarin or aspirin is given to patients with a score of 1, according to the presence of additional risk factors and the wishes of the patient.[9]

Much effort is now being expended in seeking better stroke risk prediction, coupled with a wish to identify better the risk of bleeding in response to therapy. This has become much more important with the development of new anticoagulants with better therapeutic indices than warfarin and fewer potential complications related to innate resistance, metabolic interactions with food, alcohol and medications, adherence to therapy and co-morbidities.

New drug therapies

Direct thrombin inhibitors may be better than warfarin for the treatment of patients with AF.

Oral factor Xa inhibitors also hold promise to be significantly better than current therapy, although no clinical trial has yet reported.

A galaxy of further direct thrombin and factor Xa inhibitors is being developed, with many in the late stages of phase III clinical trials. The anticoagulation therapy for AF will change considerably as information accrues and new drugs are approved. These new and easier methods of providing anticoagulant therapy will reduce or practically eliminate the large residue of patients who cannot, or will not, be adequately anticoagulated with warfarin.

New devices

The majority of thrombi, although not all, form in the blind-ended left atrial appendage (LAA), so another approach to reducing the stroke risk in patients with AF is to occlude the appendage with a device introduced percutaneously. There are several different designs for such an occluder. A randomised study comparing one of these devices with warfarin has demonstrated that LAA occlusion is non-inferior in reducing stroke risk, although there is a small early risk related to the introduction of the occluder.[10] When catheter-based left atrial ablation is undertaken, it seems likely that some of the risk of LAA occlusion has already been offset and this technique will become increasingly popular.

The "pill-in-the-pocket" approach

AF can now be monitored in real time using subcutaneous pacemakers or implanted loop recorders. Combined with an alert, a monitor could warn a

“AF increases the risk of stroke by approximately five fold, and one in six of all strokes is attributable to AF”

patient of the onset and continuation of AF so they could administer a rapidly acting anticoagulant, including some of the new agents being developed. In this way, it may be possible to use a "pill-in-the-pocket" anticoagulation strategy for patients with recurrent AF, minimising the risk of haemorrhage while preserving the appropriate anticoagulant effect by reducing the total duration over which the patient is anticoagulated.

Acknowledgement

Professor Camm is funded by the British Heart Foundation.

Declaration of Interest

Professor Camm has acted as a speaker/advisor for: sanofi aventis, Boehringer Ingelheim, Bayer, Daiichi, Bristol-Myers Squibb.

References

1. Go AS, Hylek EM, Phillips KA, *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370-5.
2. Schnabel RB, Sullivan LM, Levy D, *et al.* Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009; **373** (9665): 739-45.
3. De Vos CB, Pisters R, Nieuwlaat R, *et al.* Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. *J Am Coll Cardiol* 2010; **55**: 725-31.
4. Schneider MP, Hua TA, Böhm M, *et al.* Prevention of atrial fibrillation by renin-angiotensin system inhibition: a meta-analysis. *J Am Coll Cardiol* 2010; **55**: 2299-307.
5. Savelieva I, Kourliouros A, Camm J. Primary and secondary prevention of atrial fibrillation with statins and polyunsaturated fatty acids: review of evidence and clinical relevance. *Naunyn Schmiedebergs Arch Pharmacol* 2010; **381**: 1-13.
6. Haïssaguerre M, Jaïs P, Shah DC, *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339**: 659-66.
7. Connolly SJ, Crijns HJ, Torp-Pedersen C, *et al.* on behalf of the ATHENA Investigators. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009; **120**: 1174-80.
8. 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.
9. Fang MC, Go AS, Chang Y, *et al.* on behalf of the TRIA Study Group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2008; **51**: 810-5.
10. Holmes DR, Reddy VY, Turi ZG, *et al.* on behalf of the PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374** (9689); 534-42.